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HYPERTONIC/HYPERONCOTIC RESUSCITATION FROM SHOCK:
REDUCED VOLUME REQUIREMENT AND LOWER INTRACRANIAL PRESSURE

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Final Report

Donald S. Prough, M.D.

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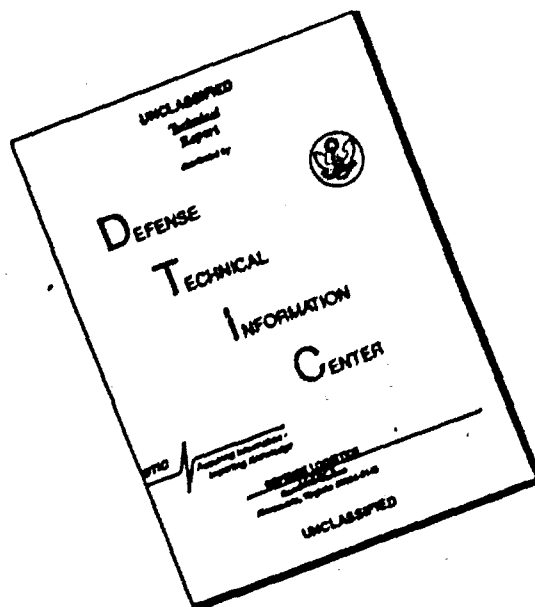
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The completed project accomplished the stated goals:

1. To determine the effects on intracranial pressure (ICP) of resuscitation from hemorrhage using conventional volumes of isotonic (SAL) resuscitation solutions in comparison to small volumes of hypertonic 7.2% saline (HS), hyperoncotic 20% hydroxyethylstarch (HES) or the combination of hypertonic 7.2% saline and 20% hydroxyethylstarch (HES/HS).
2. To determine the effects on cerebral blood flow (CBF) of resuscitation from hemorrhage using conventional volumes of isotonic (SAL) resuscitation solutions in comparison to small volumes of hypertonic 7.2% saline (HS), hyperoncotic 20% hydroxyethylstarch (HES), or the combination of hypertonic 7.2% saline and 20% hydroxyethylstarch (HES/HS). 

To accomplish that goal, we performed two series of canine experiments. The first series consisted of measuring ICP and CBF before, during and after hemorrhage in anesthetized animals without central nervous system lesions. In the second series, hemorrhage was superimposed on an intracranial mass lesion (subdural balloon). Each type of experiment was performed using one of two CBF measurement methodologies: continuous cerebral venous outflow measurements and injection of radiolabelled microspheres.

Immediately following baseline measurements, arterial blood was rapidly removed to reduce and maintain mean arterial pressure (MAP) at a target level for 30 minutes by further removal or reinfusion of shed blood. The animals then received one of four resuscitation fluids: 0.8% NaCl (137 mEq/L Na⁺; ISO); 7.2% NaCl (1233 mEq/L Na⁺; HS); 20% hydroxyethylstarch (HES); 20% hydroxyethylstarch dissolved in 7.2% saline (HES/HS).

The results indicate that:

- a. Hypertonic saline and combinations of hypertonic saline with hydroxyethylstarch are associated with lower intracranial pressure than isotonic solutions when used for resuscitation from hemorrhagic shock, with or without the presence of an intracranial mass lesion.
- b. Cerebral blood flow is improved by hypertonic resuscitation if an intracranial mass lesion is present.
- c. Under certain circumstances, hypertonic saline is associated with a delayed rise in intracranial pressure at a time when the systematic hemodynamic effects have dissipated.
- d. In general, the hemodynamic effects of hypertonic saline resuscitation are transient.
- e. The addition of hyperoncotic colloid somewhat prolongs the effects of hypertonic solutions.

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The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

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FOREWORD

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

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INTRODUCTION

The completed project accomplished the stated goals:

1. To determine the effects on intracranial pressure (ICP) of resuscitation from hemorrhage using conventional volumes of isotonic (SAL) resuscitation solutions in comparison to small volumes of hypertonic 7.2% saline (HS), hyperoncotic 20% hydroxyethylstarch (HES), or the combination of hypertonic 7.2% saline and 20% hydroxyethylstarch (HES/HS).
2. To determine the effects on cerebral blood flow (CBF) of resuscitation from hemorrhage using conventional volumes of isotonic (SAL) resuscitation solutions in comparison to small volumes of hypertonic 7.2% saline (HS), hyperoncotic 20% hydroxyethylstarch (HES), or the combination of hypertonic 7.2% saline and 20% hydroxyethylstarch (HES/HS).

To accomplish that goal, we performed two series of canine experiments. The first series (Series 1 and 1a) consisted of measuring ICP and CBF before, during and after hemorrhage in anesthetized animals without central nervous system lesions. The second series (Series 2 and 2a) consisted of studies in which hemorrhage was superimposed on an intracranial mass lesion (subdural balloon).

Each type of experiment was performed using two distinct methodologies. In the first, CBF was measured using continuous cerebral venous outflow measurements (Series 1 and 2); in the second, CBF was measured using injection of radiolabelled microspheres (Series 1a and 2a).

	Cerebral Venous Outflow	Radiolabelled Microspheres
No Mass Lesion	1	1a
Mass Lesion	2	2a

To enhance clarity, the studies were divided for analysis into two group sets. For instance, the first series 1 analysis consists of a comparison between hypertonic saline and isotonic saline in animals without a mass lesion in which CBF was measured using cerebral venous outflow.

The following summary will consist of several parts:

1. Summary of experimental methods and techniques
2. Summary of individual comparisons
3. Abstracts of presented data
4. Conclusions
5. Recommendations for further study

SUMMARY OF EXPERIMENTAL METHODS AND TECHNIQUES

Methods: Series 1. Cerebral Venous Outflow, No Mass Lesion

Animals used in this study were, handled according to guidelines established by the institution's animal care and use committee. A total of twenty-four mongrel dogs of either sex, weighing 18-22 kg were studied.

Anesthesia

Dogs were fasted overnight, then anesthetized with thiopental sodium (8.0 mg/kg), paralyzed with succinylcholine (4 mg/kg) and endotracheally intubated. Halothane 0.5% in 60% nitrous oxide maintained anesthesia and animals were ventilated, using a Edco Model 822 Large Animal Ventilator (Edco Scientific, Inc., Chapel Hill, NC), at a tidal volume (15 ml/kg) and rate sufficient to maintain normocarbica (PaCO_2 35-45 mm Hg). Additional succinylcholine, given as needed, prevented respiratory movement.

Hemodynamic Monitoring

Two femoral artery catheters were placed for monitoring of arterial blood pressure and for induction of rapid hemorrhage, respectively. A flow-directed pulmonary artery catheter was placed via the right

external jugular vein using the Seldinger technique. Systemic and pulmonary artery pressures were continuously recorded on a Grass Model 79D polygraph (Grass Instrument Co., Quincy, Mass.) with saline filled Gould Statham P23 transducers (Gould, Inc., Oxnard, CA). Pulmonary artery wedge pressure (PAWP) and central venous pressure (CVP) were monitored intermittently. Core temperature was monitored by a thermistor at the tip of the pulmonary artery catheter and maintained with a heating pad. Cardiac output (CO) was recorded intermittently using an American Edwards 9520A cardiac output computer (American Edwards, Santa Ana, CA). All transducers were intermittently calibrated with the level of the left atrium except for intracranial pressure (ICP), which was zeroed at the level of the external auditory canal.

Cerebral Venous Outflow

Following splenectomy, animals were turned to the prone "sphinx" position and the occipital musculature dissected from the underlying bone. Cerebral blood flow (CBF) was measured using a modification of the technique originally described by Rapela and Green (1), where the confluence of the sagittal and lateral sinuses was cannulated and timed samples of cerebral venous outflow measured. A 18 G catheter inserted within the cisterna magna provided continuous monitoring of ICP.

Method of Hemorrhage

After instrumentation, animals were stabilized for 30 minutes and baseline (B) data were recorded. Immediately following baseline, arterial blood was rapidly removed to reduce mean arterial pressure (MAP) to 40 mm Hg, and this level was maintained for 30 minutes by further removal or reinfusion of shed blood. Data were collected at the beginning (TO) and end of shock (T30). The animals were then randomized into one of two groups, based upon resuscitation fluid type. All fluids were rapidly infused intravenously over a 5 minute period. Group 1 (SAL) received 32 ml/kg of 0.9% NaCl (145 mEq/L Na⁺); group 2 (HS) received 4.0 ml/kg of 7.2% NaCl (1233 mEq/L Na⁺); group 3 (HES) received 4.0 ml/kg of 20% hydroxyethylstarch; and group 4 (HES/HS) received 4.0 ml/kg of 20% hydroxyethylstarch dissolved in 7.2% saline. Data were collected immediately following resuscitation (T35) and at 60 minute intervals thereafter for two hours (T95, T155).

Collected data included:

1. CBF
2. ICP
3. Systolic and diastolic blood pressure
4. Pulmonary arterial and pulmonary artery occlusion pressure
5. Central venous pressure
6. Cardiac output
7. Arterial pH, PaCO₂, PaO₂ (IL 1306, Instrumentation Laboratories, Lexington, Mass.), arterial and cerebral oxygen saturation (IL 282), and hemoglobin (hgb).

From the collected data, the following calculations were made:

1. Mean arterial pressure (MAP = diastolic blood pressure plus 1/3 systolic minus diastolic blood pressure)
2. Total peripheral resistance (TPR) = $\text{MAP} / \text{CO} \times 79.9$
3. Cerebral perfusion pressure (CPP) = MAP - ICP.

Statistical Analysis

The Kruskal-Wallis test was employed to assess differences at baseline, during early shock (TO), and during late shock (T30) among all four fluid groups. A multivariate repeated measures analysis of variance was performed to determine if interactions between group and time existed at subsequent post-resuscitation intervals. Interactions were analyzed further with the Holm's sequentially rejective multiple test procedure using a significance level of 0.05. To assess time and group differences when an interaction was not present, a multivariate repeated measures analysis of variance and an analysis of covariance were performed on the dependent variables. An α of 0.05 was used to test for group and group*time interaction effects.

METHODS: SERIES 2.

CEREBRAL VENOUS OUTFLOW, SUBDURAL MASS LESION

Animals used in this study, twenty-four mongrel dogs each weighing 18-24 kg, were handled, according to guidelines established by the institution's animal care and use committee.

Anesthesia

Dogs were fasted overnight, then anesthetized with intravenous thiopental sodium (8.0 mg/kg), paralyzed with intravenous vecuronium (0.2 mg/kg), and endotracheally intubated. Halothane 0.5% in 60% nitrous oxide maintained anesthesia. Animals were mechanically ventilated at a rate and tidal volume (15 ml/kg) sufficient to maintain normocarbica (PaCO₂ 35-45 mmHg). Additional vecuronium, given as needed, prevented respiratory movement.

Hemodynamic Monitoring

Two femoral arterial catheters were placed for monitoring of arterial blood pressure and for induction of rapid hemorrhage, respectively. A flow-directed pulmonary artery catheter was placed percutaneously via the right external jugular vein using the Seldinger technique. Systemic and pulmonary pressures were recorded continuously on a Grass model 79D polygraph (Grass Instrument Co., Quincy, Mass.) with saline filled Gould Statham P23 transducers (Gould, Inc., Oxnard, CA). Pulmonary artery occlusion (PAWP) and central venous (CVP) pressures were monitored intermittently. Cardiac output was recorded intermittently using an American Edwards Sat-1 cardiac output computer (American Edwards, Corp., Santa Ana, CA). All transducers were intermittently calibrated with the zero level established at the level of the left atrium except for ICP, which was zeroed at the level of the external auditory canal. Core temperature was monitored by a thermistor on the tip of the pulmonary artery catheter and maintained with the use of a heating pad.

Cerebral Blood Flow Measurement

Following splenectomy, animals were turned to the prone "sphinx" position, and the temporalis and occipital musculature dissected from the underlying bone prior to heparinization (500 IU/kg). Cerebral blood flow (CBF) was measured using a modification of the technique originally described by Rapela and Green (1), where the confluence of the sagittal and lateral sinuses are cannulated and timed samples of cerebral venous outflow measured. Accuracy of CBF measured using cerebral venous outflow was confirmed using the Xenon 133 clearance according to the technique of Austin et al (2).

A 18G catheter inserted within the cisterna magna provided continuous intracranial pressure (ICP) monitoring. A craniotomy was then performed over the right temporo-parietal cortex,

the dura incised and the balloon tip of a 7 Fr Foley catheter inserted subdurally for manipulation of ICP.

Collected data included:

1. CBF
2. ICP
3. Systolic and diastolic blood pressure
4. Pulmonary arterial and pulmonary artery occlusion pressure
5. Central venous pressure
6. Cardiac output
7. Arterial pH, PaCO₂, PaO₂ (IL 1306, Instrumentation Laboratories, Lexington, Mass.), arterial and cerebral oxygen saturation (IL 282), and hemoglobin (hgb).

From the collected data, the following calculations were made:

1. Mean arterial pressure (MAP = diastolic blood pressure plus 1/3 systolic minus diastolic blood pressure)
2. Total peripheral resistance (TPR) = $\text{MAP} / \text{CO} \times 79.9$
3. Cerebral perfusion pressure (CPP) = MAP - ICP
4. Cerebral arterial-venous oxygen content difference.

Method of Hemorrhage

After instrumentation, animals were stabilized for 30 minutes and baseline (B) hemodynamics recorded. Immediately following baseline, ICP was increased to 20 mmHg by inflation of the subdural balloon with saline and the ICP was maintained at 20 mmHg with further inflation as necessary throughout shock. Following balloon inflation (BI), a second data set was obtained. Arterial blood was then rapidly removed to reduce MAP to 55 mm Hg, and this level was maintained for 30 minutes by removing or reinfusing blood. Data were collected at the beginning (T0) and end (T30) of the 30 minute shock interval. Following the shock interval, animals were randomized to one of four groups, based upon resuscitation fluid type. All fluids were rapidly infused intravenously over a 5 minute period. Group 1 (SAL) received 54 ml/kg of 0.8% NaCl (137 mEq/L Na⁺); group 2 (HS) received 6.0 ml/kg of 7.2% NaCl (1233 mEq/L Na⁺) group 3 (HES) received 6.0 ml/kg of 20% hydroxyethylstarch; and group 4 (HES/HS) received 6.0 ml/kg of 20% hydroxyethylstarch dissolved in 7.2% saline. As resuscitation began, the balloon-tipped catheter was clamped and ICP allowed to vary independently. Data were collected immediately following resuscitation (T35) and at thirty minute intervals thereafter for two hours, designated as T65, T95, T125, and T155.

Statistical Analysis

The Kruskal-Wallis test was employed to assess differences at baseline, during early shock (T0), and during late shock (T30) among all four fluid groups. A multivariate repeated

time existed at subsequent post-resuscitation, intervals. Interactions were analyzed further with the Holm s sequentially rejective multiple test procedure using a significance level of 0.05. To assess time and group differences when an interaction was not present, a multivariate repeated measures analysis of variance and an analysis of covariance were performed on the dependent variables. An α of 0.05 was used to test for group and group*time interaction effects.

METHODS: SERIES 1A. MICROSPHERE CBF MEASUREMENTS, No MASS LESION

Animals used in this study, twenty-four mongrel dogs each weighing 18-24 kg, were handled according to guidelines established by the institution's animal care and use committee.

Anesthesia

Dogs were fasted overnight, then anesthetized with intravenous thiopental sodium (8.0 mg/kg), paralyzed with intravenous pancuronium bromide (.03mg/kg) and metubine iodide (.12mg/kg), and endotracheally intubated. Halothane 0.5% in 60% nitrous oxide provided maintenance anesthesia. Animals were ventilated, using a Edco Model 822 Large Animal Ventilator (Edco Scientific, Inc., Chapel Hill, NC), at a tidal volume (15 ml/kg) and rate sufficient to maintain normocarbida (PaCO₂ 35-45 mm Hg). Additional pancuronium bromide and metubine iodide, given as needed, prevented respiratory movement.

Hemodynamic Monitoring

Two brachial artery catheters were placed, the left brachial for continuous monitoring of systemic arterial blood pressure and heart rate and the right as a reference organ for organ blood flow (OBF) measurement using radioactive microspheres. A 7FR pigtail catheter was inserted into the left ventricle from the left femoral artery allowed for radioactive microsphere injection. The right femoral artery was cannulated and utilized as a second reference organ. A pulmonary artery catheter was placed percutaneously through the right external jugular vein using the Seldinger technique for measurement of cardiac output, central venous pressure and pulmonary artery wedge pressure. Body temperature was monitored continuously with the aid of a thermistor located at the tip of the pulmonary artery catheter and maintained at 37 C with a heating pad. Hemodynamic pressure monitoring utilized a Grass model 79D polygraph (Grass Instrument Co., Quincy, Mass.) with saline filled Gould Statham P23 transducers (Gould, Inc., Oxnard, CA). Systemic and pulmonary artery pressures were recorded continuously; pulinonary artery occlusion pressure (PCWP) and central venous pressure (cvp) were determined intermittently. Cardiac output (CO) was recorded intermittently using an American Edwards 9520A cardiac output computer (American Edwards Santa Ana, CA). Systemic and pulmonary artery pressures were recorded continuously; pulmonary artery occlusion pressure (PCWP) and central venous pressure (cvp) were determined intermittently. Cardiac output (CO) was recorded intermittently using an American Edwards 9520A cardiac output computer (American

Edwards, Santa Ana, CA). All transducers were intermittently calibrated with the level of the left atrium except for ICP, which was zeroed at the level of the external auditory canal.

To facilitate rapid hemorrhage animals underwent splenectomy. Animals were then turned to the prone "sphinx" position and the occipital musculature dissected from the underlying bone. The superior sagittal sinus was cannulated using a double lumen O₂ saturation catheter (American Edwards Lab., Santa Ana, CA) for continuous cerebral venous SO₂ and sagittal sinus pressure monitoring and for rapid sampling of cerebral venous blood. An 18G catheter inserted into the cisterna magna provided continuous ICP monitoring.

Organ Blood Flow Measurements

Organ blood flows, including brain, kidney, adrenal, liver and heart were measured with 15 μ m radioactive microspheres using the organ reference-sample method (3). Radioactive microspheres consisting of Gd 153, Nb 95, Sn 113, Sr 85, and Sc 46 were injected at specific times within the experimental protocol for determination of organ blood flow. The reference sample method utilized two reference organ blood samples. In this series of animals reference organs blood samples were withdrawn simultaneously from the right femoral and left brachial arteries using an Edco Model 843 Infusion-Withdrawal Syringe Pump (Edco Scientific, Inc., Chapel Hill, NC). Prior to microsphere injection, microspheres were vortexed for 4 minutes to insure adequate mixing. The number of microspheres injected were sufficient to yield greater than 400 microspheres/tissue segment with a minimum of 15,000 counts per blood reference sample. Microsphere injections were carried out over a 15 second time period. The RFS were taken beginning 30 seconds prior to microsphere injection and continuing for 60 seconds post microsphere injection at a rate of 2.06 ml/min.

Collected data included:

1. ICP
2. Systolic and diastolic blood pressure
3. Pulmonary arterial and pulmonary artery occlusion pressure
4. Central venous pressure
5. Cardiac output
6. Arterial pH, PaCO₂, PaO₂, (IL 1306, Instrumentation Laboratories, Lexington, Mass.), arterial and cerebral oxygen saturation (IL 282), and hemoglobin (hgb).
7. Blood, plasma, and urine osmolarity were measured with a 5500 Vapor Pressure Osmometer (Wescor, Inc., Logan, Utah).
8. Blood colloid osmotic pressures were measured with a 4100 Colloid Osmometer (Wescor, Inc.).

From the collected data, the following calculations were made:

1. Mean arterial pressure (MAP = diastolic blood pressure plus 1/3 systolic minus diastolic blood pressure)
2. Total peripheral resistance (TPR) = $MAP/CO \times 79.9$
3. Cerebral perfusion pressure (CPP) = $MAP - ICP$.
4. Cerebral vascular resistance (CVR = CPP / CBF)
5. Cerebral arterial-venous O₂ content differences.
6. Organ blood flows were calculated for brain, liver, kidney, adrenal and heart using the formula:

$$Z = Cz \times 5.12 / Cr \times 100$$

where Z is organ blood flow in ml/min/100gm; Cz is counts per gram of organ tissue and Cr is the total counts in both reference arterial samples.

Method of Hemorrhage

After instrumentation, animals were stabilized for 30 minutes and baseline data collected. Immediately following baseline (B) data collection, the animals were rapidly hemorrhaged via the right brachial artery to an MAP of 40 mmHg which was maintained by further removal or reinfusion of shed blood. Hemodynamic and organ blood flow measurement were obtained at the mid shock time interval (T15). Following the shock interval, animals were randomized to one of four groups, based upon resuscitation fluid type. All fluids were rapidly infused intravenously over a 5 minute period. Group 1 (SAL) received 54 ml/kg of 0.8% NaCl (137 mEq/L Na⁺); group 2 (Hs) received 6.0 ml/kg of 7.2% NaCl (1233 mEq/L Na⁺); group 3 (HES) received 6.0 ml/kg of 20% hydroxyethylstarch; and group 4 (HES/HS) received 6.0 ml/kg of 20% hydroxyethylstarch dissolved in 7.2% saline. Data were collected immediately following fluid resuscitation (T35), and thereafter at 60 minute intervals for 2 hours (T95, T155).

Statistical Analysis

The Kruskal-Wallis test was employed to assess differences at baseline, during early shock (T0), and during late shock (T30) among all four fluid groups. A multivariate repeated measures analysis of variance was performed to determine if interactions between group and time existed at subsequent post-resuscitation, intervals. Interactions were analyzed further with the Holm's sequentially rejective multiple test procedure using a significance level of 0.05. To assess time and group differences when an interaction was not present, a multivariate repeated measures analysis of variance and an analysis of covariance were performed on the dependent variables. An α of 0.05 was used to test for group and group*time interaction effects.

METHODS: SERIES 2A.
MICROSPHERE CBF MEASUREMENT, SUBDURAL MASS LESION

Animals used in this study, twenty-four mongrel dogs each weighing 18-24 kg, were, handled according to guidelines established by the institution's animal care and use committee.

Anesthesia

Dogs were fasted overnight, then anesthetized with intravenous thiopental sodium (8.0 mg/kg), paralyzed with intravenous pancuronium bromide (.03mg/kg) and metubine iodide (.12mg/kg), and endotracheally intubated. Halothane 0.5% in 60% nitrous oxide provided maintenance anesthesia. Animals were ventilated, using a Edco Model 822 Large Animal Ventilator (Edco Scientific, Inc., Chapel Hill, NC), at a tidal volume (15 ml/kg) and rate sufficient to maintain normocarbida (PaCO₂ 35-45 mm Hg). Additional pancuronium bromide and metubine iodide, given as needed, prevented respiratory movement.

Hemodynamic Monitoring

Two brachial artery catheters were placed, the left brachial for continuous monitoring of systemic arterial blood pressure and heart rate and the right as a reference organ for cerebral blood flow (CBF) determination using radioactive microspheres. A 7FR pigtail catheter was inserted into the left ventricle through the left femoral artery for injection of radioactive microspheres. The right femoral artery was cannulated and utilized as a second reference organ. A pulmonary artery catheter was placed percutaneously through the right external jugular vein using the Seldinger technique for cardiac output (CO), central venous pressure (CVP) and pulmonary artery wedge pressure (PCWP) measurement. Body temperature was monitored continuously by a thermistor at the tip of the pulmonary artery catheter and maintained at 37 C with a heating pad. Hemodynamic pressure monitoring utilized a Grass model 79D polygraph (Grass Instrument Co., Quincy, Mass.) with Gould Statham P23 transducers (Gould, Inc., Oxnard, CA). Systemic and pulmonary artery pressures were recorded continuously; PAWP and CVP were measured intermittently. CO was recorded intermittently using an American Edwards 9520A cardiac output computer (American Edwards, Santa Ana, CA). All transducers were intermittently calibrated with the level of the left atrium except for ICP, which was zeroed at the level of the external auditory canal.

To facilitate rapid hemorrhage all animals underwent splenectomy. Animals were then turned to the prone "sphinx" position and the occipital musculature dissected from the underlying bone. The superior sagittal sinus was cannulated using a double lumen 02 saturation catheter (American Edwards Lab., Santa Ana, CA) for continuous cerebral venous S_O₂ and sagittal sinus pressure monitoring and for rapid sampling of cerebral venous blood. An 18G catheter inserted into the cisterna magna provided continuous ICP monitoring. A craniotomy was then performed over the right parietal cortical area, the dura

incised and the balloon tip of a 7 Fr Foley catheter inserted subdural for manipulation of ICP.

Cerebral Blood Flow Measurement

Total and regional cerebral blood flows (CBF) were measured with radioactive microspheres (15 μ m) using the organ reference-sample method (3). Radioactive microspheres included Gd 153, Nb 95, Sn 113, Sr 85, and Sc 46. The paired reference organ blood samples (RFS) were withdrawn simultaneously from the right femoral and left brachial arteries using an Edco Model 843 Infusion-Withdrawal Syringe Pump (Edco Scientific, Inc., Chapel Hill, NC). Prior to injection, microspheres were vortexed 4 minutes to insure adequate mixing. For each microsphere type injected, an amount was chosen that would yield greater than 400 microspheres/tissue segment and a minimum of 15,000 counts per blood reference sample. Injections of each microsphere type was carried out over a 15 second period. The RFS were taken beginning 30 seconds prior to microsphere injection and continuing for 60 seconds post microsphere injection, at a withdrawal rate of 2.06 ml/min.

Collected data included:

1. ICP
2. Systolic and diastolic blood pressure
3. Pulmonary arterial and pulmonary artery occlusion pressure
4. Central venous pressure
5. Cardiac output
6. Arterial pH, PaCO₂, PaO₂ (IL 1306, Instrumentation Laboratories, Lexington, Mass.), arterial and cerebral oxygen saturation (IL 282), and hemoglobin (hgb).
7. Blood, plasma, and urine osmolarity were measured with a 5500 Vapor Pressure Osmometer (Wescor, Inc., Logan, Utah).
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From the collected data, the following calculations were made:

1. Mean arterial pressure (MAP = diastolic blood pressure plus 1/3 systolic minus diastolic blood pressure)
2. Total peripheral resistance (TPR) = MAP/CO X 79.9
3. Cerebral perfusion pressure (CPP) = MAP - ICP.
4. Cerebral vascular resistance (CVR = CPP / CBF)
5. Cerebral arterial-venous O₂ content differences.
6. Organ blood flows were calculated for brain, liver, kidney, adrenal and heart using the formula:

$$Z = Cz \times 5.12 / Cr \times 100$$

where Z is organ blood flow in ml/min/100gm; Cz is counts per gram of organ tissue and Cr is the total counts in both reference arterial samples.

Method of Hemorrhage

After instrumentation, animals were stabilized for 30 minutes and baseline (B) data collected. Immediately following baseline, ICP was increased to 15 mm Hg by balloon inflation (BI) and maintained at that level throughout the 30 minute hemorrhagic shock interval. Animals were then rapidly hemorrhaged via the right brachial artery to a MAP of 55 mm Hg which was maintained by further removing or reinfusion of shed blood. Cerebral and hemodynamic data were obtained at the mid shock time interval (T15). Following the shock interval, animals were randomized to one of four groups, based upon resuscitation fluid type. All fluids were rapidly infused intravenously over a 5 minute period. Group 1 (SAL) received 54 ml/kg of 0.8% NaCl (137 mEq/L Na⁺); group 2 (HS) received 6.0 ml/kg of 7.2% NaCl (1233 mEq/L Na⁺); group 3 (HES) received 6.0 ml/kg of 20% hydroxylethylstarch; and group 4 (HES/HS) received 6.0 ml/kg of 20% hydroxyethylstarch dissolved in 7.2% saline. Data were collected immediately following fluid resuscitation (T35), and thereafter at 60 minute intervals for 2 hours (T95, T155).

Statistical Analysis

The Kruskal-Wallis test was employed to assess differences at baseline, during early shock (T0), and during late shock (T30) among all four fluid groups. A multivariate repeated measures analysis of variance was performed to determine if interactions between group and time existed at subsequent post-resuscitation intervals. Interactions were analyzed further with the Holm's sequentially rejective multiple test procedure using a significance level of 0.05. To assess time and group differences when an interaction was not present, a multivariate repeated measures analysis of variance and an analysis of covariance were performed on the dependent variables. An α of 0.05 was used to test for group and group*time interaction effects.

SUMMARY OF INDIVIDUAL COMPARISONS

***Note:** abbreviations include:

SAL = 0.8% saline (0.9% in Series 1)

HS = 7.2% saline

HES = 20% hydroxyethylstarch in 0.8% saline

HES/HS = 20% HES in 7.2% saline

Series 1 Comparison A: SAL vs. HS

Objective:

To determine if equal sodium loads (conc. x volume) produce equivalent systemic and cerebral hemodynamic responses when administered following hypovolemic shock.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Tables 1 and 2):
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - b. Systemic variables (Tables 3-7 and Figures 1 and 2):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - no difference between groups (Figure 1)
 - 5) Mean Arterial Pressure - no difference between groups (Figure 2)
 - c. Cerebral Hemodynamics (Table 8; Figures 3-5):
 - 1) Intracranial Pressure - Despite a trend toward lower ICP in the HS group, no overall group difference was found (Figure 4)
 - 2) Cerebral Perfusion Pressure - no difference between groups (Figure 5)
 - 3) Cerebral Blood Flow - nearly identical over time in both groups. Both groups declined markedly following resuscitation and failed to compensate for hemodilution (Figure 3; see Table 1).

Series 1 Comparison B: SAL vs. HES

Objective:

To determine the equivalency of the effects of conventional rapid administration of large volumes of isotonic crystalloid versus small volumes of highly concentrated colloid (20% HES in 0.9% saline) on systemic and cerebral hemodynamic shock.

Statistical Methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Tables 9 and 10):
 - 1) PaCO₂ - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO₂ - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - b. Systemic variables (Tables 11-15 and figures 6 and 7)
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - at T35, PAP is significantly greater in the NS group ($p < 0.001$)
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - no difference between groups (Figure 6)
 - 5) Mean Arterial Pressure - no difference between groups (Figure 7)
 - c. Cerebral Hemodynamics (Table 16; Figures 8-10):
 - 1) Intracranial Pressure - no overall group difference was found (Figure 8)
 - 2) Cerebral Perfusion Pressure - significant group differences by Holm's test at T35, T65, T95, T155 (SAL greater) (Figure 9)
 - 3) Cerebral Blood Flow - significant group difference by Holm's test at T35 (Figure 10) (HES lower). Both groups declined following resuscitation and failed to compensate for hemodilution (Figure 10; see Table 9)

Series 1 Comparison C: HES vs. HS

Objective:

To determine if equal volumes of a hypertonic solution (7.2% saline) and a hyperoncotic solution (20% HES) produce equivalent systemic and cerebral hemodynamic responses when administered following hypovolemic shock.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline or during shock
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Tables 17 and 18):
 - 1) PaCO₂ - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO₂ - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - b. Systemic variables (Table 19-23 and Figures 11 and 12):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - statistically significant difference at all post-resuscitation time points
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output no difference between groups (Figure 11)
 - 5) Mean Arterial Pressure no difference between groups (Figure 12)
 - c. Cerebral Hemodynamics (Table 24; Figures 13-15):
 - 1) Intracranial Pressure - no difference between groups (Figure 13)
 - 2) Cerebral Perfusion Pressure - group difference at all time periods ($p < 0.01$) (Figure 14)
 - 3) Cerebral Blood Flow - Holm's sequential multiple test procedure shows a significant group difference at T35 (Figure 15), with CBF significantly greater in the HS group

Series 1 Comparison D:HS vs. HES/HS

Objective:

To compare the effects of equal volumes of a hypertonic solution (7.2% saline) and a hypertonic/hyperoncotic solution (20% HES in 7.2% saline) on systemic and cerebral hemodynamic responses when administered following hypovolemic shock.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline or during shock
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Tables 25 and 26):
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - b. Systemic variables (Tables 27-31; figures 16 and 17):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - no difference between groups (Figure 16)
 - 5) Mean Arterial Pressure no difference between groups (Figure 17)
 - c. Cerebral Hemodynamics (Table 32; Figures 18-20):
 - 1) Intracranial Pressure - no difference between groups (Figure 18)
 - 2) Cerebral Perfusion Pressure, statistically significant difference (Holm's) between groups (Figure 19)
 - 3) Cerebral Blood Flow - no significant group difference (Figure 20)

Series 1 Comparison E: HES vs. HES/HS

Objective:

To compare the effects of equal volumes of a hyperoncotic solution (20% HES) and a hypertonic/hyperoncotic solution (20% HES in 7.2% saline) on systemic and cerebral hemodynamic responses when administered following hypovolemic shock.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline or during shock
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Tables 33 and 34):
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - b. Systemic variables (Tables 35-39; Figures 21 and 22):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output no difference between groups (Figure 21)
 - 5) Mean Arterial Pressure no difference between groups (Figure 22)
 - c. Cerebral Hemodynamics (Figures 23-25):
 - 1) Intracranial Pressure - no difference between groups (Figure 23)
 - 2) Cerebral Perfusion Pressure - no difference between groups (Figure 24)
 - 3) Cerebral Blood Flow - no difference between groups (Figure 25)

Series 1 Comparison F: SAL vs. HES/HS

Objective:

To determine the equivalency of the effects of conventional rapid administration of large volumes of isotonic crystalloid versus small volumes of hypertonic/hyperoncotic solution (20% HES in 7.2% saline) on systemic and cerebral hemodynamic responses when administered following hypovolemic shock.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Tables 41 and 42):
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no difference between groups
 - 4) pH
 - 5) blood temperature - no difference between groups
 - b. Systemic variables (Tables 43-47; Figures 26 and 27)
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output no difference between groups (Figure 26)
 - 5) Mean Arterial Pressure no difference between groups (Figure 27)
 - c. Cerebral Hemodynamics (Table 48; Figures 28-30):
 - 1) Intracranial Pressure - no group difference (Figure 28)
 - 2) Cerebral Perfusion Pressure - no group difference (Figure 29)
 - 3) Cerebral Blood Flow - no group difference (Figure 30) Both groups declined following resuscitation and failed to compensate for hemodilution

Series 2 Comparison G: SAL vs. HS

Objective:

To determine if equal sodium loads (conc. x volume) produce equivalent systemic and cerebral hemodynamic responses when administered following hypovolemic shock in the presence of an intracranial mass lesion.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, following balloon inflation, or during shock
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Table 49-50):
 - 1) PaCO₂ - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO₂ - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO₂ - no difference between groups
 - b. Systemic variables (Tables 51-56 and Figures 31 and 32):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - no difference between groups (Figure 31)
 - 5) Mean Arterial Pressure - no difference between groups (Figure 32)
 - c. Cerebral Hemodynamics (Table 57-59 and Figures 33-35):
 - 1) Intracranial Pressure - Holm's sequential multiple test procedure shows a significant group difference (HS lower) at T35 (Figure 33)
 - 2) Cerebral Perfusion Pressure - Holm's sequential multiple test procedure shows a significant group difference at T35, T65, and T95 with CPP greater in the SAL
 - 3) Cerebral Blood Flow - no significant group effect. Both groups declined markedly following resuscitation and failed to compensate for hemodilution (Figure 34)
 - 4) Cerebral Venous Oxygen Content - no difference between groups
 - 5) Cerebral Metabolic Rate - no significant difference between groups (Figure 35)

Series 2 Comparison H: SAL vs. HES

Objective:

To determine the equivalency of the effects of conventional rapid administration of large volumes of isotonic crystalloid versus small volumes of highly concentrated colloid (20% HES in 0.9% saline) on systemic and cerebral hemodynamic responses when administered following hypovolemic shock in the presence of an intracranial mass lesion.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, following balloon inflation, or during shock
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Tables 60 and 61):
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO_2 - no difference between groups
 - b. Systemic variables (Tables 62-67 and Figures 36 and 37):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - no group difference (Figure 36)
 - 5) Mean Arterial Pressure - no significant group difference (Figure 37)
 - c. Cerebral Hemodynamics (Tables 68-70; Figures 38-41):
 - 1) Intracranial Pressure - Despite a trend toward lower ICP in the HES group, no overall group difference (Figure 38)
 - 2) Cerebral Perfusion Pressure significant group difference at T35 (Figure 39)
 - 3) Cerebral Blood Flow - nearly identical over time in both groups. Both groups recovered poorly following resuscitation and failed to compensate for hemodilution (Figure 40)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups (Table 69)
 - 5) Cerebral Metabolic Rate - no significant difference between groups (Figure 41)

Series 2 Comparison I: HES vs. HS

Objective:

To determine if equal volumes of a hypertonic solution (7.2% saline) and a hyperoncotic solution (20% HES) produce equivalent systemic and cerebral hemodynamic responses when administered following hypovolemic shock in the presence of an intracranial mass lesion.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable (MAP)
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Table 71 and 72):
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no differences between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO_2 - no difference between groups
 - b. Systemic variables (Tables 73-78; Figures 42 and 43):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - no difference between groups (Figure 42)
 - 5) Mean Arterial Pressure no difference between groups (Figure 43)
 - c. Cerebral Hemodynamics (Figures 44-47):
 - 1) Intracranial Pressure - significant group effect at T35 by Holm's sequential multiple test procedure (Figure 44)
 - 2) Cerebral Perfusion Pressure - no difference between groups (Figure 45)
 - 3) Cerebral Blood Flow no significant group difference (Figure 46)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups
 - 5) Cerebral Metabolic Rate - no significant difference between groups (Figure 47)

Series 2 Comparison J: HS vs. HES/HS

Objective:

To compare the effects of equal volumes of a hypertonic solution (7.2% saline) and a hypertonic/hyperoncotic solution (20% HES in 7.2% saline) on systemic and cerebral hemodynamic responses when administered following hypovolemic shock in the presence of an intracranial mass lesion.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Table 82):
 - 1) PaCO₂ - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO₂ - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO₂ - no difference between groups
 - b. Systemic variables (Table 83 and Figures 48 and 49):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - no difference between groups (Figure 48); note: trend toward higher CO later following resuscitation
 - 5) Mean Arterial Pressure no difference between groups (Figure 49)
 - c. Cerebral Hemodynamics (Figures 50-53):
 - 1) Intracranial Pressure significant difference between groups at T95 (Figure 50)
 - 2) Cerebral Perfusion Pressure - no difference between groups (Figure 51)
 - 3) Cerebral Blood Flow - no difference between groups (Figure 52)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups (Table 85)
 - 5) Cerebral Metabolic Rate - no significant difference between groups (Figure 53)

Series 2 Comparison K: HES vs. HES/HS

Objective:

To compare the effects of equal volumes of a hyperoncotic solution (20% HES) and a hypertonic/hyperoncotic solution (20% HES in 7.2% saline) on systemic and cerebral hemodynamic responses when administered following hypovolemic shock in the presence of an intracranial mass lesion.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Table 86 and 87):
 - 1) PaCO₂ - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO₂ - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO₂ - no difference between groups
 - b. Systemic variables (Tables 86 and 17 and Figure 54):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output no difference between groups (Figure 54)
 - 5) Mean Arterial Pressure no difference between groups
 - c. Cerebral Hemodynamics (Tables 88 and 89; Figures 55-58):
 - 1) Intracranial Pressure - no difference between groups (Figure 55)
 - 2) Cerebral Perfusion Pressure - no difference between groups (Figure 56)
 - 3) Cerebral Blood Flow - no group difference (Figure 57)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups
 - 5) Cerebral Metabolic Rate no difference between groups (Figure 58)

Series 2 Comparison L: SAL vs. HES/HS

Objective:

To determine the equivalency of the effects of conventional rapid administration of large volumes of isotonic crystalloid versus small volumes of hypertonic/hyperoncotic solution (20% HES in 7.2% saline) on systemic and cerebral hemodynamic responses when administered following hypovolemic shock in the presence of an intracranial mass lesion.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Table 90 and 91):
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO_2 - no difference between groups
 - b. Systemic variables (Tables 92-99; Figures 59 and 60):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - no difference between groups (Figure 59)
 - 5) Mean Arterial Pressure - no difference between groups (Figure 60)
 - c. Cerebral Hemodynamics (Figures 61-64):
 - 1) Intracranial Pressure - significant group effect, but no individual interval differences by Holm's sequential multiple test procedure (Figure 61)
 - 2) Cerebral Perfusion Pressure - no difference between groups (Figure 62)
 - 3) Cerebral Blood Flow - no group difference (Figure 63)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups
 - 5) Cerebral Metabolic Rate - no significant difference between groups (Figure 64)

Series 1a Comparison M: SAL vs. HS

Objective:

To determine if equal sodium loads (conc. x volume) produce equivalent systemic and cerebral hemodynamic responses (including regional distribution of cerebral blood flow) when administered following hypovolemic shock.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline or at mid-shock
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Tables 102 and 103):
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO_2 - no difference between groups
 - b. Systemic variables (Tables 104-110; Figures 65 and 66):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - significant difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - no group difference (Figure 65)
 - 5) Mean Arterial Pressure - no difference between groups (Figure 66)
 - c. Cerebral Hemodynamics (Tables 111-113; Figures 67-70):
 - 1) Intracranial Pressure - lower ICP in the HS group, with significant interval differences confirmed by Holm's sequential multiple test procedure at T35, T95, and T155 ($p < 0.0005$) (Figure 67)
 - 2) Cerebral perfusion Pressure - no difference between groups (Figure 68)
 - 3) Cerebral Blood Flow - Both groups declined following resuscitation and failed to compensate for hemodilution (Figure 69)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups (Table 112)
 - 5) Cerebral Metabolic Rate no difference between groups (Figure 70)

Series 1a Comparison N: SAL vs. HES

Objective:

To determine the equivalency of the effects of conventional rapid administration of large volumes of isotonic crystalloid versus small volumes of highly concentrated colloid (20% HES in 0.9% saline) on systemic and cerebral hemodynamic responses (including regional cerebral blood flow) when administered following hypovolemic shock.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Tables 114 and 115):
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - b. Systemic variables (Tables 116-122; Figures 71 and 72):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - significant group difference (Figure 7)
 - 5) Mean Arterial Pressure - significant group difference at T95 (Figure 72)
 - c. Cerebral Hemodynamics (Tables 123-125; Figures 73-76):
 - 1) Intracranial Pressure - lower ICP in the HES group at T35 ($P < 0.05$) (Figure 73)
 - 2) Cerebral Perfusion Pressure - significant group difference ($p < 0.05$) (Figure 74)
 - 3) Cerebral Blood Flow - consistently higher over time in HES group. Neither group compensated for hemodilution (Figure 75)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups (Table 124)
 - 5) Cerebral Metabolic Rate - no difference between groups (Figure 76)

Series 2a Comparison 0: HES vs. HS

Objective:

To determine if equal volumes of a hypertonic solution (7.2% saline) and a hyperoncotic solution (20% HES) produce equivalent systemic and cerebral hemodynamic (including regional cerebral blood flow) responses when administered following hypovolemic shock.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Tables 126 and 127):
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO_2 - no difference between groups
 - b. Systemic variables (Tables 128-134; Figures 71 and 78):
 - 1) pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - significant difference between groups; Holm's sequential multiple test procedure significant at mid-shock and T155 (Figure 77)
 - 5) Mean Arterial Pressure - no difference between groups (Figure 78)
 - c. Cerebral Hemodynamics (Tables 135-137; Figures 79-82):
 - 1) Intracranial Pressure - statistically significant difference between groups ($p < 0.01$) (Figure 79)
 - 2) Cerebral Perfusion Pressure - no difference between groups (Figure 80)
 - 3) Cerebral Blood Flow - overall group difference; no specific interval differences ($p < 0.05$) (Figure 81)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups
 - 5) Cerebral Metabolic Rate - no difference between groups (Figure 82)

Series 1a Comparison P: HS vs. HES/HS

Objective:

To compare the effects of equal volumes of a hypertonic solution (7.2% saline) and a hypertonic/hyperoncotic solution (20% HES in 7.2% saline) on systemic and cerebral hemodynamic (including regional cerebral blood flow) responses when administered following hypovolemic shock.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Tables 151 and 152):
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - b. Systemic variables (Tables 153-159; Figures 89 and 90):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - significant difference between groups ($p < 0.05$)
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - no difference between groups (Figure 89)
 - 5) Mean Arterial Pressure - no difference between groups (Figure 90)
 - c. Cerebral Hemodynamics (Tables 160-162; Figures 91-94):
 - 1) Intracranial Pressure - no difference between groups (Figure 91)
 - 2) Cerebral Perfusion Pressure - no difference between groups (Figure 92)
 - 3) Cerebral Blood Flow - no significant group difference (Figure 93)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups
 - 5) Cerebral Metabolic Rate - no difference between groups (Figure 94)

Series 1a Comparison Q: SAL vs. HES/HS

Objective:

To determine the equivalency of the effects of conventional rapid administration of large volumes of isotonic crystalloid versus small volumes of a hypertonic/hyperoncotic solution (20% HES in 7.2% saline) on systemic and cerebral hemodynamic (including regional cerebral blood flow) responses when administered following hypovolemic shock.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Tables 163 and 164)
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO_2 - no difference between groups
 - b. Systemic variables (Tables 165-171; Figures 95 and 96):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - significant difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - no difference between groups (Figure 95)
 - 5) Mean Arterial Pressure - no difference between groups (Figure 96)
 - c. Cerebral Hemodynamics (Tables 172-174; Figures 97-100):
 - 1) Intracranial Pressure - borderline group difference between groups ($p=0.0465$) (Figure 99)
 - 2) Cerebral Perfusion Pressure - no difference between groups (Figure 100)
 - 3) Cerebral Blood Flow overall group difference ($p=0.01$) (Figure 97), with CBF greater in the HES/HS group
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups
 - 5) Cerebral Metabolic Rate no difference between groups (Figure 98)

Series 2a Comparison R: SAL vs. HS

Objective:

To determine if equal sodium loads (conc. x volume) produce equivalent systemic and cerebral hemodynamic (including regional cerebral blood flow) responses when administered following hypovolemic shock in the presence of an intracranial mass lesion.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable;
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Table 175 and 176)
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups;
 - 3) PaO_2 - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO_2 - no difference between groups;
 - b. Systemic variables (Tables 178-182; Figures 101 and 102):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - Holm's sequential multiple test procedure shows a significant group difference (HS lower) at T35 (Figure 101)
 - 5) Mean Arterial Pressure no difference between groups (Figure 102)
 - c. Cerebral Hemodynamics (Table 183-186; Figures 103-106):
 - 1) Intracranial Pressure - overall group difference (HS lower) ($p < 0.05$) (Figure 103)
 - 2) Cerebral Perfusion Pressure - no significant group difference (Figure 104)
 - 3) Cerebral Blood Flow - significant group effect on right hemispheric rCBF (Table 186) by Holm's sequential multiple test procedure ($p = 0.05$). Both groups declined markedly following resuscitation and failed to compensate for hemodilution (Figure 105)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups
 - 5) Cerebral Metabolic Rate - no significant difference between groups (Figure 106)

Series 2a Comparison S: SAL vs. HES

Objective:

To determine the equivalency of the effects of conventional rapid administration of large volumes of isotonic crystalloid versus small volumes of highly concentrated colloid (20% HES in 0.9% saline) on systemic and cerebral hemodynamic (including regional cerebral blood flow) responses when administered following hypovolemic shock in the presence of an intracranial mass lesion.

Statistical methods:

1. Kruskal-Wallis: problematic differences at baseline in CBF, ICP, CPP, CMR02,
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Tables 187 and 188):
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - difference between groups at T35, baseline and mid-shock
 - 3) PaO_2 - no difference between groups
 - 4) pH - difference between groups $p=0.02$
 - 5) blood temperature - difference between groups at T35
 - 6) CaO_2 - no difference between groups
 - b. Systemic variables (Tables 189, 193; Figures 107 and 108):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - Holm's sequential multiple test procedure suggests a significant group difference (SAL higher) at T35 and at T155 (SAL lower) (Figure 107)
 - 5) Mean Arterial Pressure - different at baseline; similar thereafter (Figure 108)
 - c. Cerebral Hemodynamics (Tables 194-196; Figures 109-112):
 - 1) Intracranial Pressure - no group difference (Figure 109)
 - 2) Cerebral Perfusion Pressure - no group difference (Figure 110)
 - 3) Cerebral Blood Flow - no significant difference over time between groups. Both groups failed to compensate for hemodilution despite apparently adequate CPP (Figure 111)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups
 - 5) Cerebral Metabolic Rate - no significant difference between groups (Figure 112)

Series 2a Comparison T: HES vs. HS

Objective:

To determine if equal volumes of a hypertonic solution (7.2% saline) and a hyperoncotic solution (20% HES) produce equivalent systemic and cerebral hemodynamic (including regional cerebral blood flow) responses when administered following hypovolemic shock in the presence of an intracranial mass lesion.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Table 198):
 - 1) PaCO₂ - no difference between groups
 - 2) Hgb - difference between groups
 - 3) PaO₂ - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO₂ - no difference between groups
 - b. Systemic variables (Table 198; Figures 113 and 114):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups (check baseline)
 - 4) Cardiac Output no difference between groups (Figure 113)
 - 5) Mean Arterial Pressure no difference between groups (Figure 114);
 - c. Cerebral Hemodynamics (Tables 199 and 220; Figures 115-118):
 - 1) Intracranial Pressure significant group effect ($p < 0.05$) (Figure 115)
 - 2) Cerebral Perfusion Pressure - no difference between groups (Figure 116)
 - 3) Cerebral Blood Flow - overall group difference ($p = 0.05$) (Figure 117); subanalysis demonstrates that the right hemispheric cortical flow was significant at the .03 level
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups
 - 5) Cerebral Metabolic Rate - no significant difference between groups (Figure 118); values are greater in the HS group ($p = .0499$)

Series 2a Comparison U: HS vs. HES/HS

Objective:

To compare the effects of equal volumes of a hypertonic solution (7.2% saline) and a hypertonic/hyperoncotic solution (20% HES in 7.2% saline) on systemic and cerebral hemodynamic (including regional cerebral blood flow) responses when administered following hypovolemic shock in the presence of an intracranial mass lesion.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Table 201):
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO_2 - no difference between groups
 - b. Systemic variables (Table 201; Figures 119 and 120):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - significant difference between groups ($p=0.015$) (Figure 119)
 - 5) Mean Arterial Pressure - no difference between groups (Figure 120); at T155 MAP appears to be better maintained in the combination group
 - c. Cerebral Hemodynamics (Tables 202, 203; Figures 121, 124):
 - 1) Intracranial Pressure - significant difference between groups (Figure 121) at T35, T95, and 155
 - 2) Cerebral Perfusion Pressure - no difference between groups (Figure 122)
 - 3) Cerebral Blood Flow - no difference between groups (Figure 123)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - significant difference between groups ($p=0.0425$)
 - 5) Cerebral Metabolic Rate - significant difference between groups (Figure 124) favoring HS alone ($p=0.028$)

Series 2a Comparison V: HES vs. HES/HS

Objective:

To compare the effects of equal volumes of a hyperoncotic solution (20% HES) and a hypertonic/hyperoncotic solution (20% HES in 7.2% saline) on systemic and cerebral hemodynamic (including regional cerebral blood flow) responses when administered following hypovolemic shock in the presence of an intracranial mass lesion.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable,
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Table 204):
 - 1) PaCO₂ - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO₂ - no difference between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO₂ - difference between groups at baseline, T35, T95
 - b. Systemic variables (Table 204 and Figures 125 and 126):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - difference between groups ($p < 0.05$ at T35) (Figure 125)
 - 5) Mean Arterial Pressure - no difference between groups (Figure 126)
 - c. Cerebral Hemodynamics (Figures 127-130):
 - 1) Intracranial Pressure - no difference between groups (Figure 127), note: late increase in ICP in the HES/HS group
 - 2) Cerebral Perfusion Pressure - no difference between groups (Figure 128)
 - 3) Cerebral Blood Flow - group difference ($p = 0.0193$) (Figure 129)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups
 - 5) Cerebral Metabolic Rate no difference between groups (Figure 130)

Series 2a Comparison W: SAL vs. HES/HS

Objective:

To determine the equivalency of the effects of conventional rapid administration of large volumes of isotonic crystalloid versus small volumes of a hypertonic/hyperoncotic solution (20% HES in 7.2% saline) on systemic and cerebral hemodynamic (including regional cerebral blood flow) responses when administered following hypovolemic shock in the presence of an intracranial mass lesion.

Statistical methods:

1. Kruskal-Wallis: no differences at baseline, early shock, or late shock in any variable
2. Multivariate ANOVA (Note: By design, there are significant time effects within groups in nearly all variables. Therefore, only group effects are discussed below):
 - a. Control variables (Table 207)
 - 1) PaCO_2 - no difference between groups
 - 2) Hgb - no difference between groups
 - 3) PaO_2 - no differences between groups
 - 4) pH - no difference between groups
 - 5) blood temperature - no difference between groups
 - 6) CaO_2 - no difference between groups
 - b. Systemic variables (Tables 207-210; Figures 131 and 132):
 - 1) Pulmonary Artery Wedge Pressure (PAWP) - no difference between groups
 - 2) Pulmonary artery pressure - no significant difference between groups
 - 3) Heart Rate - no difference between groups
 - 4) Cardiac Output - no difference between groups (Figure 131)
 - 5) Mean Arterial Pressure - no difference between groups (Figure 132)
 - c. Cerebral Hemodynamics (Figures 133-135):
 - 1) Intracranial Pressure - borderline group difference between groups ($p=0.0465$) (Figure 133)
 - 2) Cerebral Perfusion Pressure - no difference between groups (Figure 134)
 - 3) Cerebral Blood Flow - no group difference (Figure 135)
 - 4) Cerebral Arteriovenous Oxygen Content Difference - no difference between groups
 - 5) Cerebral Metabolic Rate - no difference between groups (Figure 136)

3. Abstracts that have been presented based upon these data are appended.

4. Conclusions:

- a. Hypertonic saline and combinations of hypertonic saline with hydroxyethylstarch are associated with lower intracranial pressure than isotonic solutions when used for resuscitation from hemorrhagic shock, with or without the presence of an intracranial mass lesion.
- b. Cerebral blood flow is improved by hypertonic resuscitation if an intracranial mass lesion is present.
- c. Under certain circumstances, hypertonic saline is associated with a delayed rise in intracranial pressure at a time when the systemic hemodynamic effects have dissipated.
- d. In general, the hemodynamic effects of hypertonic saline resuscitation are transient.
- e. The addition of hyperoncotic colloid somewhat prolongs the effects of hypertonic solutions.

5. Recommendations for further study:

- a. The delayed rise in intracranial pressure is a most serious limitation of hypertonic saline resuscitation and should be investigated to determine the circumstances under which this is most likely to occur.
- b. Alternative colloids should be examined to determine whether they exert similar systemic and cerebral effects in combination with hypertonic saline.
- c. Careful investigation should be performed to determine whether central pontine myelinolysis, a common and devastating neurologic complication associated with rapid correction of hyponatremia, is also associated with rapid increases in serum sodium from normal to supernormal.

REFERENCES:

1. Austin G, Horn N, Rouhe S, et al. Description and early results of an intravenous radioisotope technique for measuring cerebral blood flow in man. *Eur Neurol* 1972;8:43.
2. Rapela CE, Green HD. Autoregulation of canine cerebral blood flow. *Circ Res* (Suppl I) 1964;XIV:I:205.
3. Hoffbrand BI, Forsyth RP. Validity studies of the radioactive microsphere method for the study of the distribution of cardiac output, organ blood flow, and resistance in the conscious rhesus monkey. *Cardiovasc Res* 1969;3:426.

APPENDIX A
SCIENTIFIC PRESENTATIONS

SCIENTIFIC PRESENTATIONS

Cerebral Venous Release of Thromboxane A₂ Following Hemorrhagic Shock. American Society of Anesthesiologists, San Francisco, California, 1988.

Intracranial Pressure Following Resuscitation from Hemorrhagic Shock. Society of Critical Care Medicine, Sixteenth Annual Educational and Scientific Symposium, Anaheim, California, May 28, 1987.

Hypertonic/hyperoncotic Fluid Resuscitation Following Hemorrhagic Shock: Comparison of fluids. 1987 Symposium on Hypertonic Resuscitation, Monterrey, California, June 4, 1987.

Effects of Fluid Resuscitation from Hemorrhagic Shock on Cerebral Hemodynamics in the Presence of an Intracranial Mass. 1987 Symposium on Hypertonic Resuscitation, Monterrey, California, June 5, 1987.

Shock Plus an Intracranial Mass in Dogs: Cerebrovascular Effects of Resuscitation Fluid Choices. 62nd Congress, International Anesthesia Research Society, San Diego, California, March 8, 1988. Also presented at the 1988 National Student Research Forum, Galveston, Texas, April 10, 1988.

Resuscitation From Hemorrhagic Shock in Association with an Intracranial Mass: Effects of a clinically modeled protocol on ICP. Society of Critical Care Medicine, Orlando, Florida, June 2, 1988.

Shock Plus Intracranial Hypertension Increases Cerebral Thromboxane Release. Society of Critical Care Medicine, Orlando, Florida, June 2, 1988.

A Clinically Derived Fluid Resuscitation Protocol Progressively Increases ICP in Dogs with Hemorrhagic Shock and an Intracranial Mass. Seventh International Symposium on Intracranial Pressure and Brain Injury, Ann Arbor, Michigan, June 21, 1988.

Small Volume Resuscitation from Hemorrhagic Shock in Dogs with Hypertonic Saline-Hydroxyethyl Starch Solutions. American Society of Critical Care Anesthesiologists, San Francisco, California, October 7, 1988, and at the American Society of Anesthesiologists, San Francisco, California, October 10, 1988.

Regional Cerebral Blood Flow Following Resuscitation From Hemorrhagic Shock in Dogs with a Subdural Mass. American Society of Critical Care Anesthesiologists, San Francisco, California, October 7, 1988, and at the American Society of Anesthesiologists, San Francisco, California, October 10, 1988.

Regional Cerebral Blood Flow (rCBF) Following Resuscitation From Hemorrhagic Shock with Increased Intracranial Pressure (ICP). 73 rd Annual Meeting of the Federation of American Societies for Experimental Biology, New Orleans, Louisiana, March 21, 1989.

rCBF Following Fluid Resuscitation From Hemorrhagic Shock with Isotonic or 7.2% saline with and without a subdural mass. Twelfth Annual Conference on Shock, Marco Island, florida, June 10, 1989.

APPENDIX B

PUBLISHED ABSTRACTS (10)

UNPUBLISHED ABSTRACTS (3)

ABSTRACTS

1. Olympio MA, Whitley JM, Prough DS, Petrozza PH, and Watkins WD. Cerebral Venous Release of Thromboxane A2 Following Hemorrhagic Shock. *Anesthesiology Review* 1986;13:55.
2. Whitley JM, Prough DS, Olympio MA, and Petrozza PH. Intracranial Pressure Following Resuscitation from Hemorrhagic Shock. *Critical Care Medicine* 1987;15:433.
3. Whitley JM, Prough DS, and DeWitt DS. Shock Plus an Intracranial Mass in Dogs: Cerebrovascular Effects of Resuscitation Fluid Choices. *Anesthesia and Analgesia (Suppl.)* 1988;76:S259.
4. Whitley JM, Prough DS, Deal DD, and Lamb AK. A Clinically-derived Fluid Resuscitation Protocol Progressively Increases ICP in Dogs with Hemorrhagic Shock and an Intracranial Mass. *Seventh International Symposium on Intracranial Pressure and Brain Injury. Intracranial Pressure VII* 1988:761. Publisher: Springer-Verlag, Federal Republic of Germany.
5. Whitley JM, Prough DS, Deal DD, and Lamb AK. Resuscitation From Hemorrhagic Shock in Association with an Intracranial Mass: Effects of a Clinically modeled protocol on Intracranial Pressure. *Critical Care Medicine* 1988;16:384.
6. Kong DL, Whitley JM, Prough DS, and DeWitt DS. Shock Plus Intracranial Hypertension Increases Cerebral Thromboxane Release. *Critical Care Medicine* 1988;16:383.
7. Whitley JM, Prough DS, Deal DD, Lamb AK, and DeWitt DS. Regional Cerebral Blood Flow Following Resuscitation from Hemorrhagic Shock in Dogs with a Subdural Mass. *Anesthesiology (suppl.)* 1988;69(3A):A539.
8. Whitley JM, Prough DS, Deal DD, Lamb AK, and DeWitt DS. Small Volume Resuscitation from Hemorrhagic Shock in Dogs With Hypertonic Saline-hydroxyethyl Starch Solutions. *Anesthesiology (suppl.)* 1988;69(3A):A847.
9. Whitley JM, Prough DS, Deal DD, and Lamb AK. Regional Cerebral Blood Flow (rCBF) Following Resuscitation from Hemorrhagic Shock With Increased Intracranial Pressure (ICP). Published in *Proceedings from the Federation of Association Societies of Experimental Biology* 1989:A548.
10. Whitley JM, Prough DS, Deal DD, Vines SM, and Taylor CL. rCBF Following Fluid Resuscitation from Hemorrhagic Shock with Isotonic or 7.2% Saline With and Without a Subdural Mass. *Circulatory Shock* 1989;27(4):360-361.

Title: CEREBRAL VENOUS RELEASE OF THROMBOXANE A_2 FOLLOWING HEMORRHAGIC SHOCK

Authors: M. A. Olympio, M.D., J. M. Whitley, Ph.D., D. S. Prough, M.D., P. H. Petrozza, M.D., W. D. Watkins, M.D., Ph.D

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Introduction: Following crystalloid fluid resuscitation from hemorrhagic shock, cerebral blood flow (CBF) may not be restored to control values despite hemodilution (1). In contrast, similar hemodilution produced by concurrent isovolemic replacement of blood with crystalloid increases CBF to levels greater than control (2). Recent data suggest that thromboxane B_2 (TxB_2), the stable metabolite of thromboxane A_2 , a potent vasoconstrictor, is present in increased quantities in cerebral venous blood following global cerebral ischemia (GCI) (3). We performed this study to determine if TxB_2 levels are also increased in cerebral venous blood during or after hemorrhagic shock followed by resuscitation with lactated Ringer's solution (LRS).

Methods: The protocol was approved by the institutional animal care committee. Six 15- to 25-kg mongrel dogs were anesthetized with sodium thiopental 10 mg/kg iv, paralyzed with succinylcholine 4.0 mg/kg, endotracheally intubated, and ventilated to maintain normocapnia. Halothane 1.0% in O_2 was administered during the following preparations. A pulmonary artery catheter and bilateral femoral artery catheter were placed. After splenectomy the animals were turned to the prone "sphinx" position and the occipital musculature was dissected from the skull. The animals were heparinized, the straight sinus was cannulated, and the lateral sinuses were occluded. A catheter was placed in the cisterna magna for measurement of intracranial pressure (ICP). Outflow from the straight sinus was collected and intermittently measured through a calibrated reservoir, and then was reinfused. Halothane was discontinued, 60% N_2O in O_2 was begun, and fentanyl 5.0 mcg/kg was given iv. Baseline data were obtained as follows: Samples of systemic arterial and cerebral venous blood were used for determining levels of TxB_2 by radioimmunoassay. Mean arterial pressure (MAP), cardiac output, heart rate, pulmonary artery occlusion pressure, ICP, and hemoglobin (Hgb) were also recorded. Shock was then produced by rapidly removing blood from the femoral artery catheter until an MAP of 50 mmHg was reached. That level was maintained for 30 minutes by withdrawing or reinfusing blood as needed. Sufficient LRS was then given iv to restore systolic blood pressure (BP) to control values. Measurements were repeated at 4 intervals: as soon as MAP reached 50 mmHg (early shock-ES), at the end of the shock period (late shock-LS), immediately after BP had been restored (early resuscitation-ER), and 2 hours later (late resuscitation-LR). Cerebral oxygen availability (CO_2A) was calculated as CBF x arterial oxygen content. Data were analyzed using analysis of variance of repeated measures. Individual differences were confirmed using t testing (significance = $p < 0.05$).

Results: Cerebral venous TxB_2 , CBF, Hgb, and CO_2A all changed significantly over the course of the study, as can be seen in the Table. TxB_2 increased slightly during shock, then increased markedly at LR.

CBF decreased slightly during shock, increased immediately after resuscitation, and then, despite the reduced post-resuscitation Hgb concentration, decreased to below baseline levels. CO_2A levels also increased immediately after resuscitation, then had significantly declined by LR.

Discussion: In these anesthetized dogs subjected to hemorrhagic shock and then resuscitated with LRS, there was no increase in the metabolic end-product of TxA_2 , until LR. During that same interval, CBF had declined to levels below baseline despite a concomitant reduction in Hgb. These data suggest that the previously reported failure of CBF to increase in response to decreased Hgb following resuscitation from hemorrhagic shock (1) may be related to release of TxA_2 from cell membranes. Both the decrease in CBF and the increase in cerebral venous TxB_2 were less prominent than those reported following GCI (3). The less profound CNS insult produced by hemorrhagic shock in comparison to GCI may result in release of less TxA_2 and therefore a less marked decrease in CBF.

References

1. Prough DS, Johnson JC, Stump DA, et al: Effects of hypertonic saline versus lactated Ringer's solution on cerebral oxygen transport during resuscitation from hemorrhagic shock, J Neurosurg 64:627-632, 1986
2. Todd MM, Tommasino C, Moore S, et al: The effect of hypertonic saline on intracranial pressure, cerebral blood flow and brain water content, Anesthesiology 61:A123, 1984 (Abstract).
3. Prough DS, Kong D, Watkins WD, et al: Inhibition of thromboxane A_2 production does not affect post-ischemic brain hypoperfusion in dogs, Anesth Analg 65:S122, 1986

TABLE (Means $\pm$ SE)

	B	ES	LS	ER	LR
TxB_2	430 $\pm$	463 $\pm$	593 $\pm$	513 $\pm$	1373 $\pm$ *
(pg/ml)	111	107	181	144	434
CBF	22.8 $\pm$	15.2 $\pm$	15.0 $\pm$	40.7 $\pm$ †	17.1 $\pm$
(ml $\cdot$ min $^{-1}$)	5.2	1.2	1.9	6.9	1.9
Hgb	13.3 $\pm$	12.5 $\pm$	11.4 $\pm$	9.4 $\pm$	10.0 $\pm$
(g $\cdot$ dl $^{-1}$)	0.9	0.9	1.2	1.0	0.9
CO_2A	4.4 $\pm$	2.6 $\pm$	2.4 $\pm$	5.2 $\pm$	2.4 $\pm$ §
(ml $\cdot$ min $^{-1}$)	1.3	0.2	0.4	0.8	0.4

* $p < 0.05$ compared to B, ES, and ER

† $p < 0.05$ vs. all other intervals

‡ $p < 0.05$ compared to B

§ $p < 0.05$ compared to ER

INTRACRANIAL PRESSURE FOLLOWING RESUSCITATION FROM HEMORRHAGIC SHOCK

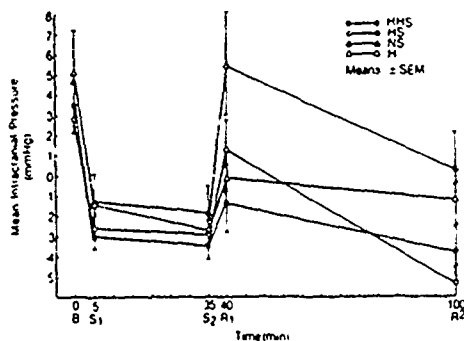
John M. Whitley, Donald S. Prough, Michael A. Olympio, Patricia H. Petrozza, Department of Anesthesia, Wake Forest University Medical Center, 300 S. Hawthorne Rd., Winston-Salem, North Carolina 27103

Purpose: We tested the hypothesis that a combination hypertonic/hyperoncotic fluid, used for resuscitation from hemorrhagic shock, would maintain a lower intracranial pressure (ICP).

Methods: In anesthetized dogs, we measured cerebral blood flow (CBF), mean arterial pressure (MAP), and cardiac output (CO). Dogs were hemorrhaged to an MAP of 40 mmHg for 30 minutes, then resuscitated using one of four fluids: (1) 0.9% NaCl 32 ml/kg (NS group), (2) 7.2% Hypertonic NaCl 4 ml/kg (HS group), (3) 20% Hetastarch in NS, 4 ml/kg, (H group) or (4) 20% H in HS, (HHS group), 4 ml/kg. Data were compared at B (baseline), S₁ (immediately after lowering MAP to 40 mmHg), S₂ (30 minutes after S₁), R₁ (immediately after resuscitation), and R₂ (one hour following R₁), using analysis of variance of repeated measures, $p < 0.05$ considered significant.

Results: ICP decreased in all groups during shock and increased following resuscitation in the NS group (Fig.). At R₂, ICP was significantly lower in the HHS and HS groups. MAP, CO, and CBF were similarly restored by all fluids.

Conclusions: The HHS resuscitation fluid produces little increase in ICP. These data extend previous observations regarding hypertonic fluid; the HHS combination may be useful for shock therapy if intracranial compliance is diminished.



References:

1. Prough DS, Johnson JC, Stump DA, Stullken EH, et al: Effects of hypertonic saline versus lactated Ringer's solution on cerebral oxygen transport during resuscitation from hemorrhagic shock. *J Neurosurg* 64:627-632, 1986

TITLE: SHOCK PLUS AN INTRACRANIAL MASS IN DOGS: CEREBROVASCULAR EFFECTS OF RESUSCITATION FLUID CHOICES
AUTHORS: J.S. Whitley, Ph.D., D.S. Prough, M.D., D.S. DeWitt, Ph.D.
AFFILIATION: Departments of Anesthesia and Neurology, Wake Forest University Medical Center, Bowman Gray School of Medicine, Winston-Salem, North Carolina 27103

Introduction: If intracranial hypertension occurs in combination with hemorrhagic shock, the choice of resuscitation fluids may strongly influence the extent of neurologic injury. In dogs, the infusion of hypertonic saline (HSS) or hydroxyethylstarch (HES) produces lower intracranial pressure (ICP) than resuscitation with isotonic crystalloid solutions (1,2). Although HSS reduces ICP to a greater extent than HES, the hemodynamic improvement following HES is more sustained than that following HSS. Recent studies of hemorrhagic shock have combined hypertonic and hyperoncotic fluid to achieve more sustained systemic hemodynamic improvement while preserving the advantages of a lower infusion volume (3). The cerebrovascular effects of such a combination have not been reported. In anesthetized dogs with a subdural mass lesion, we induced hemorrhagic shock and compared the effects of resuscitation with a hypertonic, a hyperoncotic, an isotonic, or a combined hypertonic-hyperoncotic fluid on ICP and cerebral blood flow (CBF).

Methods: 24 mongrel dogs (18-24 kg) were anesthetized with thiopental 20 mg/kg, paralyzed with vecuronium 0.2 mg/kg, and endotracheally intubated. We maintained anesthesia with nitrous oxide 60% and halothane 0.5% in oxygen and ventilated to maintain normocarbida. A pulmonary artery, a cisterna magna, and two femoral arterial catheters were placed. CBF was measured using a sagittal sinus cannula. Through a left craniotomy, a subdural balloon was placed. While ICP was maintained at 20 mmHg by balloon inflation, the animal was rapidly hemorrhaged to reduce mean arterial pressure (MAP) to 50 mmHg where it was maintained for 30 min. Resuscitation was then performed by rapid infusion (five min) of one of four randomly selected resuscitation fluids: 1. NaCl 0.8% - 54 ml/kg (NaCl group), 2. HES 20% in NaCl 0.8% - 6.0 ml/kg (HES), 3. NaCl 7.2% - 6.0 ml/kg (HSS), 4. HES 20% in NaCl 7.2% - 6.0 ml/kg (HES/HSS). As fluid infusion began, ICP was permitted to vary without further manipulation. Data were collected at baseline, after balloon inflation, at the beginning of the shock interval (T=0), at the end of the shock interval (T=30), immediately following the five-min fluid infusion (T=35), and at thirty minute intervals thereafter. We compared ICP and CBF using ANOVA of repeated measures ($p < 0.05$ considered significant) and collected descriptive data for MAP, cardiac output, arterial blood gases, heart rate, and hemoglobin.

Results: During the shock interval, ICP was experimentally maintained at 20 mmHg. Following fluid infusion, ICP increased in all groups (Fig. 1). The most significant increase occurred in the NaCl group ($p < 0.001$ in comparison to all other groups). CBF decreased in all groups during shock plus intracranial hypertension (Fig. 2), then recovered partially at T=35, only to decline steadily afterwards. The descriptive variables demonstrated several trends, the most important being MAP, which was better from T=65 through T=125 in the HES and HES/HSS groups.

Discussion: Following this severe insult, similar to a clinical head injury combined with hemorrhagic shock, a combination hypertonic/hyperoncotic resuscitation fluid (HES/HSS) or a hyperoncotic fluid (HES) produced a more sustained improvement in systemic hemodynamics than NaCl (136 mEq/L) or HSS. NaCl produced a rapid increase in ICP, while HSS

produced only a transient improvement in systemic hemodynamics. If these data are extrapolated to human trauma victims in whom head injury is combined with hemorrhagic shock, a hyperoncotic/hypertonic or a hyperoncotic solution may be preferable for acute resuscitation.

References:

1. Prough DS, et al. Effects of hypertonic saline versus lactated Ringer's solution on cerebral oxygen transport during resuscitation from hemorrhagic shock. *J Neurosurg* 1986;64:627.
2. Poole GV, et al. Effects of resuscitation from hemorrhagic shock on cerebral hemodynamics in the presence of an intracranial mass. *J Trauma* 1987;27:18, 1987.
3. Smith GC, et al. A comparison of several hypertonic solutions for resuscitation of bled sheep. *J Surg Research* 1985;39: 517.

Figure I.

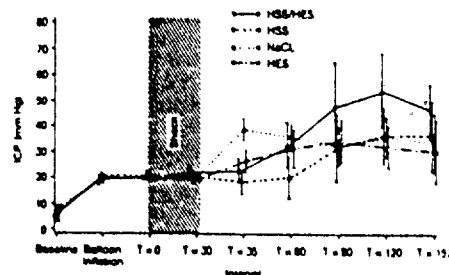
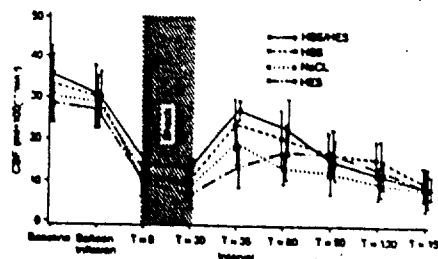


Figure II.



Effects On Intracranial Pressure In a Clinically Derived Fluid Resuscitation Protocol Following Hemorrhagic Shock with an Accompanying Intracranial Mass

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Introduction

We have previously shown, in a hemorrhagic shock - intracranial mass model, that isotonic crystalloid results in a greater and more rapid increase in ICP immediately following resuscitation than hypertonic crystalloid, colloid or a combination of crystalloid and colloid (Whitley 1988). This rapid increase in ICP may exacerbate the neurological sequelae of the shock episode by decreasing CBF following resuscitation. While the effects of resuscitation on ICP have been extensively studied, they have dealt only with the effects of a single resuscitation fluid bolus, unlike the clinical protocol where systemic hemodynamics are maintained. The present study compared the cerebrovascular effects of resuscitation with isotonic and hypertonic crystalloid, each with and without colloid (10% Pentastarch), while maintaining cardiac output above baseline levels in a hemorrhagic shock - intracranial mass model.

Methods

Twenty-four dogs were anesthetized with thiopental, intubated, and ventilated. Cardiac output (CO) was recorded using a Noninvasive Continuous Cardiac Output Monitor (NCCOM-3). Cerebral blood flow (CBF) was measured using the cerebral venous outflow technique (Rapela and Green 1964). A 18G catheter inserted into the cisterna magna provided continuous intracranial pressure (ICP) monitoring. ICP was increased to 15 mmHg before shock, by inflation of a subdural balloon overlying the left cortex, and maintained throughout the 30 minute shock period (MAP = 50 mmHg, CPP = 35 mmHg). Animals received one of four fluid groups for resuscitation: Group I: isotonic saline (40 ml/kg); Group II hypertonic saline (20 ml/kg, 250 mEq/L Na⁺); Group IP: isotonic saline (20 ml/kg) with 10% Pentastarch; Group IIP: hypertonic saline (20 ml/kg) with 10% Pentastarch. Additional fluid was infused as needed to maintain CO at or above baseline. Data were compared at: baseline (BL), elevation of ICP to 15 mmHg (BI), early (T0) and late shock (T30), following fluid resuscitation (T35), and at 30 minute intervals for two hours.

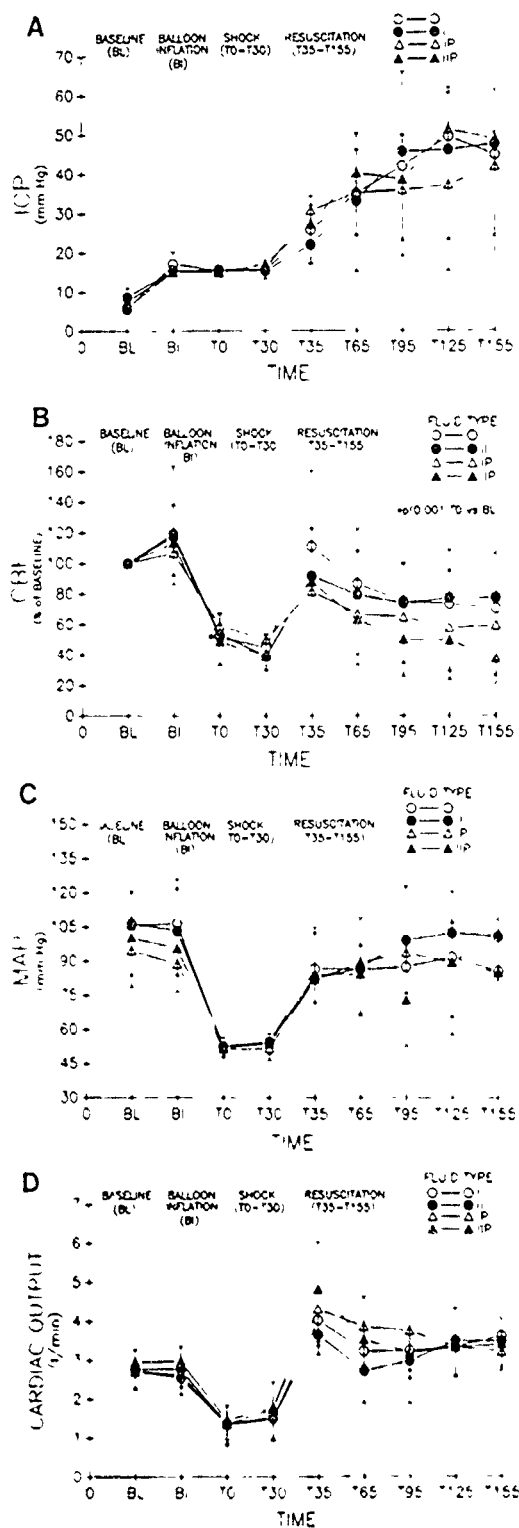


Fig. 1 A-D. Cerebrovascular and systemic hemodynamics following resuscitation from hemorrhagic shock in the presence of a intracranial mass with isotonic (I) and hypertonic (II) crystalloid alone or in combination with 10% Pent (starch (IP, IIP))

Results

Intracranial Pressure

ICP (Fig. 1 A), was increased to 15 mm Hg by balloon inflation (BI) and maintained throughout shock (T0-T30). ICP increased rapidly with the initiation of fluid resuscitation (T35) in all groups. Further increases in ICP occurred as a result of supplemental fluid infusion (T65-T155). No differences between groups were detected

Cerebral Blood Flow

Induction of hemorrhage resulted in significant reductions in CBF from BL in all groups (Fig. 1 B, $p < 0.001$). Following resuscitation, CBF declined steadily in all groups over time

Mean Arterial Pressure

During shock (T0-T30), MAP was decreased to 50 mm Hg and maintained for 30 minutes (Fig. 1 C). Following fluid resuscitation, MAP increased and then stabilized for the remainder of the experimental period

Cardiac Output

CO was maintained following resuscitation by supplemental fluid infusion (Fig. 1 D). Animals resuscitated with crystalloid required a greater fluid volume initiated at an earlier time as compared to animals receiving crystalloid plus colloid

Discussion

The deleterious effect of increased ICP is its effect on CBF. We have shown that isotonic and hypertonic crystalloid solutions alone or in combination with colloid rapidly increased ICP during the immediate post-resuscitation period. Supplemental fluid infusion, necessary to maintain CO, markedly increased ICP. As a result, CBF declined steadily over time. These results suggest that fluid resuscitation following hemorrhage in the presence of an intracranial mass may exacerbate the neurological sequelae of the shock episode.

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RESUSCITATION FROM HEMORRHAGIC SHOCK IN ASSOCIATION WITH AN INTRACRANIAL MASS: EFFECTS OF A CLINICALLY MODELLED PROTOCOL ON INTRACRANIAL PRESSURE

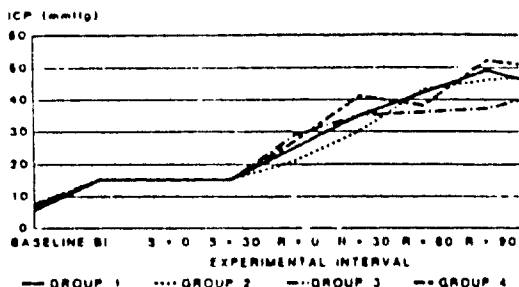
John M. Whitley, Donald S. Prough, Dwight D. Deal, Amelia K. Lamb, Douglas S. DeWitt. Departments of Anesthesia and Neurology, Bowman Gray School of Medicine, 300 S. Hawthorne Rd., Winston-Salem, N.C. 27103

Purpose: To simulate two key aspects of multiple trauma associated with head injury: 1. an expanding intracranial mass lesion, and 2. ongoing fluid resuscitation.

Methods: In 24 mongrel dogs, anesthetized with thiopental and halothane and mechanically ventilated, an intracranial balloon was inflated to maintain an intracranial pressure (ICP) of 15 mmHg during hemorrhagic shock (mean arterial pressure = 50 mmHg for 30 minutes). In random order, animals were resuscitated with balanced salt solution (BSS-Na 130 mEq/L), hypertonic solution (HSS-260mEq/L), BSS plus hetastarch (BSS/HES), or HSS/HES at a rate sufficient to maintain stable systemic hemodynamic values after resuscitation.

Results: All fluids produced a significant ($p < 0.05$), progressive rise in ICP that continued throughout the experimental period. Cerebral blood flow deteriorated as ICP increased.

Discussion: Following hemorrhagic shock, the rate of ongoing fluid infusion determines the rise of ICP. In this study, HSS (520 mOsm/L) failed to reduce ICP as a more hypertonic solution (2400 mOsm/L) had in previous studies.



CEREBROVASCULAR AND CEREBROMETABOLIC EFFECTS OF INTRACAROTID INFUSED PLATELET-ACTIVATING FACTOR IN RATS

Patrick M. Kochanek, Edwin M. Nemoto, John A. Melick, Rhobert W. Evans, and David F. Burke. Depts of Anesthesiology/Critical Care Medicine and Pediatrics, Univ of Pittsburgh, Pittsburgh, PA 15213

Platelet-activating factor (PAF) has been implicated in the pathogenesis of ischemic brain injury and endotoxic shock (1,2), but its effects on normal cerebral blood flow (CBF) and metabolism have not been described.

To test the hypothesis that PAF alters CBF and metabolism, CBF (hydrogen clearance) and cerebral metabolic rate for oxygen (CMRO₂) were measured in 2 groups of Wistar rats. Hexadecyl-PAF infused into the right carotid artery (70 pmol/min, n=10) for 1 h decreased mean arterial pressure from 122 ± 4 ($\bar{x} \pm \text{SEM}$) to 77 ± 6 mm Hg and CBF from 159 ± 12 to 116 ± 14 ml/100g/min ($p < 0.002$). In contrast, CMRO₂ increased from 9.7 ± 0.9 ml/100g/min to 11.5 ± 1.4 ml/100g/min ($p < 0.05$). In controls (n=7) rendered similarly hypotensive by blood withdrawal and infused with the PAF vehicle, CBF was 143 ± 22 and 137 ± 21 ml/100g/min and CMRO₂ 9.3 ± 1.6 and 9.6 ± 2.1 ml/100g/min at baseline and after 1 hr respectively ($p = \text{NS}$ for both).

The effects of PAF on CBF and CMRO₂ mimic those observed during postischemic reperfusion and endotoxin infusion. PAF may contribute to the hypoperfusion and hypermetabolism seen in the brain after ischemia and during septic shock.

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SHOCK PLUS INTRACRANIAL HYPERTENSION INCREASES CEREBRAL THROMBOXANE RELEASE

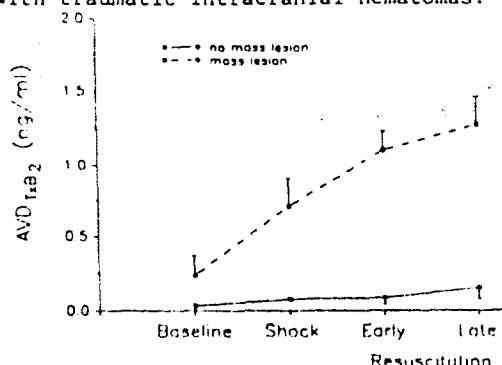
Daniel L. Kong, John M. Whitley, Donald S. Prough, Douglas S. DeWitt. Depts. of Anesthesia and Neurology, Bowman Gray School of Medicine, 300 S. Hawthorne Rd., Winston-Salem, N.C. 27103

Purpose: To determine if incomplete cerebral ischemia produced by shock and increased intracranial pressure (ICP) increases brain production of the cerebral vasoconstrictor, thromboxane A₂ (TxA₂).

Methods: 39 dogs (group 1, control, n=23, and group 2, n=16), anesthetized with pentobarbital and halothane and mechanically ventilated, underwent hemorrhagic shock to a mean arterial pressure (MAP) of 50 mmHg for 30 min, after which they were given non-blood fluid. During shock, group 2 had an intracranial balloon inflated to maintain ICP at 20 mmHg. Arterial and cerebral venous levels of TxB₂, the stable metabolite of TxA₂, were measured at intervals before, during, and after shock.

Results: In the control group, both arterial and cerebral venous TxB₂ levels remained similar to baseline. In contrast, shock plus increased ICP produced significantly more cerebral venous TxB₂ than in group 1 ($p < 0.05$).

Conclusions: Shock plus increased ICP stimulates release of the cerebral vasoconstrictor TxA₂, a mediator associated with ischemic brain injury. Related biochemical mechanisms may potentiate ischemic injury associated with traumatic intracranial hematomas.



INCREASED EEG ACTIVITY CORRELATES WITH CLINICAL SEDATION

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Currently there is no other way than EEG to assess sedation in critically ill patients when therapeutic paralysis is used. This study was done to identify power spectral EEG parameters that correlate with loss of consciousness during a slow infusion of pentothal or midazolam for anesthetic induction.

12 adult patients were randomized to receive thiopental (50 mg/min) or midazolam (2 mg/min). Every 15 secs., subjects were asked to open their eyes until unresponsive. Using bifronto-mastoid electrodes, the spectral power EEG was recorded for later analysis by an unmodified Tracor-Northern NOMAD EEG processor using 4 sec. epochs. Comparisons were made between 10 epochs at the beginning of infusion and after loss of response to verbal stimuli.

All patients were clinically sedated at loss of consciousness. All parameters were significantly ($P < 0.05$) different between control and sedation for both pentothal and midazolam. All comparisons showed increased EEG activity during the period of sedation.

	Spectral Edge(Hz)	Median freq(Hz)	Alpha (%pw)	Ratio ($\alpha + \beta / \delta$)
Thiopental (n=6)				
C	10.3±0.6	2.2±0.2	5.7±0.7	0.18±0.04
S	17.8±0.2	8.6±0.5	21.7±1.5	4.68±0.79
Midazolam (n=6)				
C	9.6±0.6	2.7±0.2	5.7±1.0	0.25±0.06
S	17.7±0.2	9.7±0.4	24.4±1.4	3.10±0.35

(C-control, S-sedation, mean±SEM)

Time from start until sedation was about 4 min. for both groups.

We conclude that the processed EEG can be used to titrate pentothal or midazolam sedation to a desired CNS effect, avoiding awareness during paralysis and minimizing adverse cardiovascular effects. The consistently increased EEG activity with both drugs cannot be readily explained, and needs further investigation.

TITLE: REGIONAL CEREBRAL BLOOD FLOW FOLLOWING RESUSCITATION FROM HEMORRHAGIC SHOCK IN DOGS WITH A SUBDURAL MASS

AUTHORS: J.M. Whitley, Ph.D., D.S. Prough, M.D., A.K. Lamb, B.S., D.D. Deal, B.S., D.S. DeWitt, Ph.D.

AFFILIATION: Department of Anesthesia, Wake Forest University Medical Center, Winston-Salem, NC 27103

Introduction. Hypertonic fluids offer potential advantages in the resuscitation of patients with hemorrhage who are at risk for intracranial hypertension. Hypertonic (7.2%) saline effectively minimizes resuscitation-induced increases in intracranial pressure (ICP) following resuscitation from hemorrhagic shock. We studied dogs with a subdural mass (a model of intracranial hypertension) to determine the effects of 7.2% NaCl on regional cerebral blood flow (rCBF) following resuscitation from hemorrhagic shock.

Methods. Twelve mongrel dogs (18-22 kg) were anesthetized with thiopental 8 mg/kg iv and halothane 0.5-1.0% in N₂O and O₂. Following intubation, they were maintained at a PaCO₂ between 34-45 mmHg. The right brachial and pulmonary arteries were cannulated for continuous monitoring of mean arterial pressure (MAP) and intermittent determination of cardiac output. The right femoral and left brachial arteries were cannulated and used as reference organs for rCBF measurements using radioactive microspheres. All animals were then splenectomized. Through a burr hole over the right cerebral hemisphere, the dura was incised and the balloon tip of a 7 Fr catheter inserted to simulate an expanding intracranial mass. Prior to hemorrhage, ICP, as measured from the cisterna magna, was slowly increased to 15 mmHg by balloon inflation and maintained at that level throughout the shock interval. Blood was rapidly removed to reduce MAP to 50 mmHg (cerebral perfusion pressure = 35 mmHg) and removed or added to maintain that MAP for 30 min (T₀-T₃₀). Animals were then randomly assigned to resuscitation with equal sodium loads consisting of either 7.2% NaCl (HS, 6 ml/kg) or 0.8% NaCl (ISO, 54 ml/kg). Once resuscitation began, ICP was permitted to vary independently. rCBF measurements on brainstem and left (LCH) and right (RCH) cerebral hemispheres were made at baseline (B), mid-shock (T₁₅), immediately following resuscitation (T₃₅), and at 60-min intervals thereafter, for 2 hours (T₉₅, T₁₅₅). Data were analyzed using repeated measures analysis of variance (P<0.05 considered significant).

Results. ICP increased markedly following resuscitation with ISO and decreased with HS (P<0.001, table 1). After T₃₅, ICP decreased in ISO while increasing slightly in HS. rCBF differed markedly between groups following resuscitation (table 2). Following resuscitation with HS, rCBF in LCH (contralateral to the mass) increased above baseline; in contrast following ISO resuscitation, rCBF remained at shock levels. Although rCBF in LCH decreased in both groups over time, HS maintained the higher blood flows. Neither fluid restored rCBF in RCH; however, rCBF increased in the HS group but was initially unchanged in the ISO group (figure). The type of resuscitation fluid strongly influenced post-resuscitation rCBF in both the RCH (P<0.01) and LCH (P<0.01). Brainstem CBF increased to pre-shock

levels in both groups with resuscitation but decreased rapidly over time with no differences between groups (table 2).

Conclusions. Hypertonic salt solutions reduce brain water by osmotic effects. Previous studies have shown that hypertonic saline, in contrast to volumes of isotonic salt solutions that provide comparable sodium loads and similar hemodynamic changes, reduces ICP following resuscitation from hemorrhagic shock. These data demonstrate that hypertonic solutions also restore or improve rCBF better than do conventional crystalloid solutions when rapid hemodynamic resuscitation must be accomplished in the presence of decreased intracranial compliance. The superior effects on ICP appear to explain this advantage of hypertonic solutions, a finding that may be clinically important.

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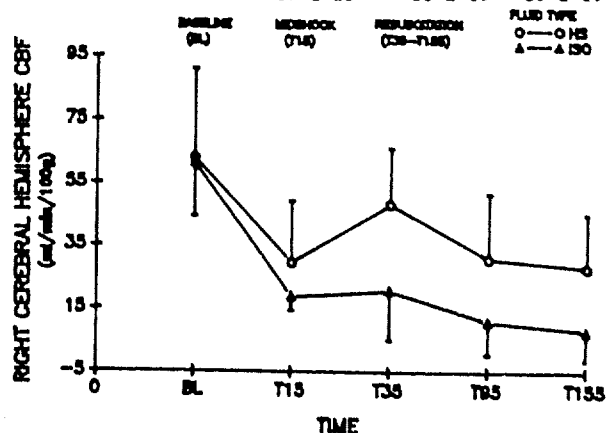
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Table 1
ICP (mmHg)

Fluid	B	T ₁₅	T ₃₅	T ₉₅	T ₁₅₅
	Pre-Mass	Mid-Shock	Post-Resuscitation		
ISO	1.92 ±1.84	14.92 ±0.73	33.67 ±7.24	28.17 ±5.90	22.50 ±9.88
HS	5.67 ±3.73	15.83 ±1.68	9.75 ±5.58	15.83 ±11.57	18.75 ±13.77

Table 2
Post-Resuscitation rCBF (ml/100g/min; mean ± SD)

Region	Fluid	T ₃₅	T ₉₅	T ₁₅₅
LCH	ISO	42 ± 19	19 ± 13	13 ± 14
	HS	67 ± 35	32 ± 24	33 ± 22
Brainstem	ISO	62 ± 19	37 ± 27	23 ± 5
	HS	67 ± 23	33 ± 19	39 ± 19



TITLE: SMALL VOLUME RESUSCITATION FROM HEMORRHAGIC SHOCK IN DOGS WITH HYPERTONIC SALINE-HYDROXYETHYL STARCH SOLUTIONS

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AFFILIATION: Departments of Anesthesia (Section on Critical Care) and Neurology, Wake Forest University Medical Center, Winston-Salem, NC 27103

Introduction. Small volumes of hypertonic saline effectively restore cardiovascular function following hemorrhage. Likewise, small volumes of colloid effectively expand and maintain the plasma volume for a longer interval than do small volumes of isotonic crystalloid following hemorrhage. We compared canine systemic hemodynamics and organ blood flow following conventional large-volume resuscitation with isotonic 0.8% saline (ISO) to small volume resuscitation with hypertonic (7.2%) saline (HS), a concentrated colloid (20% hydroxyethyl starch [HES]) and a combination fluid of 20% HES dissolved in HS.

Methods. Twenty-four mongrel dogs (18-22 kg) were anesthetized with thiopental 8 mg/kg iv, endotracheally intubated, then maintained using halothane 0.5% in 70% nitrous oxide. They were ventilated to a PaCO₂ between 35-45 mmHg. The right brachial artery and pulmonary artery were cannulated for continuous monitoring of mean arterial pressure (MAP) and cardiac output (CO). The right femoral and left brachial arteries were cannulated and used as reference organs for measurement of organ blood flow, using radioactive microspheres. All animals were then splenectomized. Following baseline (B) measurements, animals underwent a 30 minute period of hemorrhagic shock, designated T(time)0-T30, at a fixed MAP of 45 mm Hg, following which they were randomly assigned to one of four intravenous resuscitation fluid groups: ISO (54 ml/kg), HS (6 ml/kg), HES (6 ml/kg), or HES/HS (6 ml/kg). Data were collected at baseline, mid-shock (T15), immediately following resuscitation (T35) and at 60 min intervals for 2 hours (T95, T155).

Results. MAP decreased during shock, then increased in all groups following resuscitation (Table 1A). Resuscitation failed to return MAP to pre-shock levels. MAP continued to increase over the first 60 min following resuscitation in the HES and HES/HS groups, whereas it remained constant in the ISO and declined in the HS groups. CO increased with resuscitation in all groups, exceeding baseline in the ISO and HES/HS groups ($p < 0.05$ compared to HS or HES). One hour following resuscitation (T95), CO was significantly improved in either of the two colloid-containing groups than the CO at T95 in the ISO group ($p < 0.05$). Following resuscitation, cerebral blood flow, myocardial blood flow, and renal blood flow were statistically similar among groups. Renal blood flow (RBF) increased with resuscitation in all groups except HES. Over two hours following resuscitation, RBF decreased in all groups to the levels present during shock. Reperfusion of hepatic tissue following shock demonstrated a significant variation among resuscitation groups ($p < 0.05$). ISO

resulted in marked increases in hepatic blood flow (HBF) which exceeded pre-shock levels. While HES/HS immediately increased HBF to near pre-shock levels, HS and HES did not. At T155, HBF had decreased in all groups, with HS decreasing to levels present during shock.

Conclusion. These results demonstrate that small volume resuscitation with HS in combination with HES is comparable to large volumes of isotonic saline, and is superior to HS or HES in the ability to sustain adequate systemic pressure and improve organ blood flow following resuscitation from hemorrhagic shock. Further studies are necessary to determine if the combination similarly preserves or improves organ function following severe hemorrhagic shock.

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Table 1A Mean Arterial Pressure (means $\pm$ SD)

Fluid	B	T15 Mid-Shock	T35 Post-Resuscitation	T95	T155
ISO	118 $\pm$ 17	45 $\pm$ 5	86 $\pm$ 10	87 $\pm$ 6	81 $\pm$ 17
HS	113 $\pm$ 9	48 $\pm$ 9	79 $\pm$ 10	74 $\pm$ 27	66 $\pm$ 34
HES	109 $\pm$ 19	47 $\pm$ 5	78 $\pm$ 9	97 $\pm$ 4	81 $\pm$ 30
HES/HS	100 $\pm$ 15	43 $\pm$ 6	72 $\pm$ 16	93 $\pm$ 17	72 $\pm$ 18

Table 1B Cardiac Output (means $\pm$ SD)

Fluid	B	T15	T35	T95	T155
ISO	3.9 $\pm$.5	1.4 $\pm$.3	4.9 $\pm$ 1.0	2.7 $\pm$.6	7.2 $\pm$.8
HS	3.2 $\pm$ 1.0	1.2 $\pm$.1	3.0 $\pm$.6	1.7 $\pm$.3	1.5 $\pm$.3
HES	3.9 $\pm$.6	1.7 $\pm$.2	3.0 $\pm$.4	3.1 $\pm$ 1.0	2.6 $\pm$ 1.2
HES/HS	4.4 $\pm$ 1.0	1.9 $\pm$.3	4.7 $\pm$.8	3.5 $\pm$ 1.5	2.2 $\pm$ 1.0

Table 2 Hepatic Blood Flow (ml/min/100g)

	ISO	HS	HES	HES/HS
BL	46.3	36.5	33.9	33.3
T15	23.9	14.7	10.0	17.8
T35	65.7	28.7	17.4	34.8
T95	44.8	15.9	36.8	30.6
T155	31.2	12.0	27.9	26.9

1871

BACTERIAL SEPSIS ALTERS PULMONARY VASCULAR REACTIVITY TO U46619 IN ISOLATED PERFUSED RAT LUNGS. M. J. Schneidkraut, M. D. Pons, A. M. Corbin, and R. W. Carlson. Wayne State Univ. Sch. of Med., Detroit, MI 48201.

Male Sprague-Dawley rats (n=8-10 per group, 200-250 g) were anesthetized (30 mg/kg sodium pentobarbital, i.v.) and bacterial sepsis was initiated by cecal ligation and puncture. Four hours after cecal ligation, bolus injections of the thromboxane A₂ mimic, U46619 (5-200 ng) were made into the pulmonary artery of lungs isolated from control (no surgery), sham (surgery-no cecal ligation), or septic (cecal ligation peritonitis) animals. Lungs from septic rats had a decreased slope of the U46619 dose-response curve compared to the lungs from control (30.4%, p<.05) or sham (27.8%, p<.05) animals. Wet-dry lung weight ratios of all three groups were not significantly different. Lungs from rats pretreated with ibuprofen (15 mg/kg, i.v.) 30 minutes before cecal ligation and perfused *in vitro* four hours after the initiation of bacterial sepsis, showed a pressor response to U46619 that was not significantly different than control. It is concluded that a decreased vascular responsiveness to a TXA₂ mimic is present shortly after the induction of bacterial sepsis. This altered vascular response is not due to surgical trauma or the presence of pulmonary edema. The decreased vascular reactivity appears to be related to an increased endogenous release of cyclooxygenase products.

1873

REGIONAL CEREBRAL BLOOD FLOW (rCBF) FOLLOWING RESUSCITATION FROM HEMORRHAGIC SHOCK WITH INCREASED INTRACRANIAL PRESSURE (ICP)

JM. Whitley, PhD, DS Prough, MD, AK Lamb, BS, DD Deal, BS, (SPON: P. Hutchins), Department of Anesthesia, Wake Forest University Medical Center, Winston-Salem, NC 27103

If an intracranial mass is present, fluid resuscitation increases ICP. Recent data has shown 7.2% NaCl to be effective in minimizing increases in ICP and increasing CBF following resuscitation. We studied the effects of 7.2% NaCl on rCBF following resuscitation from hemorrhagic shock.

Twelve dogs were anesthetized, and maintained with halothane. ICP was continuously monitored. rCBF measurements were made using radioactive microspheres. A subdural balloon was placed over left cortex and ICP elevated to 15 mmHg and maintained throughout the 30 minute shock interval. Blood was removed to reduce mean pressure to 55 mmHg. Animals were then assigned to one of two fluid groups: 7.2% NaCl (6 ml/kg) or 0.3% NaCl (54 ml/kg). rCBF measurements on brainstem (BBB), left and right cerebral hemispheres (LCH, RCH) were made at baseline, mid-shock, after resuscitation, and at hourly intervals for 2 hours.

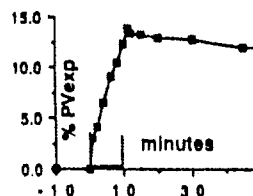
rCBF was variable between groups. rCBF in RCH increased with resuscitation above baseline with HS but not ISO. CBF in RCH decreased in both groups over time. Neither fluid restored CBF in LCH. BBF increased to baseline in both groups with resuscitation but decreased rapidly over time.

These data demonstrate that 7.2% saline restores or improves rCBF compared to conventional crystalloid solutions.

1875

PLASMA VOLUME AND LYMPH DYNAMICS DURING INFUSION OF HYPERTONIC SALINE DEXTRAN (HSD). L. Halvorsen, PR Perron, KD Ashley, RA Gunther, JW Holcroft, and GC Kramer. Depts. of Human Physiology and Surgery, Univ. of Calif., Davis, CA 95616.

HSD causes rapid restoration of cardiovascular function in hypovolemic animals. The predominant mechanism of this rapid action is controversial, having been attributed to rapid plasma volume expansion (PVexp), cardiac stimulation, and venous capacitance changes. In this study highly concentrated 25% NaCl/24% dextran 70 was infused into euvoletic sheep (1 ml/kg/10 min). Rapid blood sampling during and after infusion allowed estimation of PVexp from plasma protein [P]. Results were compared to J Evans blue measurements of PV. PVexp began immediately upon infusion and was 90% complete by the end of the infusion. Each ml of HSD expanded PV 6.4±2.2 ml while blood pressure rose 1-15 mmHg, cardiac output increased 0.8-1.3 l/min and right atrial pressure increased 3-6 mmHg. Pre-femoral lymph flow increased 2-3x. These data suggest that the predominant mechanism of action of HSD is rapid PVexp caused by a sudden shift of intracellular fluid into the interstitial and intravascular spaces in response to the large osmotic forces.



1872

NPC 205, A POTENT ADENOSINE ANTAGONIST, IMPROVES SURVIVAL FOLLOWING HEMORRHAGIC SHOCK IN RATS. Lawrence de Garaville, NOVA Pharmaceutical Corporation, Baltimore, MD 21224

It is postulated that elevated circulating adenosine levels play a role in the deterioration in cardiovascular function and death due to hemorrhagic shock (HS). It has already been shown that NPC 205 (1,3-di-n-propyl-8-(4-hydroxyphenyl)xanthine) improves cardiovascular function during HS in rats. The study herein was, therefore, designed to test the effects of NPC 205 on survivability following HS. Rats (350-450g) were anesthetized with ketamine (75 mg/kg, ip), and a catheter was placed in the left carotid artery for measurement of arterial blood pressure (ABP) and for blood withdrawal and reinfusion. Prior to HS animals were administered 100 U of heparin while the shed blood was mixed with 200 U. Blood was then withdrawn (2cc/min) until a mean ABP of 30 mmHg was achieved. HS was maintained for 60 min at which time NPC 205 (10 or 30 mg/kg, ip) or the vehicle (n=10 per group) were administered and blood was reinfused (2cc/min). Survival 6-h post-reinfusion in the control group was 30%, as compared to 90% in the 10 mg/kg group (p<.05) and 50% at 30 mg/kg NPC 205. In all groups, survival decreased over time and was no longer significantly different from control at 48-h post-reinfusion. In conclusion, NPC 205 provided a dramatic improvement in survival 6-h following HS, which suggests an adenosine antagonist may prove to be a useful therapeutic agent in the resuscitation from HS.

1874

HYPERTONIC SALINE - DEXTRAN RESUSCITATION OF MAJOR BURNS. H. Onatheim, A. Matsavage, G. S. Kramer, R. Gunther, Dept. of Human Physiology and Surgery, Univ. of Calif., Davis, CA 95616.

Small volume infusions of hypertonic saline dextran (HSD) have efficiently expanded vascular volume and reduced fluid requirements following hemorrhage. Major burns induce rapid plasma extravasation and hypovolemia. The present study was performed to determine the effect of using an initial infusion of HSD in the treatment of large cutaneous burns.

Halothane-anesthetized adult sheep were provided with intravascular catheters for hemodynamic monitoring. A full thickness burn injury was inflicted on 35-40% of the body surface area. Sheep remained anesthetized throughout the entire experiment until sacrifice. To mimic a clinical situation fluid therapy was withheld until 1 h postburn and was then started with a 2 min infusion of 4 ml/kg of either 7.5% NaCl in Dextran 70 6% (HSD-group, n=6) or normal saline (NS-group, n=6). Later lactated Ringer's infusion was given as needed to maintain CO at 90% of baseline.

At 60 min postburn MAP was reduced from 111±15 (mean±SD) to 74±20 mmHg and CO was reduced from 3.5±0.6 to 1.8±0.1 l/min (p<.01 vs. preburn). Following HSD bolus MAP was 111±12 mmHg and CO increased to 3.9±0.3 l/min whereas MAP was 93±19 mmHg and CO 2.7±0.7 l/min after NS bolus (p<.01 vs. HSD-group). The effect of HSD bolus only lasted 30-60 min. Additional lactated Ringer's infusion was needed slightly earlier after NS bolus (30±7 vs. 36±18 min, p<.05). Total fluid requirements in the first 6 h postburn were not reduced by the initial HSD bolus (2990±1470 ml vs. 2740±1220 ml in the NS-group, n.s.).

Conclusions: Small volume resuscitation with HSD is only transiently effective for volume expansion after thermal injury. This suggests that HSD resuscitation may not be effective in the presence of a large capillary leak.

Supported by NATO Collaborative Research Grant 0245/66 and Pacific Firefighters Burns Institute.

1876

Effects of a Highly Concentrated Hypertonic Saline/Dextran (HSD) Infusion in the Unanesthetized Horse. L. Snyder, G. Kramer, R. Gunther, Z. Reizan. Univ. Calif. Sch. Vet. Med., Davis, CA 95616

Infusion of various NaCl/dextran solutions have been shown to rapidly restore cardiovascular function during hemorrhagic shock. In the present study, we evaluated the cardiovascular effects of a highly concentrated 25% NaCl/24% dextran solution in 6 normal awake horses. The HSD was administered at 1 ml/kg IV over a 10 minute period. Plasma volume was determined by Evans blue dilution before infusion, and 5 and 35 minutes after administration of the NaCl-Dex solution. Clotting profiles were measured before, during and after infusion. The plasma volume increased 9.6 ± 2.8 ml/kg (mean ± SEM) and 4.0 ± 2.8 ml/kg at 5 and 35 minutes after infusion, respectively. The mean results shown for heart rate (HR), carotid (AP) and pulmonary pressures (PP), and plasma hematocrit (HCT), hemoglobin (Hb), plasma protein (Prot), osmolality (Osm), sodium (Na), and potassium (K).

Parameters	Pre	5 min. during infusion	5 min. post-infusion	20 min. post-infusion	60 min. post-infusion
HR/min.	38	45	45	46	47
AP mmHg	135	143	147	149	149
PP mmHg	24	33	29	28	30
HCT %	35.2	32.3	29.6	27	26.8
Hb g/dl	7.5	6.9	6.7	6.4	6.5
Prot g/dl	12.9	12	11.1	10	9.7
Osm mosm/L	283.2	304	310.6	300	296.5
Na mmol/L	138.7	148	151.9	144	143.5
K mmol/L	3.5	3.2	3.0	3.1	3.2

There was no evidence of either gross hemolysis or increases in plasma Hb after infusion. No changes occurred in the clotting profiles. Concentrated HSD solution appears to be safely administered in the awake horse in a dose of 1 ml/kg induces a rapid increase in plasma volume (approximately 10 ml/kg).

170 EARLY POST BURN LIPID PEROXIDATION (EFFECT OF IBUPROFEN AND ALLOPURINOL).

C. Lalonde* and R. Demling. Longwood Area Trauma Center at Beth Israel, Brigham and Women's, and Children's Hospitals, Boston, MA 02115.

We measured plasma lung and liver lipid peroxidation in anesthetized sheep after a 30% of total body surface, third degree burn. Animals were resuscitated to baseline filling pressures with Lactated Ringers and killed 10 hours post burn. Six sheep were pretreated with ibuprofen (12.5mg/kg) and five with allopurinol (50mg/kg). We used conjugated dienes and malondialdehyde as measures of lipid peroxidation. Circulating conjugated dienes increased from baseline of 4.4 ± 0.1 to 1.6 ± 0.05 after burn, while protein rich burn tissue lymph flow increased up to 8 fold. We also noted a significant increase in lung tissue malondialdehyde, MDA, from 45 ± 4 to 60 ± 6 nmol/g and liver MDA from 110 ± 20 to 271 ± 34 nmol/g along with increased tissue neutrophil sequestration. Ibuprofen attenuated lung tissue MDA but had not effect on lung inflammation, circulating lipid peroxides, or burn edema, indicating that ibuprofen most likely decreased O_2 radical release in lung tissue by the already sequestered neutrophils. Allopurinol, possibly via xanthine oxidase inhibition, markedly attenuated burn O_2 , circulating lipid peroxides, and prevented all pulmonary lipid peroxidation and inflammation, indicating that burn tissue oxidant release was in part responsible for local burn edema as well as distant inflammation and oxidant release, the latter most likely from complement activation. Neither antioxidant decreased the liver lipid peroxidation, indicating that its mechanism of production was different from that seen in burn tissue, plasma, or the lung.

171 CROSS-LINKED HEMOGLOBIN SOLUTION AS A RESUSCITATIVE FLUID FOLLOWING HEMORRHAGE IN THE RAT.

Jana Malcolm, Robert Przybelski* and David Burris*. Uniformed Services University of the Health Sciences, Bethesda, MD 20814, Walter Reed Army Institute of Research and Walter Reed Army Medical Center, Washington, D.C. 20307

Human cross-linked hemoglobin (HBXL) solution was used to resuscitate rats at 20 ml/kg bleed under anesthesia. Rats (Sprague-Dawley, 300-350 g) were bled (10 ml/kg) from the femoral artery and reinfused (1.5 ml/min) via the jugular vein with shed blood (20 ml/kg), Ringer's Lactate (RL; 40 ml/kg) or 14% HBXL (10 and 20 ml/kg). Following hemorrhage, mean arterial pressure (MAP) dropped to 40% of baseline (100 ± 5 mmHg); blood and both HBXL infusions promptly restored MAP to 100% of baseline. Within 15 min, MAP returned to baseline in the blood infused rats, but remained at 125% of baseline in the HBXL treated rats for at least 60 min. Heart rate (HR), which dropped to 60% of baseline (350-20 BPM) was returned to and remained at baseline value with both HBXL solutions and blood. RL infusion restored MAP and HR, however, its effects were transient (15 min) after which MAP and HR fell to 60% and 70% of baseline, respectively. Cutaneous pO_2 (Roche) fell to less than 5% of baseline (49.5 ± 1.4 mmHg) following the bleed, and was quickly restored to baseline with both blood and HBXL. RL also restored pO_2 values to normal, however, after infusion was complete, pO_2 values fell to 40% of baseline. Interestingly, 10 ml/kg of HBXL was as effective as 20 ml/kg in restoring and maintaining hemodynamic tissue oxygenation. These findings suggest that HBXL is a useful blood substitute in acute, non-lethal hemorrhage. Furthermore, HBXL is as effective as blood in improving hemodynamics and tissue perfusion at half the volume of blood.

172 rCBF FOLLOWING FLUID RESUSCITATION FROM HEMORRHAGIC SHOCK WITH ISOTONIC OR 7.2% NaCl WITH AND WITHOUT A SUBDURAL MASS.

J. M. Whitley*, D.S. Prough*, D. Deal*, S. Viner*, and G. Taylor*. (Spon: G. Zaloga). Wake Forest Univ., Winston-Salem, NC 27103.

Hypertonic saline successfully restores hemodynamics with severe hemorrhage, lowers intracranial pressure (ICP). The lower ICP following resuscitation suggests an advantage in terms of restoration of cerebral perfusion and improved regional cerebral blood flow (rCBF). The purpose of this study was to compare the effects of rCBF following resuscitation from hemorrhage with isotonic or 7.2% NaCl with and without an intracranial mass. Experiments were carried out on ventilated dogs divided into two groups: Group 1 (n=12) were subjected to 30 minutes of hemorrhage by rapid removal of blood (MAP 50-55 mmHg), and then resuscitated with 56 ml/kg of 0.9% NaCl

(n=6), or 6.0 ml/kg of 7.2% NaCl (n=6). Group II (n=12) animals were prepared similarly with the addition of a subdural balloon inserted over the right parietal cortex and inflated to increase ICP to 15 mmHg prior to hemorrhage. rCBF was measured using radioactive microspheres before, during shock and following resuscitation for 40 hours. Brains were sectioned into 3 regions for analysis: right (RC) and left (LC) cerebral hemispheres and praesstem (BR). Group I rCBF values revealed no significant differences over time between fluid groups. Group II rCBF values were significantly different over time with 7.2% NaCl promoting higher blood flows in RC ($p < 0.04$, by T test) and LC ($p < 0.001$). BR values revealed no differences between fluid groups. These data demonstrate that 7.2% NaCl improves rCBF better than isotonic crystalloid when a subdural mass is present.

173 EFFECT OF IMPAIRED HEPATIC MITOCHONDRIAL FUNCTION (HMF) ON SYSTEMIC METABOLISM IN MULTIPLE ORGAN FAILURE (MOF) PATIENTS AND ITS TREATMENT WITH ATP-MgCl₂.
Hirasawa, T., Sugai, Y., Ohtake, G., Ogasawara, T., Shiga, T., Aoe, and Y. Ohnawa. Department of Emergency and CCM, Chiba University School of Medicine, Chiba, Japan. 280

Previous study from our laboratory has shown that HMF is impaired among MOF patients. The present study was undertaken to investigate the effect of impaired HMF on systemic metabolism and the effect of ATP-MgCl₂ administration on HMF and systemic metabolism in MOF patients. In 33 MOF patients (45 survivors and 42 non-survivors) indirect calorimetry was performed using a metabolic computer while they were receiving TPN. Arterial ketone body ratio (AKBR) and blood levels of retinol binding protein and prealbumin were also measured. Non-protein respiratory quotient (npRQ) and energy burned as fat (%fat) were calculated from the data of indirect calorimetry. Some patients with impaired HMF received intravenous ATP-MgCl₂ administration (3000 μ moles/kg) during TPN and the same parameters were studied. Non-survived MOF patients showed lower AKBR compared to postoperative controls and survived MOF patients. There were a significant positive correlation between AKBR and npRQ, and a significant negative correlation between AKBR and %fat, respectively, indicating that impaired HMF suppressed utilization of exogenous glucose. Blood levels of retinol binding protein and prealbumin showed significant positive correlations to AKBR. ATP-MgCl₂ administration increased AKBR and npRQ, and decreased %fat. These results indicate that impaired HMF adversely affects systemic energy metabolism and protein synthesis. The results also suggest a possible role of ATP-MgCl₂ as a metabolic modulator among MOF patients.

174 IMPROVED SURVIVAL FROM HEMORRHAGIC SHOCK WITH INOSITOL AND ATP-MgCl₂ ADMINISTRATION. M.J. Shapiro, M. Jellinek, B. Chandel, G. Tadros, A.E. Baue. St. Louis University Medical Center, St. Louis, MO 63110

Phosphoinositides are structural components of membranes and hormonal receptor mediators. Hypovolemic shock may cause their loss and thus contribute to the mortality observed when hemorrhage occurs. In addition, in hypovolemic shock, the loss of ATP and the decline in ATP generating capacity intensifies such losses since phosphoinositide regeneration is dependent upon an adequate supply of ATP. Thus, in order to examine the effect of ATP, inositol and ATP + inositol administration on survival, 76 male Sprague-Dawley rats were anesthetized with 1.25 volume percent halothane. With additional local anesthesia, the right femoral artery was cannulated for continuous blood pressure recording. The left femoral artery was cannulated for blood withdrawal and infusion. The animals were awakened in a restraining cage. By withdrawing blood, 40mm Hg shock was maintained for 105 minutes. The blood was then reinfused and the animals received either placebo (15 ml/kg 0.9% N.S.), ATP-MgCl₂ (27 μ moles/kg/hr), inositol (27 μ moles/kg/hr), or ATP-MgCl₂ + inositol infused over one hour. The cannulae were then removed, and 24 hour survival recorded. Fifteen of 35 (43%) control animals survived, whereas 7 of 10 (70%) treated with ATP-MgCl₂ survived ($p > 0.1$). Twelve of 15 (80%) treated with inositol survived ($p < .02$), whereas 13 of 16 (81%) of the ATP-MgCl₂ + inositol group survived ($p < .01$). The use of inositol and ATP-MgCl₂ appear to be useful agents in improving survival from hemorrhagic hypovolemic shock.

UNPUBLISHED ABSTRACTS

1. Whitley JM, Olympio MA, Prough DS. Hypertonic/Hyperoncotic Fluid Resuscitation Following Hemorrhagic Shock: Comparison of Fluids.
2. Whitley JM, Prough DS. Effects of Fluid Resuscitation From Hemorrhagic Shock on Cerebral Hemodynamics in the Presence of an Intracranial Mass.
3. Whitley JM, Prough DS, Deal DD, Lamb AK. Effects on Intracranial Pressure in a Clinically Derived Fluid Resuscitation Protocol Following Hemorrhagic Shock with an Accompanying Intracranial Mass.

ABSTRACT FORM

1987 Symposium on Hypertonic Resuscitation SAL II June 3 to 5, Monterey, California

Directions: Please type entire abstract in the box below. Use all capital letters for the title, then list all authors with the presenter's name first and then the institution. Skip a line before the body of the abstract. The abstract will be photocopied for the program. Tables and figures may be used.

Mail to arrive by May 7 to: George C. Kramer, Ph.D.
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HYPERTONIC/HYPERONCOTIC FLUID RESUSCITATION FOLLOWING HEMORRHAGIC SHOCK: COMPARISON OF FLUIDS

John M. Whitley, PhD, Michael A. Olympio, MD, Donald S. Prough, MD
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The effects of four resuscitation fluids on systemic and cerebral hemodynamics were studied in a canine hemorrhagic shock preparation. In anesthetized animals, cerebral blood flow (CBF), mean arterial pressure (MAP), and intracranial pressure (ICP) were collected and compared. CBF was measured using a cerebral venous outflow preparation which involved cannulation of the sagittal sinus and by the Xenon 133 clearance method. Dogs were hemorrhaged to a MAP of 40 mmHg for 30 minutes, then resuscitated with one of four fluid groups: (1) 0.9% NaCl (NS 32 ml/kg), (2) 7.2% NaCl (HS 4 ml/kg), (3) 20% hetastarch (H 4 ml/kg) or (4) 20% hetastarch dissolved in 7.2/5 NaCl (HHS 4 ml/kg). Data were analyzed at B (baseline), S1 (immediately after lowering MAP to 40 mmHg), S2 (30 minutes following S1), R1 (immediately after resuscitation), and R2 (one hour after resuscitation), using analysis of variance of repeated measures with p values < 0.05 considered significant.

Results: CBF declined in all fluid groups during shock. Following resuscitation, CBF increased and exceeded baseline in the NS, HS and HHS fluid groups. By R2, CBF had declined to near shock values in all groups. There were no differences in CBF between groups at R2. MAP declined during shock and was maintained at 40 mmHg. Following resuscitation, MAP increased in all groups with NS producing the highest MAP. By R2, MAP had declined in the NS and H groups and increased in the HHS group as compared to R1. MAP in the HS group did not change. ICP also declined during shock and increased following resuscitation in all groups with values exceeding baseline in the NS group. At R2, ICP was significantly lower in the HHS and HS groups as compared to NS and H fluid groups ($p < 0.05$).

Conclusion: These results indicate that differences in ICP were present between fluid groups following resuscitation from hemorrhagic shock. While these results extend previous observations regarding hypertonic and hyperoncotic fluid resuscitation, these results also suggest that a hypertonic/hyperoncotic fluid combination may be useful shock therapy if intracranial compliance is diminished.

Presenter's signature: _____

1987 Symposium on Hypertonic Resuscitation

SALT II

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Mail to arrive by May 7 to: George C. Kramer, Ph.D.
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EFFECTS OF FLUID RESUSCITATION FROM HEMORRHAGIC SHOCK ON CEREBRAL HEMODYNAMICS IN THE PRESENCE OF AN INTRACRANIAL MASS

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Department of Anesthesia, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina 27103

The effects of fluid resuscitation on intracranial pressure (ICP) and cerebral blood flow (CBF) in the presence of an intracranial mass were studied in a canine hemorrhagic shock preparation with an expanding subdural balloon. In anesthetized dogs, ICP, CBF and mean arterial pressure (MAP) were collected and analyzed at B (baseline), IP (after increasing ICP to 20 mmHg), S1, S2, R0 (immediately after resuscitation), and at 30, 60, 90 and 120 minutes. Prior to hemorrhage, ICP was elevated and maintained during shock. Animals were then hemorrhaged to a MAP of 55 mmHg for 30 minutes and resuscitated with either: (1) 0.8% NaCl (54 ml/kg), (2) 7.2% NaCl (HS 6 ml/kg), (3) 20% hetastarch (H 6 ml/kg) or (4) 20% hetastarch dissolved in 7.2% NaCl (HHS 6 ml/kg).

Results: CBF decreased in all fluid groups following elevation of ICP. During shock, CBF was 27-35% of baseline. Following resuscitation, CBF increased in all groups. By R30, CBF had decreased from the 0.8% NaCl, HS and HHS groups, a trend which continued to R120 with CBF values 35% of baseline. CBF peaked at 66% of baseline at R30 in the H group and decreased to 58% at R120. MAP decreased slightly at IP and was maintained at 55 mmHg during shock. MAP increased in all groups following resuscitation. By R30, MAP was > 110 mmHg in the HHS and H groups and < 90 mmHg in 0.8% NaCl and HS. From R30 to R120, MAP stabilized at 110 mmHg in HHS, decreased to 80 mmHg in H and HS and increased to 95 mmHg in 0.8% NaCl. ICP increased in all groups at R0 with the 0.8% NaCl group increasing rapidly to 36 mmHg. ICP continued to increase at R30 in all fluid groups except 0.8% NaCl which showed a slight decrease. By R120, ICP was approximately 40 mmHg in the 0.8% NaCl, HS and H groups and 55 mmHg in HHS.

Conclusions: Although preliminary, these results indicate a complex association between MAP, ICP and CBF following resuscitation in the presence of an intracranial mass. While the HHS fluid was clearly superior in restoring hemodynamics following shock, ICP was substantially increased. In contrast, hyperoncotic fluid resuscitation resulted in improved CBF and lower ICP. These results suggest that hyperoncotic fluid resuscitation may be useful in shock therapy with an accompanying intracranial mass.

Presenter's signature: _____

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TITLE: EFFECTS ON INTRACRANIAL PRESSURE IN A CLINICALLY DERIVED FLUID RESUSCITATION PROTOCOL FOLLOWING HEMORRHAGIC SHOCK WITH AN ACCOMPANYING INTRACRANIAL MASS.

AUTHORS: JM Whitley, PHD, DS Prough, MD, DD Deal BS, and AK Lamb BS.

AFFILIATION: Department of Anesthesia, Section on Critical Care, Wake Forest University Medical Center, Winston-Salem, NC

INTRODUCTION: Intracranial pressure (ICP) is reduced following hemorrhagic shock. In the presence of an intracranial mass, fluid resuscitation results in significant increases in ICP. To date, no study has addressed the impact on ICP of conventional fluid resuscitation using a protocol comparable to that employed in clinical practice, in which systemic hemodynamics continue to be supported at a target level following initial resuscitation.

METHODS: Mongrel dogs were anesthetized with thiopental, intubated, paralyzed with pancuronium bromide and ventilated under halothane .5% in oxygen. Blood pressure and cardiac output (CO) were continuously monitored. A subdural balloon was placed over the left cerebral hemisphere and ICP elevated to 15 mm Hg by balloon inflation with saline and maintained at that level during a 30 minute interval of hemorrhagic shock (MAP 50 mm Hg). Following the shock interval, the 24 animals were randomly assigned to one of four fluid groups for resuscitation: 1) isotonic, 2) hypertonic, 3) isotonic plus colloid and 4) hypertonic plus colloid. ICP was allowed to fluctuate independently during resuscitation. Following initial resuscitation, additional fluid was infused as necessary to maintain CO at or above baseline values.

RESULTS: ICP increased progressively in all fluid groups during the initial resuscitation period; a trend which continued as a result of additional fluid infusion. Cerebral blood flow (CBF) increased with resuscitation, but declined steadily over time in all groups with group 2 maintaining the higher flows.

CONCLUSIONS: These results suggest that implementation of current fluid resuscitation practices may exacerbate intracranial hypertension in patients with both head trauma and hemorrhage resulting in significant decreases in CBF.

*JCP-VII
J. L. Prough '88*

*file SA 7/11/88
L. L. L.
DS*

*1988 Meeting of the N C Society of Neurosurgeons
Duke University
1988*

APPENDIX C
MANUSCRIPTS ACCEPTED, SUBMITTED,
AND IN PREPARATION

Descriptive Statistics

Series 1

ISO vs. HS

Table 1

ARMY 1: ISO vs HS

TIME PERIOD	PACO2				HGB				PAO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	40.26	0.57	37.72	0.40	12.20	0.50	11.82	0.49	231.22	4.48	227.33	12.95
EARLY SHOCK	30.08	1.18	31.20	3.14	10.47	0.51	10.75	0.35	216.22	5.87	213.83	10.18
LATE SHOCK	38.39	1.53	37.00	2.28	9.68	0.44	9.58	0.33	261.11	37.51	200.67	15.04
T35	50.81	3.40	51.20	2.78	7.86	0.46	7.25	0.27	243.44	16.90	217.00	10.75
T95	34.43	1.76	35.63	2.19	7.50	.	8.65	0.45	225.75	5.84	220.50	18.30
T155	32.52	0.99	32.34	3.89	9.41	0.55	8.18	0.70	225.67	5.48	210.80	16.11

Table 2

ARMY 1: ISO vs HS

TIME PERIOD	PH				TEMP			
	GROUP				GROUP			
	HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	7.37	0.01	7.38	0.01	37.78	0.37	37.84	0.28
EARLY SHOCK	7.41	0.02	7.40	0.02	37.98	0.41	37.83	0.27
LATE SHOCK	7.19	0.02	7.19	0.03	37.77	0.36	38.14	0.47
T35	7.05	0.04	7.04	0.03	37.63	0.39	37.25	0.29
T95	7.21	0.04	7.22	0.07	.	.	37.54	.
T155	7.13	0.03	7.15	0.06	37.61	0.46	37.32	0.27

Table 3

ARMY 1: ISO vs HS

TIME PERIOD	CO				HR				PAMP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	2.47	0.18	2.67	0.51	153.33	5.77	170.83	13.19	4.00	0.74	3.10	1.02
EARLY SHOCK	0.69	0.04	0.79	0.03	160.00	6.01	166.67	14.53	3.11	1.31	1.75	0.63
LATE SHOCK	0.67	0.03	0.68	0.05	157.22	9.32	170.83	11.29	4.00	1.31	3.10	1.26
T35	1.79	0.12	2.83	0.30	150.00	9.86	154.17	11.72	2.83	0.70	3.60	0.91
T95	1.13	0.12	0.89	0.07	160.00	9.13	160.00	.	4.75	1.25	.	.
T155	0.68	0.05	0.63	0.07	164.44	9.30	155.00	11.76	2.94	1.33	3.60	0.53

Table 4

ARMY 1: ISO vs HS

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	24.44	1.38	18.83	1.87	5.11	0.95	5.17	1.05
EARLY SHOCK	11.78	0.66	11.67	1.02	0.78	0.86	1.67	1.09
LATE SHOCK	14.11	0.77	13.50	0.72	1.67	0.83	2.67	0.76
T35	21.78	1.80	27.50	2.11	4.33	0.93	5.83	1.14
T95	18.56	1.62	16.75	1.18	2.44	0.77	5.00	1.78
T155	16.44	0.65	14.90	1.24	2.44	0.82	4.17	0.70

Table 5

ARMY 1: ISO vs NS

TIME PERIOD	SBP				DBP				MAP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	NS		ISO		NS		ISO		NS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	169.44	7.19	157.50	8.83	117.78	5.01	113.33	7.26	135.00	5.33	128.17	7.28
EARLY SHOCK	55.56	1.55	52.50	2.81	33.67	1.11	31.67	1.67	40.89	1.10	38.67	1.74
LATE SHOCK	56.33	1.82	55.83	1.54	28.00	0.82	29.17	1.54	37.33	0.85	38.00	1.39
T35	89.22	5.84	128.33	9.46	42.78	4.17	58.33	12.56	58.33	4.46	90.33	5.58
T95	95.63	7.82	105.00	18.71	36.67	7.31	61.25	14.77	58.89	5.64	77.00	15.88
T155	45.22	7.92	51.67	10.93	18.00	5.00	25.83	6.38	27.22	5.84	34.50	7.78

Table 6

ARMY 1: ISO vs HS

TIME PERIOD	LVSW				CVP			
	GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDEPR
BASELINE	0.03	0.003	0.03	0.007	-2.33	0.837	-1.17	0.715
EARLY SHOCK	0.00	0.000	0.00	0.001	-4.56	0.543	-4.50	0.548
LATE SHOCK	0.00	0.000	0.00	0.000	-4.28	0.534	-4.33	0.587
T35	0.01	0.001	0.02	0.005	-3.50	0.874	-0.75	0.574
T95	0.00	0.002	0.00	.	-4.75	1.250	.	.
T155	0.00	0.001	0.00	0.001	-3.17	0.661	-4.00	0.606

Table 7

ARMY 1: ISO vs HS

TIME PERIOD	RESP				SVR			
	GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	13.89	0.61	12.83	1.28	4693.54	473.09	4936.56	1342.43
EARLY SHOCK	12.89	0.61	11.75	1.45	5422.92	336.96	4371.13	364.79
LATE SHOCK	10.50	0.68	9.90	0.68	4930.47	178.35	5211.32	639.32
T35	13.75	1.08	12.70	1.77	2841.94	145.19	2721.82	308.69
T95	14.00	0.00	18.00	.	3407.37	782.18	3008.91	801.41
T155	12.88	0.61	11.83	1.08	4212.77	710.51	5307.06	832.61

Table 8

ARMY 1: ISO vs HS

TIME PERIOD	CBF				ICP				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	35.11	3.40	40.00	5.01	2.83	0.70	4.33	1.50	132.17	5.24	128.03	9.30
EARLY SHOCK	21.78	2.28	26.20	2.63	-2.61	0.82	-1.58	1.71	43.57	1.10	39.83	1.01
LATE SHOCK	23.67	2.36	24.50	1.36	-2.83	0.52	-2.42	1.45	40.27	0.77	40.38	4.17
T35	47.67	2.76	53.50	5.08	1.33	1.48	5.50	2.56	56.93	3.67	88.30	7.42
T95	27.44	2.81	31.00	2.80	-5.44	0.97	0.00	2.44	63.96	5.47	58.03	9.51
T155	21.44	3.14	21.58	2.12	-5.11	1.16	-0.50	1.58	38.17	9.28	39.67	8.58

Descriptive Statistics

Series 1

ISO vs. HES

Table 9

ARMY 1: ISO vs HES

TIME PERIOD	PACO2				HGB				PAO2			
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	41.26	1.14	37.72	0.40	11.58	1.01	11.82	0.49	210.60	17.65	227.33	12.95
EARLY SHOCK	31.30	2.56	31.20	3.14	10.50	0.71	10.75	0.35	207.00	5.81	213.83	10.18
LATE SHOCK	46.74	6.13	37.00	2.28	10.18	0.68	9.58	0.33	207.00	12.39	200.67	15.04
T35	49.90	1.28	51.20	2.78	8.94	0.54	7.25	0.27	215.00	9.26	217.00	10.75
T95	34.70	2.51	35.63	2.19	8.40	1.30	8.65	0.45	215.20	5.31	220.50	18.30
T155	34.12	3.12	32.34	3.89	8.92	0.76	8.18	0.70	210.20	8.95	210.80	16.11

Table 10

ARMY 1: ISO vs NES

TIME PERIOD	PH				TEMP			
	GROUP				GROUP			
	NES		ISO		NES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	7.36	0.01	7.38	0.01	37.26	0.48	37.84	0.28
EARLY SHOCK	7.41	0.02	7.40	0.02	37.04	0.29	37.83	0.27
LATE SHOCK	7.15	0.04	7.19	0.03	37.45	0.49	38.14	0.47
T35	7.09	0.02	7.04	0.03	37.47	0.57	37.23	0.29
T95	7.22	0.05	7.22	0.07	37.20	0.56	37.54	.
T155	7.20	0.05	7.15	0.06	38.04	0.40	37.32	0.27

Table 11

ARMY 1: ISO vs NES

TIME PERIOD	CO				HR				PALP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	NES		ISO		NES		ISO		NES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	2.73	0.57	2.67	0.51	164.00	6.78	170.85	13.19	2.70	0.46	3.10	1.02
EARLY SHOCK	0.82	0.16	0.79	0.03	161.00	12.08	166.67	14.53	1.70	0.72	1.75	0.63
LATE SHOCK	0.86	0.16	0.68	0.05	162.00	9.70	170.83	11.29	3.20	0.72	3.10	1.26
T35	1.74	0.36	2.83	0.30	166.00	9.27	154.17	11.72	3.75	0.72	3.60	0.91
T95	1.43	0.44	0.89	0.07	192.50	11.09	160.00	.	2.88	1.59	.	.
T155	1.06	0.22	0.63	0.07	175.00	8.66	155.00	11.76	3.50	0.71	3.60	0.53

Table 12

ARMY 1: ISO vs HES

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	19.20	2.44	18.83	1.87	2.80	1.24	5.17	1.05
EARLY SHOCK	12.00	0.77	11.67	1.02	1.80	0.80	1.67	1.09
LATE SHOCK	14.80	1.36	13.50	0.72	2.80	0.86	2.67	0.76
T35	18.60	1.66	27.50	2.11	5.00	1.26	5.83	1.14
T95	18.20	0.80	16.75	1.18	4.80	0.73	3.00	1.78
T155	16.80	1.20	14.00	1.24	4.40	1.29	4.17	0.70

Table 13

ARMY 1: ISO vs HES

TIME PERIOD	SSP				DSP				MAP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	178.00	7.84	157.50	8.83	121.00	2.45	113.33	7.26	140.00	3.44	128.17	7.28
EARLY SHOCK	52.00	1.22	52.50	2.81	32.00	1.22	31.67	1.67	39.00	1.22	38.67	1.74
LATE SHOCK	56.00	2.92	55.83	1.54	28.00	1.22	29.17	1.54	37.40	0.81	38.00	1.39
T35	84.40	8.39	128.33	9.46	46.60	8.72	58.33	12.56	59.00	8.58	90.33	5.58
T95	84.00	16.61	105.00	18.71	47.40	16.16	61.25	14.77	59.60	16.12	77.00	15.88
T155	61.00	15.03	51.67	10.93	33.00	9.03	25.83	6.38	42.40	11.03	34.50	7.78

Table 14

ARMY 1: ISO vs HES

TIME PERIOD	LVSU				CVP			
	GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	0.03	0.008	0.03	0.007	-1.80	1.271	-1.17	0.715
EARLY SHOCK	0.00	0.000	0.00	0.001	-4.50	0.570	-4.50	0.548
LATE SHOCK	0.00	0.000	0.00	0.000	-4.30	0.255	-4.33	0.587
T35	0.01	0.002	0.02	0.005	-3.40	0.400	-0.75	0.574
T95	0.00	0.001	0.00	.	-2.83	0.333	.	.
T155	0.08	0.072	0.00	0.001	-0.40	1.812	-4.00	0.606

Table 15

ARMY 1: ISO vs HES

TIME PERIOD	RESP				SVR			
	GROUP				GROUP			
	HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	13.60	0.87	12.83	1.28	4671.56	1004.02	4936.56	1342.43
EARLY SHOCK	12.80	0.97	11.75	1.45	4747.19	836.06	4371.13	364.79
LATE SHOCK	10.60	1.40	9.90	0.68	4260.26	551.41	5211.32	639.32
T35	14.60	1.08	12.70	1.77	3275.17	752.91	2721.82	308.69
T95	16.00	1.15	18.00	.	3458.95	865.55	3008.91	801.41
T155	14.40	1.47	11.83	1.08	5918.34	808.93	5307.06	832.61

ARMY 1: ISO vs HES

All variables
Table 16

TIME PERIOD	CSF				ICP				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	38.60	5.54	40.00	5.01	2.70	1.42	4.33	1.50	137.33	3.51	128.03	9.30
EARLY SHOCK	21.60	4.13	26.20	2.63	-4.40	1.44	-1.58	1.71	43.07	1.19	39.83	1.01
LATE SHOCK	23.60	3.40	24.50	1.36	-4.10	0.87	-2.42	1.45	41.43	0.78	40.38	4.17
T35	27.60	4.50	53.50	5.08	-2.60	1.31	5.50	2.56	61.80	6.86	88.30	7.42
T95	25.20	3.25	31.00	2.80	-3.20	2.12	0.00	2.44	62.80	14.39	58.03	9.51
T155	22.40	3.56	21.58	2.12	-2.70	2.84	-0.50	1.58	66.08	7.58	39.67	8.58

Descriptive Statistics

Series 1

HES vs. HS

Table 17

ARMY 1: HS vs HES

TIME PERIOD	PACO2				HGB				PAO2			
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	41.26	1.14	40.26	0.57	11.58	1.01	12.20	0.50	210.60	17.65	231.22	4.48
EARLY SHOCK	31.30	2.56	30.08	1.18	10.50	0.71	10.47	0.51	207.00	5.81	216.22	5.87
LATE SHOCK	46.74	6.13	38.39	1.53	10.18	0.68	9.68	0.44	207.00	12.39	261.11	37.51
T35	49.90	1.28	50.81	3.40	8.94	0.54	7.86	0.46	215.00	9.26	243.44	16.90
T95	34.70	2.51	34.43	1.76	8.40	1.30	7.50	.	215.20	5.31	225.75	5.84
T155	34.12	3.12	32.52	0.99	8.92	0.76	9.41	0.55	210.20	8.95	225.67	5.48

Table 18

ARMY 1: HIS vs HES

TIME PERIOD	PH				TEMP			
	GROUP				GROUP			
	HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	7.36	0.01	7.37	0.01	37.26	0.48	37.78	0.37
EARLY SHOCK	7.41	0.02	7.41	0.02	37.04	0.29	37.98	0.41
LATE SHOCK	7.15	0.04	7.19	0.02	37.45	0.49	37.77	0.36
T35	7.09	0.02	7.05	0.04	37.47	0.57	37.63	0.39
T95	7.22	0.05	7.21	0.04	37.20	0.56	.	.
T155	7.20	0.05	7.13	0.03	38.04	0.40	37.61	0.46

Table 19

ARMY 1: HS vs HES

TIME PERIOD	CO				HR				PAWP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	2.73	0.57	2.47	0.18	164.00	6.78	153.33	5.77	2.70	0.46	4.00	0.74
EARLY SHOCK	0.82	0.16	0.69	0.04	161.00	12.08	160.00	6.01	1.70	0.72	3.11	1.31
LATE SHOCK	0.86	0.16	0.67	0.03	162.00	9.70	157.22	9.32	3.20	0.72	4.00	1.31
T35	1.74	0.36	1.79	0.12	166.00	9.27	150.00	9.86	3.75	0.72	2.83	0.70
T95	1.43	0.44	1.13	0.12	192.50	11.09	160.00	9.13	2.88	1.59	4.75	1.25
T155	1.06	0.22	0.68	0.05	175.00	8.66	164.44	9.30	3.50	0.71	2.94	1.33

Table 20

ARMY 1: HS vs HES

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	19.20	2.44	24.44	1.38	2.80	1.24	5.11	0.95
EARLY SHOCK	12.00	0.77	11.78	0.66	1.80	0.80	0.78	0.86
LATE SHOCK	14.80	1.36	14.11	0.77	2.80	0.86	1.67	0.83
T35	18.60	1.66	21.78	1.80	5.00	1.26	4.33	0.93
T95	18.20	0.80	18.56	1.62	4.80	0.73	2.44	0.77
T155	16.80	1.20	16.44	0.65	4.40	1.29	2.44	0.82

Table 21

ARMY 1: HS vs HES

TIME PERIOD	SBP				DBP				MAP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	178.00	7.84	169.44	7.19	121.00	2.45	117.78	5.01	140.00	3.44	135.00	5.33
EARLY SHOCK	52.00	1.22	55.56	1.55	32.00	1.22	33.67	1.11	39.00	1.22	40.89	1.10
LATE SHOCK	56.00	2.92	56.33	1.82	28.00	1.22	28.00	0.82	37.40	0.81	37.33	0.85
T35	84.40	8.39	89.22	5.84	46.60	8.72	42.78	4.17	59.00	8.58	58.33	4.46
T95	84.00	16.61	95.63	7.82	47.40	16.16	36.67	7.31	59.60	16.12	58.89	5.64
T155	61.00	15.03	45.22	7.92	33.00	9.03	18.00	5.00	42.40	11.03	27.22	5.84

Table 22

ARMY 1: HS vs HES

TIME PERIOD	LVSW				CVP			
	GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	0.03	0.008	0.03	0.003	-1.80	1.271	-2.33	0.837
EARLY SHOCK	0.00	0.000	0.00	0.000	-4.50	0.570	-4.56	0.543
LATE SHOCK	0.00	0.000	0.00	0.000	-4.30	0.255	-4.28	0.534
T35	0.01	0.002	0.01	0.001	-3.40	0.400	-3.50	0.874
T95	0.00	0.001	0.00	0.002	-2.83	0.333	-4.75	1.250
T155	0.08	0.072	0.00	0.001	-0.40	1.812	-3.17	0.661

Table 23

ARMY 1: HS vs HES

TIME PERIOD	RESP				SVR			
	GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	13.60	0.87	13.89	0.61	4671.56	1004.02	4693.54	473.09
EARLY SHOCK	12.80	0.97	12.89	0.61	4747.19	836.06	5422.92	336.96
LATE SHOCK	10.60	1.40	10.50	0.68	4260.26	551.41	4930.47	178.35
T35	14.60	1.08	13.75	1.08	3275.17	752.91	2841.94	145.19
T95	16.00	1.15	14.00	0.00	3458.95	865.55	3407.37	782.18
T155	14.40	1.47	12.88	0.61	5918.34	808.93	4212.77	710.51

Descriptive Statistics

Series 1

HS vs. HES/HS

Table 25

ARMY 1: HS vs HES/HS

TIME PERIOD	PACO2				HGB				PAO2			
	HES/HS		HS		HES/HS		HS		HES/HS		HS	
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	39.15	0.56	40.26	0.57	12.92	0.77	12.20	0.50	235.00	9.72	231.22	4.48
EARLY SHOCK	30.40	1.35	30.08	1.18	10.77	0.38	10.47	0.51	224.33	9.99	216.22	5.87
LATE SHOCK	39.32	0.91	38.39	1.53	11.15	0.42	9.68	0.44	220.50	8.81	261.11	37.51
T35	48.87	2.75	50.81	3.40	8.53	0.25	7.86	0.46	206.17	16.93	243.44	16.90
T95	33.54	0.79	34.43	1.76	10.30	0.46	7.50	.	223.20	4.28	225.75	5.84
T155	35.73	2.80	32.52	0.99	8.94	0.56	9.41	0.55	214.83	9.09	225.67	5.48

Table 26

ARMY 1: HS vs HES/HS

TIME PERIOD	PH				TEMP			
	GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	7.38	0.01	7.37	0.01	37.03	0.10	37.78	0.37
EARLY SHOCK	7.39	0.04	7.41	0.02	37.15	0.12	37.98	0.41
LATE SHOCK	7.20	0.03	7.19	0.02	37.46	0.21	37.77	0.36
T35	7.10	0.03	7.05	0.04	37.56	0.18	37.63	0.39
T95	7.27	0.02	7.21	0.04	38.43	0.13	.	.
T155	7.16	0.02	7.13	0.03	37.99	0.31	37.61	0.46

Table 27

ARMY 1: HS vs HES/HS

TIME PERIOD	CO				HR				PAWP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	2.52	0.26	2.47	0.18	160.00	5.16	153.33	5.77	2.90	0.62	4.00	0.74
EARLY SHOCK	0.67	0.05	0.69	0.04	148.33	4.77	160.00	6.01	1.25	0.78	3.11	1.31
LATE SHOCK	0.72	0.07	0.67	0.03	168.33	12.22	157.22	9.32	2.83	0.83	4.00	1.31
T35	1.69	0.23	1.79	0.12	170.00	11.83	150.00	9.86	2.30	0.58	2.83	0.70
T95	1.14	0.43	1.13	0.12	200.00	9.13	160.00	9.13	2.75	1.25	4.75	1.25
T155	0.73	0.14	0.68	0.05	190.00	7.75	164.44	9.30	3.00	1.19	2.94	1.33

Table 28

ARMY 1: HS vs HES/HS

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	22.00	0.82	24.44	1.38	5.67	1.20	5.11	0.95
EARLY SHOCK	11.33	0.80	11.78	0.66	0.00	1.03	0.78	0.86
LATE SHOCK	13.67	0.80	14.11	0.77	2.50	1.06	1.67	0.83
T35	21.50	1.38	21.78	1.80	4.83	0.54	4.33	0.93
T95	18.40	1.25	18.56	1.62	3.80	0.73	2.44	0.77
T155	18.83	1.40	16.44	0.65	3.83	1.35	2.44	0.82

Table 29

ARMY 1: HS vs HES/HS

TIME PERIOD	SBP				DBP				MAP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	176.67	3.80	169.44	7.19	120.00	4.08	117.76	5.01	138.83	3.59	135.00	5.33
EARLY SHOCK	52.00	2.94	55.56	1.55	33.33	1.65	33.67	1.11	39.33	1.02	40.89	1.10
LATE SHOCK	55.00	2.24	56.33	1.82	32.50	1.12	28.00	0.82	40.00	0.77	37.33	0.85
T35	94.17	6.76	89.22	5.84	55.83	11.21	42.78	4.17	68.50	9.45	58.33	4.46
T95	106.67	3.33	95.63	7.82	67.50	5.44	36.67	7.31	80.50	4.22	58.89	5.64
T155	67.50	7.39	45.22	7.92	32.50	3.10	18.00	5.00	44.17	3.77	27.22	5.84

Table 30

ARMY 1: HS vs HES/HS

TIME PERIOD	LVSW				CVP			
	GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	0.03	0.003	0.03	0.003	-2.83	0.760	-2.33	0.837
EARLY SHOCK	0.00	0.000	0.00	0.000	-4.92	0.664	-4.56	0.543
LATE SHOCK	0.00	0.000	0.00	0.000	-4.75	0.616	-4.28	0.534
T35	0.01	0.002	0.01	0.001	-3.42	0.625	-3.50	0.874
T95	0.01	0.001	0.00	0.002	-4.00	0.577	-4.75	1.250
T155	0.00	0.000	0.00	0.001	-3.58	0.860	-3.17	0.661

Table 31

ARMY 1: HS vs HES/HS

TIME PERIOD	RESP				SVR			
	GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	14.17	0.87	13.89	0.61	4642.76	395.56	4693.54	473.09
EARLY SHOCK	12.33	0.76	12.89	0.61	5554.80	519.45	5422.92	336.96
LATE SHOCK	11.17	0.65	10.50	0.68	5246.29	595.60	4930.47	178.35
T35	13.83	0.98	13.75	1.08	3806.17	464.67	2841.94	145.19
T95	13.50	0.29	14.00	0.00	7114.17	1814.19	3407.37	782.18
T155	14.00	0.63	12.88	0.61	5879.82	1858.07	4212.77	710.51

Table 32

ARMY 1: HS vs HES/HS

TIME PERIOD	CBF				ICP				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	32.17	2.17	35.11	3.40	3.50	1.28	2.83	0.70	135.13	5.08	132.17	5.24
EARLY SHOCK	19.00	1.53	21.78	2.28	-3.00	0.63	-2.61	0.82	43.10	1.32	43.57	1.10
LATE SHOCK	22.33	1.28	23.67	2.36	-3.42	0.71	-2.83	0.52	43.70	1.19	40.27	0.77
T35	36.83	5.15	47.67	2.76	-1.33	1.55	1.33	1.48	73.93	9.39	56.93	3.67
T95	26.00	1.77	27.44	2.81	-3.90	0.75	-5.44	0.97	81.93	5.18	63.96	5.47
T155	22.83	2.02	21.44	3.14	-3.67	0.83	-5.11	1.16	47.30	4.49	38.17	9.28

Descriptive Statistics

Series 1

HES vs. HES/HS

Table 33

ARMY 1: HES/HS vs HES

TIME PERIOD	PACO ₂				HGB				PAO ₂			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HES/HS		HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	41.26	1.14	39.15	0.56	11.58	1.01	12.92	0.77	210.60	17.65	235.00	9.72
EARLY SHOCK	31.30	2.56	30.40	1.35	10.50	0.71	10.77	0.38	207.00	5.81	224.33	9.99
LATE SHOCK	46.74	6.13	39.32	0.91	10.18	0.68	11.15	0.42	207.00	12.39	220.50	8.81
T35	49.90	1.28	48.87	2.75	8.94	0.54	8.53	0.25	215.00	9.26	206.17	16.93
T95	34.70	2.51	33.54	0.79	8.40	1.30	10.30	0.46	215.20	5.31	223.20	4.28
T155	34.12	3.12	35.73	2.80	8.92	0.76	8.94	0.56	210.20	8.95	214.83	9.09

Table 34

ARMY 1: HES/HS vs HES

TIME PERIOD	PH				TEMP			
	GROUP		GROUP		GROUP		GROUP	
	HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	7.36	0.01	7.38	0.01	37.26	0.48	37.03	0.10
EARLY SHOCK	7.41	0.02	7.39	0.04	37.04	0.29	37.15	0.12
LATE SHOCK	7.15	0.04	7.20	0.03	37.45	0.49	37.46	0.21
T35	7.09	0.02	7.10	0.03	37.47	0.57	37.56	0.18
T95	7.22	0.05	7.27	0.02	37.20	0.56	38.43	0.13
T155	7.20	0.05	7.16	0.02	38.04	0.40	37.99	0.31

ARMY 1: HES/HS vs HES

TIME PERIOD	CO				HR				PAMP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HES/HS		HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	2.73	0.57	2.52	0.26	164.00	6.78	160.00	5.16	2.70	0.46	2.90	0.62
EARLY SHOCK	0.82	0.16	0.67	0.05	161.00	12.08	148.33	4.77	1.70	0.72	1.25	0.78
LATE SHOCK	0.86	0.16	0.72	0.07	162.00	9.70	168.33	12.22	3.20	0.72	2.83	0.83
T35	1.74	0.36	1.69	0.23	166.00	9.27	170.00	11.83	3.75	0.72	2.30	0.58
T95	1.43	0.44	1.14	0.43	192.50	11.09	200.00	9.13	2.88	1.59	2.75	1.25
T155	1.06	0.22	0.73	0.14	175.00	8.66	190.00	7.75	3.50	0.71	3.00	1.19

Table 36

ARMY 1: HES/HS vs HES

TIME PERIOD	PAP1				PAP2			
	GROUP				GROUP			
	HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	19.20	2.44	22.00	0.82	2.80	1.24	5.67	1.20
EARLY SHOCK	12.00	0.77	11.33	0.80	1.80	0.80	0.00	1.03
LATE SHOCK	14.80	1.36	13.67	0.80	2.80	0.86	2.50	1.06
T35	18.60	1.66	21.50	1.38	5.00	1.26	4.83	0.54
T95	18.20	0.80	18.40	1.25	4.80	0.73	3.80	0.73
T155	16.80	1.20	18.83	1.40	4.40	1.29	3.83	1.35

Table 37

ARMY 1: HES/HS vs HES

TIME PERIOD	SBP				DBP				MAP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HES/HS		HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	178.00	7.84	176.67	3.80	121.00	2.45	120.00	4.08	140.00	3.44	138.83	3.59
EARLY SHOCK	52.00	1.22	52.00	2.94	32.00	1.22	33.33	1.65	39.00	1.22	39.33	1.02
LATE SHOCK	56.00	2.92	55.00	2.24	28.00	1.22	32.50	1.12	37.40	0.81	40.00	0.77
T35	84.40	8.39	94.17	6.76	46.60	8.72	55.83	11.21	59.00	8.58	68.50	9.45
T95	84.00	16.61	106.67	3.33	47.40	16.16	67.50	5.44	59.60	16.12	80.50	4.22
T155	61.00	15.03	67.50	7.39	33.00	9.03	32.50	3.10	42.40	11.03	44.17	3.77

Table 38

ARMY 1: HES/HS vs HES

TIME PERIOD	LVSW				CVP			
	GROUP				GROUP			
	HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	0.03	0.008	0.03	0.003	-1.80	1.271	-2.83	0.760
EARLY SHOCK	0.00	0.000	0.00	0.000	-4.50	0.570	-4.92	0.664
LATE SHOCK	0.00	0.000	0.00	0.000	-4.30	0.255	-4.75	0.616
T35	0.01	0.002	0.01	0.002	-3.40	0.400	-3.42	0.625
T95	0.00	0.001	0.01	0.001	-2.83	0.333	-4.00	0.577
T155	0.08	0.072	0.00	0.000	-0.40	1.812	-3.58	0.860

Table 39

ARMY 1: HES/HS vs HES

TIME PERIOD	RESP				SVR			
	GROUP		GROUP		GROUP		GROUP	
	HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	13.60	0.87	14.17	0.87	4671.56	1004.02	4642.76	395.56
EARLY SHOCK	12.80	0.97	12.33	0.76	4747.19	836.06	5554.80	519.45
LATE SHOCK	10.60	1.40	11.17	0.65	4260.26	551.41	5246.29	595.60
T35	14.60	1.08	13.83	0.98	3275.17	752.91	3806.17	464.67
T95	16.00	1.15	13.50	0.29	3458.95	865.55	7114.17	1814.19
T155	14.40	1.47	14.00	0.63	5918.34	808.93	5879.82	1858.07

Table 40

ARMY 1: HES/HS vs HES

TIME PERIOD	CBF				ICP				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HES/HS		HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	38.60	5.54	32.17	2.17	2.70	1.42	3.50	1.28	137.33	3.51	135.13	5.08
EARLY SHOCK	21.60	4.13	19.00	1.53	-4.40	1.44	-3.00	0.63	43.07	1.19	43.10	1.32
LATE SHOCK	23.60	3.40	22.33	1.28	-4.10	0.87	-3.42	0.71	41.43	0.78	43.70	1.19
T35	27.60	4.50	36.83	5.15	-2.60	1.31	-1.33	1.55	61.80	8.86	73.93	9.39
T95	25.20	3.25	26.00	1.77	-3.20	2.12	-3.90	0.75	62.80	14.39	81.93	5.18
T155	22.40	3.56	22.83	2.02	-2.70	2.84	-3.67	0.83	66.08	7.58	47.30	4.49

Descriptive Statistics

Series 1

ISO vs. HES/HS

Table 41

ARMY 1: ISO vs HES/HS

TIME PERIOD	PACO2				HGB				PAO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	39.15	0.56	37.72	0.40	12.92	0.77	11.82	0.49	235.00	9.72	227.33	12.95
EARLY SHOCK	30.40	1.35	31.20	3.14	10.77	0.38	10.75	0.35	224.33	9.99	213.83	10.18
LATE SHOCK	39.32	0.91	37.00	2.28	11.15	0.42	9.58	0.33	220.50	8.81	200.67	15.04
T35	48.87	2.75	51.20	2.78	8.53	0.25	7.25	0.27	206.17	16.93	217.00	10.75
T95	33.54	0.79	35.63	2.19	10.30	0.46	8.65	0.45	223.20	4.28	220.50	18.30
T155	35.73	2.80	32.34	3.89	8.94	0.56	8.18	0.70	214.83	9.09	210.80	16.11

Table 42

ARMY 1: ISO vs HES/HS

TIME PERIOD	PH				TEMP			
	GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	7.38	0.01	7.38	0.01	37.03	0.10	37.84	0.28
EARLY SHOCK	7.39	0.04	7.40	0.02	37.15	0.12	37.83	0.27
LATE SHOCK	7.20	0.03	7.19	0.03	37.46	0.21	38.14	0.47
T35	7.10	0.03	7.04	0.03	37.56	0.18	37.23	0.29
T95	7.27	0.02	7.22	0.07	38.43	0.13	37.54	.
T155	7.16	0.02	7.15	0.06	37.99	0.31	37.32	0.27

ARMY 1: ISO vs HES/HS

TIME PERIOD	CO				HR				PAWP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	2.52	0.26	2.67	0.51	160.00	5.16	170.83	13.19	2.90	0.62	3.10	1.02
EARLY SHOCK	0.67	0.05	0.79	0.03	148.33	4.77	166.67	14.53	1.25	0.78	1.75	0.63
LATE SHOCK	0.72	0.07	0.68	0.05	168.33	12.22	170.83	11.29	2.83	0.83	3.10	1.26
T35	1.69	0.23	2.83	0.30	170.00	11.83	154.17	11.72	2.30	0.58	3.60	0.91
T95	1.14	0.43	0.89	0.07	200.00	9.13	160.00	.	2.75	1.25	.	.
T155	0.73	0.14	0.63	0.07	190.00	7.75	155.00	11.76	3.00	1.19	3.60	0.53

Table 44

ARMY 1: ISO vs HES/HS

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	22.00	0.82	18.83	1.87	5.67	1.20	5.17	1.05
EARLY SHOCK	11.33	0.80	11.67	1.02	0.00	1.03	1.67	1.09
LATE SHOCK	13.67	0.80	13.50	0.72	2.50	1.06	2.67	0.76
T35	21.50	1.38	27.50	2.11	4.83	0.54	5.83	1.14
T95	18.40	1.25	16.75	1.18	3.80	0.73	5.00	1.78
T155	18.83	1.40	14.00	1.24	3.83	1.35	4.17	0.70

Table 45

ARMY 1: ISO vs HES/HS

TIME PERIOD	SBP				DBP				MAP			
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	176.67	3.80	157.50	8.83	120.00	4.08	113.33	7.26	138.83	3.59	128.17	7.28
EARLY SHOCK	52.00	2.94	52.50	2.81	33.33	1.65	31.67	1.67	39.33	1.02	38.67	1.74
LATE SHOCK	55.00	2.24	55.83	1.54	32.50	1.12	29.17	1.54	40.00	0.77	38.00	1.39
T35	94.17	6.76	128.33	9.46	55.83	11.21	58.33	12.56	68.50	9.45	90.33	5.58
T95	106.67	3.33	105.00	18.71	67.50	5.44	61.25	14.77	80.50	4.22	77.00	15.88
T155	67.50	7.39	51.67	10.93	32.50	3.10	25.83	6.38	44.17	3.77	34.50	7.78

Table 46

ARMY 1: ISO vs HES/HS

TIME PERIOD	LVSW				CVP			
	GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	0.03	0.003	0.03	0.007	-2.83	0.760	-1.17	0.715
EARLY SHOCK	0.00	0.000	0.00	0.001	-4.92	0.664	-4.50	0.548
LATE SHOCK	0.00	0.000	0.00	0.000	-4.75	0.616	-4.33	0.587
T35	0.01	0.002	0.02	0.005	-3.42	0.625	-0.75	0.574
T95	0.01	0.001	0.00	.	-4.00	0.577	.	.
T155	0.00	0.000	0.00	0.001	-3.58	0.860	-4.00	0.606

Table 47

ARMY 1: ISO vs HES/HS

TIME PERIOD	RESP				SVR			
	GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	14.17	0.87	12.83	1.28	4642.76	395.56	4936.56	1342.43
EARLY SHOCK	12.33	0.76	11.75	1.45	5554.80	519.45	4371.13	364.79
LATE SHOCK	11.17	0.65	9.90	0.68	5246.29	595.60	5211.32	639.32
T35	13.83	0.98	12.70	1.77	3806.17	464.67	2721.82	308.69
T95	13.50	0.29	18.00	.	7114.17	1814.19	3008.91	801.41
T155	14.00	0.63	11.83	1.08	5879.82	1858.07	5307.06	832.61

Table 48

ARMY 1: ISO vs HES/HS

TIME PERIOD	CBF				ICP				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	32.17	2.17	40.00	5.01	3.50	1.28	4.33	1.50	135.13	5.03	128.03	9.30
EARLY SHOCK	19.00	1.53	26.20	2.63	-3.00	0.63	-1.58	1.71	43.10	1.32	39.83	1.01
LATE SHOCK	22.33	1.28	24.50	1.36	-3.42	0.71	-2.42	1.45	43.70	1.19	40.38	4.17
T35	36.83	5.15	53.50	5.08	-1.33	1.55	5.50	2.56	73.93	9.39	88.30	7.42
T95	26.00	1.77	31.00	2.80	-3.90	0.75	0.00	2.44	81.93	5.18	58.03	9.51
T155	22.83	2.02	21.58	2.12	-3.67	0.83	-0.50	1.58	47.30	4.49	39.67	8.58

Descriptive Statistics

Series 2

ISO vs. HS

Table 49

Army 2: ISO vs HS

TIME PERIOD	PACO2A				HGBA				PAO2A			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	38.48	0.85	36.87	0.85	14.33	0.64	11.81	1.10	254.94	32.73	295.71	34.21
BALLOON INFLATION	39.60	1.17	35.73	0.98	14.28	0.63	12.60	0.96	275.83	31.16	291.40	38.01
EARLY SHOCK	32.29	1.66	33.74	1.84	12.19	0.76	10.99	0.93	208.75	27.06	289.00	39.27
LATE SHOCK	41.53	1.99	42.97	1.36	12.54	0.67	11.41	1.03	210.75	29.07	258.33	33.29
T35	52.35	2.53	38.61	1.04	9.70	0.79	8.26	0.85	241.63	27.17	300.57	32.92
T65	37.78	0.73	35.67	0.99	11.35	0.76	9.62	0.87	231.63	27.77	292.00	35.19
T95	39.60	0.90	39.44	1.63	12.40	0.51	10.37	0.96	246.25	30.60	289.00	35.58
T125	37.51	0.76	36.52	1.50	12.10	0.64	10.65	1.13	241.13	27.37	272.50	35.78
T155	38.23	1.24	39.34	1.49	12.21	0.58	11.92	0.58	237.00	24.45	253.00	35.10

Table 50

Army 2: ISO vs HS

TIME PERIOD	PHA				TEMP				CAO2			
	GROUP				GROUP				GROUP			
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	7.36	0.01	7.38	0.01	38.19	0.25	37.03	0.49	17.52	2.00	18.15	1.25
BALLOON INFLATION	7.35	0.01	7.38	0.02	38.20	0.35	37.07	0.58	18.09	1.89	18.39	1.24
EARLY SHOCK	7.37	0.01	7.38	0.02	38.33	0.36	37.05	0.60	16.05	1.59	16.82	1.03
LATE SHOCK	7.24	0.03	7.27	0.02	39.12	0.28	37.47	0.72	16.20	1.69	17.55	1.04
T35	7.14	0.03	7.22	0.04	38.70	0.19	36.81	0.55	12.46	1.86	13.34	0.77
T65	7.23	0.02	7.26	0.02	38.90	0.17	36.93	0.57	14.65	1.94	14.68	0.69
T95	7.24	0.02	7.24	0.02	39.24	0.23	37.21	0.65	15.32	1.60	16.26	0.92
T125	7.22	0.03	7.25	0.02	39.38	0.25	37.82	0.63	14.95	1.75	16.33	1.12
T155	7.21	0.04	7.26	0.03	39.30	0.35	37.89	0.87	15.04	1.68	15.75	0.72

Table 51

Army 2: ISO vs HS

TIME PERIOD	CO				HR				PAOP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	2.72	0.29	3.60	0.85	121.25	6.39	132.86	8.37	3.63	1.80	2.71	1.24
BALLOON INFLATION	2.80	0.37	3.09	0.74	116.67	6.15	132.86	7.78	2.57	1.89	1.50	1.04
EARLY SHOCK	1.35	0.13	1.79	0.34	121.38	7.64	130.00	7.24	1.25	1.63	0.01	0.72
LATE SHOCK	1.60	0.16	2.38	0.57	147.50	9.40	145.71	8.41	1.13	1.50	-0.43	0.69
T35	3.66	0.19	6.17	0.54	131.57	6.91	141.43	10.33	3.25	1.92	7.14	0.91
T65	2.29	0.16	3.95	0.72	150.00	5.35	145.71	9.97	2.14	1.78	0.93	0.64
T95	1.97	0.22	3.22	0.62	160.50	6.27	156.57	9.68	2.07	1.69	0.36	1.02
T125	1.93	0.22	3.21	0.71	160.00	9.06	159.17	8.98	2.50	1.82	0.75	1.30
T155	1.78	0.24	2.88	0.61	166.63	8.06	158.00	8.60	2.21	1.85	0.33	1.15

Table 52

Army 2: ISO vs HS

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	19.88	1.92	17.43	1.19	5.75	1.67	4.00	2.10
BALLOON INFLATION	19.43	2.31	16.71	1.19	4.57	2.30	3.21	1.91
EARLY SHOCK	12.63	1.66	12.00	0.69	1.88	1.82	0.14	1.06
LATE SHOCK	14.63	1.61	13.71	0.57	3.13	1.89	0.86	1.14
T35	24.75	1.91	25.71	1.17	5.63	2.60	5.71	1.39
T65	16.38	1.34	18.14	0.99	2.88	1.64	1.43	1.21
T95	53.63	36.64	17.14	1.35	3.25	1.85	1.71	1.48
T125	18.00	1.67	18.00	1.84	3.63	1.85	1.67	0.76
T155	17.75	1.92	17.17	1.82	4.38	1.97	2.00	1.29

Table 33

Army 2: ISO vs HS

TIME PERIOD	SBP				DBP				MAP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	143.13	9.49	132.43	11.59	100.63	8.15	95.29	8.87	114.88	8.28	109.29	8.33
BALLOON INFLATION	141.43	5.42	127.57	10.07	97.14	6.06	89.29	7.67	111.86	5.48	100.04	9.23
EARLY SHOCK	77.43	4.50	71.33	3.18	49.43	1.43	51.67	3.33	57.75	1.36	55.67	1.34
LATE SHOCK	76.14	2.96	67.50	4.33	48.57	1.21	49.50	2.47	56.63	1.25	55.24	1.56
T35	94.00	6.20	106.14	7.18	49.13	3.90	66.43	5.15	64.13	4.47	79.76	5.83
T65	109.63	6.94	97.14	3.43	76.00	4.94	67.57	2.06	87.63	5.24	77.33	2.39
T95	107.50	7.32	102.71	8.37	72.38	4.61	72.86	6.31	83.25	5.32	82.50	6.66
T125	115.63	9.61	111.67	8.23	73.50	5.65	77.67	7.67	87.63	6.53	88.83	7.66
T155	107.50	10.73	103.17	6.27	63.13	6.12	76.50	11.51	77.88	7.13	85.33	9.57

Table 34

Army 2: ISO vs HS

TIME PERIOD	SO2T				SVR				LVSW			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	470.24	190.954	731.87	158.429	3721.41	523.229	3006.80	481.666	0.03	0.004	0.04	0.010
BALLOON INFLATION	438.96	162.378	640.80	144.031	3608.42	562.839	3370.65	492.988	0.04	0.007	0.03	0.008
EARLY SHOCK	145.92	71.017	318.19	56.640	4140.02	470.365	3161.62	440.506	1.15	1.142	0.01	0.002
LATE SHOCK	288.44	47.803	444.05	100.945	3327.31	427.411	2571.25	423.941	0.01	0.002	0.01	0.003
T35	477.90	102.925	867.96	47.944	1417.20	79.168	1051.73	92.528	0.02	0.003	0.04	0.006
T65	297.00	83.355	595.28	124.269	3338.00	427.481	1846.22	214.958	0.02	0.001	0.03	0.004
T95	263.69	79.522	561.22	92.589	3880.28	490.447	2492.08	361.149	0.01	0.002	0.03	0.006
T125	319.32	59.480	531.43	126.332	4037.82	418.369	2816.63	569.188	0.02	0.003	0.02	0.009
T155	297.30	70.375	528.17	84.443	3923.69	357.944	2858.97	414.742	0.01	0.003	0.02	0.006

Table 55

Army 2: ISO vs HS

TIME PERIOD	CVP				VO2				RESP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	-0.81	1.48	-2.89	0.83	196.94	50.45	232.10	45.95	13.00	0.73	14.00	1.15
BALLOON INFLATION	-2.07	1.82	-3.36	0.68	227.16	48.88	210.83	31.37	13.14	0.83	13.86	1.16
EARLY SHOCK	-3.31	1.62	-4.68	0.74	100.29	30.55	190.14	25.77	12.75	0.88	12.00	1.18
LATE SHOCK	-4.38	1.46	-5.64	0.61	131.91	12.71	211.98	44.76	12.88	0.40	12.00	1.05
T35	-0.81	1.81	1.07	1.17	189.20	25.63	362.23	27.68	16.88	0.99	15.14	1.32
T65	-3.19	1.73	-3.93	0.49	156.78	26.47	267.00	48.73	16.75	1.01	14.43	1.19
T95	-3.50	1.65	-4.50	0.72	124.51	31.40	244.39	29.02	16.50	1.04	14.14	1.24
T125	-3.19	1.71	-4.00	1.18	179.61	22.56	180.86	41.79	16.00	1.38	15.17	0.60
T155	-3.44	1.78	-4.08	1.11	146.04	23.77	188.00	46.75	15.88	1.30	15.50	0.62

Table 56

Army 2: ISO vs HS

TIME PERIOD	PACO2V				HGBV				PAO2V			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	49.40	0.74	46.36	2.32	14.24	0.86	12.12	1.27	49.63	2.74	43.71	2.88
BALLOON INFLATION	48.88	1.86	46.12	1.72	14.06	0.78	12.80	0.83	49.33	3.09	42.00	3.79
EARLY SHOCK	50.70	3.10	48.10	3.78	12.96	0.74	11.01	0.93	29.75	1.83	34.14	2.96
LATE SHOCK	59.51	5.68	50.71	3.93	13.68	0.80	11.49	0.88	44.14	2.32	38.86	1.94
T35	51.55	7.35	48.20	3.17	10.14	0.83	8.06	0.79	57.13	3.89	45.14	2.94
T65	48.51	2.78	50.41	1.38	11.80	0.76	9.76	0.96	44.75	2.72	39.57	1.84
T95	52.08	3.78	50.57	3.01	12.57	0.62	10.46	0.97	42.00	2.00	38.71	1.92
T125	54.24	2.00	43.63	2.50	12.55	0.54	10.78	1.08	38.88	3.14	43.00	2.58
T155	53.33	4.62	44.60	2.34	12.63	0.60	11.98	0.57	37.50	3.45	50.50	6.64

Table 57

Army 2: ISO vs HS

TIME PERIOD	CEREBREAL BLOOD FLOW				INTRACRANIAL PRESSURE				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	32.25	3.81	29.71	2.57	6.81	1.34	6.14	1.41	107.98	8.28	102.81	8.39
BALLOON INFLATION	29.14	3.47	27.71	2.98	20.57	0.57	19.14	0.82	91.33	5.73	81.00	9.65
EARLY SHOCK	8.63	1.84	11.86	1.28	20.63	0.80	19.79	0.31	37.42	1.85	35.89	1.46
LATE SHOCK	9.38	2.11	8.29	1.61	20.63	0.92	21.29	0.80	36.17	2.00	34.04	1.20
T35	24.75	3.12	17.43	3.08	18.94	1.71	38.21	1.91	45.08	4.33	41.45	4.19
T65	18.75	2.90	12.43	1.94	20.88	3.33	35.64	2.09	66.75	6.74	40.12	2.48
T95	14.75	2.47	11.57	2.40	29.81	5.07	31.93	3.13	53.90	6.36	53.69	9.45
T125	13.88	2.15	10.00	2.03	37.63	4.20	35.90	3.86	49.92	6.32	52.97	9.97
T155	9.13	1.72	8.50	2.63	36.19	5.08	33.67	5.69	41.79	3.92	51.67	9.81

Table 58

Army 2: ISO vs HS

TIME PERIOD	MAP				CVO2				AVDO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	114.88	8.28	109.29	8.33	11.47	1.69	12.18	1.20	6.04	0.73	5.97	0.56
BALLOON INFLATION	111.86	5.48	100.04	9.23	10.93	1.60	11.86	1.25	7.16	0.89	6.54	0.75
EARLY SHOCK	57.75	1.36	55.67	1.34	6.44	1.08	6.37	0.87	9.61	0.89	10.45	0.94
LATE SHOCK	56.63	1.25	55.24	1.56	8.40	2.10	9.12	0.84	7.79	1.10	8.43	0.50
T35	64.13	4.47	79.76	5.83	7.45	1.66	7.78	0.76	5.02	0.34	5.57	0.46
T65	87.63	5.24	77.33	2.39	8.31	1.24	8.00	0.78	6.34	0.97	6.68	0.40
T95	83.25	5.32	82.50	6.66	7.76	1.78	8.84	0.56	7.56	0.66	7.42	0.93
T125	87.63	6.53	88.83	7.66	6.26	2.03	9.34	0.95	8.69	0.97	6.45	1.31
T155	77.88	7.13	85.33	9.57	6.97	2.40	10.50	1.22	8.07	1.33	6.24	1.47

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Army 2: ISO vs HS

TIME PERIOD	CMRO2				CO2T				CVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	1.59	0.38	1.85	0.08	4.57	1.10	5.75	0.56	3.97	0.79	3.47	0.35
BALLOON INFLATION	1.74	0.33	1.96	0.17	4.39	0.78	5.65	0.55	3.51	0.56	3.17	0.46
EARLY SHOCK	0.71	0.20	1.26	0.21	1.17	0.32	2.05	0.33	5.69	1.36	3.26	0.38
LATE SHOCK	0.71	0.26	0.74	0.16	1.38	0.51	1.55	0.38	6.34	1.98	6.16	2.12
T35	1.32	0.32	1.14	0.20	3.09	0.71	2.74	0.44	2.17	0.48	3.24	0.65
T65	1.08	0.33	0.85	0.13	2.46	0.70	1.90	0.32	4.69	1.21	4.05	1.01
T95	1.09	0.34	0.77	0.13	2.12	0.67	1.85	0.42	5.05	1.33	6.75	3.35
T125	1.13	0.27	0.73	0.18	1.86	0.44	1.77	0.35	5.10	1.45	4.20	0.55
T155	0.82	0.23	0.70	0.26	1.46	0.41	1.57	0.49	6.13	1.41	11.89	6.60

Descriptive Statistics

Series 2

ISO vs. HES

Table 60

Army 2: ISO vs HES

TIME PERIOD	PACO2A				HGBA				PAO2A			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	35.37	0.71	36.87	0.85	13.82	0.82	11.81	1.10	295.50	29.74	295.71	34.21
BALLOON INFLATION	35.62	1.38	35.73	0.98	13.67	0.85	12.60	0.96	306.00	33.83	291.40	38.01
EARLY SHOCK	34.17	1.94	33.74	1.84	12.18	0.73	10.99	0.93	275.83	25.71	289.00	39.27
LATE SHOCK	41.63	2.51	42.97	1.36	12.45	0.62	11.41	1.03	274.50	26.23	258.33	33.29
T35	41.83	1.67	38.61	1.04	10.44	0.59	8.26	0.85	289.17	25.05	300.57	32.92
T65	37.88	1.22	35.67	0.99	10.08	0.62	9.62	0.87	290.17	22.37	292.00	35.19
T95	36.67	0.97	39.44	1.63	10.40	0.68	10.37	0.96	292.83	24.63	289.00	35.58
T125	36.95	1.09	36.52	1.50	10.30	0.75	10.65	1.13	293.17	21.51	272.50	35.78
T155	38.00	1.57	39.34	1.49	10.18	0.70	11.92	0.58	287.83	24.76	253.00	35.10

Table 61

Army 2: ISO vs HES

TIME PERIOD	PHA				TEMP				CAO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	7.39	0.01	7.38	0.01	36.85	0.50	37.03	0.49	20.83	0.39	18.15	1.25
BALLOON INFLATION	7.37	0.02	7.38	0.02	36.91	0.52	37.07	0.58	20.54	0.12	18.39	1.24
EARLY SHOCK	7.37	0.04	7.38	0.02	37.07	0.51	37.05	0.60	18.39	0.32	16.82	1.03
LATE SHOCK	7.26	0.02	7.27	0.02	37.62	0.53	37.47	0.72	18.30	0.39	17.55	1.04
T35	7.25	0.02	7.22	0.04	37.39	0.47	36.81	0.55	15.28	0.42	13.34	0.77
T65	7.28	0.03	7.26	0.02	37.22	0.53	36.93	0.57	14.88	0.94	14.68	0.69
T95	7.32	0.02	7.24	0.02	37.17	0.63	37.21	0.65	15.62	0.87	16.26	0.92
T125	7.29	0.02	7.25	0.02	37.44	0.69	37.82	0.63	15.51	1.35	16.33	1.12
T155	7.27	0.01	7.26	0.03	37.79	0.68	37.89	0.87	15.42	1.11	16.75	0.72

Table 62

Army 2: ISO vs HES

TIME PERIOD	CO				HR				PAOP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	2.89	0.47	3.60	0.85	146.17	14.70	132.86	8.37	1.00	0.92	2.71	1.24
BALLOON INFLATION	2.59	0.40	3.09	0.74	137.83	17.11	132.86	7.78	1.00	0.79	1.50	1.04
EARLY SHOCK	1.36	0.15	1.79	0.34	141.20	12.88	130.00	7.24	-1.08	1.00	0.01	0.72
LATE SHOCK	1.59	0.12	2.38	0.57	165.00	7.42	145.71	8.41	-0.25	0.75	-0.43	0.69
T35	2.64	0.24	6.17	0.54	161.67	8.72	141.43	10.33	0.92	0.68	7.14	0.91
T65	2.93	0.33	3.95	0.72	151.33	12.56	145.71	9.97	0.33	0.77	0.93	0.64
T95	2.29	0.27	3.22	0.62	143.83	14.90	156.57	9.68	0.17	1.09	0.36	1.02
T125	2.15	0.32	3.21	0.71	152.17	14.79	159.17	8.98	-0.17	1.14	0.75	1.30
T155	1.98	0.22	2.88	0.61	156.67	12.82	158.00	8.60	0.42	1.09	0.33	1.15

Table 63

Army 2: ISO vs HES

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	16.67	1.20	17.43	1.19	3.50	1.18	4.00	2.10
BALLOON INFLATION	16.50	1.28	16.71	1.19	3.17	1.25	3.21	1.91
EARLY SHOCK	11.17	1.25	12.00	0.69	0.33	1.17	0.14	1.06
LATE SHOCK	12.50	1.15	13.71	0.57	2.00	0.93	0.86	1.14
T35	17.33	1.02	25.71	1.17	4.67	0.95	5.71	1.39
T65	17.50	0.96	18.14	0.99	4.17	0.95	1.43	1.21
T95	15.83	1.01	17.14	1.35	3.17	1.08	1.71	1.48
T125	15.00	1.77	18.00	1.84	2.83	1.11	1.67	0.76
T155	16.17	1.78	17.17	1.82	3.17	1.14	2.00	1.29

Table 64

Army 2: ISO vs HES

TIME PERIOD	SBP				DBP				MAP			
	HES		ISO		HES		ISO		HES		ISO	
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	157.50	6.55	132.43	11.59	111.33	3.84	95.29	8.87	126.67	4.54	109.29	8.33
BALLOON INFLATION	153.17	6.20	127.57	10.07	112.17	3.17	89.29	7.67	125.67	4.14	100.04	9.23
EARLY SHOCK	78.50	1.50	71.33	3.18	49.00	6.00	51.67	3.33	56.17	1.17	55.67	1.34
LATE SHOCK	67.67	11.20	67.50	4.33	50.33	2.33	49.50	2.47	54.33	2.78	55.24	1.56
T35	93.33	8.13	106.14	7.18	63.33	3.57	66.43	5.15	73.17	4.92	79.76	5.83
T65	132.50	7.04	97.14	3.43	89.50	5.09	67.57	2.06	103.83	5.40	77.33	2.39
T95	138.33	6.67	102.71	8.37	91.67	3.80	72.86	6.31	110.00	4.15	82.50	6.66
T125	121.83	11.03	111.67	8.23	78.33	6.91	77.67	7.67	96.17	6.18	88.83	7.66
T155	108.67	9.60	103.17	6.27	73.60	6.16	76.50	11.51	81.83	7.32	85.33	9.57

Table 65

Army 2: ISO vs HES

TIME PERIOD	SO2T				SVR				LVSW			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	814.17	59.940	731.87	158.429	4078.13	599.078	3006.80	481.666	0.03	0.006	0.04	0.010
BALLOON INFLATION	681.82	10.065	640.80	144.031	4469.84	630.797	3370.65	492.988	0.03	0.004	0.03	0.008
EARLY SHOCK	317.28	13.330	318.19	56.640	4352.77	435.934	3161.62	440.506	0.01	0.001	0.01	0.002
LATE SHOCK	306.61	31.184	444.05	100.945	3087.25	204.000	2571.25	423.941	0.01	0.001	0.01	0.003
T35	450.29	59.021	867.96	47.944	2424.51	214.839	1051.73	92.528	0.02	0.003	0.04	0.006
T65	497.14	46.125	595.28	124.269	3068.42	256.811	1846.22	214.958	0.03	0.005	0.03	0.004
T95	404.81	41.922	561.22	92.589	4253.81	491.527	2492.08	361.149	0.03	0.005	0.03	0.006
T125	349.14	50.569	531.43	126.332	4150.14	684.954	2816.63	569.188	0.02	0.006	0.02	0.009
T155	300.52	35.031	528.17	84.443	3536.40	166.007	2858.97	414.742	0.02	0.004	0.02	0.006

Table 66

Army 2: ISO vs HES

TIME PERIOD	CVP				VO2				RESP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	-4.00	0.88	-2.89	0.83	266.53	26.92	232.10	45.95	14.50	0.96	14.00	1.15
BALLOON INFLATION	-3.42	0.94	-3.36	0.68	217.67	25.29	210.83	31.37	13.50	1.02	13.86	1.16
EARLY SHOCK	-5.33	0.95	-4.68	0.74	192.40	14.76	190.14	25.77	12.67	0.71	12.00	1.18
LATE SHOCK	-5.58	0.77	-5.64	0.61	134.26	8.28	211.98	44.76	12.17	0.83	12.00	1.05
T35	-4.42	0.91	1.07	1.17	188.48	26.53	362.23	27.68	15.00	1.10	15.14	1.32
T65	-4.17	0.60	-3.93	0.49	148.12	35.47	267.00	48.73	16.00	1.18	14.43	1.19
T95	-4.33	0.70	-4.50	0.72	143.34	20.47	244.39	29.02	16.67	1.20	14.14	1.24
T125	-4.63	0.75	-4.00	1.18	137.21	11.58	180.86	41.79	15.83	1.30	15.17	0.60
T155	-5.00	0.72	-4.08	1.11	108.42	44.72	188.00	46.75	17.50	1.15	15.50	0.62

Table 67

Army 2: ISO vs HES

TIME PERIOD	PACO2V				HGBV				PAO2V			
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	45.67	1.24	46.36	2.32	13.72	0.86	12.12	1.27	43.33	1.58	43.71	2.88
BALLOON INFLATION	45.96	2.85	46.12	1.72	13.83	0.79	12.80	0.83	40.25	3.98	42.00	3.79
EARLY SHOCK	48.60	4.63	48.10	3.78	12.64	0.86	11.01	0.93	34.00	4.00	34.14	2.96
LATE SHOCK	50.52	4.44	50.71	3.93	12.58	0.74	11.49	0.88	37.60	2.48	38.86	1.94
T35	55.67	4.14	48.20	3.17	10.98	0.58	8.06	0.79	41.33	1.15	45.14	2.94
T65	51.97	2.96	50.41	1.38	10.70	0.61	9.76	0.96	41.67	2.59	39.57	1.84
T95	49.28	2.95	50.57	3.01	10.48	0.64	10.46	0.97	38.67	2.73	38.71	1.92
T125	52.62	3.57	43.63	2.50	10.78	0.82	10.78	1.08	39.50	1.18	43.00	2.58
T155	56.65	3.04	44.60	2.34	10.43	0.67	11.98	0.57	37.67	4.07	50.50	6.64

Army 2: ISO vs HES

all variables Table 68

TIME PERIOD	CEREBREAL BLOOD FLOW				INTRACRANIAL PRESSURE				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	28.67	2.42	29.71	2.57	6.08	1.62	6.14	1.41	120.64	4.17	102.81	8.39
BALLOON INFLATION	27.17	2.17	27.71	2.98	20.00	0.00	19.14	0.82	105.72	4.14	81.00	9.65
EARLY SHOCK	9.67	2.08	11.86	1.28	19.83	0.54	19.79	0.31	36.44	1.30	35.89	1.46
LATE SHOCK	8.50	1.26	8.29	1.61	19.33	0.33	21.29	0.80	35.00	2.74	34.04	1.20
T35	13.67	2.51	17.43	3.08	24.83	0.79	38.21	1.91	48.44	4.64	41.45	4.19
T65	17.50	3.32	12.43	1.94	31.33	3.61	35.64	2.09	72.64	5.98	40.12	2.48
T95	17.17	2.77	11.57	2.40	34.25	4.07	31.93	3.13	76.22	6.37	53.69	9.45
T125	13.50	3.36	10.00	2.03	31.92	4.10	35.90	3.86	64.25	7.53	52.97	9.97
T155	9.00	2.44	8.50	2.63	30.33	6.15	33.67	5.69	51.50	7.20	51.67	9.81

Table 69

Army 2: ISO vs HES

TIME PERIOD	MAP				CVO2				AVDO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	126.67	4.54	109.29	8.33	14.02	0.07	12.18	1.20	6.81	0.39	5.97	0.56
BALLOON INFLATION	125.67	4.14	100.04	9.23	14.15	0.37	11.86	1.25	6.55	0.70	6.54	0.75
EARLY SHOCK	56.17	1.17	55.67	1.34	8.45	1.39	6.37	0.87	9.94	1.70	10.45	0.94
LATE SHOCK	54.33	2.78	55.24	1.56	10.03	1.00	9.12	0.84	8.27	1.24	8.43	0.50
T35	73.17	4.92	79.76	5.83	8.89	0.11	7.78	0.76	6.38	0.32	5.57	0.46
T65	103.83	5.40	77.33	2.39	10.05	0.84	8.00	0.78	4.83	1.55	6.68	0.40
T95	110.00	4.15	82.50	6.66	9.72	0.68	8.84	0.56	5.91	1.50	7.42	0.93
T125	96.17	6.18	88.83	7.66	9.14	0.40	9.34	0.95	6.36	1.22	6.45	1.31
T155	81.83	7.32	85.33	9.57	9.74	1.85	10.50	1.22	4.72	0.86	6.24	1.47

Table 70

Army 2: ISO vs HES

TIME PERIOD	CMRO2				CO2T				CVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	1.94	0.42	1.85	0.08	5.87	1.07	5.75	0.56	4.46	0.45	3.47	0.35
BALLOON INFLATION	1.83	0.20	1.96	0.17	5.75	0.03	5.65	0.55	3.97	0.20	3.17	0.46
EARLY SHOCK	1.06	0.36	1.26	0.21	2.01	0.65	2.05	0.33	4.92	1.28	3.26	0.38
LATE SHOCK	0.90	0.26	0.74	0.16	1.90	0.34	1.55	0.38	4.65	0.79	6.16	2.12
T35	1.21	0.06	1.14	0.20	2.90	0.11	2.74	0.44	4.25	1.00	3.24	0.65
T65	1.12	0.33	0.85	0.13	3.61	0.34	1.90	0.32	4.88	0.83	4.05	1.01
T95	1.31	0.26	0.77	0.13	3.57	0.13	1.85	0.42	4.94	0.75	6.75	3.35
T125	1.27	0.15	0.73	0.18	3.16	0.06	1.77	0.35	6.51	1.89	4.20	0.55
T155	0.66	0.01	0.70	0.26	2.17	0.29	1.57	0.49	10.57	4.32	11.89	6.60

Descriptive Statistics

Series 2

HES vs. HS

Table 71

Army 2: HS vs HES

TIME PERIOD	PACO2A				HGBA				PAO2A			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	35.37	0.71	38.48	0.85	13.82	0.82	14.33	0.64	295.50	29.74	254.94	32.73
BALLOON INFLATION	35.62	1.38	39.60	1.17	13.67	0.85	14.28	0.63	306.00	33.83	275.83	31.16
EARLY SHOCK	34.17	1.94	32.29	1.66	12.18	0.73	12.19	0.76	275.83	25.71	208.75	27.06
LATE SHOCK	41.63	2.51	41.53	1.99	12.45	0.62	12.54	0.67	274.50	26.23	210.75	29.07
T35	41.83	1.67	52.35	2.53	10.44	0.59	9.70	0.79	289.17	25.05	241.63	27.17
T65	37.88	1.22	37.78	0.73	10.08	0.62	11.35	0.76	290.17	22.37	231.63	27.77
T95	36.67	0.97	39.60	0.90	10.40	0.68	12.40	0.51	292.83	24.63	246.25	30.60
T125	36.95	1.09	37.51	0.76	10.30	0.75	12.10	0.64	293.17	21.51	241.13	27.37
T155	38.00	1.57	38.23	1.24	10.18	0.70	12.21	0.58	287.83	24.76	237.00	24.45

Table 72

Army 2: HS vs HES

TIME PERIOD	PHA				TEMP				CAO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	7.39	0.01	7.36	0.01	36.85	0.50	38.19	0.25	20.83	0.39	17.52	2.00
BALLOON INFLATION	7.37	0.02	7.35	0.01	36.91	0.52	38.20	0.35	20.54	0.12	18.09	1.89
EARLY SHOCK	7.37	0.04	7.37	0.01	37.07	0.51	38.33	0.36	18.39	0.32	16.05	1.59
LATE SHOCK	7.26	0.02	7.24	0.03	37.62	0.53	39.12	0.28	18.30	0.39	16.20	1.69
T35	7.25	0.02	7.14	0.03	37.39	0.47	38.70	0.19	15.28	0.42	12.46	1.86
T65	7.28	0.03	7.23	0.02	37.22	0.53	38.90	0.17	14.88	0.94	14.65	1.94
T95	7.32	0.02	7.24	0.02	37.17	0.63	39.24	0.23	15.62	0.87	15.32	1.60
T125	7.29	0.02	7.22	0.03	37.44	0.69	39.38	0.25	15.51	1.35	14.95	1.75
T155	7.27	0.01	7.21	0.04	37.79	0.68	39.30	0.35	15.42	1.11	15.04	1.68

Table 73

Army 2: HS vs HES

TIME PERIOD	CO				HR				PAOP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	2.89	0.47	2.72	0.29	146.17	14.70	121.25	6.39	1.00	0.92	3.63	1.80
BALLOON INFLATION	2.59	0.40	2.80	0.37	137.83	17.11	116.67	6.15	1.00	0.79	2.57	1.89
EARLY SHOCK	1.36	0.15	1.35	0.13	141.20	12.88	121.38	7.64	-1.08	1.00	1.25	1.63
LATE SHOCK	1.59	0.12	1.60	0.16	165.00	7.42	147.50	9.40	-0.25	0.75	1.13	1.50
T35	2.64	0.24	3.66	0.19	161.67	8.72	131.57	6.91	0.92	0.68	3.25	1.92
T65	2.93	0.33	2.29	0.16	151.33	12.56	150.00	5.35	0.33	0.77	2.14	1.78
T95	2.29	0.27	1.97	0.22	143.83	14.90	160.50	6.27	0.17	1.09	2.07	1.69
T125	2.15	0.32	1.93	0.22	152.17	14.79	160.00	9.06	-0.17	1.14	2.50	1.82
T155	1.98	0.22	1.78	0.24	156.67	12.82	166.63	8.06	0.42	1.09	2.21	1.85

Table 74

Army 2: HS vs HES

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	16.67	1.20	19.88	1.92	3.50	1.18	5.75	1.67
BALLOON INFLATION	16.50	1.28	19.43	2.31	3.17	1.25	4.57	2.30
EARLY SHOCK	11.17	1.25	12.63	1.66	0.33	1.17	1.88	1.82
LATE SHOCK	12.50	1.15	14.63	1.61	2.00	0.93	3.13	1.89
T35	17.33	1.02	24.75	1.91	4.67	0.95	5.63	2.60
T65	17.50	0.96	16.38	1.34	4.17	0.95	2.88	1.64
T95	15.83	1.01	53.63	36.64	3.17	1.08	3.25	1.85
T125	15.00	1.77	18.00	1.67	2.83	1.11	3.63	1.85
T155	16.17	1.78	17.75	1.92	3.17	1.14	4.38	1.97

Table 75

Army 2: HS vs HES

TIME PERIOD	SBP				DBP				MAP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	108.83	7.70	108.33	5.80	10.31	2.08	9.80	0.90	4.65	0.58	4.91	0.68
MID SHOCK	55.50	0.50	55.00	1.51	5.96	1.03	6.24	0.58	6.48	0.72	7.03	0.59
RO	84.50	4.64	78.50	8.01	5.90	0.73	5.97	0.50	3.84	0.42	4.85	0.37
EARLY SHOCK	78.50	1.50	77.43	4.50	49.00	6.00	49.43	1.43	56.17	1.17	57.75	1.36
LATE SHOCK	67.67	11.20	76.14	2.96	50.33	2.33	48.57	1.21	54.33	2.78	56.63	1.25
T35	93.33	8.13	94.00	6.20	63.33	3.57	49.13	3.90	73.17	4.92	64.13	4.47
T65	132.50	7.04	109.63	6.94	89.50	5.09	76.00	4.94	103.83	5.40	87.63	5.24
T95	138.33	6.67	107.50	7.32	91.67	3.80	72.38	4.61	110.00	4.15	83.25	5.32
T125	121.83	11.03	115.63	9.61	78.33	6.91	73.50	5.65	96.17	6.18	87.63	6.53
T155	108.67	9.60	107.50	10.73	73.60	6.16	63.13	6.12	81.83	7.32	77.88	7.13

Table 76

Army 2: HS vs HES

TIME PERIOD	S02T				SVR				LVSW			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	814.17	59.940	470.24	190.954	4078.13	599.078	3721.41	523.229	0.03	0.006	0.03	0.004
BALLOON INFLATION	681.82	10.065	438.96	162.378	4469.84	630.797	3608.42	562.839	0.03	0.004	0.04	0.007
EARLY SHOCK	317.28	13.330	145.92	71.017	4352.77	435.934	4140.02	470.365	0.01	0.001	1.15	1.142
LATE SHOCK	306.61	31.184	288.44	47.803	3087.25	204.000	3327.31	427.411	0.01	0.001	0.01	0.002
T35	450.29	59.021	477.90	102.925	2424.51	214.839	1417.20	79.168	0.02	0.003	0.02	0.003
T65	497.14	46.125	297.00	83.355	3068.42	256.811	3338.00	427.481	0.03	0.005	0.02	0.001
T95	404.81	41.922	263.69	79.522	4253.81	491.527	3880.28	490.447	0.03	0.005	0.01	0.002
T125	349.14	50.569	319.32	59.480	4150.14	684.954	4037.82	418.369	0.02	0.006	0.02	0.003
T155	300.52	35.031	297.30	70.375	3536.40	166.007	3923.69	367.944	0.02	0.004	0.01	0.003

Table 77

Army 2: HS vs HES

TIME PERIOD	CVP				VO2				RESP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	-4.00	0.88	-0.81	1.48	266.53	26.92	196.94	50.45	14.50	0.96	13.00	0.73
BALLOON INFLATION	-3.42	0.94	-2.07	1.82	217.67	25.29	227.16	48.88	13.50	1.02	13.14	0.83
EARLY SHOCK	-5.33	0.95	-3.31	1.62	192.40	14.76	100.29	30.55	12.67	0.71	12.75	0.88
LATE SHOCK	-5.58	0.77	-4.38	1.46	134.26	8.28	131.91	12.71	12.17	0.83	12.88	0.40
T35	-4.42	0.91	-0.81	1.81	188.48	26.53	189.20	25.63	15.00	1.10	16.88	0.99
T65	-4.17	0.60	-3.19	1.73	148.12	35.47	156.78	26.47	16.00	1.18	16.75	1.01
T95	-4.33	0.70	-3.50	1.65	143.34	20.47	124.51	31.40	16.67	1.20	16.50	1.04
T125	-4.63	0.75	-3.19	1.71	137.21	11.58	179.61	22.56	15.83	1.30	16.00	1.38
T155	-5.00	0.72	-3.44	1.78	108.42	44.72	146.04	23.77	17.50	1.15	15.88	1.30

Table 78

Army 2: HS vs HES

TIME PERIOD	PACO2V				HGBV				PAO2V			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	45.67	1.24	49.40	0.74	13.72	0.86	14.24	0.86	43.33	1.58	49.63	2.74
BALLOON INFLATION	43.93	2.85	48.88	1.86	13.83	0.79	14.06	0.78	40.25	3.98	49.33	3.09
EARLY SHOCK	48.60	4.63	50.70	3.10	12.64	0.86	12.96	0.74	34.00	4.00	29.75	1.83
LATE SHOCK	50.52	4.44	59.51	5.68	12.58	0.74	13.68	0.80	37.60	2.48	44.14	2.32
T35	55.67	4.14	51.55	7.35	10.98	0.58	10.14	0.83	41.33	1.15	57.13	3.89
T65	51.97	2.96	48.51	2.78	10.70	0.61	11.80	0.76	41.67	2.59	44.75	2.72
T95	49.28	2.95	52.08	3.78	10.48	0.64	12.57	0.62	38.67	2.73	42.00	2.00
T125	52.62	3.57	54.24	2.00	10.78	0.82	12.55	0.54	39.50	1.18	38.88	3.14
T155	56.65	3.04	53.33	4.62	10.43	0.67	12.63	0.60	37.67	4.07	37.50	3.45

Table 78

Army 2: HS vs HES

TIME PERIOD	CEREBREAL BLOOD FLOW				INTRACRANIAL PRESSURE				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	28.67	2.42	32.25	3.81	6.08	1.62	6.81	1.34	120.64	4.17	107.98	8.28
BALLOON INFLATION	27.17	2.17	29.14	3.47	20.00	0.00	20.57	0.57	105.72	4.14	91.33	5.73
EARLY SHOCK	9.67	2.08	8.63	1.84	19.83	0.54	20.63	0.80	36.44	1.30	37.42	1.85
LATE SHOCK	8.50	1.26	9.38	2.11	19.33	0.33	20.63	0.92	35.00	2.74	36.17	2.00
T35	13.67	2.51	24.75	3.12	24.83	0.79	18.94	1.71	48.44	4.64	45.08	4.33
T65	17.50	3.32	18.75	2.90	31.33	3.61	20.88	3.33	72.64	5.98	66.75	6.74
T95	17.17	2.77	14.75	2.47	34.25	4.07	29.81	5.07	76.22	6.37	53.90	6.36
T125	13.50	3.36	13.88	2.15	31.92	4.10	37.63	4.20	64.25	7.53	49.92	6.32
T155	9.00	2.44	9.13	1.72	30.33	6.15	36.19	5.08	51.50	7.20	41.79	3.92

Table 80

Army 2: HS vs HES

TIME PERIOD	MAP				CV02				AV02			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	126.67	4.54	114.88	8.28	14.02	0.07	11.47	1.69	6.81	0.39	6.04	0.73
BALLOON INFLATION	125.67	4.14	111.86	5.48	14.15	0.37	10.93	1.60	6.55	0.70	7.16	0.89
EARLY SHOCK	56.17	1.17	57.75	1.36	8.45	1.39	6.44	1.08	9.94	1.70	9.61	0.89
LATE SHOCK	54.33	2.78	56.63	1.25	10.03	1.00	8.40	2.10	8.27	1.24	7.79	1.10
T35	73.17	4.92	64.13	4.47	8.89	0.11	7.45	1.66	6.38	0.32	5.02	0.34
T65	103.83	5.40	87.63	5.24	10.05	0.84	8.31	1.24	4.83	1.55	6.34	0.97
T95	110.00	4.15	83.25	5.32	9.72	0.68	7.76	1.78	5.91	1.50	7.56	0.66
T125	96.17	6.18	87.63	6.53	9.14	0.40	6.26	2.03	6.36	1.22	8.69	0.97
T155	81.83	7.32	77.88	7.13	9.74	1.85	6.97	2.40	4.72	0.86	8.07	1.33

Table 81

Army 2: HS vs HES

TIME PERIOD	CMRO2				CO2T				CVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	1.94	0.42	1.59	0.38	5.87	1.07	4.57	1.10	4.46	0.45	3.97	0.79
BALLOON INFLATION	1.83	0.20	1.74	0.33	5.75	0.03	4.39	0.78	3.97	0.20	3.51	0.56
EARLY SHOCK	1.06	0.36	0.71	0.20	2.01	0.65	1.17	0.32	4.92	1.28	5.69	1.36
LATE SHOCK	0.90	0.26	0.71	0.26	1.90	0.34	1.38	0.51	4.65	0.79	6.34	1.98
T35	1.21	0.06	1.32	0.32	2.90	0.11	3.09	0.71	4.25	1.00	2.17	0.48
T65	1.12	0.33	1.08	0.33	3.61	0.34	2.46	0.70	4.88	0.83	4.69	1.21
T95	1.31	0.26	1.09	0.34	3.57	0.13	2.12	0.67	4.94	0.75	5.05	1.33
T125	1.27	0.15	1.13	0.27	3.16	0.06	1.86	0.44	6.51	1.89	5.10	1.45
T155	0.66	0.01	0.82	0.23	2.17	0.29	1.46	0.41	10.57	4.32	6.13	1.41

Descriptive Statistics

Series 2

HS vs. HES/HS

Table 82

Army 2: HS/HES vs HS

		NTIME																	
		BALLOON																	
		BASELINE		INFLATION		EARLY SHOCK		LATE SHOCK		T35		T65		T95		T125		T155	
		STD-		STD-		STD-		STD-		STD-		STD-		STD-		STD-		STD-	
		MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR
PA- GRO-																			
CO- UP																			
2A																			
NES-																			
/HS		38.3	1.1	36.7	0.7	33.0	1.5	43.4	1.7	44.6	1.4	37.1	0.6	37.9	1.1	36.9	0.7	38.4	1.5
HS		38.5	0.9	39.6	1.2	32.3	1.7	41.5	2.0	52.4	2.5	37.8	0.7	39.6	0.9	37.5	0.8	38.2	1.2
HG- NES-																			
BA /HS		15.0	0.8	14.9	0.8	13.7	0.7	13.6	0.6	10.1	0.6	11.2	0.5	11.5	0.6	11.4	0.5	11.8	0.5
HS		14.3	0.6	14.3	0.6	12.2	0.8	12.5	0.7	9.7	0.8	11.4	0.8	12.4	0.5	12.1	0.6	12.2	0.6
PA- NES-																			
O2A /HS		266.6	17.8	257.7	16.0	248.7	19.5	242.6	19.6	260.7	18.8	270.3	20.5	265.0	20.7	259.4	21.3	263.4	26.3
HS		254.9	32.7	275.8	31.2	208.8	27.1	210.8	29.1	241.6	27.2	231.6	27.8	246.3	30.6	241.1	27.4	237.0	24.4
PHA NES-																			
/HS		7.4	0.0	7.4	0.0	7.4	0.0	7.3	0.0	7.2	0.0	7.3	0.0	7.3	0.0	7.3	0.0	7.3	0.0
HS		7.4	0.0	7.4	0.0	7.4	0.0	7.2	0.0	7.1	0.0	7.2	0.0	7.2	0.0	7.2	0.0	7.2	0.0
TE- NES-																			
MP /HS		37.6	0.4	37.5	0.4	37.6	0.5	37.9	0.5	37.6	0.5	37.6	0.5	37.7	0.6	38.1	0.6	37.7	0.7
HS		38.2	0.2	38.2	0.4	38.3	0.4	39.1	0.3	38.7	0.2	38.9	0.2	39.2	0.2	39.4	0.2	39.3	0.4
MAP NES-																			
/HS		128.1	9.9	118.6	11.4	53.3	0.9	51.1	3.6	72.9	4.1	108.6	8.4	105.9	10.5	97.4	14.2	89.8	9.5
HS		114.9	8.3	111.9	5.5	57.8	1.4	56.6	1.3	64.1	4.5	87.6	5.2	83.3	5.3	87.6	6.5	77.9	7.1
CO NES-																			
/HS		2.7	0.3	2.4	0.3	1.4	0.2	1.5	0.2	3.3	0.5	2.4	0.3	2.3	0.4	2.0	0.4	2.4	0.4
HS		2.7	0.3	2.8	0.4	1.3	0.1	1.6	0.2	3.7	0.2	2.3	0.2	2.0	0.2	1.9	0.2	1.8	0.2
PA- NES-																			
OP /HS		1.6	0.8	1.3	0.7	0.1	1.0	-0.4	0.9	1.3	1.4	0.6	0.6	0.5	0.4	-0.9	0.8	-0.6	0.6
HS		3.6	1.8	2.6	1.9	1.3	1.6	1.1	1.5	3.3	1.9	2.1	1.8	2.1	1.7	2.5	1.8	2.2	1.9

(CONTINUED)

Table 83

Army 2: HS/HES vs HS

		NTIME																	
		BALLOON																	
		BASELINE		INFLATION		EARLY SHOCK		LATE SHOCK		T35		T65		T95		T125		T155	
		STD-		STD-		STD-		STD-		STD-		STD-		STD-		STD-		STD-	
		MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR
PA- GRO- CO- UP 2V	NES-																		
	/HS	45.4	1.6	45.2	1.0	45.6	2.6	56.9	1.9	57.5	1.3	46.1	1.6	49.4	1.7	50.5	2.2	55.5	5.7
	HS	49.4	0.7	48.9	1.9	50.7	3.1	59.5	5.7	51.6	7.4	48.5	2.8	52.1	3.8	54.2	2.0	53.3	4.6
HG- NES- BV	/HS	15.1	0.8	15.0	0.7	13.4	0.8	14.0	0.6	11.4	0.4	11.5	0.4	11.6	0.5	11.9	0.4	11.6	0.4
	HS	14.2	0.9	14.1	0.8	13.0	0.7	13.7	0.8	10.1	0.8	11.8	0.8	12.6	0.6	12.6	0.5	12.6	0.6
PA- NES- O2V	/HS	46.7	1.8	46.0	2.8	31.0	2.6	37.8	1.3	47.6	1.4	37.3	2.1	32.0	2.0	31.5	2.1	31.0	2.3
	HS	49.6	2.7	49.3	3.1	29.8	1.8	44.1	2.3	57.1	3.9	44.8	2.7	42.0	2.0	38.9	3.1	37.5	3.4

Table 54

Army 2: HS/HES vs HS

		N TIME																	
		BALLOON								T35		T65		T95		T125		T155	
		BASELINE		INFLATION		EARLY SHOCK		LATE SHOCK											
		STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR
CBF GRO- UP	HES- /HS	36.4	2.2	35.0	4.8	14.6	1.6	13.1	1.0	26.4	1.4	22.9	2.9	14.6	2.1	10.6	2.2	9.0	1.6
	HS	32.3	3.8	29.1	3.5	8.6	1.8	9.4	2.1	24.8	3.1	18.8	2.9	14.8	2.5	13.9	2.2	9.1	1.7
ICP HES- /HS		5.9	1.1	20.0	0.0	19.6	0.2	22.2	1.1	22.9	1.9	35.0	4.3	49.0	6.9	51.4	6.7	45.8	5.4
	HS	6.8	1.3	20.6	0.6	20.6	0.8	20.6	0.9	18.9	1.7	20.9	3.3	29.8	5.1	37.6	4.2	36.2	5.1
CPP HES- /HS		122.2	10.0	98.3	11.4	33.7	1.1	30.1	4.6	50.3	4.1	73.6	7.9	56.8	5.4	46.6	9.0	45.4	6.6
	HS	108.0	8.3	91.3	5.7	37.4	1.8	36.2	2.0	45.1	4.3	66.8	6.7	53.9	6.4	49.9	6.3	41.8	3.9

Table 85

Army 2: HS/HES vs HS

		NTIME																	
		BALLOON								T35		T65		T95		T125		T155	
		BASELINE	INFLATION		EARLY SHOCK		LATE SHOCK												
		STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR
CA- GRO- O2 UP																			
	HES- /HS	20.2	1.1	20.0	1.0	18.5	0.9	18.6	1.0	14.1	0.9	15.5	0.9	15.8	1.0	16.2	0.6	16.2	0.6
	HS	17.5	2.0	18.1	1.9	16.0	1.6	16.2	1.7	12.5	1.9	14.6	1.9	15.3	1.6	15.0	1.7	15.0	1.7
CV- HES- O2 /HS		14.0	1.1	13.6	1.3	6.9	0.8	9.0	0.8	8.9	0.6	7.6	0.6	6.4	0.6	5.9	0.5	6.1	1.0
	HS	11.5	1.7	10.9	1.6	6.4	1.1	8.4	2.1	7.4	1.7	8.3	1.2	7.8	1.8	6.3	2.0	7.0	2.4
AV- HES- DO2 /HS		6.2	0.4	6.4	0.8	11.6	0.6	10.0	1.5	5.2	0.7	7.9	0.6	9.4	1.0	10.3	1.0	10.7	1.5
	HS	6.0	0.7	7.2	0.9	9.6	0.9	7.8	1.1	5.0	0.3	6.3	1.0	7.6	0.7	8.7	1.0	8.1	1.3
CM- HES- RO2 /HS		2.2	0.2	2.1	0.2	1.8	0.2	1.2	0.1	1.3	0.2	1.5	0.2	1.2	0.1	0.9	0.2	0.8	0.1
	HS	1.6	0.4	1.7	0.3	0.7	0.2	0.7	0.3	1.3	0.3	1.1	0.3	1.1	0.3	1.1	0.3	0.8	0.2
CO- HES- 2T /HS		7.2	0.7	7.2	1.5	2.9	0.3	2.4	0.1	3.6	0.2	3.0	0.3	2.1	0.3	1.3	0.4	1.2	0.1
	HS	4.6	1.1	4.4	0.8	1.2	0.3	1.4	0.5	3.1	0.7	2.5	0.7	2.1	0.7	1.9	0.4	1.5	0.4

Descriptive Statistics

Series 2

HES vs. HES/HS

Table 86

Army 2: HS/HES vs HES

		NTIME																			
		BASELINE		BALLOON INFLATION		EARLY SHOCK		LATE SHOCK		T35		T65		T95		T125		T155			
		STD-MEAN		STD-ERR		STD-MEAN		STD-ERR		STD-MEAN		STD-ERR		STD-MEAN		STD-ERR		STD-MEAN		STD-ERR	
PA-TRT	CO-																				
2A	1	38.3	1.1	36.7	0.7	33.0	1.5	43.4	1.7	44.6	1.4	37.1	0.6	37.9	1.1	36.9	0.7	38.4	1.5		
	2	35.4	0.7	35.6	1.4	34.2	1.9	41.6	2.5	41.8	1.7	37.9	1.2	36.7	1.0	37.0	1.1	38.0	1.6		
HG-BA	1	15.0	0.8	14.9	0.8	13.7	0.7	13.6	0.6	10.1	0.6	11.2	0.5	11.5	0.6	11.4	0.5	11.8	0.5		
	2	13.8	0.8	13.7	0.8	12.2	0.7	12.5	0.6	10.4	0.6	10.1	0.6	10.4	0.7	10.3	0.8	10.2	0.7		
PA-O2A	1	266.6	17.8	257.7	16.0	248.7	19.5	242.6	19.6	260.7	18.8	270.3	20.5	265.0	20.7	259.4	21.3	263.4	26.3		
	2	295.5	29.7	306.0	33.8	275.8	25.7	274.5	26.2	289.2	25.1	290.2	22.4	292.8	24.6	293.2	21.5	287.8	24.8		
PHA	1	7.4	0.0	7.4	0.0	7.4	0.0	7.3	0.0	7.2	0.0	7.3	0.0	7.3	0.0	7.3	0.0	7.3	0.0		
	2	7.4	0.0	7.4	0.0	7.4	0.0	7.3	0.0	7.2	0.0	7.3	0.0	7.3	0.0	7.3	0.0	7.3	0.0		
TE-MP	1	37.6	0.4	37.5	0.4	37.6	0.5	37.9	0.5	37.6	0.5	37.6	0.5	37.7	0.6	38.1	0.6	37.7	0.7		
	2	36.8	0.5	36.9	0.5	37.1	0.5	37.6	0.5	37.4	0.5	37.2	0.5	37.2	0.6	37.4	0.7	37.8	0.7		
NAP	1	128.1	9.9	118.6	11.4	53.3	0.9	51.1	3.6	72.9	4.1	108.6	8.4	105.9	10.5	97.4	14.2	89.8	9.5		
	2	126.7	4.5	125.7	4.1	56.2	1.2	54.3	2.8	73.2	4.9	103.8	5.4	110.0	4.1	96.2	6.2	81.8	7.3		
CO	1	2.7	0.3	2.4	0.3	1.4	0.2	1.5	0.2	3.3	0.5	2.4	0.3	2.3	0.4	2.0	0.4	2.4	0.4		
	2	2.9	0.5	2.6	0.4	1.4	0.2	1.6	0.1	2.6	0.2	2.9	0.3	2.3	0.3	2.2	0.3	2.0	0.2		
PA-OP	1	1.6	0.8	1.3	0.7	0.1	1.0	-0.4	0.9	1.3	1.4	0.6	0.6	0.5	0.4	-0.9	0.8	-0.6	0.6		
	2	1.0	0.9	1.0	0.8	-1.1	1.0	-0.3	0.8	0.9	0.7	0.3	0.8	0.2	1.1	-0.2	1.1	0.4	1.1		
PA-CO-2V	1	45.4	1.6	45.2	1.0	45.6	2.6	56.9	1.9	57.5	1.3	46.1	1.6	49.4	1.7	50.5	2.2	55.5	5.7		
	2	45.7	1.2	43.9	2.8	48.6	4.6	50.5	4.4	55.7	4.1	52.0	3.0	49.3	3.0	52.6	3.6	56.7	3.0		
HG-BV	1	15.1	0.8	15.0	0.7	13.4	0.8	14.0	0.6	11.4	0.4	11.5	0.4	11.6	0.5	11.9	0.4	11.6	0.4		
	2	13.7	0.9	13.8	0.8	12.6	0.9	12.6	0.7	11.0	0.6	10.7	0.6	10.5	0.6	10.8	0.8	10.4	0.7		

(CONTINUED)

Table 87

Army 2: HS/HES vs HES

		NTIME																	
		BALLOON																	
		BASELINE		INFLATION		EARLY SHOCK		LATE SHOCK		T35		T65		T95		T125		T155	
		STD-		STD-		STD-		STD-		STD-		STD-		STD-		STD-		STD-	
		MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR	MEAN	ERR
PA- TRT																			
O2V																			
1		46.7	1.8	46.0	2.8	31.0	2.4	37.8	1.3	47.6	1.4	37.3	2.1	32.0	2.0	31.5	2.1	31.0	2.3
2		43.3	1.6	40.3	4.0	34.0	4.0	37.6	2.5	41.3	1.1	41.7	2.6	38.7	2.7	39.5	1.2	37.7	4.1

Table 88

Army 2: NS/WES vs WES

	NTIME																	
	BALLOON								T35		T65		T95		T125		T155	
	BASELINE		INFLATION		EARLY SHOCK		LATE SHOCK											
	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR	STD- MEAN	ERR
CBF TRT																		
1	36.4	2.2	35.0	4.8	14.6	1.6	13.1	1.0	26.4	1.4	22.9	2.9	14.6	2.1	10.6	2.2	9.0	1.6
2	28.7	2.4	27.2	2.2	9.7	2.1	8.5	1.3	13.7	2.5	17.5	3.3	17.2	2.8	13.5	3.4	9.0	2.4
ICP 1	5.9	1.1	20.0	0.0	19.6	0.2	22.2	1.1	22.9	1.9	35.0	4.3	49.0	6.9	51.4	6.7	45.8	5.4
2	6.1	1.6	20.0	0.0	19.8	0.5	19.3	0.3	24.8	0.8	31.3	3.6	34.3	4.1	31.9	4.1	30.3	6.1
CPP 1	122.2	10.0	98.3	11.4	33.7	1.1	30.1	4.6	50.3	4.1	73.6	7.9	56.8	5.4	46.6	9.0	45.4	6.6
2	120.6	4.2	105.7	4.1	36.4	1.3	35.0	2.7	48.4	4.6	72.6	6.0	76.2	6.4	64.3	7.5	51.5	7.2

Table 89

Army 2: HS/MES vs MES

		NTIME																	
		BALLOON																	
		BASELINE		INFLATION		EARLY SHOCK		LATE SHOCK		T35		T65		T95		T125		T155	
		STD- MEAN ERR		STD- MEAN ERR		STD- MEAN ERR		STD- MEAN ERR		STD- MEAN ERR		STD- MEAN ERR		STD- MEAN ERR		STD- MEAN ERR		STD- MEAN ERR	
CA- TRT O2	1	20.2	1.1	20.0	1.0	18.5	0.9	18.6	1.0	14.1	0.9	15.5	0.9	15.8	1.0	16.2	0.6	16.2	0.6
	2	20.8	0.4	20.5	0.1	18.4	0.3	18.3	0.4	15.3	0.4	14.9	0.9	15.6	0.9	15.5	1.4	15.4	1.1
CV- 1 O2	1	14.0	1.1	13.6	1.3	6.9	0.8	9.0	0.8	8.9	0.6	7.6	0.6	6.4	0.6	5.9	0.5	6.1	1.0
	2	14.0	0.1	14.1	0.4	8.5	1.4	10.0	1.0	8.9	0.1	10.1	0.8	9.7	0.7	9.1	0.4	9.7	1.9
AV- 1 DO2	1	6.2	0.4	6.4	0.8	11.6	0.6	10.0	1.5	5.2	0.7	7.9	0.6	9.4	1.0	10.3	1.0	10.7	1.5
	2	6.8	0.4	6.6	0.7	9.9	1.7	8.3	1.2	6.4	0.3	4.8	1.5	5.9	1.5	6.4	1.2	4.7	0.9
CM- 1 RO2	1	2.2	0.2	2.1	0.2	1.8	0.2	1.2	0.1	1.3	0.2	1.5	0.2	1.2	0.1	0.9	0.2	0.8	0.1
	2	1.9	0.4	1.8	0.2	1.1	0.4	0.9	0.3	1.2	0.1	1.1	0.3	1.3	0.3	1.3	0.1	0.7	0.0
CO- 1 2T	1	7.2	0.7	7.2	1.5	2.9	0.3	2.4	0.1	3.6	0.2	3.0	0.3	2.1	0.3	1.3	0.4	1.2	0.1
	2	5.9	1.1	5.8	0.0	2.0	0.7	1.9	0.3	2.9	0.1	3.6	0.3	3.6	0.1	3.2	0.1	2.2	0.3

Descriptive Statistics

Series 2

ISO vs. HES/HS

Table 90

Army 2: ISO vs HES/HS

TIME PERIOD	PACO2A				HGBA				PAO2A			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	38.34	1.08	36.87	0.85	15.01	0.77	11.81	1.10	266.57	17.79	295.71	34.21
BALLOON INFLATION	36.73	0.69	35.73	0.98	14.89	0.76	12.60	0.96	257.71	16.04	291.40	38.01
EARLY SHOCK	33.03	1.50	33.74	1.84	13.71	0.67	10.99	0.93	248.71	19.53	289.00	39.27
LATE SHOCK	43.39	1.70	42.97	1.36	13.63	0.60	11.41	1.03	242.57	19.65	258.33	33.29
T35	44.60	1.42	38.61	1.04	10.12	0.65	8.26	0.85	260.71	18.78	300.57	32.92
T65	37.11	0.58	35.67	0.99	11.23	0.46	9.62	0.87	270.29	20.54	292.00	35.19
T95	37.86	1.13	39.44	1.63	11.46	0.61	10.37	0.96	265.00	20.67	289.00	35.58
T125	36.93	0.72	36.52	1.50	11.36	0.53	10.65	1.13	259.43	21.29	272.50	35.78
T155	38.40	1.47	39.34	1.49	11.75	0.49	11.92	0.58	263.40	26.33	253.00	35.10

Table 91

Army 2: ISO vs HES/HS

TIME PERIOD	PHA				TEMP				CAO2			
	GROUP				GROUP				GROUP			
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	7.40	0.01	7.38	0.01	37.60	0.39	37.03	0.49	20.24	1.14	18.15	1.25
BALLOON INFLATION	7.40	0.02	7.38	0.02	37.53	0.40	37.07	0.58	19.96	1.03	18.39	1.24
EARLY SHOCK	7.42	0.02	7.38	0.02	37.63	0.47	37.05	0.60	18.48	0.92	16.82	1.03
LATE SHOCK	7.31	0.03	7.27	0.02	37.94	0.46	37.47	0.72	18.59	1.00	17.55	1.04
T35	7.23	0.02	7.22	0.04	37.62	0.46	36.81	0.55	14.15	0.89	13.34	0.77
T65	7.32	0.01	7.26	0.02	37.57	0.51	36.93	0.57	15.53	0.89	14.68	0.69
T95	7.32	0.01	7.24	0.02	37.73	0.57	37.21	0.65	15.79	1.00	16.26	0.92
T125	7.30	0.02	7.25	0.02	38.07	0.64	37.82	0.63	16.22	0.59	16.33	1.12
T155	7.29	0.01	7.26	0.03	37.73	0.69	37.89	0.87	16.21	0.64	16.75	0.72

Table 93

Army 2: ISO vs HES/HS

TIME PERIOD	CO				HR				PAOP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	2.68	0.29	3.60	0.85	128.57	5.95	132.86	8.37	1.57	0.85	2.71	1.24
BALLOON INFLATION	2.36	0.29	3.09	0.74	122.86	5.22	132.86	7.78	1.29	0.71	1.50	1.04
EARLY SHOCK	1.40	0.21	1.79	0.34	116.00	4.00	130.00	7.24	0.14	1.04	0.01	0.72
LATE SHOCK	1.53	0.24	2.38	0.57	135.00	5.63	145.71	8.41	-0.36	0.88	-0.43	0.69
T35	3.34	0.49	6.17	0.54	144.29	13.56	141.43	10.33	1.25	1.36	7.14	0.91
T65	2.41	0.27	3.95	0.72	147.14	13.75	145.71	9.97	0.58	0.62	0.93	0.64
T95	2.26	0.37	3.22	0.62	152.86	17.55	156.57	9.68	0.50	0.39	0.36	1.02
T125	1.98	0.40	3.21	0.71	145.00	10.88	159.17	8.98	-0.90	0.78	0.75	1.30
T155	2.44	0.42	2.88	0.61	148.00	12.41	158.00	8.60	-0.60	0.64	0.33	1.15

Table 94

Army 2: ISO vs HES/HS

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	17.00	0.44	17.43	1.19	3.29	1.43	4.00	2.10
BALLOON INFLATION	16.14	0.55	16.71	1.19	2.00	0.90	3.21	1.91
EARLY SHOCK	11.29	0.68	12.00	0.69	-0.86	0.63	0.14	1.06
LATE SHOCK	12.57	0.92	13.71	0.57	0.00	0.93	0.86	1.14
T35	19.43	1.27	25.71	1.17	3.14	1.18	5.71	1.39
T65	16.57	1.13	18.14	0.99	0.71	0.71	1.43	1.21
T95	15.71	1.19	17.14	1.35	0.43	0.84	1.71	1.48
T125	14.43	0.87	18.00	1.84	-0.14	0.88	1.67	0.76
T155	13.20	1.85	17.17	1.82	-0.40	0.93	2.00	1.29

Table 95

Army 2: ISO vs HES/HS

TIME PERIOD	SBP				DBP				MAP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	158.57	10.39	132.43	11.59	112.86	9.99	95.29	8.87	128.14	9.92	109.29	8.33
BALLOON INFLATION	150.71	10.26	127.57	10.07	105.43	9.01	89.29	7.67	118.57	11.43	100.04	9.23
EARLY SHOCK	64.00	1.53	71.33	3.18	44.33	1.86	51.67	3.33	53.29	0.92	55.67	1.34
LATE SHOCK	57.33	8.69	67.50	4.33	39.00	7.37	49.50	2.47	51.14	3.62	55.24	1.56
T35	97.14	4.74	106.14	7.18	62.71	3.52	66.43	5.15	72.86	4.11	79.76	5.83
T65	137.43	10.10	97.14	3.43	94.29	7.60	67.57	2.06	108.57	8.36	77.33	2.39
T95	137.00	13.30	102.71	8.37	90.14	9.28	72.86	6.31	105.86	10.53	82.50	6.66
T125	122.57	17.47	111.67	8.23	84.86	12.65	77.67	7.67	97.43	14.16	88.83	7.66
T155	120.50	12.49	103.17	6.27	78.40	9.38	76.50	11.51	89.80	9.53	85.33	9.57

Table 96

Army 2: ISO vs HES/HS

TIME PERIOD	SO2T				SVR				LVSW			
	GROUP				GROUP				GROUP			
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	537.65	61.564	731.87	158.429	4259.91	520.457	3006.80	481.666	0.04	0.003	0.04	0.010
BALLOON INFLATION	384.63	89.614	640.80	144.031	4692.44	645.368	3370.65	492.988	0.03	0.003	0.03	0.008
EARLY SHOCK	236.30	39.545	318.19	56.640	3710.44	388.059	3161.62	440.506	0.01	0.002	0.01	0.002
LATE SHOCK	279.05	41.364	444.05	100.945	3333.54	460.516	2571.25	423.941	0.01	0.002	0.01	0.003
T35	491.07	82.264	867.96	47.944	2083.63	275.213	1051.73	92.528	0.03	0.004	0.04	0.006
T65	353.38	52.433	595.28	124.269	4030.76	483.557	1846.22	214.958	0.03	0.004	0.03	0.004
T95	358.29	65.813	561.22	92.589	4454.29	598.353	2492.08	361.149	0.02	0.004	0.03	0.006
T125	316.82	65.091	531.43	126.332	4645.15	990.609	2816.63	569.188	0.02	0.002	0.02	0.009
T155	408.34	74.095	528.17	84.443	3789.17	1006.64	2858.97	414.742	0.02	0.003	0.02	0.006

Table 97

Army 2: ISO vs HES/HS

TIME PERIOD	CVP				VO2				RESP			
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	-4.29	0.85	-2.89	0.83	160.68	10.71	232.10	45.95	14.14	0.94	14.00	1.15
BALLOON INFLATION	-4.07	0.73	-3.36	0.68	196.62	57.17	210.83	31.37	14.86	0.83	13.86	1.16
EARLY SHOCK	-5.64	0.86	-4.68	0.74	138.93	33.60	190.14	25.77	13.43	0.61	12.00	1.18
LATE SHOCK	-5.50	0.72	-5.64	0.61	148.52	17.67	211.98	44.76	12.00	0.62	12.00	1.05
T35	-3.29	0.84	1.07	1.17	171.24	24.25	362.23	27.68	17.00	1.29	15.14	1.32
T65	-3.93	0.51	-3.93	0.49	173.91	24.65	267.00	48.73	16.71	0.78	14.43	1.19
T95	-4.29	0.47	-4.50	0.72	203.04	27.99	244.39	29.02	14.57	0.37	14.14	1.24
T125	-5.08	0.84	-4.00	1.18	196.41	35.08	180.86	41.79	13.86	0.40	15.17	0.60
T155	-5.30	0.85	-4.08	1.11	281.21	42.27	188.00	46.75	14.40	0.51	15.50	0.62

Table 98

Army 2: ISO vs HES/HS

TIME PERIOD	PACO2V				HGBV				PAO2V			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	45.44	1.62	46.36	2.32	15.13	0.77	12.12	1.27	46.71	1.85	43.71	2.88
BALLOON INFLATION	45.17	0.93	46.12	1.72	15.01	0.72	12.80	0.83	46.00	2.83	42.00	3.79
EARLY SHOCK	45.57	2.63	48.10	3.78	13.36	0.80	11.01	0.93	31.00	2.44	34.14	2.96
LATE SHOCK	56.90	1.93	50.71	3.93	13.95	0.62	11.49	0.88	37.83	1.33	38.86	1.94
T35	57.51	1.28	48.20	3.17	11.39	0.37	8.06	0.79	47.57	1.43	45.14	2.94
T65	46.13	1.65	50.41	1.38	11.49	0.39	9.76	0.96	37.29	2.10	39.57	1.84
T95	49.41	1.69	50.57	3.01	11.57	0.45	10.46	0.97	32.00	2.01	38.71	1.92
T125	50.52	2.22	43.63	2.50	11.87	0.36	10.78	1.08	31.50	2.06	43.00	2.58
T155	55.52	5.72	44.60	2.34	11.58	0.40	11.98	0.57	31.00	2.35	50.50	6.64

Table 99

Army 2: ISO vs HES/HS

TIME PERIOD	MAP				CVO2				AVDO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	128.14	9.92	109.29	8.33	14.04	1.12	12.18	1.20	6.21	0.44	5.97	0.56
BALLOON INFLATION	118.57	11.43	100.04	9.23	13.56	1.31	11.86	1.25	6.39	0.75	6.54	0.75
EARLY SHOCK	53.29	0.92	55.67	1.34	6.89	0.83	6.37	0.87	11.58	0.58	10.45	0.94
LATE SHOCK	51.14	3.62	55.24	1.56	8.99	0.80	9.12	0.84	10.02	1.51	8.43	0.50
T35	72.86	4.11	79.76	5.83	8.94	0.56	7.78	0.76	5.20	0.67	5.57	0.46
T65	108.57	8.36	77.33	2.39	7.60	0.56	8.00	0.78	7.93	0.55	6.68	0.40
T95	105.86	10.53	82.50	6.66	6.38	0.60	8.84	0.56	9.41	1.02	7.42	0.93
T125	97.43	14.16	88.83	7.66	5.90	0.51	9.34	0.95	10.31	0.97	6.45	1.31
T155	89.80	9.53	85.33	9.57	6.12	0.98	10.50	1.22	10.75	1.51	6.24	1.47

Table 100

Army 2: ISO vs HES/HS

TIME PERIOD	CEREBREAL BLOOD FLOW				INTRACRANIAL PRESSURE				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	36.43	2.21	29.71	2.57	5.93	1.14	6.14	1.41	122.17	9.97	102.81	8.39
BALLOON INFLATION	35.00	4.80	27.71	2.98	20.00	0.00	19.14	0.82	98.33	11.43	81.00	9.65
EARLY SHOCK	14.57	1.56	11.86	1.28	19.57	0.20	19.79	0.31	33.67	1.05	35.89	1.46
LATE SHOCK	13.14	1.03	8.29	1.61	22.21	1.10	21.29	0.80	30.12	4.60	34.04	1.20
T35	26.43	1.45	17.43	3.08	22.94	1.89	38.21	1.91	50.31	4.10	41.45	4.19
T65	22.86	2.88	12.43	1.94	35.00	4.27	35.64	2.09	73.57	7.86	40.12	2.48
T95	14.57	2.14	11.57	2.40	49.00	6.88	31.93	3.13	56.81	5.43	53.69	9.45
T125	10.57	2.22	10.00	2.03	51.43	6.69	35.90	3.86	46.57	9.01	52.97	9.97
T155	9.00	1.58	8.50	2.63	45.80	5.42	33.67	5.69	45.40	6.63	51.67	9.81

Table 101

Army 2: ISO vs HES/HS

TIME PERIOD	CHRO2				CO2T				CVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	2.18	0.19	1.85	0.08	7.21	0.75	5.75	0.56	3.36	0.24	3.47	0.35
BALLOON INFLATION	2.08	0.15	1.96	0.17	7.19	1.45	5.65	0.55	3.06	0.44	3.17	0.46
EARLY SHOCK	1.80	0.17	1.26	0.21	2.92	0.31	2.05	0.33	3.10	0.47	3.26	0.38
LATE SHOCK	1.25	0.08	0.74	0.16	2.43	0.13	1.55	0.38	2.09	0.40	6.16	2.12
T35	1.34	0.17	1.14	0.20	3.64	0.25	2.74	0.44	1.91	0.14	3.24	0.65
T65	1.53	0.17	0.85	0.13	2.97	0.26	1.90	0.32	3.33	0.29	4.05	1.01
T95	1.23	0.14	0.77	0.13	2.10	0.27	1.85	0.42	4.18	0.43	6.75	3.35
T125	0.86	0.25	0.73	0.18	1.35	0.39	1.77	0.35	3.79	1.58	4.20	0.55
T155	0.79	0.09	0.70	0.26	1.21	0.09	1.57	0.49	5.03	0.39	11.89	6.60

Descriptive Statistics

Series 1a

ISO vs. HS

Table 102

ARMY 1A: ISO vs HS

TIME PERIOD	PACOZA				HBA				PAO2A			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	39.52	0.57	41.24	0.64	13.75	0.98	14.14	0.81	190.50	13.23	169.60	7.86
MID SHOCK	40.18	1.74	41.16	0.43	11.32	0.98	11.32	0.66	187.67	8.97	155.00	9.82
R0	40.35	0.92	39.54	0.52	8.40	0.74	7.28	0.46	196.50	9.39	186.00	6.12
R60	41.82	2.44	40.78	1.28	10.73	0.70	9.68	0.68	176.00	5.09	168.00	7.40
R120	38.90	0.49	41.18	1.35	10.22	1.30	10.84	0.92	183.20	14.32	162.60	6.14

Table 103

ARMY 1A: ISO vs HS

TIME PERIOD	PHA				TEMP				CAO2			
	GROUP				GROUP				GROUP			
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	7.39	0.01	7.39	0.02	37.38	0.39	37.32	0.42	18.81	1.16	19.47	1.08
MID SHOCK	7.31	0.03	7.32	0.01	38.06	0.41	38.06	0.45	15.60	1.17	15.71	0.94
R0	7.22	0.02	7.28	0.02	37.80	0.22	36.61	0.31	11.75	0.92	10.34	0.63
R60	7.23	0.03	7.29	0.02	38.34	0.53	37.85	0.30	14.95	0.93	13.50	0.93
R120	7.23	0.01	7.25	0.03	38.95	0.39	38.69	0.23	14.31	1.69	14.86	1.24

Table 104

ARMY 1A: ISO vs HS

TIME PERIOD	CO				HR				PAOP			
	GROUP				GROUP				GROUP			
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	3.22	0.42	3.85	0.22	134.17	8.34	136.80	9.75	3.83	2.07	5.40	0.58
MID SHOCK	1.21	0.06	1.42	0.15	145.00	15.52	141.60	11.63	0.08	1.19	3.00	0.76
R0	2.95	0.25	4.86	0.48	148.67	11.24	132.00	7.59	3.08	1.75	8.50	1.43
R60	1.72	0.14	2.65	0.27	176.50	11.71	148.80	2.94	3.10	0.58	3.88	0.72
R120	1.52	0.12	2.16	0.42	177.60	14.89	177.60	9.60	2.38	0.66	3.13	0.59

Table 105

ARMY 1A: ISO vs HS

TIME PERIOD	PAP1				PAP2			
	GROUP				GROUP			
	HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	23.67	2.78	24.00	0.84	4.50	2.08	6.60	2.04
MID SHOCK	15.67	1.80	15.40	1.33	0.83	1.30	2.20	0.86
R0	30.00	3.76	26.80	1.02	1.83	2.12	8.00	1.79
R60	23.50	1.52	18.80	1.53	2.67	0.33	3.00	1.48
R120	23.80	1.93	20.00	1.38	3.20	0.73	3.60	1.29

Table 106

ARMY 1A: ISO vs HS

TIME PERIOD	SBP				DBP				MAP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	141.50	6.35	147.40	7.43	99.17	4.56	103.00	9.70	113.17	4.44	118.20	8.99
MID SHOCK	77.33	6.10	67.67	8.19	34.17	2.82	30.00	1.73	48.60	3.50	44.80	2.44
R0	133.33	9.55	126.60	4.48	55.83	3.96	66.00	6.40	81.72	3.83	86.20	4.99
R60	128.33	9.28	119.00	3.67	57.50	13.27	71.00	3.67	81.67	10.45	86.80	2.84
R120	114.00	12.39	115.00	8.94	49.60	14.41	65.00	8.37	77.66	12.79	80.80	3.70

Table 107

ARMY 1A: ISO vs HS

TIME PERIOD	SO2T				RESP .				COP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	596.08	64.52	749.47	60.05	13.83	0.65	13.20	0.66	11.07	0.90	12.34	0.36
MID SHOCK	188.42	16.48	219.00	11.87	13.33	1.02	12.80	0.66	9.30	0.38	10.40	0.54
R0	343.87	35.04	499.74	54.76	18.00	0.52	15.80	0.97	6.07	0.25	5.50	0.39
R60	225.64	44.70	356.94	43.35	12.83	0.87	13.20	0.58	7.90	0.40	7.78	0.55
R120	215.80	28.82	315.65	60.71	14.00	0.89	13.40	0.68	7.72	0.48	8.28	0.41

Table 108

ARMY 1A: ISO vs HS

TIME PERIOD	COSM				CVP				SVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	0.93	0.26	0.99	0.31	-0.75	1.14	-0.20	0.92	3026.56	304.70	2484.56	249.92
MID SHOCK	0.98	0.07	0.99	0.27	-4.08	1.05	-2.90	0.64	3529.15	279.24	2765.21	228.98
R0	1.11	0.07	0.93	0.15	-1.92	1.36	1.80	1.34	2320.47	128.75	1419.27	82.78
R60	0.94	0.13	1.17	0.67	-2.92	0.69	-2.40	0.83	3683.72	353.48	2811.90	286.84
R120	0.89	0.14	0.64	0.14	-2.60	0.58	-3.20	0.72	3812.48	464.94	3589.67	636.51

Table 108

ARMY 1A: ISO vs HS

TIME PERIOD	VO2			
	GROUP			
	HS		ISO	
	MEAN	STDERR	MEAN	STDERR
BASELINE	167.58	30.31	213.39	13.64
MID SHOCK	91.88	13.24	114.46	12.39
R0	123.16	15.26	232.55	18.68
R60	111.88	9.13	175.90	18.16
R120	109.45	10.67	157.25	23.85

Table 110

ARMY 1A: ISO vs HS

TIME PERIOD	LVSU			
	GROUP			
	HS		ISO	
	MEAN	STDERR	MEAN	STDERR
BASELINE	0.04	0.007	0.04	0.003
MID SHOCK	0.01	0.001	0.01	0.001
R0	0.02	0.004	0.04	0.005
R60	0.01	0.002	0.02	0.003
R120	0.01	0.003	0.02	0.003

Table III

ARMY 1A: ISO vs HS

TIME PERIOD	CEREBREAL BLOOD FLOW				INTRACRANIAL PRESSURE				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	56.27	5.58	46.28	3.32	7.17	2.02	4.60	3.23	106.00	3.13	113.60	10.02
MID SHOCK	45.86	7.48	38.36	2.97	2.00	2.16	-2.60	2.62	46.67	2.26	48.00	4.48
R0	86.19	15.51	53.12	6.34	2.83	1.87	11.80	3.15	79.05	2.48	74.40	3.97
R60	53.30	8.30	48.67	5.46	2.17	3.00	7.80	2.35	79.50	10.19	79.00	2.35
R120	46.76	4.92	44.10	4.22	3.60	3.04	7.40	2.56	74.06	13.68	73.40	8.32

Table 112

ARMY 1A: ISO vs HS

TIME PERIOD	MAP				CVO2				AVDO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	113.17	4.44	118.20	8.99	13.53	1.11	13.83	0.88	5.27	0.89	5.64	0.55
MID SHOCK	48.60	3.50	44.80	2.44	7.97	0.72	7.64	1.00	7.64	1.22	8.07	0.41
R0	81.72	3.83	86.20	4.99	7.60	0.70	5.37	0.57	4.15	0.35	4.97	0.64
R60	81.67	10.45	86.80	2.84	8.20	0.75	6.79	0.77	6.74	0.88	6.71	0.57
R120	77.66	12.79	80.80	8.70	6.92	1.45	7.11	0.66	7.39	0.88	7.75	1.05

Table 113

ARMY 1A: ISO vs HS

TIME PERIOD	CMRO2				CO2T				CVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HS		ISO		HS		ISO		HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	2.79	0.41	2.59	0.26	10.55	1.16	8.96	0.65	2.12	0.23	2.51	0.33
MID SHOCK	3.18	0.40	3.17	0.17	6.89	0.79	5.94	0.28	1.13	0.18	1.20	0.10
R0	3.48	0.63	2.57	0.31	9.93	1.82	5.38	0.39	1.12	0.25	1.47	0.17
R60	3.41	0.39	3.21	0.35	7.76	1.00	6.50	0.79	1.68	0.34	1.73	0.25
R120	3.34	0.35	3.28	0.34	6.65	1.02	6.37	0.39	1.47	0.31	1.84	0.46

Descriptive Statistics

Series 1a

ISO vs. HES

Table 114

ARMY 1A: ISO vs HES

TIME PERIOD	PACO2A				HBA				PACO2A			
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	40.86	0.31	41.24	0.64	12.93	0.94	14.14	0.81	169.71	13.22	169.60	7.86
MID SHOCK	40.63	0.45	41.16	0.43	10.77	0.82	11.32	0.66	154.29	10.79	155.00	9.82
R0	41.33	0.40	39.54	0.52	8.60	0.65	7.28	0.46	167.14	13.79	186.00	6.12
R60	39.94	1.02	40.78	1.28	9.13	0.58	9.68	0.68	175.14	12.40	168.00	7.40
R120	40.69	0.48	41.18	1.35	9.53	0.79	10.84	0.92	183.29	13.14	162.60	6.14

ARMY 1A: ISO vs HES

TIME PERIOD	PHA				TEMP				CAO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	7.39	0.00	7.39	0.02	37.51	0.22	37.32	0.42	17.58	1.36	19.47	1.08
MID SHOCK	7.34	0.01	7.32	0.01	38.03	0.22	38.06	0.45	14.69	1.17	15.71	0.94
R0	7.29	0.01	7.28	0.02	37.92	0.23	36.61	0.31	11.83	0.94	10.34	0.63
R60	7.33	0.02	7.29	0.02	37.88	0.35	37.85	0.30	12.56	0.86	13.50	0.93
R120	7.29	0.03	7.25	0.03	38.29	0.42	38.69	0.23	13.09	1.11	14.86	1.24

Table 116

ARMY 1A: ISO vs HES

TIME PERIOD	CO				HR				PAOP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	3.85	0.21	3.85	0.22	130.29	5.51	136.80	9.75	5.36	1.37	5.40	0.58
MID SHOCK	1.69	0.10	1.42	0.15	128.57	9.34	141.60	11.63	1.25	0.52	3.00	0.76
R0	3.05	0.13	4.86	0.48	149.14	8.22	132.00	7.59	0.92	1.27	8.50	1.43
R60	3.11	0.38	2.65	0.27	157.71	10.93	148.80	2.94	2.08	0.83	3.88	0.72
R120	2.64	0.46	2.16	0.42	159.43	11.92	177.60	9.60	3.00	1.30	3.13	0.59

Table 117

ARMY 1A: ISO vs HES

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	27.86	1.65	24.00	0.84	5.71	1.38	6.60	2.04
MID SHOCK	17.43	1.59	15.40	1.33	1.86	1.34	2.20	0.86
R0	24.00	2.12	26.80	1.02	4.14	1.42	8.00	1.79
R60	23.14	1.98	18.80	1.53	1.71	1.36	3.00	1.48
R120	22.57	2.39	20.00	1.38	0.86	1.56	3.60	1.29

Table 118

ARMY 1A: ISO vs HES

TIME PERIOD	SBP				DBP				MAP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	141.43	5.95	147.40	7.43	92.14	8.85	103.00	9.70	108.61	7.59	118.20	8.99
MID SHOCK	71.17	3.16	67.67	8.19	33.83	2.39	30.00	1.73	46.86	2.09	44.80	2.44
R0	114.29	3.35	126.60	4.48	59.29	4.29	66.00	6.40	77.67	3.47	86.20	4.99
R60	140.71	4.42	119.00	3.67	76.14	3.22	71.00	3.67	96.86	1.77	86.80	2.84
R120	122.86	13.58	115.00	8.94	60.00	11.90	65.00	8.37	80.86	12.02	80.80	8.70

Table 119

ARMY 1A: ISO vs HES

TIME PERIOD	SO2T				RESP				COP			
	GROUP				GROUP				GROUP			
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	553.43	92.29	749.47	60.05	14.57	0.81	13.20	0.66	11.13	0.82	12.34	0.36
MID SHOCK	205.08	37.61	219.00	11.87	13.86	0.46	12.80	0.66	9.87	0.48	10.40	0.54
R0	308.03	51.70	499.74	54.76	16.43	1.09	15.80	0.97	14.80	0.85	5.50	0.39
R60	382.30	39.15	356.94	43.35	14.71	0.64	13.20	0.58	12.21	0.70	7.78	0.55
R120	341.74	55.25	315.65	60.71	13.43	0.53	13.40	0.68	12.11	1.11	8.28	0.41

Table 126

ARMY 1A: ISO vs HES

TIME PERIOD	COSM				CVP				SVR			
	GROUP				GROUP				GROUP			
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	1.07	0.26	0.99	0.31	0.71	1.19	-0.20	0.92	1967.27	325.37	2484.56	249.92
MID SHOCK	0.98	0.22	0.99	0.27	-3.75	0.95	-2.90	0.64	2425.43	195.41	2765.21	228.98
R0	0.98	0.21	0.93	0.15	-2.42	0.83	1.80	1.34	2108.69	134.52	1419.27	82.78
R60	0.91	0.21	1.17	0.67	-1.67	1.09	-2.40	0.83	2769.99	302.10	2811.90	286.84
R120	0.91	.	0.64	0.14	-1.50	1.01	-3.20	0.72	2659.64	316.32	3589.67	636.51

Table 121

ARMY 1A: ISO vs HES

VO2

GROUP

HES

ISO

MEAN STDERR MEAN STDERR

TIME
PERIOD

BASELINE	214.75	16.80	213.39	13.64
MID SHOCK	116.09	10.51	114.46	12.39
R0	164.90	17.53	232.55	18.68
R60	139.06	19.13	175.90	18.16
R120	173.50	21.31	157.25	23.85

Table 122

ARMY 1A: ISO vs HES

TIME PERIOD	LVSU			
	GROUP			
	HES		ISO	
	MEAN	STDERR	MEAN	STDERR
BASELINE	0.04	0.005	0.04	0.003
MID SHOCK	0.01	0.000	0.01	0.001
R0	0.02	0.002	0.04	0.005
R60	0.02	0.003	0.02	0.003
R120	0.02	0.005	0.02	0.003

All Table 123 Variables

ARMY 1A: ISO vs HES

TIME PERIOD	CBF				ICP				CPP			
	HES		ISO		HES		ISO		HES		ISO	
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	63.40	6.29	46.28	3.32	4.57	1.93	4.60	3.23	104.00	7.58	113.60	10.02
MID SHOCK	50.99	5.80	38.36	2.97	-3.14	1.88	-2.60	2.62	50.00	2.81	48.00	4.48
R0	63.50	6.90	53.12	6.34	0.00	2.06	11.80	3.15	80.57	5.08	74.40	3.97
R60	54.79	5.06	48.67	5.46	3.14	2.48	7.80	2.35	93.43	3.70	79.00	2.35
R120	45.66	6.70	44.10	4.22	4.00	2.56	7.40	2.56	76.86	11.29	73.40	8.32

Table 124

ARMY 1A: ISO vs HES

TIME PERIOD	MAP				CVO2				AVO2			
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	108.61	7.59	118.20	8.99	12.03	1.34	13.83	0.88	5.55	0.21	5.64	0.55
MID SHOCK	46.86	2.09	44.80	2.44	7.49	0.60	7.64	1.00	7.20	0.72	8.07	0.41
R0	77.67	3.47	86.20	4.99	6.34	0.57	5.37	0.57	5.49	0.64	4.97	0.64
R60	96.86	1.77	86.80	2.84	6.34	0.55	6.79	0.77	6.23	0.44	6.71	0.57
R120	80.86	12.02	80.80	8.70	5.72	1.18	7.11	0.66	7.37	0.89	7.75	1.05

Table 125

ARMY 1A: ISO vs HES

TIME PERIOD	CMRO2				CO2T				CVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		ISO		HES		ISO		HES		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	3.54	0.42	2.59	0.26	10.92	1.08	8.96	0.65	1.82	0.33	2.51	0.33
MID SHOCK	3.48	0.22	3.17	0.17	7.13	0.41	5.94	0.28	1.00	0.13	1.20	0.10
R0	3.35	0.44	2.57	0.31	7.16	0.49	5.38	0.39	1.36	0.25	1.47	0.17
R60	3.31	0.21	3.21	0.35	6.68	0.36	6.50	0.79	1.82	0.19	1.73	0.25
R120	3.04	0.25	3.28	0.34	5.89	0.82	6.37	0.39	1.75	0.23	1.84	0.46

Descriptive Statistics

Series 1a

HES vs. HS

Table 126

ARMY 1A: HS vs HES

TIME PERIOD	PACO2A				HBA				PAO2A			
	HES		HS		HES		HS		HES		HS	
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	40.86	0.31	39.52	0.57	12.93	0.94	13.75	0.98	169.71	13.22	190.50	13.23
MID SHOCK	40.63	0.45	40.18	1.74	10.77	0.82	11.32	0.98	154.29	10.79	187.67	8.97
R0	41.33	0.40	40.35	0.92	8.60	0.65	8.40	0.74	167.14	13.79	196.50	9.39
R60	39.94	1.02	41.82	2.44	9.13	0.58	10.73	0.70	175.14	12.40	176.00	5.09
R120	40.69	0.48	38.90	0.49	9.53	0.79	10.22	1.30	183.29	13.14	183.20	14.32

Table 12.7

ARMY 1A: HS vs HES

TIME PERIOD	PHA				TEMP				CAO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	7.39	0.00	7.39	0.01	37.51	0.22	37.38	0.39	17.58	1.36	18.81	1.16
MID SHOCK	7.34	0.01	7.31	0.03	38.03	0.22	38.06	0.41	14.69	1.17	15.60	1.17
R0	7.29	0.01	7.22	0.02	37.92	0.23	37.80	0.22	11.83	0.94	11.75	0.92
R60	7.33	0.02	7.23	0.03	37.88	0.35	38.34	0.53	12.56	0.86	14.95	0.93
R120	7.29	0.03	7.23	0.01	38.29	0.42	38.95	0.39	13.09	1.11	14.31	1.69

Table 128

ARMY 1A: HS vs HES

TIME PERIOD	CO				HR				PAOP			
	HES		HS		HES		HS		HES		HS	
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	3.85	0.21	3.22	0.42	130.29	5.51	134.17	8.34	5.36	1.37	3.83	2.07
MID SHOCK	1.69	0.10	1.21	0.06	128.57	9.34	145.00	15.52	1.25	0.52	0.08	1.19
R0	3.05	0.13	2.95	0.25	149.14	8.22	148.67	11.24	0.92	1.27	3.08	1.75
R60	3.11	0.38	1.72	0.14	157.71	10.93	176.50	11.71	2.08	0.83	3.10	0.58
R120	2.64	0.46	1.52	0.12	159.43	11.92	177.60	14.89	3.00	1.30	2.38	0.66

Table 129

ARMY 1A: HS vs HES

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	27.86	1.65	23.67	2.78	5.71	1.38	4.50	2.08
MID SHOCK	17.43	1.59	15.67	1.80	1.86	1.34	0.83	1.30
R0	24.00	2.12	30.00	3.76	4.14	1.42	1.83	2.12
R60	23.14	1.98	23.50	1.52	1.71	1.36	2.67	0.33
R120	22.57	2.39	23.80	1.93	0.86	1.56	3.20	0.73

Table 130

ARMY 1A: HS vs HES

TIME PERIOD	SBP				DBP				MAP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	141.43	5.95	141.50	6.35	92.14	8.85	99.17	4.56	108.61	7.59	113.17	4.44
MID SHOCK	71.17	3.16	77.33	6.10	33.83	2.39	34.17	2.82	46.86	2.09	48.60	3.50
R0	114.29	3.35	133.33	9.55	59.29	4.29	55.83	3.96	77.67	3.47	81.72	3.83
R60	140.71	4.42	128.33	9.28	76.14	3.22	57.50	13.27	96.86	1.77	81.67	10.45
R120	122.86	13.58	114.00	12.39	60.00	11.90	49.60	14.41	80.86	12.02	77.66	12.79

Table 131

ARMY 1A: HS vs NES

TIME PERIOD	SO2T				RESP				COP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	NES		HS		NES		HS		NES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	553.43	92.29	596.08	64.52	14.57	0.81	13.83	0.65	11.13	0.82	11.07	0.90
MID SHOCK	205.08	37.61	188.42	16.48	13.86	0.46	13.33	1.02	9.87	0.48	9.30	0.38
R0	308.03	51.70	343.87	35.04	16.43	1.09	18.00	0.52	14.80	0.85	6.07	0.25
R60	382.30	39.15	225.64	44.70	14.71	0.64	12.83	0.87	12.21	0.70	7.90	0.40
R120	341.74	55.25	215.80	28.82	13.43	0.53	14.00	0.89	12.11	1.11	7.72	0.48

Table 132

ARMY 1A: HS vs HES

TIME PERIOD	COSM				CVP				SVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	1.07	0.26	0.93	0.26	0.71	1.19	-0.75	1.14	1967.27	325.37	3026.56	304.70
MID SHOCK	0.98	0.22	0.98	0.07	-3.75	0.95	-4.08	1.05	2425.43	195.41	3529.15	279.24
R0	0.98	0.21	1.11	0.07	-2.42	0.83	-1.92	1.36	2108.69	134.52	2320.47	128.75
R60	0.91	0.21	0.94	0.13	-1.67	1.09	-2.92	0.69	2769.99	302.10	3883.72	353.48
R120	0.91	.	0.89	0.14	-1.50	1.01	-2.60	0.58	2659.64	316.32	3812.48	464.94

Table 133

ARMY 1A: HS vs HES

VO2

GROUP

HES

HS

MEAN STDERR MEAN STDERR

TIME
PERIOD

BASELINE	214.75	16.20	167.58	30.31
MID SHOCK	116.09	10.51	91.88	13.24
R0	164.90	17.53	123.16	15.26
R60	189.06	19.13	111.88	9.13
R120	173.50	21.31	109.45	10.67

Table 134

ARMY 1A: NS vs HES

LVSW

GROUP

HES

NS

MEAN STDERR MEAN STDERR

TIME
PERIOD

BASELINE	0.04	0.005	0.04	0.007
MID SHOCK	0.01	0.000	0.01	0.001
R0	0.02	0.002	0.02	0.004
R60	0.02	0.003	0.01	0.002
R120	0.02	0.005	0.01	0.003

Table 135

ARMY 1A: NS vs NES

TIME PERIOD	CEREBREAL BLOOD FLOW				INTRACRANIAL PRESSURE				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	NES		HS		NES		HS		NES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	63.40	6.29	56.27	5.58	4.57	1.93	7.17	2.02	104.00	7.58	105.00	3.13
MID SHOCK	50.99	5.80	45.86	7.48	-3.14	1.88	2.00	2.16	50.00	2.81	46.67	2.26
R0	63.50	6.90	86.19	15.51	0.00	2.06	2.83	1.87	80.57	5.08	79.05	2.48
R60	54.79	5.06	53.30	8.30	3.14	2.48	2.17	3.00	93.43	3.70	79.50	10.19
R120	45.66	6.70	46.76	4.92	4.00	2.56	3.60	3.04	76.86	11.29	74.06	13.68

Table 136

ARMY 1A: HS vs HES

TIME PERIOD	MAP				CVO2				AVO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	108.61	7.59	113.17	4.44	12.03	1.34	13.53	1.11	5.55	0.21	5.27	0.89
MID SHOCK	46.86	2.09	48.60	3.50	7.49	0.60	7.97	0.72	7.20	0.72	7.64	1.22
R0	77.67	3.47	81.72	3.83	6.34	0.57	7.60	0.70	5.49	0.64	4.15	0.35
R60	96.86	1.77	81.67	10.45	6.34	0.55	8.20	0.75	6.23	0.44	6.74	0.88
R120	80.86	12.02	77.66	12.79	5.72	1.18	6.92	1.45	7.37	0.89	7.39	0.88

Table 137

ARMY 1A: HS vs HES

TIME PERIOD	CMRO2				CO2T				CVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HS		HES		HS		HES		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	3.54	0.42	2.79	0.41	10.92	1.08	10.55	1.16	1.82	0.33	2.12	0.23
MID SHOCK	3.48	0.22	3.18	0.40	7.13	0.41	6.89	0.79	1.00	0.13	1.13	0.18
R0	3.35	0.44	3.48	0.63	7.16	0.49	9.93	1.82	1.36	0.25	1.12	0.25
R60	3.31	0.21	3.41	0.39	6.68	0.36	7.76	1.00	1.82	0.19	1.68	0.34
R120	3.04	0.25	3.34	0.35	5.89	0.82	6.65	1.02	1.75	0.25	1.47	0.31

Descriptive Statistics

Series 1a

HES vs. HES/HS

Table 138

ARMY 1A: HES/HS vs HES

TIME PERIOD	PAC02A				HBA				PA02A			
	HES		HES/HS		HES		HES/HS		HES		HES/HS	
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	40.86	0.31	38.82	1.44	12.93	0.94	12.12	0.88	169.71	13.22	180.20	10.64
MID SHOCK	40.63	0.45	42.04	0.63	10.77	0.82	10.28	0.64	154.29	10.79	168.80	10.13
R0	41.33	0.40	38.04	0.79	8.60	0.65	7.36	0.50	167.14	13.79	191.80	13.75
R60	39.94	1.02	40.82	0.63	9.13	0.58	8.86	0.48	175.14	12.40	191.60	16.41
R120	40.69	0.48	39.02	0.81	9.53	0.79	10.02	0.56	183.29	13.14	178.20	9.86

Table 139

ARMY 1A: HES/HS vs HES

TIME PERIOD	PHA				TEMP				CAO2			
	GROUP				GROUP				GROUP			
	HES		HES/HS		HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	7.39	0.00	7.40	0.01	37.51	0.22	37.16	0.26	17.58	1.36	17.65	0.76
MID SHOCK	7.34	0.01	7.33	0.01	38.03	0.22	37.81	0.17	14.69	1.17	15.00	0.59
R0	7.29	0.01	7.31	0.02	37.92	0.23	37.81	0.17	11.83	0.94	10.90	0.67
R60	7.33	0.02	7.30	0.02	37.88	0.35	37.87	0.43	12.56	0.86	12.49	0.88
R120	7.29	0.03	7.24	0.06	38.29	0.42	38.84	0.53	13.09	1.11	14.25	1.36

Table 140

ARMY 1A: HES/HS vs HES

TIME PERIOD	SBP				DBP				MAP			
	GROUP		HES/HS		GROUP		HES/HS		GROUP		HES/HS	
	HES		MEAN	STDERR	HES		MEAN	STDERR	HES		MEAN	STDERR
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	141.43	5.95	132.80	7.87	92.14	8.85	81.00	7.48	108.61	7.59	98.40	7.58
MID SHOCK	71.17	3.16	76.00	5.94	33.83	2.39	33.50	2.53	46.86	2.09	43.20	2.52
R0	114.29	3.35	115.00	5.24	59.29	4.29	51.00	4.30	77.67	3.47	72.40	4.48
R60	140.71	4.42	138.60	8.06	76.14	3.22	71.00	9.32	96.86	1.77	93.40	7.68
R120	122.86	13.58	117.00	8.00	60.00	11.90	52.60	12.38	80.86	12.02	74.06	10.50

Table 141

ARMY 1A: HES/HS vs HES

TIME PERIOD	CO				HR				PAOP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HES/HS		HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	3.85	0.21	4.39	0.48	130.29	5.51	146.40	19.12	5.36	1.37	5.00	0.88
MID SHOCK	1.69	0.10	1.94	0.12	128.57	9.34	133.20	11.13	1.25	0.52	2.25	0.92
R0	3.05	0.13	4.73	0.34	149.14	8.22	141.60	11.00	0.92	1.27	4.13	0.99
R60	3.11	0.38	3.50	0.67	157.71	10.93	158.40	8.82	2.08	0.83	2.40	0.73
R120	2.64	0.46	2.19	0.44	159.43	11.92	168.00	18.59	3.00	1.30	2.40	0.73

Table 143

ARMY 1A: HES/HS vs HES

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	27.86	1.65	24.60	2.18	5.71	1.38	4.00	1.61
MID SHOCK	17.43	1.59	16.40	1.60	1.86	1.34	-0.80	0.37
R0	24.00	2.12	26.80	2.73	4.14	1.42	3.20	1.28
R60	23.14	1.98	23.60	4.45	1.71	1.36	1.40	1.50
R120	22.57	2.39	19.40	1.44	0.86	1.56	1.80	0.97

Table 144

ARMY 1A: HES/HES vs HES

TIME PERIOD	SO2T				RESP				COP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HES/HS		HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	553.43	92.29	794.80	80.40	14.57	0.81	14.60	0.40	11.13	0.82	11.34	1.13
MID SHOCK	205.08	37.61	290.15	20.87	13.86	0.46	14.00	0.55	9.87	0.48	10.32	1.00
R0	308.03	51.70	540.04	44.87	16.43	1.09	20.20	0.66	14.80	0.85	12.18	1.08
R60	382.30	39.15	481.42	63.27	14.71	0.64	14.20	0.86	12.21	0.70	11.74	0.73
R120	341.74	55.25	299.90	28.35	13.43	0.53	14.20	0.86	12.11	1.11	11.04	1.02

Table 145

ARMY 1A: HES/HES vs HES

TIME PERIOD	COSM				CVP				SVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HES/HS		HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	1.07	0.26	0.76	0.06	0.71	1.19	-0.70	0.98	1967.27	325.37	1852.82	124.31
MID SHOCK	0.98	0.22	0.67	0.02	-3.75	0.95	-2.88	0.55	2425.43	195.41	2074.48	261.55
R0	0.98	0.21	0.62	0.11	-2.42	0.83	-0.63	0.77	2108.69	134.52	1244.90	68.84
R60	0.91	0.21	0.73	0.04	-1.67	1.09	-2.40	0.43	2769.99	302.10	2382.62	433.65
R120	0.91	.	0.67	0.02	-1.50	1.01	-3.00	0.57	2659.64	316.32	3184.36	311.75

ARMY 1A: HES/HES vs HES

TIME PERIOD	VO2			
	GROUP			
	HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR
BASELINE	214.75	16.80	242.27	32.87
MID SHOCK	116.09	10.51	120.56	5.37
R0	164.90	17.53	211.49	44.60
R60	189.06	19.13	217.35	23.36
R120	173.50	21.31	154.41	21.85

Table 147

ARMY 1A: HES/HS vs HES

TIME PERIOD	LVSU			
	GROUP			
	HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR
BASELINE	0.04	0.005	0.04	0.009
MID SHOCK	0.01	0.000	0.01	0.001
R0	0.02	0.002	0.03	0.007
R60	0.02	0.003	0.03	0.005
R120	0.02	0.005	0.04	0.028

Table 148

ARMY 1A: HES/HS vs HES

TIME PERIOD	CEREBREAL BLOOD FLOW				INTRACRANIAL PRESSURE				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HES/HS		HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	63.40	6.29	54.60	6.23	4.57	1.93	7.60	2.58	104.00	7.58	90.80	6.83
MID SHOCK	50.99	5.80	48.22	2.28	-3.14	1.88	2.40	0.24	50.00	2.81	40.80	2.60
R0	63.50	6.90	84.03	7.50	0.00	2.06	4.20	1.69	80.57	5.08	68.20	3.95
R60	54.79	5.06	57.95	2.36	3.14	2.48	-0.80	2.82	93.43	3.70	94.20	5.84
R120	45.66	6.70	51.35	5.44	4.00	2.56	1.40	4.32	76.86	11.29	72.60	6.43

Table 149

ARMY 1A: HES/HS vs HES

TIME PERIOD	MAP				CV02				AV002			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HES/HS		HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	108.61	7.59	98.40	7.58	12.03	1.34	12.32	0.62	5.55	0.21	5.33	0.33
MID SHOCK	46.86	2.09	43.20	2.52	7.49	0.60	8.92	0.63	7.20	0.72	6.26	0.30
R0	77.67	3.47	72.40	4.48	6.34	0.57	6.56	0.55	5.49	0.64	4.34	0.92
R60	96.86	1.77	93.40	7.68	6.34	0.55	6.78	0.51	6.23	0.44	5.71	0.51
R120	80.86	12.92	74.06	10.50	5.72	1.18	6.85	0.98	7.37	0.89	7.40	1.23

Table 150

ARMY 1A: HES/HS vs HES

TIME PERIOD	CMRO2				CO2T				CVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES		HES/HS		HES		HES/HS		HES		HES/HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	3.54	0.42	2.73	0.24	10.92	1.08	9.15	1.04	1.82	0.33	1.75	0.26
MID SHOCK	3.48	0.22	2.83	0.09	7.13	0.41	6.82	0.56	1.00	0.13	0.90	0.07
R0	3.35	0.44	3.19	0.85	7.16	0.49	8.88	0.58	1.36	0.25	1.05	0.24
R60	3.31	0.21	3.64	0.33	6.68	0.36	8.05	0.88	1.82	0.19	1.45	0.17
R120	3.04	0.25	3.41	0.28	5.89	0.82	6.66	0.33	1.75	0.23	1.48	0.17

Descriptive Statistics

Series 1a

HS vs. HES/HS

Table 151

ARMY 1A: HS vs HES/HS

TIME PERIOD	PACO2A				HBA				PAO2A			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	38.82	1.44	39.52	0.57	12.12	0.88	13.75	0.98	180.20	10.64	190.50	13.23
MID SHOCK	42.04	0.63	40.18	1.74	10.28	0.64	11.32	0.98	168.80	10.13	187.67	8.97
R0	38.04	0.79	40.35	0.92	7.36	0.50	8.40	0.74	191.80	13.75	196.50	9.39
R60	40.82	0.63	41.82	2.44	8.86	0.48	10.73	0.70	191.60	16.41	176.00	5.09
R120	39.02	0.81	38.90	0.49	10.02	0.56	10.22	1.30	178.20	9.86	183.20	14.32

Table 132

ARMY 1A: HS vs HES/HS

TIME PERIOD	PHA				TEMP				CAO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	7.40	0.01	7.39	0.01	37.16	0.26	37.38	0.39	17.65	0.76	18.81	1.16
MID SHOCK	7.33	0.01	7.31	0.03	37.81	0.17	38.06	0.41	15.00	0.59	15.60	1.17
R0	7.31	0.02	7.22	0.02	37.81	0.17	37.80	0.22	10.90	0.67	11.75	0.92
R60	7.30	0.02	7.23	0.03	37.87	0.43	38.34	0.53	12.49	0.88	14.95	0.93
R120	7.24	0.06	7.23	0.01	38.84	0.53	38.95	0.39	14.25	1.36	14.31	1.69

Table 133

ARMY 1A: HS vs HES/HS

TIME PERIOD	CO				HR				PAOP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	4.39	0.48	3.22	0.42	146.40	19.12	134.17	8.34	5.00	0.88	3.83	2.07
MID SHOCK	1.94	0.12	1.21	0.06	133.20	11.13	145.00	15.52	2.25	0.92	0.08	1.19
R0	4.73	0.34	2.95	0.25	141.60	11.00	148.67	11.24	4.13	0.99	3.08	1.75
R60	3.50	0.67	1.72	0.14	158.40	8.82	176.50	11.71	2.40	0.73	3.10	0.58
R120	2.19	0.44	1.52	0.12	168.00	18.59	177.60	14.89	2.40	0.73	2.38	0.66

Table 154

ARMY 1A: NS vs HES/HS

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HES/HS		NS		HES/HS		NS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	24.60	2.18	23.67	2.78	4.00	1.61	4.50	2.08
MID SHOCK	16.40	1.60	15.67	1.80	-0.80	0.37	0.83	1.30
R0	26.80	2.73	30.00	3.76	3.20	1.28	1.83	2.12
R60	23.60	4.45	23.50	1.52	1.40	1.50	2.67	0.33
R120	19.40	1.44	23.80	1.93	1.80	0.97	3.20	0.73

Table 135

ARMY 1A: HS vs HES/HS

TIME PERIOD	SO2T				RESP				COP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	794.80	80.40	596.08	64.52	14.60	0.40	13.83	0.65	11.34	1.13	11.07	0.90
MID SHOCK	290.15	20.87	188.42	16.48	14.00	0.55	13.33	1.02	10.32	1.00	9.30	0.38
R0	540.04	44.87	343.87	35.04	20.20	0.66	18.00	0.52	12.18	1.08	6.07	0.25
R60	481.42	63.27	225.64	44.70	14.20	0.86	12.83	0.87	11.74	0.73	7.90	0.40
R120	299.90	28.35	215.80	28.82	14.20	0.86	14.00	0.89	11.04	1.02	7.72	0.48

Table 156

ARMY 1A: HS vs HES/HS

TIME PERIOD	COSM				CVP				SVR			
	HES/HS		HS		HES/HS		HS		HES/HS		HS	
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	0.76	0.06	0.93	0.26	-0.70	0.98	-0.75	1.14	1852.82	124.31	3026.56	304.70
MID SHOCK	0.67	0.02	0.98	0.07	-2.88	0.55	-4.08	1.05	2074.48	261.55	3529.15	279.24
R0	0.62	0.11	1.11	0.07	-0.63	0.77	-1.92	1.36	1244.90	68.84	2320.47	128.75
R60	0.73	0.04	0.94	0.13	-2.40	0.43	-2.92	0.69	2382.62	433.65	3883.72	353.48
R120	0.67	0.02	0.89	0.14	-3.00	0.57	-2.60	0.58	3184.36	311.75	3812.48	464.94

7/20/15

ARMY 1A: HS vs HES/HS

VO2

GROUP

HES/HS

HS

MEAN STDERR MEAN STDERR

TIME
PERIOD

BASELINE	242.27	32.87	167.58	30.31
MID SHOCK	120.56	5.37	91.88	13.24
R0	211.49	44.60	123.16	15.26
R60	217.35	23.36	111.88	9.13
R120	154.41	21.85	109.45	10.67

Table 158

ARMY 1A: HS vs HES/HS

LVSU

GROUP

HES/HS

HS

MEAN STDERR MEAN STDERR

TIME
PERIOD

BASELINE	0.04	0.009	0.04	0.007
MID SHOCK	0.01	0.001	0.01	0.001
R0	0.03	0.007	0.02	0.004
R60	0.03	0.005	0.01	0.002
R120	0.04	0.028	0.01	0.003

Table 159

ARMY 1A: NS vs NES/NS

TIME PERIOD	SBP				DBP				MAP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	NES/NS		NS		NES/NS		NS		NES/NS		NS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	132.80	7.87	141.50	6.35	81.00	7.48	99.17	4.56	98.40	7.58	113.17	4.44
MID SHOCK	76.00	5.94	77.33	6.10	33.50	2.53	34.17	2.82	43.20	2.52	48.60	3.50
R0	115.00	5.24	133.33	9.55	51.00	4.30	55.83	3.96	72.40	4.48	81.72	3.83
R60	138.60	8.06	128.33	9.28	71.00	9.32	57.50	13.27	93.40	7.68	81.67	10.45
R120	117.00	8.00	114.00	12.39	52.60	12.38	49.60	14.41	74.06	10.50	77.66	12.79

Table 160

ARMY 1A: HS vs HES/HS

TIME PERIOD	CEREBREAL BLOOD FLOW				INTRACRANIAL PRESSURE				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	54.60	6.23	56.27	5.58	7.60	2.58	7.17	2.02	90.80	6.83	106.00	3.13
MID SHOCK	48.22	2.28	45.86	7.48	2.40	0.24	2.00	2.16	40.80	2.60	46.67	2.26
R0	84.03	7.50	86.19	15.51	4.20	1.69	2.83	1.87	68.20	3.95	79.05	2.48
R60	57.95	2.36	53.30	8.30	-0.80	2.82	2.17	3.00	94.20	5.84	79.50	10.19
R120	51.35	5.44	46.76	4.92	1.40	4.32	3.60	3.04	72.60	6.43	74.06	13.68

Table 161

ARMY 1A: NS vs HES/NS

TIME PERIOD	MAP				CVO2				AVDO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	98.40	7.58	113.17	4.44	12.32	0.62	13.53	1.11	5.33	0.33	5.27	0.89
MID SHOCK	43.20	2.52	48.60	3.50	8.92	0.63	7.97	0.72	6.26	0.30	7.64	1.22
R0	72.40	4.48	81.72	3.83	6.56	0.55	7.60	0.70	4.34	0.92	4.15	0.35
R60	93.40	7.68	81.67	10.45	6.78	0.51	8.20	0.75	5.71	0.51	6.74	0.88
R120	74.06	10.50	77.66	12.79	6.85	0.98	6.92	1.45	7.40	1.23	7.39	0.88

Table 162

ARMY 1A: HS vs HES/HS

TIME PERIOD	CHRO2				CO2T				CVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		HS		HES/HS		HS		HES/HS		HS	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	2.73	0.24	2.79	0.41	9.15	1.04	10.55	1.16	1.75	0.26	2.12	0.23
MID SHOCK	2.83	0.09	3.18	0.40	6.82	0.56	6.89	0.79	0.90	0.07	1.13	0.18
R0	3.19	0.85	3.48	0.63	8.88	0.58	9.93	1.82	1.05	0.24	1.12	0.25
R60	3.64	0.33	3.41	0.39	8.05	0.88	7.76	1.00	1.45	0.17	1.68	0.34
R120	3.41	0.28	3.34	0.35	6.66	0.33	6.65	1.02	1.48	0.17	1.47	0.31

Descriptive Statistics

Series 1a

ISO vs. HES/HS

Tab 163

ARMY 1A: ISO vs HES/HS

TIME PERIOD	PACO2A				HBA				PAO2A			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASLINE	38.82	1.44	41.24	0.64	12.12	0.88	14.14	0.81	180.20	10.64	169.60	7.86
MID SHOCK	42.04	0.63	41.16	0.43	10.28	0.64	11.32	0.66	168.80	10.13	155.00	9.82
R0	38.04	0.79	39.54	0.52	7.36	0.50	7.28	0.46	191.80	13.75	186.00	6.12
R60	40.82	0.63	40.78	1.28	8.86	0.48	9.68	0.68	191.60	16.41	168.00	7.40
R120	39.02	0.81	41.18	1.35	10.02	0.56	10.84	0.92	178.20	9.86	162.60	6.14

Table 164

ARMY 1A: ISO vs HES/HS

TIME PERIOD	PHA				TEMP				CAO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	7.40	0.01	7.39	0.02	37.16	0.26	37.32	0.42	17.65	0.76	19.47	1.08
MID SHOCK	7.33	0.01	7.32	0.01	37.81	0.17	38.06	0.45	15.00	0.59	15.71	0.94
R0	7.31	0.02	7.28	0.02	37.81	0.17	36.61	0.31	10.90	0.67	10.34	0.63
R60	7.30	0.02	7.29	0.02	37.87	0.43	37.85	0.30	12.49	0.88	13.50	0.93
R120	7.24	0.06	7.25	0.03	38.84	0.53	38.69	0.23	14.25	1.36	14.86	1.24

Table 165

ARMY 1A: ISO vs HES/HS

TIME PERIOD	CO				HR				PAOP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	4.39	0.48	3.85	0.22	146.40	19.12	136.80	9.75	5.00	0.88	5.40	0.58
MID SHOCK	1.94	0.12	1.42	0.15	133.20	11.13	141.60	11.63	2.25	0.92	3.00	0.76
R0	4.73	0.34	4.86	0.48	141.60	11.00	132.00	7.59	4.13	0.99	8.50	1.43
R60	3.50	0.67	2.65	0.27	158.40	8.82	148.80	2.94	2.40	0.73	3.88	0.72
R120	2.19	0.44	2.16	0.42	168.00	18.59	177.60	9.60	2.40	0.73	3.13	0.59

Table 164

ARMY 1A: ISO vs HES/HS

TIME PERIOD	PAP1				PAP2			
	GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	24.60	2.18	24.00	0.84	4.00	1.61	6.60	2.04
MID SHOCK	16.40	1.60	15.40	1.33	-0.80	0.37	2.20	0.86
R0	26.80	2.73	26.80	1.02	3.20	1.28	8.00	1.79
R60	23.60	4.45	18.80	1.53	1.40	1.50	3.00	1.48
R120	19.40	1.44	20.00	1.38	1.80	0.97	3.60	1.29

Table H66167

ARMY 1A: ISU vs HES/MS

TIME PERIOD	SBP				DBP				MAP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/MS		ISO		HES/MS		ISO		HES/MS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	132.80	7.87	147.40	7.43	81.00	7.48	103.00	9.70	98.40	7.58	118.20	8.99
MID SHOCK	76.00	5.94	67.67	8.19	33.50	2.53	30.00	1.73	43.20	2.52	44.80	2.44
R0	115.00	5.24	126.60	4.48	51.00	4.30	66.00	6.40	72.40	4.48	86.20	4.99
R60	138.60	8.06	119.00	3.67	71.00	9.32	71.00	3.67	93.40	7.68	86.80	2.84
R120	117.00	8.00	115.00	8.94	52.60	12.38	65.00	8.37	74.06	10.50	80.80	8.70

Table #67/68

ARMY 1A: ISO vs HES/HS

TIME PERIOD	SO2T				RESP				COP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	794.80	80.40	749.47	60.05	14.60	0.40	13.20	0.66	11.34	1.13	12.34	0.36
MID SHOCK	290.15	20.87	219.00	11.87	14.00	0.55	12.80	0.66	10.32	1.00	10.40	0.54
R0	540.04	44.87	499.74	54.76	20.20	0.66	15.80	0.97	12.18	1.08	5.50	0.39
R60	481.42	63.27	356.94	43.35	14.20	0.86	13.20	0.58	11.74	0.73	7.78	0.55
R120	299.90	28.35	315.65	60.71	14.20	0.86	13.40	0.68	11.04	1.02	8.28	0.41

Table 168/169

ARMY 1A: ISO vs HES/HS

TIME PERIOD	COSM				CVP				SVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	0.76	0.06	0.99	0.31	-0.70	0.98	-0.20	0.92	1852.82	124.31	2484.56	249.92
MID SHOCK	0.67	0.02	0.99	0.27	-2.88	0.55	-2.90	0.64	2074.48	261.55	2765.21	228.98
R0	0.62	0.11	0.93	0.15	-0.63	0.77	1.80	1.34	1244.90	68.84	1419.27	82.78
R60	0.73	0.04	1.17	0.67	-2.40	0.43	-2.40	0.83	2382.62	433.65	2811.90	286.84
R120	0.67	0.02	0.64	0.14	-3.00	0.57	-3.20	0.72	3184.36	311.75	3589.67	636.51

Table 165
170

ARMY 1A: ISO vs HES/HS

VO2

GROUP

HES/HS

ISO

MEAN STDERR MEAN STDERR

TIME
PERIOD

BASELINE	242.27	32.87	213.39	13.64
MID SHOCK	120.56	5.37	114.46	12.39
R0	211.49	44.60	232.55	18.68
R60	217.35	23.36	175.90	18.16
R120	154.41	21.85	157.25	23.85

ARMY 1A: ISO vs HES/HS

Table D-10
166
171

TIME PERIOD	LVSU			
	GROUP			
	HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR
BASELINE	0.04	0.009	0.04	0.003
MID SHOCK	0.01	0.001	0.01	0.001
R0	0.03	0.007	0.04	0.005
R60	0.03	0.005	0.02	0.003
R120	0.04	0.028	0.02	0.003

Table 172

ARMY 1A: ISO vs HES/HS

TIME PERIOD	CEREBREAL BLOOD FLOW				INTRACRANIAL PRESSURE				CPP			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	54.60	6.23	46.28	3.32	7.60	2.58	4.60	3.23	90.80	6.83	113.60	10.02
HID SHOCK	48.22	2.28	38.36	2.97	2.40	0.24	-2.60	2.62	40.80	2.60	48.00	4.48
R0	84.03	7.50	53.12	6.34	4.20	1.69	11.80	3.15	68.20	3.95	74.40	3.97
R60	57.95	2.36	48.67	5.46	-0.80	2.82	7.80	2.35	94.20	5.84	79.00	2.35
R120	51.35	5.44	44.10	4.22	1.40	4.32	7.40	2.56	72.60	6.43	73.40	8.32

ARMY 1A: ISO vs HES/HS

Table 173

TIME PERIOD	MAP				CVO2				AVDO2			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	98.40	7.58	118.20	8.99	12.32	0.62	13.83	0.88	5.33	0.33	5.64	0.55
MID SHOCK	43.20	2.52	44.80	2.44	8.92	0.63	7.64	1.00	6.26	0.30	8.07	0.41
R0	72.40	4.48	86.20	4.99	6.56	0.55	5.37	0.57	4.34	0.92	4.97	0.64
R60	93.40	7.68	86.80	2.84	6.78	0.51	6.79	0.77	5.71	0.51	6.71	0.57
R120	74.06	10.50	80.80	8.70	6.85	0.98	7.11	0.66	7.40	1.23	7.75	1.05

Table 174

ARMY 1A: ISO vs HES/HS

TIME PERIOD	CMRO2				CO2T				CVR			
	GROUP		GROUP		GROUP		GROUP		GROUP		GROUP	
	HES/HS		ISO		HES/HS		ISO		HES/HS		ISO	
	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR	MEAN	STDERR
BASELINE	2.73	0.24	2.59	0.26	9.15	1.04	8.96	0.65	1.75	0.26	2.51	0.33
MID SHOCK	2.83	0.09	3.17	0.17	6.82	0.56	5.94	0.28	0.90	0.07	1.20	0.10
R0	3.19	0.85	2.57	0.31	8.88	0.58	5.38	0.39	1.05	0.24	1.47	0.17
R60	3.64	0.33	3.21	0.35	8.05	0.88	6.50	0.79	1.45	0.17	1.73	0.25
R120	3.41	0.28	3.28	0.34	6.66	0.33	6.37	0.39	1.48	0.17	1.84	0.46

MANUSCRIPTS

- Small Volume Resuscitation From Hemorrhagic Shock in Dogs: Effects on Systemic Hemodynamics and Systemic Blood Flow
DS Prough, JM Whitley, CL Taylor, DD Deal, DS DeWitt

Accepted: Critical Care Medicine

- Cerebral and Hemodynamic Effects of a Clinically Derived Fluid Resuscitation Protocol Following Hemorrhagic Shock With An Intracranial Mass
JM Whitley, DS Prough, JK Brockschmidt, SM Vines, DS DeWitt

Submitted: Surgery

- Resuscitation From Hemorrhagic Shock With Small Volumes of Hypertonic/Hyperoncotic Solutions In the Presence of a Subdural Mass
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Submitted: Journal of Neurosurgery

Hemorrhage and Intracranial Hypertension in Combination Increase Cerebral Production of Thromboxane A₂
DL Kong, DS Prough, JM Whitley, CL Taylor, SM Vines, DS DeWitt

Submitted: Critical Care Medicine

- Cerebrovascular Effects of Small Volume Resuscitation From Hemorrhagic Shock: Comparison of Hypertonic Saline and Concentrated Hydroxyethyl Starch in Dogs
JM Whitley, DS Prough, CL Taylor, DD Deal, DS DeWitt

Submitted: Journal of Trauma

Regional Cerebral Blood Flow Following Resuscitation from Hemorrhagic Shock with Hypertonic Saline: Influence of a Subdural Mass
DS Prough, JM Whitley, CL Taylor, DD Deal, SM Vines, DS DeWitt

Submitted: Anesthesiology

MANUSCRIPTS READY FOR SUBMISSION

Resuscitation from Hemorrhagic Shock with Hypertonic Saline in the Presence of a Subdural Mass

JM Whitley, DS Prough, CL Taylor, DD Deal, DS DeWitt

To: J. Trauma

Hypertonic/hyperoncotic Fluid Resuscitation Following Hemorrhagic Shock

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Small Volume Resuscitation with 7.2% Saline with and without hydroxyethyl Starch in a Model of Hemorrhagic Shock and Intracranial Hypertension

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To: Critical Care Medicine or Resuscitation

SMALL VOLUME RESUSCITATION FROM HEMORRHAGIC SHOCK IN DOGS:
EFFECTS ON SYSTEMIC HEMODYNAMICS AND SYSTEMIC BLOOD FLOW

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ABSTRACT

We compared canine systemic hemodynamics and organ blood flow (radioactive microsphere technique) following resuscitation with 0.8% saline (SAL; Na^+ 137 $\text{mEq} \cdot \text{L}^{-1}$) to resuscitation with 7.2% saline (HS; Na^+ 1233 $\text{mEq} \cdot \text{L}^{-1}$), 20% hydroxyethyl starch (HES) in 0.8% saline, or a combination fluid consisting of 20% hydroxyethyl starch in 7.2% saline (HS/HES), each in a volume approximating 15% of shed blood volume. Twenty-four endotracheally intubated mongrel dogs (18-24 kg) were ventilated to maintain normocarbica with halothane 0.5% in nitrous oxide and oxygen (60:40). Following a 30-minute period of hemorrhagic shock (mean arterial pressure = 45 mm Hg), extending from time (T) 0 to T30, animals received one of four randomly assigned intravenous resuscitation fluids: SAL (54 $\text{ml} \cdot \text{kg}^{-1}$), HS (6.0 $\text{ml} \cdot \text{kg}^{-1}$), HES (6.0 $\text{ml} \cdot \text{kg}^{-1}$) or HS/HES (6.0 $\text{ml} \cdot \text{kg}^{-1}$). Data were collected at baseline (BL), mid-shock (T15), immediately after fluid infusion (T35) and at 60-minute intervals for two hours (T95, T155). Mean arterial pressure (MAP) increased in all groups following resuscitation. Cardiac output (CO) increased with resuscitation in all groups, exceeding baseline in the SAL and HS/HES groups ($p < 0.05$ compared to HS or HES). At T95, CO was significantly greater in either of the two colloid-containing groups than in the HS group ($p < 0.05$). Following resuscitation, brain blood flow, myocardial blood flow, and renal blood flow were similar among groups. Hepatic arterial flow (HAF) following shock varied significantly among groups ($p < 0.05$). HS and HES produced minimal improvements in HAF, SAL markedly increased HAF to levels exceeding baseline ($p < 0.05$ SAL vs HES), and HS/HES increased HAF to near baseline levels. At T155, HAF had decreased in all groups; HAF in the HS group had decreased to levels comparable to those during

shock. Small volume resuscitation with the combination of HS/HES is comparable to much larger volumes of 0.8% saline, and is equal or superior to HS or HES in the ability to restore and sustain systemic arterial pressure and improve organ blood flow following resuscitation from hemorrhagic shock.

INTRODUCTION

Prompt restoration of blood pressure and cardiac output is essential in the acute resuscitation of trauma victims. Ideally, the fluid infused should restore systemic hemodynamics when administered rapidly in a small volume constituting a fraction of shed blood volume. Recently, small volumes of hypertonic salt solutions have been used to effectively restore systemic hemodynamics. Velasco and colleagues initially reported that as little as $4.0 \text{ ml} \cdot \text{kg}^{-1}$ of 7.5% saline could effectively restore blood pressure and cardiac output and produce 100% survival in dogs subjected to hemorrhage approximating $40 \text{ ml} \cdot \text{kg}^{-1}$ (1-3). Subsequent investigators have demonstrated that hypertonic saline, in a variety of concentrations, with and without added colloid, produces acute stabilization when administered in a volume much smaller than the original shed blood volume (4-12). The addition of colloid, usually 6.0% low-molecular weight dextran, has been used to extend the relatively short-lived hemodynamic effects of hypertonic saline alone (4,9,10,13). Maningas and colleagues resuscitated unanesthetized swine after five minutes of shock, using a mixture of 7.5% saline and 6.0% dextran-70, and demonstrated that the combination restores cardiac output, renal, splanchnic, pancreatic, and small intestinal blood flow significantly better than 0.9% saline administered in a volume equal to 25% of shed blood volume (14). Although dextran solutions are commonly used in Europe for resuscitation, the more commonly employed synthetic colloid in this country is hydroxyethyl starch. Highly concentrated solutions of hydroxyethyl starch have not been studied in combination with either isotonic or hypertonic saline solutions.

Therefore, we performed the following study to compare the effects on systemic hemodynamics and systemic blood flow of acute resuscitation with a volume of 0.8%

saline, exceeding the original shed blood volume, to equal, small volumes of 7.2% saline, 20% hydroxyethyl starch in 0.8% saline, and 20% hydroxyethyl starch in 7.2% saline.

METHODS

Animals were handled according to guidelines established by the institution's Animal Care and Use Committee. Twenty-four mongrel dogs of either sex, weighing 18-24 kg, were anesthetized with thiopental sodium ($8.0 \text{ mg} \cdot \text{kg}^{-1}$ iv), paralyzed with pancuronium ($0.2 \text{ mg} \cdot \text{kg}^{-1}$ iv), and endotracheally intubated. Halothane 0.5% in nitrous oxide and oxygen (60:40) maintained anesthesia. Animals were ventilated using an Edco Model 822 large-animal ventilator (Edco Scientific, Inc., Chapel Hill, NC), at a tidal volume of $15 \text{ ml} \cdot \text{kg}^{-1}$ and a rate sufficient to maintain normocarbica (PaCO_2 35-45 mm Hg). Additional pancuronium, given as needed, prevented respiratory movement.

Bilateral brachial artery catheters were placed, the right for continuous monitoring of systemic arterial blood pressure and the left as a reference organ for organ blood flow determinations using radioactive microspheres. A 7-Fr pigtail catheter was inserted into the left ventricle through the left femoral artery for injection of radioactive microspheres. The right femoral artery was cannulated and utilized as a second reference organ. A flow-directed, pulmonary artery catheter was placed via the right external jugular vein to measure cardiac output (CO) and pulmonary artery occlusion pressure (PAOP). Hemodynamic pressure monitoring utilized a Grass 79D polygraph (Grass Instrument Co., Quincy, Mass.) with Gould-Statham P23 transducers (Gould, Inc., Oxnard, Ca.). Systemic and pulmonary artery pressures were recorded continuously; PAOP was measured intermittently. Body temperature was monitored continuously by a thermistor on the tip of the pulmonary artery catheter and was maintained with the use of a heating pad applied to the trunk and extremities. CO was recorded intermittently using an American Edwards 9520A

CO computer (American Edwards, Santa Ana, Ca.). All transducers were intermittently calibrated at the level of the left atrium.

Organ Blood Flow Measurement

Organ blood flow measurements were obtained using radioactive microspheres (15 μm) using the organ reference-sample method (15). Radioactive microspheres included Gd 153, Nb 95, Sn 113, Sr 85, and Sc 46. Paired reference organ blood samples (ROBS) were withdrawn simultaneously from the right femoral and left brachial arteries using an Edco Model 843 Infusion-Withdrawal Syringe Pump (Edco Scientific, Inc., Chapel Hill, NC). Counts per minute (CPM) from the ROBS were averaged for use in evaluating CBF. Prior to injection, microspheres were vortexed for 4 minutes to insure adequate mixing. The dose of each microsphere type was calculated to yield ≥ 400 microspheres per tissue segment and a minimum of 15,000 counts per ROBS. Injection of each microsphere type was carried out over 15 seconds. Each ROBS was taken beginning 30 seconds prior to microsphere injection and continuing for 60 seconds post-injection, at a withdrawal rate of $2.06 \text{ ml} \cdot \text{min}^{-1}$. At the conclusion of the experiment, the organs were removed and counted along with the arterial reference samples in a well-type gamma counter (Auto-Gamma 5000, Packard Instruments, Downers Grove, IL). Aliquots of microspheres labelled with each radionuclide were counted along with the blood and tissue samples and curve stripping to correct for isotope overlap was performed using a microcomputer connected to the gamma counter. Organ blood flows were derived from the formula:

$$\text{Blood flow} = \frac{C_t \times \text{withdrawal rate} \times 100}{C_r \times Wt} \quad \text{Eq. 1}$$

where C_t = CPM in the tissue sample, C_r = CPM in the reference sample, and Wt = weight of the tissue sample.

Method of Hemorrhage

After instrumentation, all animals were left undisturbed for 30 minutes, after which baseline (BL) data were recorded. Recorded data consisted of organ blood flow, systolic and diastolic arterial pressures (SAP and DAP), CO, PAOP, pulmonary arterial systemic and diastolic pressure (PAS and PAD), core temperature, arterial pH, PaCO_2 , PaO_2 (IL 1306 Instrumentation Laboratory, Lexington, Mass.), arterial and cerebral O_2 saturation, hemoglobin (Hgb) (IL 282; Instrumentation Laboratory, Lexington, Mass.), serum osmolality (5500 Vapor Pressure Osmometer, Wescor, Inc., Logan, Utah), and colloid oncotic pressure (4100 Colloid Osmometer, Wescor, Inc.). Mean arterial pressure (MAP) was calculated from the formula:

$$\text{MAP} = \text{DAP} + 1/3 (\text{SAP} - \text{DAP}) \quad \text{Eq. 2}$$

Systemic oxygen transport (DO_2) was calculated from the equation:

$$\text{DO}_2 = \text{CO} \times \text{CaO}_2 \quad \text{Eq. 3}$$

After anti-coagulation with heparin ($500 \text{ IU} \cdot \text{kg}^{-1}$ iv), blood was rapidly withdrawn through the right brachial artery catheter to reduce MAP to 45 mm Hg; MAP was maintained at that level for 30 minutes by removing or reinfusing shed blood. Hemodynamic data were obtained at the mid-shock time interval, designated T15, indicating the number of minutes elapsed from the onset of shock. Following

the shock interval, animals were randomly assigned to one of four groups, based upon the composition of resuscitation fluid: Group SAL received $54 \text{ ml} \cdot \text{kg}^{-1}$ of 0.8% saline ($137 \text{ mEq} \cdot \text{L}^{-1}$ sodium), Group HS received $6.0 \text{ ml} \cdot \text{kg}^{-1}$ of 7.2% hypertonic saline ($1233 \text{ mEq} \cdot \text{L}^{-1}$ sodium), Group HES received $6.0 \text{ ml} \cdot \text{kg}^{-1}$ of 20% hydroxyethyl starch dissolved in 0.8% saline, and Group HS/HES received $6.0 \text{ ml} \cdot \text{kg}^{-1}$ of 20% hydroxyethyl starch dissolved in 7.2% saline. Additional data were collected immediately after infusion of the resuscitation fluid over 5 minutes (T35) and thereafter at hourly intervals for two hours (T95, T155). Figure 1 summarizes the experimental preparation.

Statistical Analysis

The Kruskal-Wallis test was employed to assess differences among the groups at baseline and during shock, before randomization. A multivariate repeated measures analysis of variance (ANOVA) was performed to determine if interactions between groups and time existed at subsequent post-resuscitation intervals (16). Interactions were analyzed further with the Holm's sequentially rejective multiple test procedure using a significance level of 0.05 (17). To assess time and group differences when an interaction was not present, a multivariate repeated measures ANOVA and an analysis of covariance were performed on the dependent variables. When a statistically significant group effect was evident, Holm's sequentially rejective multiple test procedure was used to determine which groups differed.

RESULTS

Mean body weights, shed blood volume, and resuscitation volumes for the SAL, HS, HES, and HS/HES groups are listed in Table 1. No significant differences were detected in body weights or volumes of shed blood among groups. All subsequent values in the text, tables, and figures are expressed as means $\pm$ SEM.

SYSTEMIC VARIABLES

Kruskal-Wallis testing detected no difference in MAP at baseline or during shock among the four groups (Table 2). With resuscitation, MAP increased similarly in all groups, but did not return to baseline. SAP nearly equalled baseline in all groups; DAP was less than baseline. SAP continued to increase during the first 60 minutes in both the HES and HS/HES groups, whereas it remained constant in SAL and HS (Figure 2). No statistical differences among fluid groups were apparent at any time period.

CO, unlike MAP, differed significantly following resuscitation (Figure 3A). CO increased at T35 in all four fluid groups, exceeding baseline in the SAL and HS/HES groups ($p < 0.05$ compared to the HS or HES groups). One hour following resuscitation (T95), CO was significantly greater in the HES and HS/HES groups than in the HS group, in which CO had declined to levels present during shock ($p < 0.05$). By T155, CO had decreased in all groups but remained greater than shock levels in all but the HS group.

At T35, PAOP was highest ($p < 0.05$) and Hgb was lowest in the SAL group (Table 2). DO_2 was similar among groups at all time intervals (Figure 3B), except at T35 where a significant difference ($p < 0.05$) was detected in groups SAL and HS/HES

compared to groups HS and HES. Other variables including pH, PaCO₂, PaO₂ and blood temperature were similar among groups at all time intervals.

Increases in serum osmolality were greatest in the HS and HS/HES groups. Colloid oncotic pressure, as percent of baseline, increased with resuscitation in the HES and HS/HES groups compared to SAL and HS, which decreased (Table 4).

ORGAN BLOOD FLOWS

Brain

Kruskal-Wallis testing disclosed no differences in brain blood flow (BBF) among groups at baseline (Figure 4A). Hemorrhagic shock resulted in comparable, statistically insignificant reductions in total BBF. Following resuscitation (T35), BBF was restored at least to baseline in all fluid groups with those fluids containing 7.2% saline exceeding baseline. The HS and HS/HES groups significantly exceeded the HES and SAL groups ($p < 0.05$). BBF subsequent to T35 was comparable in all groups for the duration of the experiment.

Heart

Myocardial blood flow (MBF) (Figure 4B) was comparable among groups at baseline. Induction of hemorrhage was associated with a reduction of approximately 50% in MBF. Resuscitation resulted in marked increases in MBF in all groups. There were no significant differences among groups at any time interval.

KIDNEY

Renal blood flow (RBF) (Figure 4C) was statistically similar among groups at baseline. Hemorrhage produced a 50% reduction in RBF in all groups. At T35, RBF was restored to baseline levels in all groups. However, by T95, RBF had declined to shock levels in all four fluid groups. No statistically significant group effects were detected.

LIVER

Hepatic arterial flow (HAF) was comparable at baseline in the four groups (Figure 4D). During shock, HAF decreased by 50% compared to baseline. Resuscitation with SAL markedly increased HAF to levels exceeding baseline. HS and HS/HES increased HAF to near baseline levels while HES produced minimal improvements in HAF ($p < 0.05$ SAL vs HES). At T155, HAF had decreased in all groups; HAF in the HS group had decreased to levels comparable to those during shock.

DISCUSSION

Interest in the applicability of small-volume resuscitation for trauma patients was stimulated by studies performed by Velasco and colleagues in the early 1980's. They first demonstrated that dogs, subjected to hemorrhage equal to approximately one-half of estimated blood volume, could be effectively resuscitated using 7.5% saline in a dose of $40 \text{ ml} \cdot \text{kg}^{-1}$, a volume that was equal only to about one-tenth of the initial shed blood volume (1). Subsequently, they demonstrated that hypertonic saline failed to improve systemic hemodynamics if a vagally mediated reflex arc were abolished or if hypertonic saline solution were infused into the aorta rather than into the inferior vena cava (2). However, hypertonic resuscitation fluids produced a relatively short-lived improvement in blood pressure and CO (4,9,10). As a consequence, subsequent investigators added colloid, usually 6.0% low-molecular weight dextran, to the hypertonic solution (9,10,18).

Previous investigators have not investigated the effects of the addition of highly concentrated hydroxyethyl starch to hypertonic resuscitation solutions. However, the present study suggests that this combination, like the combination of hypertonic saline with 6.0% low-molecular weight dextran, extends the duration of systemic hemodynamic improvement without interfering with the immediate hemodynamic responses. Kramer and colleagues bled unanesthetized adult sheep to maintain MAP at 50 mm Hg for three hours (shed blood volume = $42 \pm 7 \text{ ml} \cdot \text{kg}^{-1}$). They then administered 200 ml of either 0.9% saline or 7.2% saline with 6.0% dextran-70. Only the combination fluid restored blood pressure and CO. Thirty minutes following the initial bolus, lactated Ringer's solution was given as necessary to both groups to restore and maintain CO at baseline values. The combination fluid necessitated the

administration of only one-sixth the quantity of lactated Ringer's solution required by the control group (18). Smith and colleagues compared the effects of $4 \text{ ml} \cdot \text{kg}^{-1}$ in sheep who had been bled to a MAP of 50 mm Hg for two hours. They demonstrated that the combination of 7.2% saline and 6.0% dextran 70 sustained a significantly higher CO over the three-hour, post-resuscitation observation period than did hypertonic saline alone or a combination of hypertonic saline and sodium acetate (9). Maningas and colleagues studied the effects of 0.9% saline, 7.5% saline, 6.0% dextran 70, or 7.5% saline in 6.0% dextran 70 following potentially lethal hemorrhage in swine. Each fluid was given in a volume equal to 25% of the shed blood volume. The combination fluid was associated with 100% survival for 96 hours in comparison to significantly poorer survival in the group that received 0.9% saline alone or 7.5% saline alone (10). Most recently, Velasco and colleagues demonstrated that the combination of 7.5% saline and 6.0% dextran 70 was associated with somewhat higher survival and more sustained improvement in plasma volume than 6.0% dextran 70 or 7.5% saline alone (19).

These data demonstrate that the three, small-volume resuscitation fluids are comparably effective in restoring and maintaining MAP when administered in volumes approximating 15% of shed blood volume. Furthermore, they improve MAP in a manner that cannot be distinguished from the improvements produced by much larger volumes of a solution containing $137 \text{ mEq} \cdot \text{L}^{-1}$. However, the three fluids are not equivalent in their effect on CO. Both 0.8% saline and the combination of 20% HES in 7.2% saline improve CO to values exceeding baseline immediately following resuscitation. Neither 20% HES in 0.8% saline nor 7.2% HS alone restored CO to

baseline values. In the group that had received 7.2% saline alone, CO had declined nearly to the values present during shock by 60 minutes following fluid administration.

The present study demonstrates not only that the improvement in CO produced by hypertonic saline alone is transient but also that the improvements in blood flow to essential systemic organs such as the kidneys and liver is transient. RBF was restored by all four fluids to baseline values, but by 60 minutes following resuscitation, it had declined to levels present during shock with all four fluids. HAF exceeded baseline values following resuscitation only in the group that received 0.8% saline. 7.2% HS failed to restore HAF to baseline values following resuscitation and was associated with a rapid decline in the 120 minutes following resuscitation. In contrast, HAF was well-maintained in the three groups that received either a large volume of SAL (a slightly hypotonic fluid) or small volumes of the colloid-containing fluids HES and HS/HES. Changes in MBF appear to relate most closely to changes in heart rate and blood pressure in the two hours following resuscitation. Based upon all of the above information, the combination of 20% HES in 7.2% saline appears to be the most effective of the three alternative, small-volume resuscitation fluids in its ability to restore and maintain perfusion pressure and blood flow.

These data extend those of Maningas in which 0.9% saline and a combination of 7.5% saline with 6.0% dextran-70 were compared in a volume equal to 25% of shed blood volume (14). He evaluated organ blood flow 5 min and 30 min following resuscitation with the two fluids, whereas the present study continued measurements for two hours. In contrast to the present study, Maningas compared a small volume of 0.9% saline to a combination hypertonic/hyperoncotic fluid, whereas the present study evaluated a volume of 0.8% saline exceeding shed blood volume. As in

Maningas' study, the combination hypertonic/hyperoncotic fluid (HS/HES) restored RBF 5 minutes following resuscitation. At that interval we demonstrated that a large volume of 0.8% saline and small volumes of HES and HS were equally effective at restoring RBF. Sixty-minutes later, the colloid-containing fluids (HES and HS/HES) were associated with superior RBF. Maningas reported that liver blood flow, similar in baseline to that in the present study, was restored by the combination of 7.5% saline and 6.0% dextran 70. Our data support those observations and further demonstrate that HAF is well preserved even 60 minutes following resuscitation with a combination fluid. However, the immediate effects of HS/HES on HAF are less profound than the effects of a large volume of 0.8% saline.

The selection of experimental endpoints for resuscitation following hemorrhagic shock necessitates careful definition of the clinical situation of interest because the use of those endpoints influences subsequent measurements. A variety of endpoints may be used to achieve comparability among groups. One approach is to infuse whatever volume of fluid is required to maintain a pre-determined level of a physiologic endpoint such as blood pressure, CO, or PAOP. Clinical resuscitation normally utilizes blood pressure for its endpoint. However, blood pressure remains similar, despite progressively declining CO, if systemic vascular resistance increases. The use of central venous pressure (CVP) and PAOP data provides an estimate of filling pressure. However, CVP and PAOP are determined by a complex interaction among blood volume, venous capacitance, and ventricular distensibility, contractility, and afterload. Intermittent determinations of CO using thermodilution also can be used to guide therapy. If resuscitation is carried out with red-cell-free solutions, thereby reducing Hgb and CaO_2 , CO will constitute a less accurate estimate of the adequacy

of resuscitation than DO_2 , a calculation that incorporates both CO and CaO_2 (see Eq. 3).

This study was designed to duplicate acute resuscitation such as might occur at the scene of an accident or on a battlefield. The most practical method under such circumstances is to rapidly infuse a limited volume of fluid during stabilization or transport. Therefore, the fluids chosen for comparison in this study consisted of three small-volume alternatives as well as a much larger volume of slightly hypotonic saline. The stability of systemic hemodynamics following infusion of various types of fluids differs markedly. The infusion of solutions containing colloid, such as those used in the HES and HS/HES groups, is associated with a more sustained increase in plasma volume than that produced by a slightly hypotonic or hypertonic saline solution (4,20,21). Thus, CO, RBF, and HAF declined more rapidly in the 0.8% and 7.2% saline groups than in the two groups that received colloid.

The more sustained effects of the colloid containing solutions would be of greatest value if a substantial time interval separated acute resuscitation from subsequent efforts. However, if definitive treatment will be minimally delayed, only the acute effects of the various fluid choices should be compared. Under those circumstances, if circumstances permit infusion of only a small volume, the combination HS/HES appears to have the most favorable immediate effects. Further studies are necessary to determine if the superiority of the combination fluid is also evident after more severe hemorrhage or more protracted hypotension. Depending upon such studies, this combination may have practical utility for the management of acute hemorrhagic shock in man.

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Table 1. Body Weight, Shed Blood, and Resuscitation Volumes (Means $\pm$ SEM)

Group	Weight (kg)	Blood Loss (ml $\cdot$ kg ⁻¹)	Resus. Volume (ml $\cdot$ kg ⁻¹)
SAL	22.3 $\pm$ 1.06	37.1 $\pm$ 2.42	54
HS	20.3 $\pm$ 1.25	35.3 $\pm$ 2.80	6
HES	21.8 $\pm$.57	32.1 $\pm$ 3.55	6
HS/HES	20.4 $\pm$.68	36.5 $\pm$ 2.80	6

Table 2. Major Systemic Variables (Means $\pm$ SEM)

Group		BL	T15	T35	T95	T155
MAP	SAL	118 $\pm$ 9	45 $\pm$ 2	86 $\pm$ 5	87 $\pm$ 3	81 $\pm$ 9
	HS	113 $\pm$ 4	49 $\pm$ 4	82 $\pm$ 4	82 $\pm$ 10	78 $\pm$ 13
	HES	109 $\pm$ 8	47 $\pm$ 2	78 $\pm$ 3	97 $\pm$ 2	81 $\pm$ 12
	HS/HES	98 $\pm$ 8	43 $\pm$ 3	72 $\pm$ 5	93 $\pm$ 8	74 $\pm$ 11
SAP (mm Hg)	SAL	147 $\pm$ 7	67 $\pm$ 8	126 $\pm$ 4	119 $\pm$ 4	115 $\pm$ 9
	HS	141 $\pm$ 6	77 $\pm$ 6	133 $\pm$ 10	128 $\pm$ 9	114 $\pm$ 12
	HES	141 $\pm$ 6	71 $\pm$ 3	114 $\pm$ 3	141 $\pm$ 4	123 $\pm$ 14
	HS/HES	133 $\pm$ 8	76 $\pm$ 6	115 $\pm$ 5	138 $\pm$ 8	117 $\pm$ 8
DAP (mm Hg)	SAL	103 $\pm$ 10	30 $\pm$ 2	66 $\pm$ 6	71 $\pm$ 4	65 $\pm$ 8
	HS	99 $\pm$ 5	34 $\pm$ 3	56 $\pm$ 4	58 $\pm$ 13	50 $\pm$ 14
	HES	92 $\pm$ 9	34 $\pm$ 2	60 $\pm$ 4	76 $\pm$ 3	60 $\pm$ 12
	HS/HES	81 $\pm$ 7	34 $\pm$ 3	51 $\pm$ 4	71 $\pm$ 9	53 $\pm$ 12
PAOP (mm Hg)	SAL	5.4 $\pm$ 0.6	3.0 $\pm$ 0.8	8.5 $\pm$ 1.4*	3.9 $\pm$ 0.7	3.1 $\pm$ 0.6
	HS	3.8 $\pm$ 2.1	0.1 $\pm$ 1.2	3.1 $\pm$ 1.7	3.1 $\pm$ 0.6	2.4 $\pm$ 0.7
	HES	5.4 $\pm$ 1.4	1.3 $\pm$ 0.5	0.9 $\pm$ 1.3	2.1 $\pm$ 0.8	3.0 $\pm$ 1.3
	HS/HES	5.0 $\pm$ 0.9	2.3 $\pm$ 0.9	4.1 $\pm$ 1.0	2.4 $\pm$ 0.7	2.4 $\pm$ 0.7
Hgb (g $\cdot$ dl $^{-1}$)	SAL	14.1 $\pm$ 0.8	11.3 $\pm$ 0.7	7.3 $\pm$ 0.5	9.7 $\pm$ 0.7	10.8 $\pm$ 0.9
	HS	13.8 $\pm$ 1.0	11.3 $\pm$ 1.0	9.4 $\pm$ 0.7	10.7 $\pm$ 0.7	10.2 $\pm$ 1.3
	HES	12.9 $\pm$ 0.9	10.2 $\pm$ 0.8	8.6 $\pm$ 0.7	9.1 $\pm$ 0.6	9.5 $\pm$ 0.8
	HS/HES	12.1 $\pm$ 0.9	10.3 $\pm$ 0.6	7.4 $\pm$ 0.5	8.9 $\pm$ 0.5	10.0 $\pm$ 0.6
DO $_2$ (ml ^{2} min $^{-1}$)	SAL	750 $\pm$ 60	219 $\pm$ 12	500 $\pm$ 55**	357 $\pm$ 44	316 $\pm$ 61
	HS	596 $\pm$ 65	188 $\pm$ 16	344 $\pm$ 35	226 $\pm$ 45	216 $\pm$ 29
	HES	553 $\pm$ 92	205 $\pm$ 38	308 $\pm$ 52	382 $\pm$ 39	342 $\pm$ 55
	HS/HES	795 $\pm$ 80	290 $\pm$ 21	540 $\pm$ 45**	481 $\pm$ 63	300 $\pm$ 28

* p<0.05 SAL vs HS, HES, and HS/HES.

** p<0.05 SAL vs HS and HES
HS/HES vs HS and HES

Table 3. Major Systemic Variables (Means $\pm$ SEM)

	Group	BL	T15	T35	T95	T155
pH	SAL	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.0
	HS	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0
	HES	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0
	HS/HES	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.1
PaCO ₂ (mm Hg)	SAL	41.2 $\pm$ 0.6	41.2 $\pm$ 0.4	39.5 $\pm$ 0.5	40.8 $\pm$ 1.3	41.2 $\pm$ 1.4
	HS	39.5 $\pm$ 0.6	40.2 $\pm$ 1.7	40.4 $\pm$ 0.9	41.8 $\pm$ 2.4	38.9 $\pm$ 0.5
	HES	40.9 $\pm$ 0.3	40.6 $\pm$ 0.4	41.3 $\pm$ 0.4	39.9 $\pm$ 1.0	40.7 $\pm$ 0.5
	HS/HES	38.8 $\pm$ 1.4	42.0 $\pm$ 0.6	38.0 $\pm$ 0.8	40.8 $\pm$ 0.6	39.0 $\pm$ 0.8
PaO ₂ (mm Hg)	SAL	170 $\pm$ 8	155 $\pm$ 10	186 $\pm$ 6	168 $\pm$ 7	163 $\pm$ 6
	HS	191 $\pm$ 13	188 $\pm$ 9	197 $\pm$ 10	176 $\pm$ 5	183 $\pm$ 14
	HES	170 $\pm$ 13	154 $\pm$ 11	167 $\pm$ 14	175 $\pm$ 12	183 $\pm$ 13
	HS/HES	180 $\pm$ 11	169 $\pm$ 10	192 $\pm$ 14	192 $\pm$ 18	178 $\pm$ 10
Temp (°C)	SAL	37.3 $\pm$ 0.4	38.1 $\pm$ 0.5	36.6 $\pm$ 0.3	37.9 $\pm$ 0.3	38.7 $\pm$ 0.2
	HS	37.4 $\pm$ 0.4	38.1 $\pm$ 0.4	37.8 $\pm$ 0.2	39.3 $\pm$ 0.5	38.9 $\pm$ 0.4
	HES	37.5 $\pm$ 0.2	38.0 $\pm$ 0.2	37.9 $\pm$ 0.0	37.9 $\pm$ 0.4	38.3 $\pm$ 0.4
	HS/HES	37.2 $\pm$ 0.3	37.8 $\pm$ 0.2	37.8 $\pm$ 0.2	37.9 $\pm$ 0.4	38.8 $\pm$ 0.5

Table 4. Serum Osmolality and Colloid Oncotic Pressure (Means $\pm$ SEM)

	Group	BL	T95	T155
Serum Osmolality (mOsm $\cdot$ L ⁻¹)	SAL	292 $\pm$ 7	281 $\pm$ 14	299 $\pm$ 0
	HS	292 $\pm$ 12	318 $\pm$ 6	324 $\pm$ 4
	HES	291 $\pm$ 8	313 $\pm$ 14	307 $\pm$ 6
	HS/HES	290 $\pm$ 8	311 $\pm$ 7	322 $\pm$ 4
Colloid Oncotic Pressure (% Baseline)	SAL	100 $\pm$ 0	63 $\pm$ 4	67 $\pm$ 3
	HS	100 $\pm$ 0	71 $\pm$ 4	70 $\pm$ 4
	HES	100 $\pm$ 0	110 $\pm$ 1	110 $\pm$ 1
	HS/HES	100 $\pm$ 0	110 $\pm$ 1	110 $\pm$ 1

LEGENDS

- Figure 1. Summary of experimental procedure.
- Figure 2. Response of systolic arterial pressure following resuscitation from hemorrhagic shock with 0.8% saline (SAL), 7.2% saline (HS), 20% hydroxyethyl starch (HES) in 0.8% saline, or HES dissolved in 7.2% saline (HS/HES).
- Figure 3. Changes in cardiac output (A) and systemic organ transport (B) following resuscitation from hemorrhagic shock with 0.8% saline (SAL), 7.2% saline (HS), 20% hydroxyethyl starch (HES) in 0.8% saline, or HES dissolved in 7.2% saline (HS/HES).
- Figure 4. Changes in brain (A), myocardium (B), renal (C), and hepatic (D) blood flow following resuscitation from hemorrhagic shock with 0.8% saline (SAL), 7.2% saline (HS), 20% hydroxyethyl starch (HES) in 0.8% saline, or HES dissolved in 7.2% saline (HS/HES).

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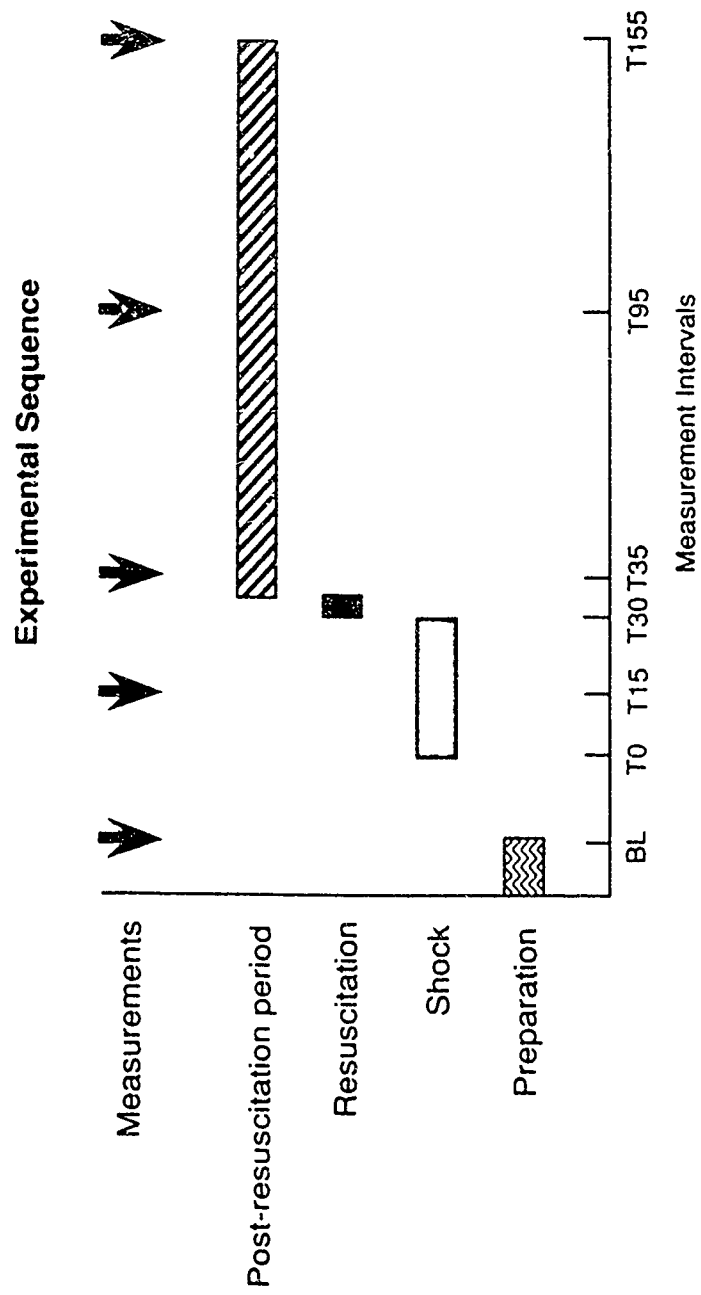
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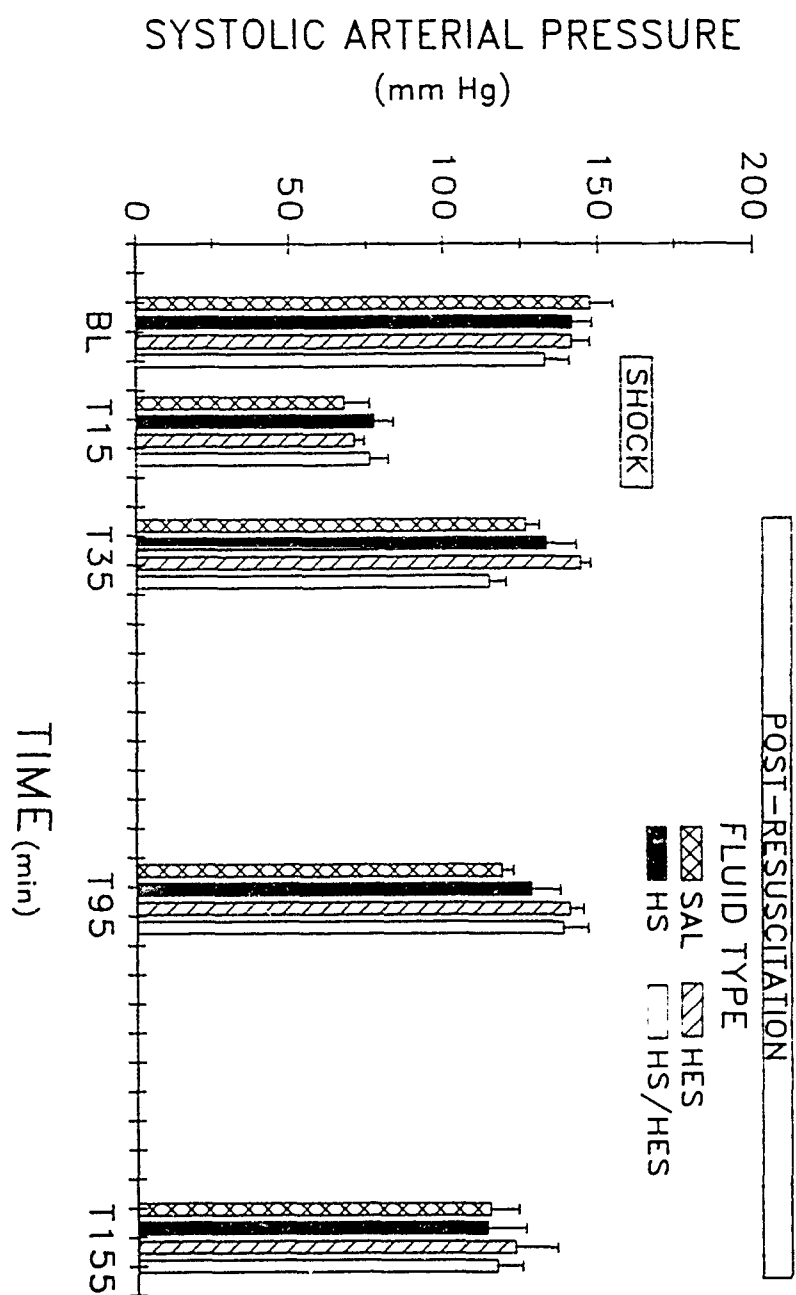
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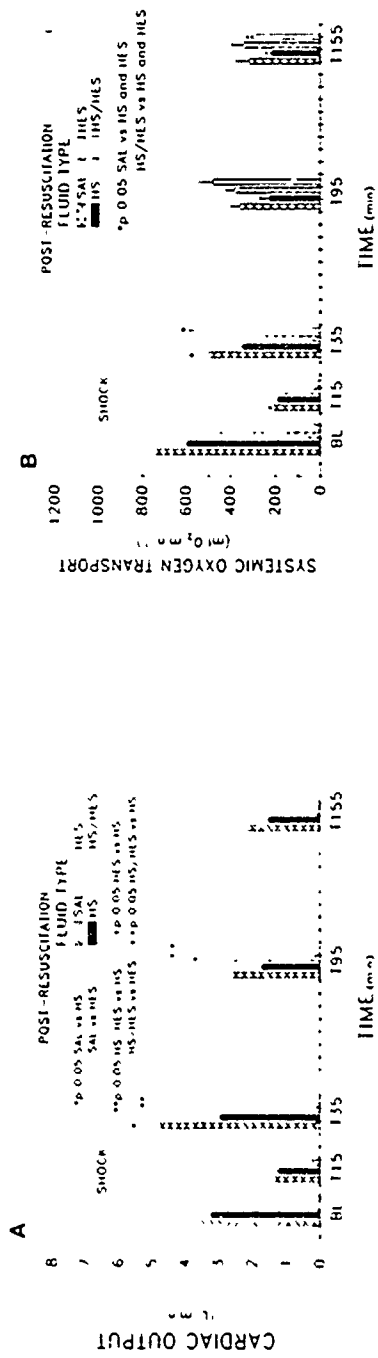
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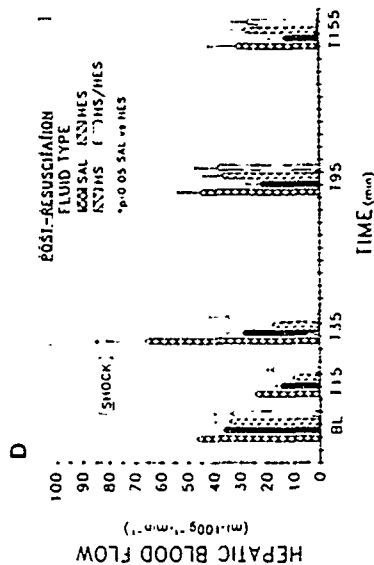
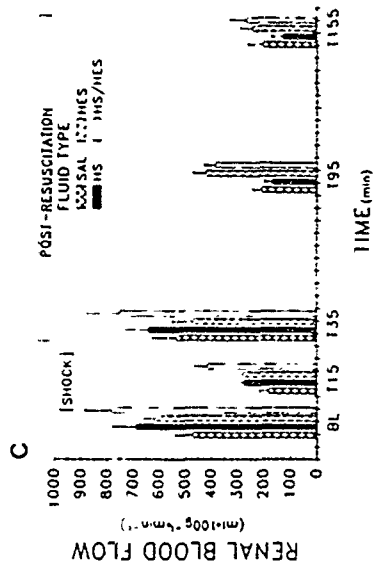
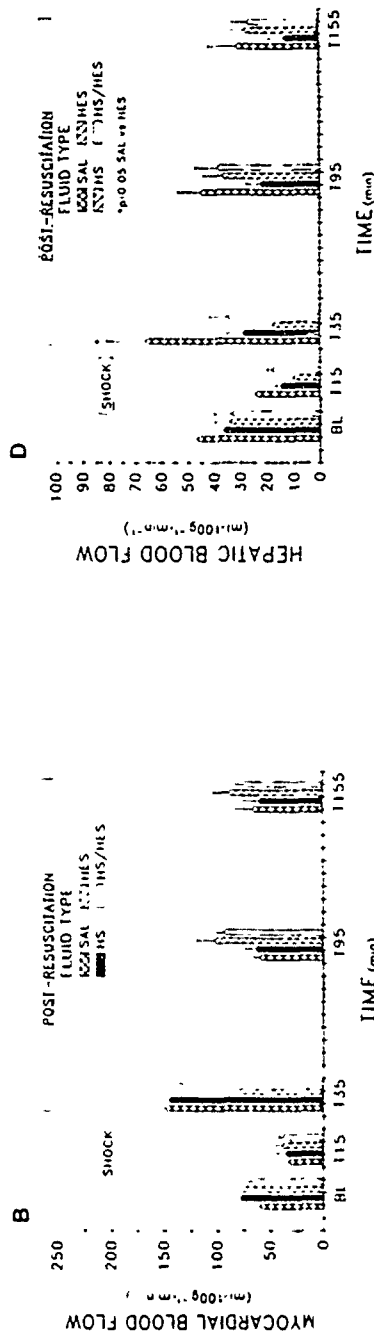
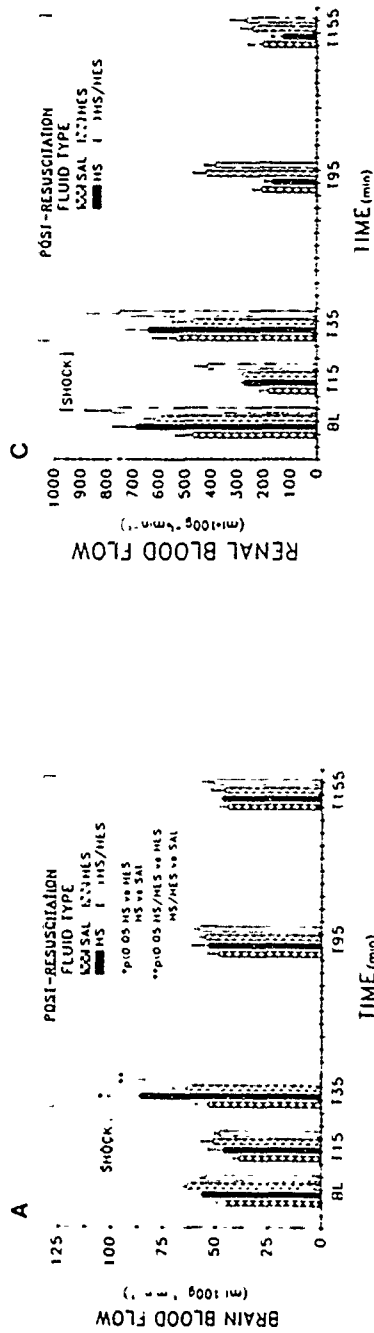
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CEREBRAL HEMODYNAMIC EFFECTS OF FLUID RESUSCITATION IN THE PRESENCE OF AN EXPERIMENTAL INTRACRANIAL MASS

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FLUID RESUSCITATION PROTOCOL FOLLOWING MEMBRANE SKULL
WITH AN EXPERIMENTAL INTRACRANIAL MASS.*

Whole Paper

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Abstract

We addressed the impact on intracranial pressure (ICP) of post-hemorrhage fluid resuscitation using a protocol in which additional fluid was infused to maintain a stable cardiac output after an initial bolus of fluid was infused. Anesthetized, mechanically ventilated, mongrel dogs ($n = 27$) underwent a 30-minute interval of hemorrhagic shock (mean arterial pressure = 55 mm Hg) during which inflation of a subdural balloon maintained ICP at 15 mm Hg. Following shock, animals were resuscitated with one of four randomly assigned fluids: 1) slightly hypotonic crystalloid ($\text{Na}^+ 125 \text{ mEq} \cdot \text{L}^{-1}$; designated Na-125); 2) hypertonic crystalloid ($\text{Na}^+ 250 \text{ mEq} \cdot \text{L}^{-1}$; designated Na-250); 3) slightly hypotonic crystalloid plus 10% pentastarch (Na-125P); or 4) hypertonic crystalloid plus 10% pentastarch (Na-250P). Supplemental fluid was administered as needed to maintain cardiac output comparable to baseline values. ICP increased progressively in all fluid groups during resuscitation. Cerebral blood flow, measured using the cerebral venous outflow method, increased immediately following resuscitation, then declined steadily over time in all groups. Fluids containing pentastarch maintained hemodynamic stability with minimal supplementation throughout most of the post-resuscitation period, compared to crystalloid alone, which required substantial additional volume. If decreased intracranial compliance and hemorrhage are combined, ongoing resuscitation is associated with significantly increased ICP and significantly decreased cerebral blood flow, independent of the tonicity and oncotic pressure of the infused fluid.

Key words: Shock, hemorrhagic
 Intracranial pressure
 Cerebral blood flow
 Intravenous fluids, colloid
 Intravenous fluids, crystalloid
 Intravenous fluids, hypertonic

Running head: Fluid resuscitation

Introduction

Hypotension is associated with increased mortality and also appears to worsen neurologic outcome in patients with acute head injury (Glasgow Scale ≤ 8).^{1,2} Yet effective treatment of hemorrhagic shock in patients with head injury represents a therapeutic problem. In experimental animals, hemorrhagic hypotension is associated with a decline in intracranial pressure (ICP);³⁻⁷ restoration of blood pressure increases ICP.³⁻⁷ If ICP increases sufficiently to reduce cerebral perfusion pressure, a decline in cerebral blood flow (CBF) will result. While systemic hemodynamic values can be restored comparably with appropriately administered crystalloid or colloid solutions, significant differences in post-resuscitation ICP may accompany different fluid resuscitation regimens. Slightly hypotonic crystalloid solutions (i.e., lactated Ringer's solution) increase ICP to a greater extent immediately following resuscitation than do hypertonic crystalloid³ or colloid.^{4,5,8}

While the changes in ICP following fluid resuscitation have been characterized, most studies have dealt only with the effects of a single bolus of resuscitation fluid.³⁻⁵ In contrast, clinical resuscitation consists of initial stabilization followed by supplemental fluid infusion based upon clinical assessment to more accurately duplicate clinical practice. The present study combines an intracranial mass with hemorrhagic shock to compare the cerebrovascular effects of ongoing resuscitation with either slightly hypotonic or hypertonic crystalloid, each with and without concentrated colloid, at a rate sufficient to maintain cardiac output at least equal to pre-shock levels.

Methods

Animals were handled according to guidelines established by the institution's Animal Care and Use Committee. Twenty-seven mongrel dogs (18-24 kg), randomized to one of four resuscitation groups (see below), were fasted overnight, anesthetized with intravenous thiopental sodium ($8.0 \text{ mg} \cdot \text{kg}^{-1}$), paralyzed with intravenous metubine iodide ($0.12 \text{ mg} \cdot \text{kg}^{-1}$) and pancuronium bromide ($0.03 \text{ mg} \cdot \text{kg}^{-1}$), and endotracheally intubated. Halothane 0.5% in nitrous oxide and oxygen (60:40) provided maintenance anesthesia. Animals were ventilated, using a Harvard Respiration Pump Model 607 (Harvard Apparatus Co., Inc., Millis, MA), at a tidal volume of $15 \text{ ml} \cdot \text{kg}^{-1}$ and a rate adjusted to maintain normocarbida. Additional metubine iodide and pancuronium bromide, given as needed, prevented respiratory movement.

Hemodynamic Measurements

Bilateral femoral arterial catheters were placed for continuous monitoring of systemic arterial pressure, and induction of rapid hemorrhage. A pulmonary artery catheter was placed percutaneously through the right external jugular vein for determination of cardiac output (CO) by thermodilution, and for measurement of central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP). Hemodynamic pressure measurements utilized a Grass 7SD polygraph (Grass Instrument Co., Quincy, MA) and Gould Statham P23 transducers (Gould, Inc., Oxnard, CA). Body temperature was monitored continuously by the thermistor on the tip of the pulmonary artery catheter and was maintained at 37°C with a heating pad applied to the trunk and extremities. CO was measured intermittently using an American Edwards 9520A CO computer

(American Edwards, Corp., Santa Ana, CA) and monitored continuously using a Noninvasive Continuous Cardiac Output Monitor (NCCOM-3, Biomed Medical Manufacturing, Ltd., Irvine, CA). All transducers were intermittently calibrated with the zero level established at the level of the left atrium except for ICP, which was zeroed at the level of the external auditory canal (7 cm above left atrial level).

After splenectomy, animals were turned to the prone "sphinx" position and the occipital musculature was dissected from the cranium. Following administration of heparin ($500 \text{ IU} \cdot \text{kg}^{-1} \text{ iv}$), the confluence of the sagittal and lateral sinuses was cannulated for measurement of CBF using the cerebral venous outflow technique developed by Rapela and Green.⁹ CBF in $\text{ml} \cdot \text{min}^{-1}$ was monitored continuously using a Square-Wave Electromagnetic Flowmeter (Carolina Medical Electronics, Inc., King, NC). Transient obstruction of the venous cannula confirmed bilateral lateral sinus occlusion. An 18-ga catheter in the cisterna magna provided continuous measurement of ICP. Through a one-cm twist-drill hole created in the right parietal skull, the dura was incised and the balloon tip of a 7-Fr Foley catheter was inserted subdurally for manipulation of ICP.

Collected data included: CBF, ICP, systolic and diastolic arterial pressures (SAP and DAP), pulmonary artery systolic and diastolic pressures (PAS and PAD), PAOP, temperature, arterial and cerebral venous pH, PCO_2 , PO_2 (IL 1306, Instrumentation Laboratory, Lexington, MA), oxygen saturation and hemoglobin (IL 282, Instrumentation Laboratory, Lexington, MA), serum osmolality (5500 Vapor Pressure Osmometer,

Wescor, Inc., Logan, UT), and colloid oncotic pressure (4100 Colloid Osmometer, Wescor, Inc.). From the collected data, the following calculations were made:

1. Mean arterial pressure (MAP) = $DAP + 1/3 (SAP - DAP)$
2. cerebral perfusion pressure (CPP) = $MAP - ICP$
3. oxygen content (CxO_2) = $PxO_2 \times 0.0031 + Hgb \times 1.39 \times \% SxO_2$

where x = arterial or venous.

After instrumentation, animals were stabilized for 30 minutes and baseline (BL) data were collected. Immediately after baseline measurements, ICP was increased to 15 mm Hg by balloon inflation (BI) with saline and was maintained at that level throughout the 30-minute hemorrhagic shock period. Animals were rapidly hemorrhaged via the left femoral artery to a MAP of 55 mm Hg (CPP = 40 mm Hg) and maintained at that level by further removal or reinfusion of shed blood. Systemic and cerebral hemodynamic data were obtained at the beginning (T0) and end (T30) of the 30-minute shock period. Resuscitation consisted of one of four randomly assigned fluids. The initial bolus of fluid was chosen to provide an equal sodium load in groups 1, 2, and 4. Groups 2, 3, and 4 received equal volumes for the initial bolus but the sodium and colloid loads differed. Group 1 (Na-125, n=6) received $40 \text{ ml} \cdot \text{kg}^{-1}$ of a solution containing $\text{Na}^+ 125 \text{ mEq} \cdot \text{L}^{-1}$, $\text{Cl}^- 75 \text{ mEq} \cdot \text{L}^{-1}$, and lactate $50 \text{ mEq} \cdot \text{L}^{-1}$; Group 2 (Na-250, n=7) received $20 \text{ ml} \cdot \text{kg}^{-1}$ of a solution containing $\text{Na}^+ 250 \text{ mEq} \cdot \text{L}^{-1}$, $\text{Cl}^- 150 \text{ mEq} \cdot \text{L}^{-1}$, and lactate $100 \text{ mEq} \cdot \text{L}^{-1}$; Group 3 (Na-125P; n=7) received $20 \text{ ml} \cdot \text{kg}^{-1}$ of a solution containing 10% pentastarch dissolved in a fluid with the same electrolyte concentrations as Group 1; and Group 4 (Na-250P, n=7) received $20 \text{ ml} \cdot \text{kg}^{-1}$ of a solution containing 10% pentastarch dissolved

in a fluid with the same electrolyte concentration as group 4. The subdural balloon was clamped at T30 as resuscitation was initiated; ICP was then allowed to vary spontaneously (i.e., the subdural balloon inflation volume was held constant). CO in each animal was monitored continuously using the NCCOM-3. If CO declined below baseline, the originally assigned fluid was infused at a rate of $1.0 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ until CO equalled baseline. Data were collected at baseline (BL), immediately following elevation of ICP to 15 mm Hg (balloon inflation; BI), at the beginning (T0) and end (T30) of the shock period, immediately following fluid resuscitation (T35), and thereafter at 30-minute intervals for two hours (T65, T95, T125, and T155).

Statistical Analysis

The Kruskal-Wallis test was used to confirm similarity among the four groups at baseline and during shock before randomization. A multivariate repeated measures analysis of variance (ANOVA) was performed to determine if interactions between group and time existed at subsequent post-resuscitation intervals.¹⁰ Interactions were analyzed further using Holm's sequentially rejective multiple test procedure using a significance level of 0.05.¹¹ To assess time and group differences when an interaction was not present, a multivariate repeated measures ANOVA and an analysis of covariance were performed on the dependent variables. When a statistically significant group effect was evident, Holm's sequentially rejective multiple test procedure was used to determine which groups differed.

Results

No significant differences were detected in body weights or volumes of shed blood among groups (Table 1). The Na-125 group required the most additional fluid after the initial bolus, averaging $68.7 \pm 14.9 \text{ ml} \cdot \text{kg}^{-1}$ (mean total fluid infused $1475 \pm 337 \text{ ml}$), with Na-250 requiring $45.6 \pm 6.2 \text{ ml} \cdot \text{kg}^{-1}$ (mean total fluid infused $865 \pm 126 \text{ ml}$). The animals that had received fluids containing 10% pentastarch required less additional volume, $8.3 \pm 2.1 \text{ ml} \cdot \text{kg}^{-1}$ for Na-125P ($p < 0.001$ vs. Na-125) and $11.6 \pm 3.4 \text{ ml} \cdot \text{kg}^{-1}$ for Na-250P ($p < 0.001$ vs. Na-250). The time at which supplemental fluid was first required also differed significantly ($p < 0.05$) among groups (Table 1). Serum osmolality was similar among groups at baseline (Table 2). There were no significant differences in osmolality throughout the post-resuscitation interval although osmolality was greatest in the Na-250 group. Colloid oncotic pressure (COP) was comparable at baseline and during shock among groups. Resuscitation with Na-125P and Na-250P resulted in significant increases in COP when compared to Na-125 and Na-250 (Na-125 vs. Na-125P; $p < 0.001$) (Na-250 vs. Na-250P; $p < 0.001$).

Hemodynamic Data

With the onset of hemorrhage, MAP decreased rapidly to 55 mm Hg where it was maintained for 30 minutes (Figure 1). In response to fluid resuscitation (T35), MAP increased similarly in all four groups and remained similar throughout the experimental period. Hemorrhagic shock decreased CO by approximately 50% in all groups (Figure 2). Following the initial fluid bolus, CO increased, exceeding baseline levels in all groups. After T35, CO was supported by supplemental fluid infusion to maintain CO

above baseline for the remainder of the experimental period. Systemic oxygen transport (DO_2) was comparable among groups (Table 2). After resuscitation, DO_2 remained at approximately 80% of baseline values, representing the combined effects of preserved CO and hemodilution.

Systemic Variables

PaCO_2 , PaO_2 , pH, body temperature, Hgb, and CaO_2 were similar among groups. All groups were normocarbic at all intervals. PaO_2 consistently exceeded 200 mm Hg; pH remained ≥ 7.30 in all groups at all intervals except for T35 in the Na-250 group (7.2). All animals remained normothermic throughout. Hemoglobin levels decreased insignificantly during shock in all groups (Table 3); there was a further, similar reduction during resuscitation in all groups. Hgb remained at T35 levels throughout the remainder of the experimental period with no differences detected among groups. Changes in arterial oxygen content (CaO_2) paralleled changes in hemoglobin (Table 3).

Cerebral Hemodynamics

Intracranial Pressure

Prior to balloon inflation, there were no differences in ICP among groups (Figure 3). ICP was maintained at 15 mm Hg in all groups during shock. Resuscitation (T35) increased ICP in all groups. Further increases in ICP occurred in all groups as supplemental fluid infusion continued. No differences were detected among groups at any post-resuscitation time interval.

Cerebral Perfusion Pressure

CPP (Figure 4) decreased with elevation of ICP and further decreased following induction of hemorrhage. Resuscitation (T35) increased CPP in all groups, although it was not restored to baseline by any of the fluid choices. No differences in CPP were detected among groups following resuscitation.

Cerebral Blood Flow

CBF was similar at baseline in all groups (Figure 5). Hemorrhage was associated with a marked reduction in CBF in all groups compared to baseline. Fluid resuscitation initially increased CBF in all groups. Statistical analysis failed to detect a difference among groups at any time period, although a difference approaching significance ($p = 0.08$) was found between Na-250 and Na-250P at T155. There were no differences detected between groups in other cerebral variables including cerebral oxygen transport (CO_2T), cerebral arteriovenous oxygen content difference (A-VDO_2) and the cerebral metabolic rate for oxygen consumption (CMRO_2) following resuscitation (Table 4).

Discussion

In dogs with intracranial hypertension, acute, bolus fluid resuscitation from hemorrhagic shock is associated with progressive intracranial hypertension. Supplemental fluid infusion, given as necessary to maintain CO, further exacerbates intracranial hypertension. This effect appears to be independent of the type of fluid infused within the range of sodium and colloid concentrations examined in this study. In contrast, Gunnar et al.^{7,12} and Ducey et al.,⁸ demonstrated that more highly hypertonic resuscitation solutions were associated with significantly lower ICP than were isotonic resuscitation solutions. The present data suggest that a sodium concentration of 250 mEq•L⁻¹ is insufficient to exert an important therapeutic effect on ICP.

The effects of fluid resuscitation on ICP requires consideration of several factors, including cerebral arterial and venous blood volume, brain tissue volume (i.e., water content), and cerebrospinal fluid volume. Although ICP during resuscitation was comparable in all groups, the four fluids may nevertheless have caused differential changes in the components of intracranial volume. Hypertonic salt solutions reduce brain water and therefore tend to reduce ICP, regardless of whether antecedent shock is present.^{3,6-8,12,13} Colloid solutions do not decrease brain water,¹⁴⁻¹⁷ although both isovolemic hemodilution¹⁸ and resuscitation with colloid have been associated with a lower ICP than resuscitation with conventional, slightly hypotonic, crystalloid solutions.^{4,5,8} Cerebral arterial flow tended to be best preserved in the group that received the hypertonic resuscitation fluid without colloid. Therefore, these data prompt the hypothesis that hypertonic resuscitation solutions may result in a primary decline in

cerebrovascular resistance. It is also noteworthy that the two groups that received colloid-containing fluids tended to have lower CBF. This observation also merits further study in light of the demonstration by Muizelaar and others that the cerebral vasculature responds poorly to increases in viscosity if autoregulation is impaired.¹⁹ Further studies are necessary to differentiate the effects of varying constituents of resuscitation fluid on the components that determine ICP.

The effects of our fluid resuscitation regimen on ICP are best contrasted with the studies by Gunnar and colleagues,^{6,7,17} who studied the effects on ICP of three complex fluid resuscitation regimens following 60 minutes of hemorrhagic shock produced by removing 40% of calculated blood volume. Resuscitation consisted of the return of one-half of the shed blood volume, accompanied by either 0.9% saline, 3.0% saline (513 mEq/L), or 10% dextran-40 in a volume equal to the amount of shed blood. 0.9% saline was then infused in a volume of 1500 mL over the subsequent 75 minutes.⁶ ICP was lowest in the animals that had received hypertonic saline prior to the normal saline infusion. ICP in the animals that had received 0.9% saline was similar to ICP in those that had received dextran-40. Although the maximum increase in ICP was similar in animals receiving 0.9% saline and those receiving dextran-40, the peak increase in ICP in the 0.9% saline animals occurred immediately following resuscitation and well before the peak increase in animals receiving 10% dextran-40. However, the greater mean pulmonary artery pressure and mean PAOP in the animals that received dextran-40 suggest relative hypervolemia in comparison to the other two groups. Gunnar and colleagues subsequently compared the effects of normal saline, 10% dextran-40, and

hypertonic (3.0%) saline in animals that had been subjected to hemorrhagic shock combined with epidural balloon inflation.⁷ ICP increased most dramatically in the normal saline and dextran-40 groups and increased little in the hypertonic saline group. Considered in relationship to the present study, these data necessitate greater definition of the effects of blood administration, sodium concentration, total osmolar load, and intravascular volume on ICP following resuscitation.

In relation to the present study, perhaps the most important observation of Gunnar and colleagues is that shock combined with inflation of an epidural balloon produces increased permeability of the blood-brain barrier to Evan's blue dye, an albumin-bound tracer.⁷ Further studies are required to determine the influence of intracranial mass lesions, increased ICP, and decreased cerebral perfusion pressure on blood brain barrier function. Gunnar and colleagues permitted ICP to decline during the shock interval. Therefore, cerebral perfusion pressure was substantially greater during shock in that study than in the present study, increasing from a low of approximately 40 mm Hg at the beginning of shock to approximately 65 mm Hg by the end of the shock interval. Consequently, it is possible that blood-brain barrier function was more severely damaged by cerebral hypoperfusion in the present study.

It is important to consider the comparability of this model to the clinical situation. Experimental studies that compare various fluid regimens for resuscitation from hemorrhagic shock must select one of a variety of endpoints in order to achieve comparability among groups. Perhaps the simplest alternative is simply to infuse a fixed volume of each of the test fluids as a bolus, after which the acute effects of the

treatments can be compared. However, the infusion of solutions containing colloid, such as those used in groups Na-125P and Na-250P, is associated with a more sustained increase in plasma volume than the increase produced by either an isotonic or a hypertonic solution.³⁻⁵ A second alternative is to infuse sufficient fluid to maintain a predetermined level of a physiologic endpoint such as blood pressure, ventricular filling pressures, or CO. Blood pressure, the endpoint used during routine clinical resuscitation, may remain misleadingly high despite progressively declining CO, as intravascular volume declines. Severely traumatized, hypovolemic patients may be monitored with a CVP catheter or a pulmonary artery catheter, either of which provides an estimate of filling pressure. However, CVP and PAOP are determined by complex interactions among blood volume, venous capacitance, and ventricular distensibility, contractility, and afterload.

Intermittent determinations of CO using thermodilution have been used as a physiologic endpoint for resuscitation of high-risk surgical patients.²⁰ Certain data suggest that this approach to hemodynamic management may improve survival and decrease morbidity, in comparison to conventional management using blood pressure or filling pressures to guide therapy.²⁰ Therefore, the present study utilized continuous CO to monitor resuscitation. Using that endpoint, we achieved comparable, stable levels of hemodilution and stable, similar levels of CO and systemic oxygen transport during the interval from T65 to T155.

In summary, in the presence of an intracranial mass lesion, resuscitation from hemorrhagic shock is associated with a progressive increase in ICP, regardless of the

tonicity or oncotic pressure of resuscitation fluid, if comparable levels of systemic hemodynamic stability are achieved. If these data can be confirmed in humans, monitoring of ICP or other variables related to the adequacy of cerebral circulation in the immediate post-resuscitation interval may exert a favorable effect on outcome following acute head injury in conjunction with multiple trauma. Mortality in head-injured patients correlates with the severity of intracranial hypertension. If ICP exceeds 20 mm Hg but can be reduced, the mortality rate approaches 45%; if ICP exceeds 20 mm Hg and cannot be reduced, the mortality rate is 95%.²¹ Because therapy with fluids of the tonicities and colloid concentrations utilized in this study was uniformly associated with intracranial hypertension and gradually declining CBF during resuscitation, other techniques of improving systemic perfusion require further investigation. Particular attention should be paid to the possibility that positive inotropic agents might improve cardiac output and systemic oxygen transport while exerting less deleterious effects on the cerebral circulation than does aggressive fluid resuscitation.

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Table 1. Characteristics of Hemorrhage and Resuscitation (means $\pm$ SEM)

Fluid Group	N	Body Weight (kg)	Blood Loss (ml•kg ⁻¹)	Bolus Volume (ml•kg ⁻¹)	Supplemental Volume (ml•kg ⁻¹)	Supplementation Required (Time)
Na-125	6	21.2 $\pm$ 0.9	20.5 $\pm$ 2.0	40	68.7 $\pm$ 14.9*	T95 $\pm$ 6.1**
Na-250	7	18.9 $\pm$ 0.4	25.9 $\pm$ 3.7	20	45.6 $\pm$ 6.2*	T101 $\pm$ 6.2**
Na-125P	7	21.1 $\pm$ 1.0	22.3 $\pm$ 3.9	20	8.3 $\pm$ 2.1	T135 $\pm$ 15.4
Na-250P	7	20.5 $\pm$ 0.6	19.3 $\pm$ 5.1	20	11.6 $\pm$ 3.4	T142 $\pm$ 10.4

* group difference in volume of supplemental fluid required to maintain CO. Groups Na-125 and Na-125P differed significantly ($p < 0.001$) as did Groups Na-250 and Na-250P ($p < 0.001$).

** group difference in time of onset of supplemental fluid infusion. Groups Na-125 and Na-125P differed significantly ($p < 0.05$) as did Groups Na-250 and Na-250P ($p < 0.05$).

Table 2. Serum Osmolality and Colloid Oncotic Pressure

Group	Serum Osmolality (mOsm•L ⁻¹)				Colloid Oncotic Pressure (% of Baseline)			
	Time Interval				Time Interval			
	BL	T30	T95	T155	BL	T30	T95	T155
Na-125	294±9	301±8	297±5	300±8	100±0.0	89±8	60±1*	56±1*
Na-125P	284±10	299±7	307±4	296±6	100±0.0	91±4	135±8	138±7
Na-250	284±7	302±9	334±6	347±14	100±0.0	90±3	69±3**	66±6**
Na-250P	285±7	296±16	313±7	319±8	100±0.0	92±5	117±8	122±7

p<0.001; *Na-125 vs Na-125P

p<0.001; **Na-250 vs Na-250P

Table 3. Major Systemic Variables (Means $\pm$ SEH)

	Group	BL	BL	IO	T30	T35	T65	T95	T125	T155
Hgb (g $\cdot$ dl $^{-1}$)	Na-125	12.3 $\pm$ 0.8	12.3 $\pm$ 0.8	11.1 $\pm$ 0.8	10.0 $\pm$ 0.8	8.1 $\pm$ 0.6	8.9 $\pm$ 0.7	8.6 $\pm$ 0.4	8.3 $\pm$ 0.3	8.6 $\pm$ 0.5
	Na-125P	11.5 $\pm$ 1.1	11.4 $\pm$ 1.1	10.3 $\pm$ 1.0	10.7 $\pm$ 1.0	7.9 $\pm$ 0.7	8.1 $\pm$ 0.6	8.1 $\pm$ 0.7	8.3 $\pm$ 0.8	8.8 $\pm$ 0.7
	Na-250	11.6 $\pm$ 0.6	11.6 $\pm$ 0.5	10.3 $\pm$ 0.5	10.5 $\pm$ 0.6	8.1 $\pm$ 0.4	8.9 $\pm$ 0.4	8.3 $\pm$ 0.6	8.1 $\pm$ 0.6	8.2 $\pm$ 0.6
	Na-250P	11.4 $\pm$ 1.0	11.5 $\pm$ 1.1	10.1 $\pm$ 1.0	10.4 $\pm$ 1.1	7.3 $\pm$ 0.9	7.8 $\pm$ 0.9	7.8 $\pm$ 1.0	7.6 $\pm$ 0.9	8.1 $\pm$ 1.0
CaO $_2$ (ml $\cdot$ 100ml $^{-1}$)	Na-125	17.4 $\pm$ 1.1	17.2 $\pm$ 1.2	15.6 $\pm$ 1.2	15.2 $\pm$ 1.2	11.6 $\pm$ 1.0	12.7 $\pm$ 1.0	10.3 $\pm$ 0.7	11.8 $\pm$ 0.5	12.2 $\pm$ 0.8
	Na-125P	16.2 $\pm$ 1.5	16.1 $\pm$ 1.4	14.6 $\pm$ 1.3	15.0 $\pm$ 1.3	11.4 $\pm$ 0.9	11.6 $\pm$ 0.8	11.6 $\pm$ 1.0	11.9 $\pm$ 1.1	12.6 $\pm$ 1.0
	Na-250	16.3 $\pm$ 0.8	16.3 $\pm$ 0.6	14.1 $\pm$ 0.8	14.7 $\pm$ 0.8	11.7 $\pm$ 0.6	12.6 $\pm$ 0.5	11.9 $\pm$ 0.8	11.7 $\pm$ 0.8	11.8 $\pm$ 0.9
	Na-250P	15.9 $\pm$ 1.4	16.2 $\pm$ 1.4	14.3 $\pm$ 1.3	14.7 $\pm$ 1.5	10.7 $\pm$ 1.2	11.2 $\pm$ 1.2	11.3 $\pm$ 1.3	10.9 $\pm$ 1.3	11.6 $\pm$ 1.3
DO $_2$ (mlO $_2$ $\cdot$ min $^{-1}$)	Na-125	47.6 $\pm$ 5	43.7 $\pm$ 4	20.8 $\pm$ 3	22.6 $\pm$ 3	46.3 $\pm$ 4	40.9 $\pm$ 4	40.4 $\pm$ 5	39.7 $\pm$ 4	43.6 $\pm$ 4
	Na-125P	50.2 $\pm$ 9	49.6 $\pm$ 8	21.8 $\pm$ 4	26.5 $\pm$ 5	50.6 $\pm$ 8	44.9 $\pm$ 6	43.6 $\pm$ 6	40.9 $\pm$ 7	41.3 $\pm$ 6
	Na-250	47.7 $\pm$ 3	44.3 $\pm$ 3	18.8 $\pm$ 2	22.2 $\pm$ 4	42.9 $\pm$ 4	34.7 $\pm$ 5	34.3 $\pm$ 3	39.7 $\pm$ 3	40.0 $\pm$ 2
	Na-250P	42.2 $\pm$ 4	41.7 $\pm$ 5	19.1 $\pm$ 3	25.3 $\pm$ 5	52.0 $\pm$ 9	40.0 $\pm$ 8	34.6 $\pm$ 5	35.4 $\pm$ 5	40.2 $\pm$ 6

Hgb = hemoglobin; CaO $_2$ = arterial oxygen content; DO $_2$ = systemic oxygen transport

Table 4. Major Cerebral Variables (Means $\pm$ SEM)

Group	BL	BI	TO	T30	T35	T65	T95	T125	T155
CO_2T ($\text{ml}\cdot\text{min}^{-1}$)	Na-125	4.7 $\pm$ 0.6	5.3 $\pm$ 0.6	2.2 $\pm$ 0.4	1.9 $\pm$ 0.3	3.2 $\pm$ 0.6	2.7 $\pm$ 0.3	2.3 $\pm$ 0.3	2.3 $\pm$ 0.5
	Na-125F	4.4 $\pm$ 0.6	4.8 $\pm$ 0.7	2.5 $\pm$ 0.4	2.0 $\pm$ 0.3	2.7 $\pm$ 0.6	2.3 $\pm$ 0.6	2.0 $\pm$ 0.4	2.1 $\pm$ 0.5
	Na-250	6.2 $\pm$ 0.6	6.3 $\pm$ 0.6	2.5 $\pm$ 0.2	1.8 $\pm$ 0.2	3.4 $\pm$ 0.4	3.2 $\pm$ 0.4	3.1 $\pm$ 0.4	3.2 $\pm$ 0.5
	Na-250P	4.3 $\pm$ 0.3	4.8 $\pm$ 0.7	1.8 $\pm$ 0.3	1.5 $\pm$ 0.2	2.3 $\pm$ 0.2	1.7 $\pm$ 0.3	1.3 $\pm$ 0.2	1.0 $\pm$ 0.2
	Na-125	6.8 $\pm$ 0.6	6.1 $\pm$ 0.7	9.5 $\pm$ 0.5	8.7 $\pm$ 0.5	4.8 $\pm$ 0.5	5.9 $\pm$ 1.1	5.0 $\pm$ 0.7	5.3 $\pm$ 0.8
Cerebral A-VO ₂ ($\text{ml}\cdot 100\text{ml}^{-1}$)	Na-125P	6.0 $\pm$ 0.4	6.5 $\pm$ 0.7	9.0 $\pm$ 1.0	8.3 $\pm$ 0.8	5.1 $\pm$ 0.8	5.7 $\pm$ 0.5	5.7 $\pm$ 0.6	6.6 $\pm$ 0.4
	Na-250	4.1 $\pm$ 1.0	5.1 $\pm$ 0.4	7.0 $\pm$ 1.2	8.4 $\pm$ 0.8	4.6 $\pm$ 0.4	6.1 $\pm$ 0.5	5.6 $\pm$ 0.4	5.8 $\pm$ 0.4
	Na-250P	6.2 $\pm$ 0.8	5.9 $\pm$ 0.7	8.2 $\pm$ 0.9	8.3 $\pm$ 0.9	5.0 $\pm$ 0.5	5.3 $\pm$ 1.0	5.2 $\pm$ 1.1	5.5 $\pm$ 1.0
	Na-125	1.8 $\pm$ 0.2	1.9 $\pm$ 0.3	1.3 $\pm$ 0.3	1.1 $\pm$ 0.2	1.3 $\pm$ 0.1	1.1 $\pm$ 0.1	0.9 $\pm$ 0.1	0.9 $\pm$ 0.2
	Na-125P	1.6 $\pm$ 0.2	1.9 $\pm$ 0.1	0.5 $\pm$ 0.2	1.1 $\pm$ 0.2	1.0 $\pm$ 0.2	1.1 $\pm$ 0.3	0.9 $\pm$ 0.2	1.2 $\pm$ 0.3
CMRO ₂ ($\text{ml}\cdot\text{min}^{-1}$)	Na-250	1.5 $\pm$ 0.3	1.9 $\pm$ 0.1	1.1 $\pm$ 0.2	1.0 $\pm$ 0.1	1.3 $\pm$ 0.1	1.5 $\pm$ 0.1	1.5 $\pm$ 0.2	1.6 $\pm$ 0.2
	Na-250P	1.6 $\pm$ 0.2	1.7 $\pm$ 0.2	1.0 $\pm$ 0.2	0.8 $\pm$ 0.1	1.1 $\pm$ 0.1	0.9 $\pm$ 0.2	0.7 $\pm$ 0.9	0.5 $\pm$ 0.1

CO_2T = cerebral oxygen transport; cerebral A-VO₂ = cerebral arteriovenous oxygen content difference; CMRO₂ = cerebral oxygen consumption

Legends

- Figure 1. Changes in mean arterial pressure (MAP) following resuscitation from hemorrhage with hypotonic lactated saline (Na-125), hypertonic lactated saline (Na-250), hypotonic lactated saline with 10% pentastarch (Na-125P), or hypertonic lactated saline with pentastarch (Na-250P).
- Figure 2. Changes in cardiac output (CO) following resuscitation from hemorrhage with hypotonic lactated saline (Na-125), hypertonic lactated saline (Na-250), hypotonic lactated saline with 10% pentastarch (Na-125P), or hypertonic lactated saline with pentastarch (Na-250P).
- Figure 3. Changes in intracranial pressure following resuscitation from hemorrhage with hypotonic lactated saline (Na-125), hypertonic lactated saline (Na-250), hypotonic lactated saline with 10% pentastarch (Na-125P), or hypertonic lactated saline with pentastarch (Na-250P).
- Figure 4. Changes in cerebral perfusion pressure (CPP) following resuscitation from hemorrhage with hypotonic lactated saline (Na-125), hypertonic lactated saline (Na-250), hypotonic lactated saline with 10% pentastarch (Na-125P), or hypertonic lactated saline with pentastarch (Na-250P).
- Figure 5. Changes in total brain blood flow (BBF) following resuscitation from hemorrhage with hypotonic lactated saline (Na-125), hypertonic lactated saline (Na-250), hypotonic lactated saline with 10% pentastarch (Na-125P), or hypertonic lactated saline with pentastarch (Na-250P).

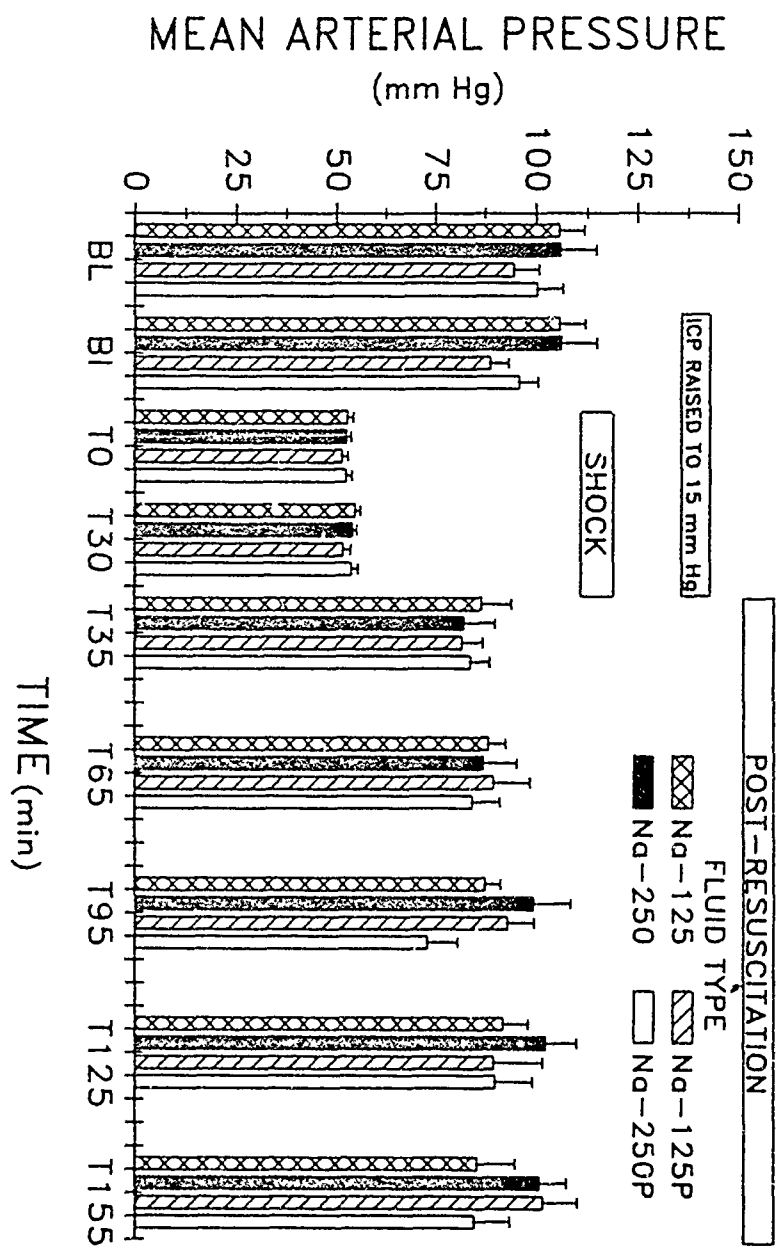
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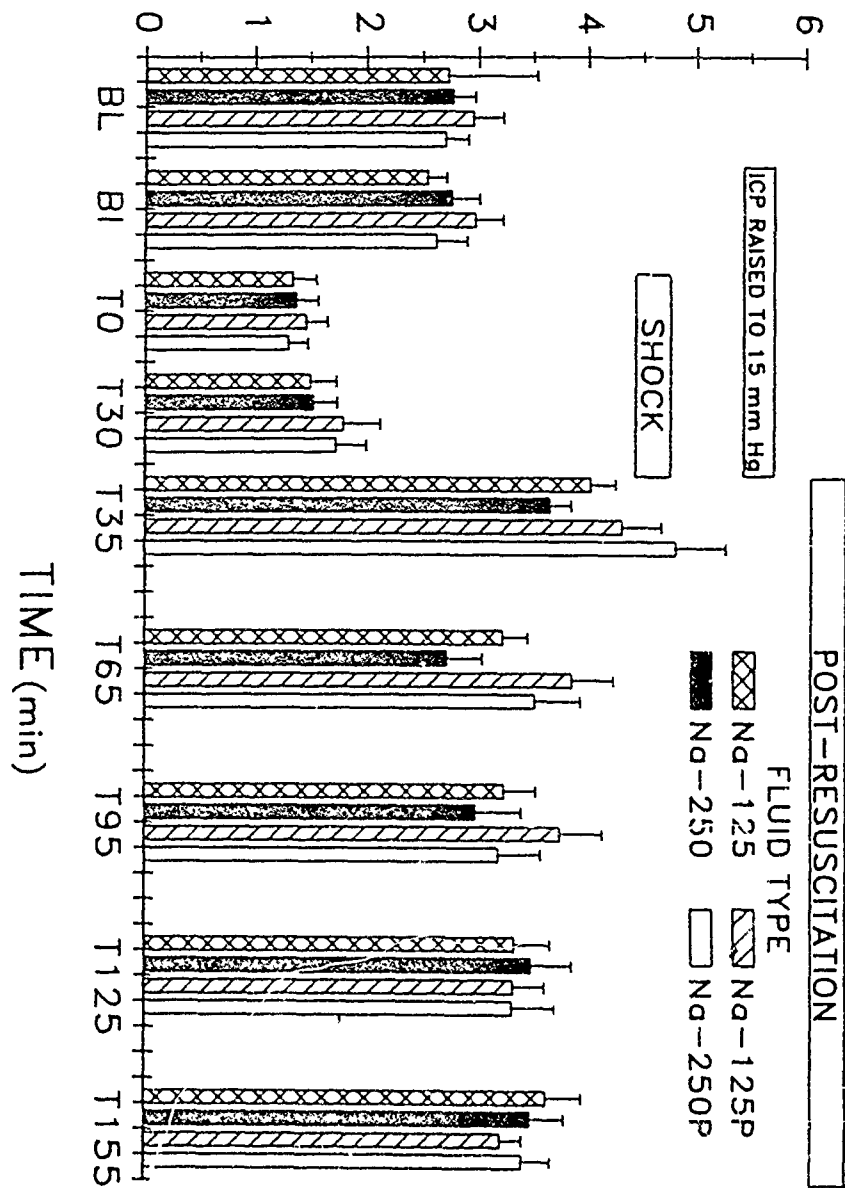
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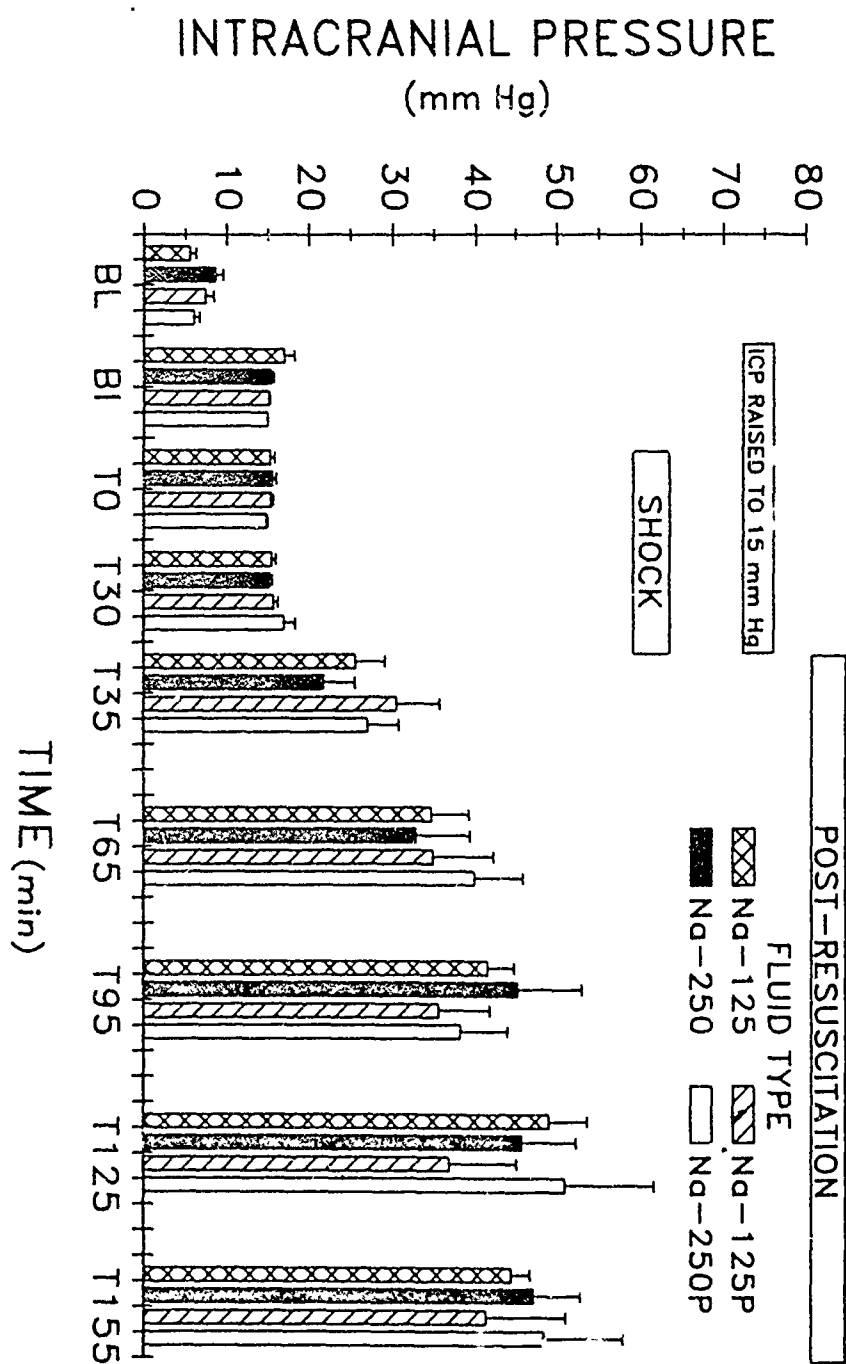
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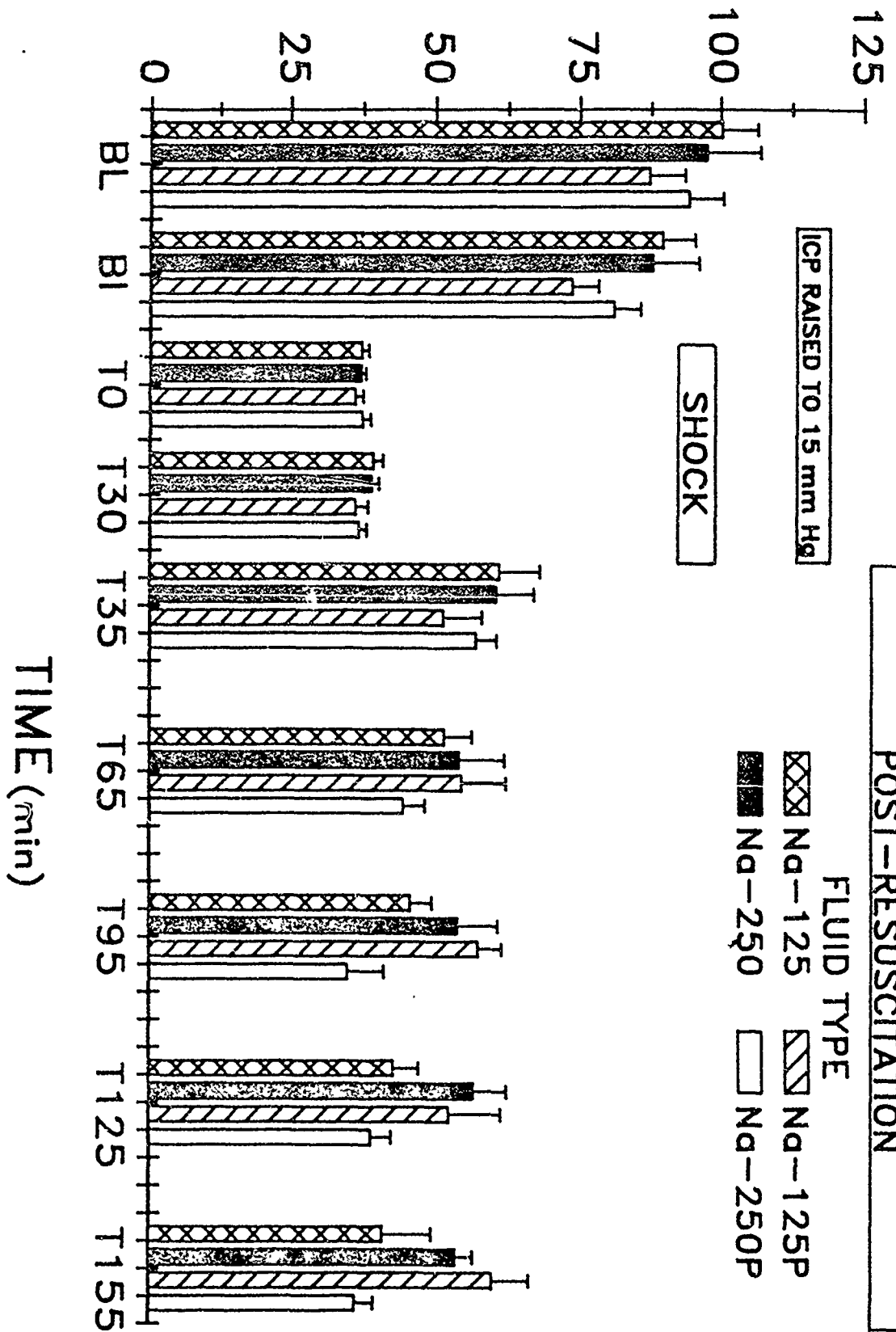


CARDIAC OUTPUT (L · min⁻¹)

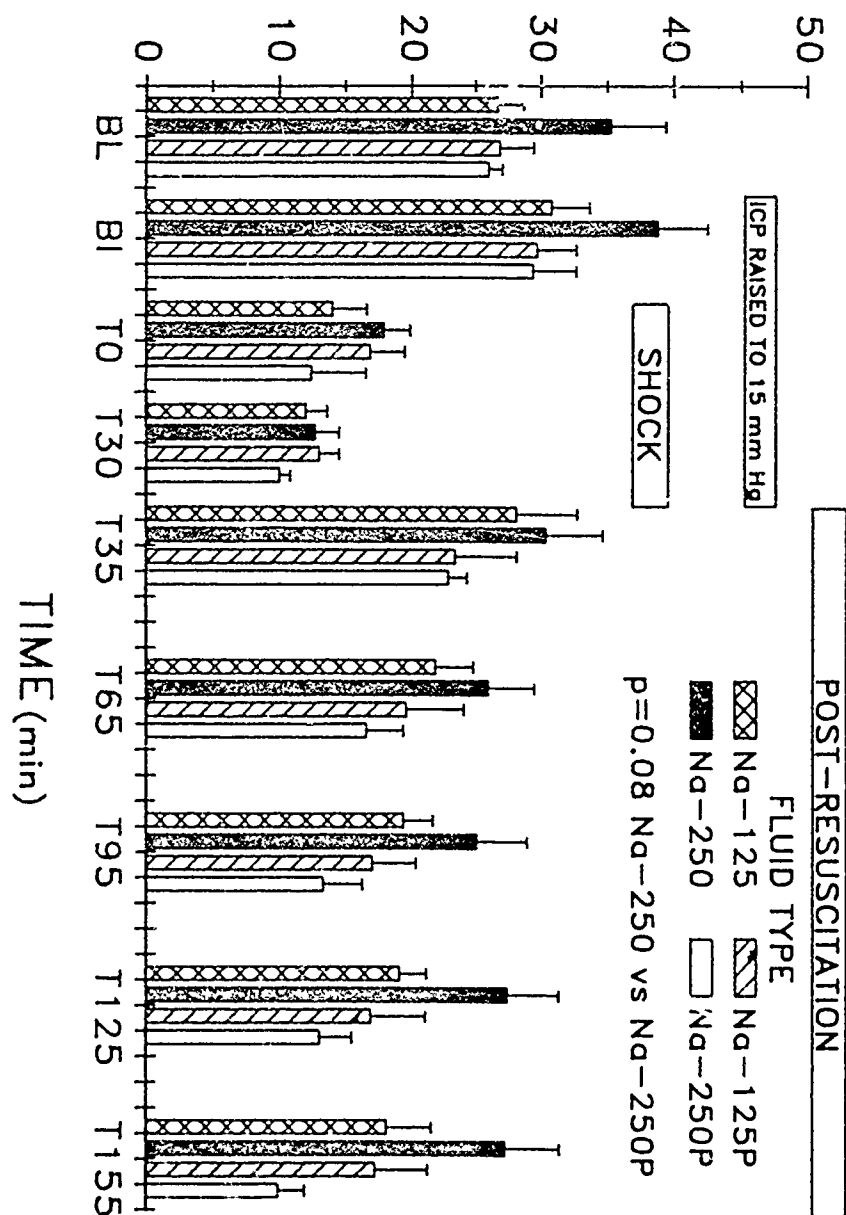




CEREBRAL PERFUSION PRESSURE (mm Hg)



BRAIN BLOOD FLOW (ml · min⁻¹)



RESUSCITATION FROM HEMORRHAGIC SHOCK WITH SMALL
VOLUMES OF HYPERTONIC/HYPERONCOTIC SOLUTIONS IN
THE PRESENCE OF A SUBDURAL MASS

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ABSTRACT

We compared canine cerebrovascular and systemic hemodynamics following fluid resuscitation with small, equal volumes of 7.2% saline, 20% hydroxyethyl starch, or a combination of the two in a model of intracranial hypertension (produced by inflation of a subdural balloon) and hemorrhagic shock. Twenty-one anesthetized, intubated mongrel dogs were ventilated with 0.5% halothane in nitrous oxide and oxygen (60:40) to maintain normocarbica. While intracranial pressure (ICP) was maintained at 20 mm Hg by inflation of a right-hemispheric, subdural balloon, rapid hemorrhage reduced mean arterial pressure to 55 mm Hg and maintained it at that level for 30 minutes. Subsequently, over five minutes, one of three randomly assigned resuscitation fluids was infused in a total volume of $6.0 \text{ ml} \cdot \text{kg}^{-1}$: (1) 7.2% hypertonic saline (HS; $1232 \text{ mEq} \cdot \text{L}^{-1}$ sodium); (2) 20% hydroxyethyl starch (HES) dissolved in 0.8% saline; or (3) 20% HES dissolved in 7.2% HS (HS/HES). As fluid infusion began, ICP was permitted to vary without further manipulation. Data were collected at baseline (BL), after balloon inflation (BI), at the beginning of the shock interval (T0), at the end of the shock interval (T30), immediately following fluid infusion (T35), and at thirty-minute intervals thereafter for two hours (T65, T95, T125, T155). ICP and cerebral blood flow (cerebral venous outflow technique) were compared among groups using repeated measures ANOVA. Following rapid fluid infusion, mean arterial pressure was better maintained from T65 to T125 in the two groups that received colloid (HES and HS/HES) than in the HS group ($p < 0.05$ at T95). At T35, ICP in the HES and HS/HES groups exceeded that in the HS group ($p < 0.001$), which remained at shock levels. ICP increased further in the HS/HES group, exceeding that in both the HS and HES groups at T95 and T125 ($p < 0.05$). ICP in

the HS group increased from T95 onward, equalling ICP in the HES group but remaining lower than in the HS/HES group. Cerebral blood flow decreased in all groups during shock, partially recovered at T35, then declined steadily afterwards without statistical difference among groups. Following a severe reduction in cerebral perfusion pressure, resuscitation with hypertonic solutions fails to produce a sustained lower level of ICP than colloid resuscitation.

Key words: Hemorrhagic shock
Intracranial pressure
Subdural mass
Hypertonic saline
Hydroxyethyl starch
Resuscitation

INTRODUCTION

Traumatic hypotension is associated with increased mortality in patients who have suffered closed head injury.¹³ In patients with a Glasgow Coma Score ≤ 8 on admission to the hospital, a systolic blood pressure less than 90 mm Hg is associated with a risk of poor neurologic outcome that is 13 times greater than the risk in those patients in whom systolic arterial pressure exceeds 90 mm Hg.³ Although inadequate cerebral perfusion during shock or resuscitation could contribute to the increased mortality and morbidity, cerebral circulatory changes during acute hemorrhage and resuscitation have not been described in man. Animal models must provide basic information about changes in intracranial pressure (ICP), cerebral blood flow (CBF), and cerebral metabolism during shock and resuscitation.

Hemorrhagic shock reduces ICP in animals without intracranial pathology²¹ and reduces ICP to an even greater extent if an intracranial mass lesion exists.^{6,19} Subsequent restoration of blood pressure produces a rapid increase in ICP, the magnitude of increase depending upon the type of resuscitation fluid used.^{6,19} Small volumes ($4.0\text{--}6.0\text{ ml}\cdot\text{kg}^{-1}$) of hypertonic resuscitation solutions produce a minimal increase in ICP in comparison to the large increase associated with conventional crystalloid solutions,^{5,20,21} yet produce substantial improvements in blood pressure, cardiac output, and survival after otherwise lethal hemorrhage.^{5,15,23,28,29} Hypertonic solutions are associated with lower ICP even when employed for resuscitation in a volume sufficient to produce hyperdynamic cardiac output values.⁶⁻⁸

Unfortunately, hypertonic solutions only transiently improve systemic hemodynamic values.²¹ Several investigators have attempted to increase the duration of these effects by combining a synthetic colloid with hypertonic saline.^{12,16,17,24,30}

Such solutions retain the greatest advantage of hypertonic solutions (i.e., efficacy when infused in small volumes), an asset that is undergoing investigation as a tool for the immediate stabilization of trauma victims.¹⁷

From the perspective of cerebral hemodynamics, a combination of hypertonic crystalloid and colloid could be advantageous. Colloid-containing resuscitation solutions also appear to be associated with a smaller rise in ICP than isotonic or slightly hypotonic crystalloid solutions,^{5,18,19} although some experimental data suggest that colloid solutions are equivalent to 0.9% saline in their effects on ICP.⁶⁻⁸ However, CBF may not be improved despite lower post-resuscitation ICP.^{19,21}

Our model combined decreased intracranial compliance and hemorrhagic shock to compare the cerebrovascular and systemic hemodynamic effects of resuscitation with small, equal volumes of 7.2% saline, 20% hydroxyethyl starch, or a combination of the two.

METHODS

Twenty-one mongrel dogs weighing 18-24 kg were handled according to guidelines established by our institution's Animal Care and Use Committee. Dogs are fasted overnight, anesthetized with intravenous thiopental sodium ($8.0 \text{ mg} \cdot \text{kg}^{-1}$), paralyzed with intravenous vecuronium ($0.2 \text{ mg} \cdot \text{kg}^{-1}$), endotracheally intubated, and maintained under anesthesia with halothane 0.5% in nitrous oxide and oxygen (60:40). Animals were mechanically ventilated at a rate and tidal volume ($15 \text{ ml} \cdot \text{kg}^{-1}$) necessary to maintain normocarbida.

Two femoral arterial catheters were placed for monitoring of arterial blood pressure and for rapid hemorrhage. A flow-directed, pulmonary artery catheter was placed percutaneously via the right external jugular vein. Systemic and pulmonary pressures were recorded continuously on a Grass model 79D polygraph (Grass Instrument Co., Quincy, Mass.) with saline-filled Gould-Statham P23 transducers (Gould, Inc., Oxnard, Ca.). Pulmonary artery occlusion (PAOP) was recorded intermittently. Cardiac output (CO) was recorded intermittently using an American Edwards Sat-1 CO computer (American Edwards, Corp., Santa Ana, Ca.). All transducers were intermittently calibrated with the zero level established at the level of the left atrium. Blood temperature was monitored by a thermistor on the tip of the pulmonary artery catheter and maintained using a heating pad on the trunk and extremities.

Following splenectomy, animals were turned to the prone "sphinx" position, and the temporalis and occipital musculature dissected from the skull. After heparinization ($500 \text{ IU} \cdot \text{kg}^{-1}$), the confluence of the sagittal and lateral sinuses was cannulated. Cerebral blood flow (CBF) was measured in $\text{ml} \cdot \text{min}^{-1}$ using timed

samples of cerebral venous outflow, a technique originally described by Rapela and Green.²² An 18-ga catheter inserted into the cisterna magna, zeroed to the level of the external auditory canal (7 cm above the left atrium), provided continuous ICP monitoring. The dura was incised through a right temporoparietal burr hole and the balloon tip of a 7-Fr Foley catheter was inserted subdurally for manipulation of ICP. Animals were subjected to no further manipulation during the subsequent 30 minutes.

Baseline (BL) measurements included: CBF, ICP, systolic and diastolic arterial pressure (SAP and DAP), systolic and diastolic pulmonary artery pressure (PAS and PAD), PAOP, CO, and serum osmolality (5500 Vapor Pressure Osmometer, Wescor, Inc., Logan, Utah). Arterial and cerebral venous pH, PCO_2 , and PO_2 were measured with an IL 1306 blood gas analyzer and arterial and cerebral oxygen saturation and hemoglobin (Hgb) were analyzed in an Il 282 CO-Oximeter (Instrumentation Laboratory, Lexington, Mass.). From the collected data we calculated mean arterial pressure ($MAP = DAP + 1/3 (SAP - DAP)$), cerebral perfusion pressure ($CPP = MAP - ICP$), cerebral arteriovenous oxygen content difference (cerebral A-VDO₂), and estimated cerebral oxygen consumption (CMRO₂) in $ml \cdot min^{-1}$ as $CBF \times$ the cerebral A-VDO₂. Cerebral oxygen transport (CO₂T) in $ml \cdot min^{-1}$ was calculated as $CBF \times CaO_2$.

Immediately following baseline (BL) measurements, ICP was increased to 20 mm Hg by inflation of the subdural balloon with saline and was maintained at that level throughout shock. Following balloon inflation (BI), a second data set was obtained. Arterial blood withdrawal then rapidly reduced MAP to 55 mm Hg and maintained it at that level for 30 minutes. Data were recorded at the beginning (T0) and end (T30) of the 30-minute shock interval. Animals were then randomly assigned

to receive one of three resuscitation fluids over a five-minute interval in a volume ($6.0 \text{ ml} \cdot \text{kg}^{-1}$) equal to only a fraction of the shed blood volume. Group HS (hypertonic fluid alone) received 7.2% NaCl ($1232 \text{ mEq} \cdot \text{L}^{-1} \text{ Na}^+$), group HES (colloid alone) received 20% hydroxyethyl starch dissolved in 0.8% saline ($137 \text{ mEq} \cdot \text{L}^{-1} \text{ Na}^+$), and group HS/HES received 20% hydroxyethyl starch dissolved in 7.2% saline. As resuscitation began, ICP was allowed to vary independently. Data were collected immediately following fluid infusion (T35) and at thirty minute intervals thereafter for two hours, designated as T65, T95, T125, and T155. Figure 1 summarizes the experimental preparation.

Statistical Analysis

The Kruskal-Wallis test was employed to detect differences between the three fluid groups at BL and BI. A multivariate repeated measures analysis of variance (ANOVA) was performed to determine if interactions between groups and time existed.⁴ Interactions were analyzed further with the Holm's sequentially rejective multiple test procedure using a significant level of 0.05.⁹ To assess time or group differences when an interaction was not present, a multivariate repeated measures ANOVA and an analysis of covariance were performed on the dependent variables.

RESULTS

Mean body weights and volumes of shed blood during hemorrhage for Groups HS/HES, HS, and HES are listed in Table 1. Body weight and shed blood volume were comparable among groups.

Systemic Data

Mean Arterial Pressure

All groups exhibited comparable MAP at BL, BI, T0, and T30 (Figure 2). In response to fluid resuscitation (T35), MAP increased similarly in all three groups. At T95, MAP in the HS group was significantly lower than in the two colloid groups ($p < 0.05$). At no time did any of the three resuscitation fluids restore MAP to baseline.

Cardiac Output

CO declined during hemorrhage to approximately 50% of baseline (Figure 3). CO increased following resuscitation in all groups, returning to baseline in HES and somewhat exceeding baseline in HS and HS/HES ($p = \text{NS}$ among groups).

Other Systemic Variables

PaCO_2 , hemoglobin, PaO_2 , pH, blood temperature, and PAOP were similar among groups at all time intervals (Table 2). Increases in serum osmolality were greatest in the HS group, intermediate in the HS/HES group and lowest in the HES group. (Table 3).

Cerebral Hemodynamic Data

Intracranial Pressure

ICP (Fig. 4) was similar before balloon inflation in the three groups and was maintained at 20 mm Hg throughout the shock interval. Resuscitation resulted in initial increases in ICP in the HES and HS/HES groups compared to the HS group which remained at shock levels ($p < .001$ HS/HES vs HS and HES vs HS). By T65, ICP had increased further in both the HES and HS/HES groups, but remained at 20 ± 3 mm Hg in the HS group ($p < 0.05$ HS/HES vs HS and HES vs HS). After T65, ICP remained stable in the HES group but increased further in both groups that had received hypertonic solutions. At T95 and T125, ICP in the HS/HES group significantly exceeded ICP in the other two groups ($p < 0.05$). Resuscitation increased ICP significantly in all groups over the duration of the post-resuscitation interval ($p < 0.0001$, T35 vs T155).

Cerebral Perfusion Pressure

Cerebral perfusion pressure (Fig. 5) followed the same general pattern as MAP, although it tended to be highest in the HES group from T95 onward.

Cerebral Blood Flow

During shock, CBF declined significantly in each group compared to baseline CBF (Fig. 6) ($p < 0.05$). Resuscitation (T35) was associated with an increase in CBF in both the HS and HS/HES groups to near baseline, in contrast to HES which increased only slightly immediately following resuscitation. Analysis of covariance detected a significant difference in CBF between the HS, HS/HES, and HES groups

at T35 ($p = 0.025$ HS vs HES and HS/HES vs HES). Following T35, CBF declined in the HS and HS/HES groups, a trend that continued until the end of the experimental period.

Table 4 lists interval changes in cerebral A-VDO₂, CMRO₂, and CO₂T. Note that the units for the latter two measurements are ml·min⁻¹ to correspond to the units of CBF measurement.

DISCUSSION

This study confirms previous reports^{15,23,28,29} that small volumes of hypertonic saline increase MAP and CO following severe hemorrhage. Similar small volumes of a combination of hypertonic saline and highly concentrated hydroxyethyl starch produce acute systemic hemodynamic effects comparable to those produced by HS. These data are comparable to those that demonstrate the similarity of the acute hemodynamic effects of hypertonic saline alone and hypertonic saline combined with 6.0% dextran,^{12,16,24,30} although the present study combined a more concentrated mixture of colloid with hypertonic saline. In addition, they also demonstrate that equal small volumes of a highly concentrated solution of hydroxyethyl starch in 0.8% saline restore MAP and CO in a comparable fashion. Therefore, from the perspective of acute restoration of overall systemic perfusion, small volumes of any of the three solutions tested are equally effective.

These data further clarify the cerebral physiologic effects of hypertonic and hyperoncotic resuscitation solutions. Isovolemic hemodilution (without shock) with hypertonic lactated saline ($252 \text{ mEq} \cdot \text{L}^{-1} \text{ Na}^{+}$) decreases ICP and brain water in comparison to 0.9% saline.²⁵ Because the normal blood brain barrier is poorly permeable to sodium, changes in serum osmolality cause rapid changes in ICP and in brain water. Zornow and colleagues used plasmapheresis to acutely reduce serum osmolality and oncotic pressure in rabbits and demonstrated that small decreases in serum osmolality increased ICP and brain water, whereas decreases in oncotic pressure slightly increased ICP without increasing brain water.³³ Changes in oncotic pressure exert little effect on ICP and brain water, even in animals with experimental brain injury. Isovolemic hemodilution with lactated Ringer's solution, a slightly

hypotonic solution, increases ICP and brain water in comparison to 6.0% hydroxyethyl starch.²⁷ Following focal, cortical, cryogenic brain injury in rabbits, 45 minutes of isovolemic hemodilution with 0.9% saline, 6.0% hydroxyethyl starch, or 5.0% albumin produced no differences among groups in ICP or brain water.³²

However, hemodilution following hemorrhagic shock may exert different effects on ICP than isovolemic hemodilution in the absence of shock. Hypertonic saline also has been associated with a lower ICP than isotonic or slightly hypotonic salt solutions.^{5-8,20,21} Prough and colleagues compared a single bolus of 7.5% hypertonic saline (6.0 ml·kg⁻¹) to lactated Ringer's solution (60 ml·kg⁻¹) following a 30-minute shock interval produced by blood loss of approximately 40 ml·kg⁻¹ in mongrel dogs.²¹ Hypertonic saline was associated with a significantly lower post-resuscitation ICP but a similar, reduced level of CBF and cerebral oxygen transport. Gunnar and colleagues compared 3.0% saline, 0.9% saline, and a 10% solution of low molecular weight dextran. Following a one-hour interval of hemorrhagic shock, the investigators returned one-half of the shed blood, infused one of the test fluids in a volume equal to shed blood, then infused 1500 ml of 0.9% saline over the ensuing 1.25 hours.⁸ ICP in the group that had received 10% dextran remained similar to ICP in the group that received 0.9% saline, both of which consistently exceeded ICP in the group that had received 3.0% saline. However, the conclusion that colloid and isotonic crystalloid resuscitation produces comparable changes in ICP is complicated by the higher central venous pressure (CVP) in the group that had received low molecular weight dextran. Increases in CVP increase ICP, presumably by increasing cerebral venous blood volume. Poole and colleagues resuscitated animals both with and without intracranial mass lesions from hemorrhagic shock using a single intravenous

bolus of either 6.0% hydroxyethyl starch or lactated Ringer's solution.^{18,19} Although the latter two studies showed a lower ICP in the group that had received colloid, the difference may have been associated with the difference in resuscitation volumes rather than in changes in brain water, which were not measured. Gunnar and colleagues subsequently reported preliminary data suggesting that a resuscitation regimen equivalent to the one they had previously reported produced no differences in CBF.⁷

The present study was designed to duplicate the circumstances of acute, pre-hospital resuscitation, in which maximal hemodynamic benefit must be achieved rapidly, ideally with the infusion of a small volume of fluid. The presence of an intracranial mass lesion, limiting intracranial compliance, necessitates consideration of the effects of resuscitation on ICP. Under such circumstances, the three fluids tested produced no clinically important differences in ICP or CBF. Although the immediate effects on CO were slightly greater in the two groups that received hypertonic solutions, those differences promptly resolved. Although ICP was initially somewhat lower in the group that received HS without colloid, that difference also rapidly resolved. Although CBF was initially lowest in the group that received HES alone, no differences remained 30 minutes after resuscitation. Intuitively, the more rapid restoration of CBF in the two groups receiving hypertonic fluids might improve neurologic outcome in head-injured animals, although that has not been investigated.

The surprising observation provided by this data set is the gradual, delayed rise in ICP beginning 30-60 minutes after resuscitation in the two groups that received hypertonic solutions. Systemic variables changed in a fashion that should not have increased ICP. From T65 to T155, MAP remained stable in the HS group and

gradually declined in the group that had received HS/HES. CO similarly tended to decline over the same interval. PAD, indirectly reflecting blood volume, also declined. Nevertheless, ICP increased from 35.0 ± 4.3 mm Hg to 51.4 ± 6.7 mm Hg in the HS/HES group and from 20.9 ± 3.3 mm Hg to 37.6 ± 4.2 mm Hg in the HS group. The increase in ICP in the HS group was unexpected, based upon previous experience with hypertonic saline solutions²¹ and upon data from other authors.⁵⁻⁸

An important hypothesis that requires testing is whether the level of cerebral perfusion pressure in these animals with intracranial mass lesions, in contrast to those without lesions studied previously, was sufficiently low to produce blood-brain barrier dysfunction accompanied by a delayed increase in brain sodium and water concentration. Gunnar and colleagues compared the effects of resuscitation with 0.9% saline, 10% dextran-40, and hypertonic (3.0%) saline in animals that had been subjected to hemorrhagic shock combined with epidural balloon inflation.⁶ Resuscitation consisted of return of one-half of shed blood, followed by infusion of a volume equal to shed blood volume of one of the test fluids. Additional 0.9% saline was then administered to all animals to maintain right atrial pressure at 10 mm Hg. ICP increased dramatically in the 0.9% saline and dextran-40 groups and increased little in the hypertonic saline group. All animals showed evidence of breakdown of the blood-brain barrier.

Several important differences in experimental design require comment. First, the epidural balloon was inflated prior to shock and permitted to decline as a consequence of shock. In this respect, the methodology resembles that of Poole and colleagues¹⁹ rather than the methodology of the present study because CPP was less severely reduced. Second, resuscitation was initiated with one-half of the previously

shed blood. Infusion of blood alone increased cardiac index to control values. In contrast, in the present study, resuscitation was initiated with blood-free solutions, as usually occurs in clinical resuscitation. Third, Gunnar and colleagues resuscitated animals with equal volumes of the test solutions. Therefore, since the acute sodium load administered to the animals receiving 3.0% saline far exceeded that administered in the present study, a greater reduction in brain water would be predicted. It is also evident that an infusion of 10% dextran-40 in a volume equal to shed blood volume is not equivalent to the infusion of an equal volume of 0.9% saline. One would expect that the expansion of blood volume induced by oncotic pressure differences would substantially alter the systemic response. In fact, the decline in hematocrit reported by the authors was nearly twice as great following dextran-40 as following 0.9% saline. Although the maximum increase in ICP was similar in animals receiving 0.9% saline and those receiving dextran, the peak increase in ICP in the 0.9% saline animals occurred immediately following resuscitation and well before the peak increase in animals receiving 10% dextran-40.

Perhaps the most important observation of Gunnar and colleagues, for the purposes of the present study, is that inflation of an epidural balloon combined with shock and resuscitation produced increased permeability of the blood-brain barrier to Evan's blue dye, an albumin-bound tracer.⁶ The deterioration in blood-brain barrier function demonstrated by those authors may well explain the late rise in ICP in the present study. In fact, because Gunnar and colleagues permitted ICP to decline during the shock interval, the extent of underlying parenchymal injury may well have been less. Although the authors did not measure CBF, CPP increased from a low of approximately 40 mm Hg at the beginning of shock to approximately 65 mm Hg by

the end of the shock interval. Because CPP was substantially less in the present study, it is likely that blood-brain barrier function was more severely damaged.

Todd and colleagues have demonstrated that the duration of cerebral ischemia influences the severity of subsequent cerebral edema.²⁶ However, Todd et al. reduced CBF during ischemia nearly to zero, whereas CBF in the present study was reduced to only about one-third of baseline levels. Although preceding ischemia does not alter the rate at which sodium is transported across the blood-brain barrier into the brain, it does appear to impair clearance of sodium from the brain.^{1,14} The effects of fluid infusion on ICP following other types of brain insult have been studied. Warner and Boehland induced acute forebrain ischemia with carotid occlusion and hemorrhagic hypotension for 10 minutes in rats, then administered 0.9% saline, 6.0% hydroxyethyl starch, or returned shed blood.³¹ They demonstrated no differences in the accumulation of brain water with the exception of an isolated increase in brain water in the caudoputamen 24 hours following infusion of 6.0% hydroxyethyl starch. Kaieda and colleagues reduced colloid oncotic pressure in pentobarbital-anesthetized rabbits who had undergone cryogenic brain injury and demonstrated no effects of either brief or prolonged reductions in oncotic pressure on brain water.^{10,11} Therefore, the effects on ICP and brain water of various fluids appear to depend upon the experimental model employed.

These data confirm previous data that demonstrate that, following hemorrhagic shock, hemodilution fails to restore CBF to pre-shock levels.^{18,19,21} In each of these animal studies, despite an increase in CPP to a level compatible with preserved autoregulation,² CBF remained below baseline. This clearly contrasts with changes in CBF that accompany isovolemic hemodilution.^{25,27} At comparable levels of CPP

immediately following resuscitation, the two hypertonic solutions produced slightly higher CBF than the isotonic colloid solution, although that tendency rapidly disappeared. Further studies are necessary to confirm the possible superiority of hypertonic solutions and to determine if the effect results from a specific effect of hypertonicity on cerebrovascular resistance or on other unidentified factors.

This critical observation of the gradual increase in ICP following resuscitation with hypertonic solutions after severe reductions in cerebral perfusion pressure necessitates additional study before HS can be safely employed in patients with the potential for blood brain barrier disruption. Additional animal studies should be done in animals that have undergone other types of brain injury, particularly models that duplicate features of clinical closed head injury.

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LEGENDS

Figure 1. Summary of experimental preparation.

Figure 2. Response of mean arterial pressure following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS), 20% hydroxyethyl starch (HES), or hypertonic, hyperoncotic hydroxyethyl starch (HS/HES).

Figure 3. Changes in cardiac output following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS), 20% hydroxyethyl starch (HES), or hypertonic, hyperoncotic hydroxyethyl starch (HS/HES).

Figure 4. Response of intracranial pressure following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS), 20% hydroxyethyl starch (HES), or hypertonic, hyperoncotic hydroxyethyl starch (HS/HES). Intracranial hypertension induced by inflation of an subdural balloon accompanied hemorrhage.

Figure 5. Changes in cerebral perfusion pressure following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS), 20% hydroxyethyl starch (HES), or hypertonic, hyperoncotic hydroxyethyl starch (HS/HES). Intracranial hypertension induced by inflation of an subdural balloon accompanied hemorrhage.

Figure 6. Response of cerebral blood flow following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS), 20% hydroxyethyl starch (HES), or

hypertonic, hyperoncotic hydroxyethyl starch (HS/HES). Intracranial hypertension induced by inflation of an subdural balloon accompanied hemorrhage.

Table 1. Body Weight, Shed Blood Volume and Balloon Volume
(means $\pm$ SEM)

Group	N	Weight (kg)	Blood Loss (ml $\cdot$ kg ⁻¹)	Resus. Volume (ml $\cdot$ kg ⁻¹)	Balloon Volume (ml)
HS/HES	7	20.7 $\pm$ 1.1	22.8 $\pm$ 3	6	5.5 $\pm$.7
HES	7	23.3 $\pm$ 0.8	23.3 $\pm$ 1	6	7.6 $\pm$.5
HS	7	18.6 $\pm$ 2.7	21.5 $\pm$ 2	6	4.8 $\pm$.9

Table 2. Major Systemic Variables (Means $\pm$ SEM)

	Group	BL	Balloon Inflation	TO	T30	T35	T85	T95	T125	T155
P_{aCO_2} (mm Hg)	HS/HES	36 $\pm$ 1.1	37 $\pm$ 0.7	33 $\pm$ 1.7	43 $\pm$ 1.7	45 $\pm$ 1.4	37 $\pm$ 0.6	38 $\pm$ 1.1	37 $\pm$ 0.7	38 $\pm$ 1.5
	HS	36 $\pm$ 0.9	40 $\pm$ 1.2	32 $\pm$ 1.7	42 $\pm$ 2.0	52 $\pm$ 2.5	36 $\pm$ 0.7	40 $\pm$ 0.9	38 $\pm$ 0.8	38 $\pm$ 1.2
	HES	35 $\pm$ 0.7	36 $\pm$ 1.4	34 $\pm$ 1.9	42 $\pm$ 2.5	42 $\pm$ 1.7	38 $\pm$ 1.2	37 $\pm$ 1.0	37 $\pm$ 1.1	38 $\pm$ 1.6
Hgb (g $\cdot$ dl $^{-1}$)	HS/HES	15.0 $\pm$ 0.8	14.9 $\pm$ 0.6	13.7 $\pm$ 0.7	13.6 $\pm$ 0.6	10.1 $\pm$ 0.6	11.2 $\pm$ 0.5	11.5 $\pm$ 0.6	11.4 $\pm$ 0.5	11.6 $\pm$ 0.5
	HS	14.3 $\pm$ 0.6	14.3 $\pm$ 0.6	12.2 $\pm$ 0.6	12.5 $\pm$ 0.7	9.7 $\pm$ 0.6	11.4 $\pm$ 0.6	12.4 $\pm$ 0.5	12.1 $\pm$ 0.6	12.2 $\pm$ 0.6
	HES	13.6 $\pm$ 0.6	13.7 $\pm$ 0.6	12.2 $\pm$ 0.7	12.5 $\pm$ 0.6	10.4 $\pm$ 0.6	10.1 $\pm$ 0.6	10.4 $\pm$ 0.7	10.3 $\pm$ 0.3	10.2 $\pm$ 0.7
P_{aO_2} (mm Hg)	HS/HES	267 $\pm$ 10	256 $\pm$ 16	249 $\pm$ 20	243 $\pm$ 20	261 $\pm$ 19	270 $\pm$ 21	265 $\pm$ 21	259 $\pm$ 21	263 $\pm$ 21
	HS	255 $\pm$ 33	276 $\pm$ 31	209 $\pm$ 27	211 $\pm$ 29	242 $\pm$ 27	232 $\pm$ 26	246 $\pm$ 31	241 $\pm$ 27	231 $\pm$ 24
	HES	296 $\pm$ 30	306 $\pm$ 34	276 $\pm$ 26	275 $\pm$ 26	289 $\pm$ 25	290 $\pm$ 22	293 $\pm$ 25	293 $\pm$ 22	286 $\pm$ 25
pH	HS/HES	7.4 $\pm$ 0.0	7.4 $\pm$ 0.0	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0
	HS	7.4 $\pm$ 0.0	7.4 $\pm$ 0.0	7.4 $\pm$ 0.0	7.2 $\pm$ 0.0	7.1 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0
	HES	7.4 $\pm$ 0.0	7.4 $\pm$ 0.0	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0
Temp ($^{\circ}$ C)	HS/HES	37.6 $\pm$ 0.4	37.5 $\pm$ 0.4	37.6 $\pm$ 0.5	37.9 $\pm$ 0.5	37.6 $\pm$ 0.5	37.6 $\pm$ 0.5	37.7 $\pm$ 0.6	38.1 $\pm$ 0.6	37.7 $\pm$ 0.7
	HS	36.2 $\pm$ 0.2	36.2 $\pm$ 0.4	36.3 $\pm$ 0.4	39.1 $\pm$ 0.3	38.7 $\pm$ 0.2	38.9 $\pm$ 0.2	39.2 $\pm$ 0.2	39.4 $\pm$ 0.2	39.3 $\pm$ 0.4
	HES	36.6 $\pm$ 0.5	36.9 $\pm$ 0.5	37.1 $\pm$ 0.5	37.6 $\pm$ 0.5	37.4 $\pm$ 0.5	37.2 $\pm$ 0.5	37.2 $\pm$ 0.6	37.4 $\pm$ 0.7	37.6 $\pm$ 0.7
PAOP (mm Hg)	HS/HES	1.6 $\pm$ 0.6	1.3 $\pm$ 0.7	0.1 $\pm$ 1.0	-0.4 $\pm$ 0.9	1.3 $\pm$ 1.4	0.6 $\pm$ 0.6	0.5 $\pm$ 0.4	-0.9 $\pm$ 0.6	-0.6 $\pm$ 0.6
	HS	3.6 $\pm$ 1.6	2.6 $\pm$ 1.9	1.3 $\pm$ 1.6	1.1 $\pm$ 1.5	3.3 $\pm$ 1.9	2.1 $\pm$ 1.6	2.1 $\pm$ 1.7	2.5 $\pm$ 1.8	2.2 $\pm$ 1.9
	HES	1.0 $\pm$ 0.9	1.0 $\pm$ 0.6	-1.1 $\pm$ 1.0	-0.3 $\pm$ 0.6	0.9 $\pm$ 0.7	0.3 $\pm$ 0.6	0.2 $\pm$ 1.1	-0.2 $\pm$ 1.1	0.4 $\pm$ 1.1

Table 3. Serum Osmolality (Means $\pm$ SEM)

	Group	BL	T95	T155
Serum Osmolality (mOsm $\cdot$ L ⁻¹)	HS/HES	297 $\pm$ 5	313 $\pm$ 4	316 $\pm$ 5
	HS	287 $\pm$ 3	337 $\pm$ 13	321 $\pm$ 6
	HES	279 $\pm$ 6	302 $\pm$ 4	301 $\pm$ 5

Table 4. Major Cerebral Variables (Means $\pm$ SEM)

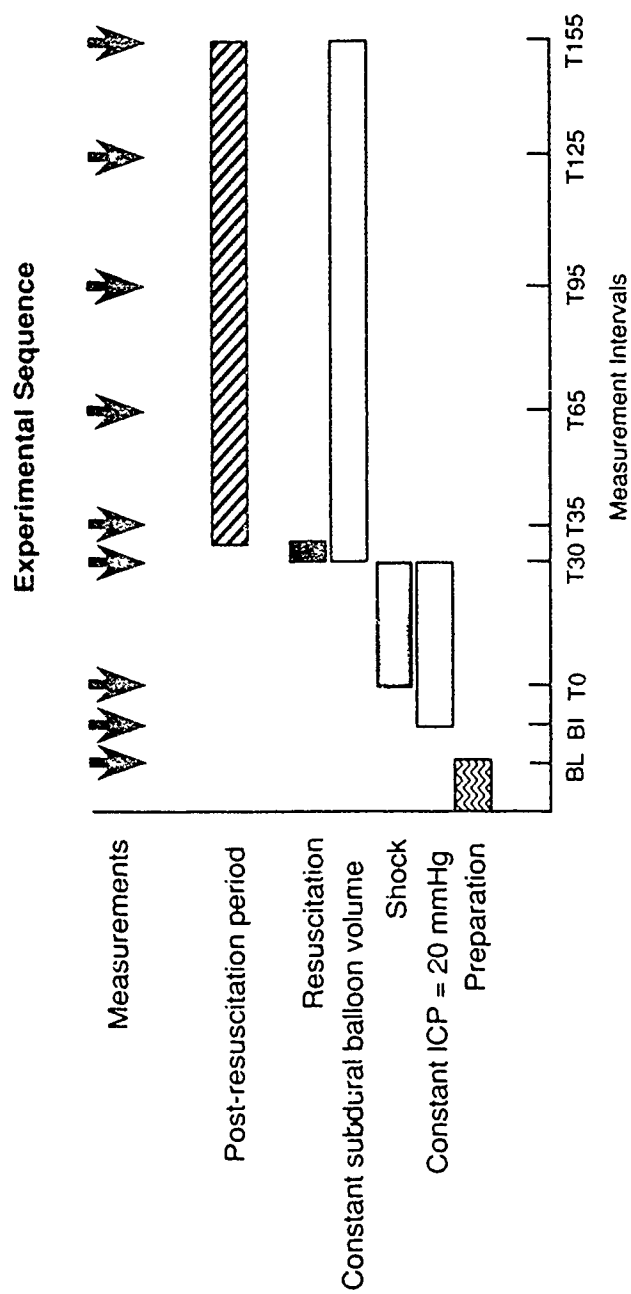
Group	BL	Balloon Inflation	T0	T30	T35	T65	T95	T125	T155
Cerebral A-VOO ₂ (ml $\cdot$ 100 ml ⁻¹)	HS/HES	6.4 $\pm$ 0.4	11.6 $\pm$ 0.6	10.0 $\pm$ 1.5	5.2 $\pm$ 0.7	7.9 $\pm$ 0.8	9.4 $\pm$ 1.0	10.3 $\pm$ 1.0	10.7 $\pm$ 1.5
	HS	6.0 $\pm$ 0.7	9.6 $\pm$ 0.9	7.8 $\pm$ 1.1	5.0 $\pm$ 0.3	6.3 $\pm$ 1.0	7.6 $\pm$ 0.7	8.7 $\pm$ 1.0	8.1 $\pm$ 1.3
	HES	6.8 $\pm$ 0.4	9.9 $\pm$ 1.7	8.3 $\pm$ 1.2	6.4 $\pm$ 0.3	4.8 $\pm$ 1.5	5.9 $\pm$ 1.5	6.4 $\pm$ 1.2	4.7 $\pm$ 0.9
CMRO ₂ 2.1 (ml $\cdot$ min ⁻¹)	HS/HES	2.2 $\pm$ 0.2	2.1 $\pm$ 0.2	1.2 $\pm$ 0.1	1.3 $\pm$ 0.2	1.5 $\pm$ 0.2	1.2 $\pm$ 0.1	0.9 $\pm$ 0.2	0.8 $\pm$ 0.1
	HS	1.6 $\pm$ 0.4	1.7 $\pm$ 0.3	0.7 $\pm$ 0.3	1.3 $\pm$ 0.3	1.1 $\pm$ 0.3	1.1 $\pm$ 0.3	1.1 $\pm$ 0.3	0.8 $\pm$ 0.2
	HES	1.9 $\pm$ 0.4	1.8 $\pm$ 0.2	0.9 $\pm$ 0.3	1.2 $\pm$ 0.1	1.1 $\pm$ 0.3	1.3 $\pm$ 0.3	1.3 $\pm$ 0.1	0.7 $\pm$ 0.0
CO ₂ T -1 (ml $\cdot$ min ⁻¹)	HS/HES	7.4 $\pm$ 0.7	7.0 $\pm$ 1.5	2.4 $\pm$ 0.1	3.7 $\pm$ 0.2	3.7 $\pm$ 0.3	2.3 $\pm$ 0.3	1.7 $\pm$ 0.4	1.5 $\pm$ 0.1
	HS	5.7 $\pm$ 1.1	5.3 $\pm$ 0.8	1.4 $\pm$ 0.3	3.1 $\pm$ 0.7	2.8 $\pm$ 0.7	2.3 $\pm$ 0.7	2.1 $\pm$ 0.4	1.4 $\pm$ 0.4
	HES	6.0 $\pm$ 1.1	5.8 $\pm$ 0.0	1.8 $\pm$ 0.7	2.1 $\pm$ 0.1	2.6 $\pm$ 0.3	2.7 $\pm$ 0.1	2.1 $\pm$ 0.1	1.4 $\pm$ 0.3

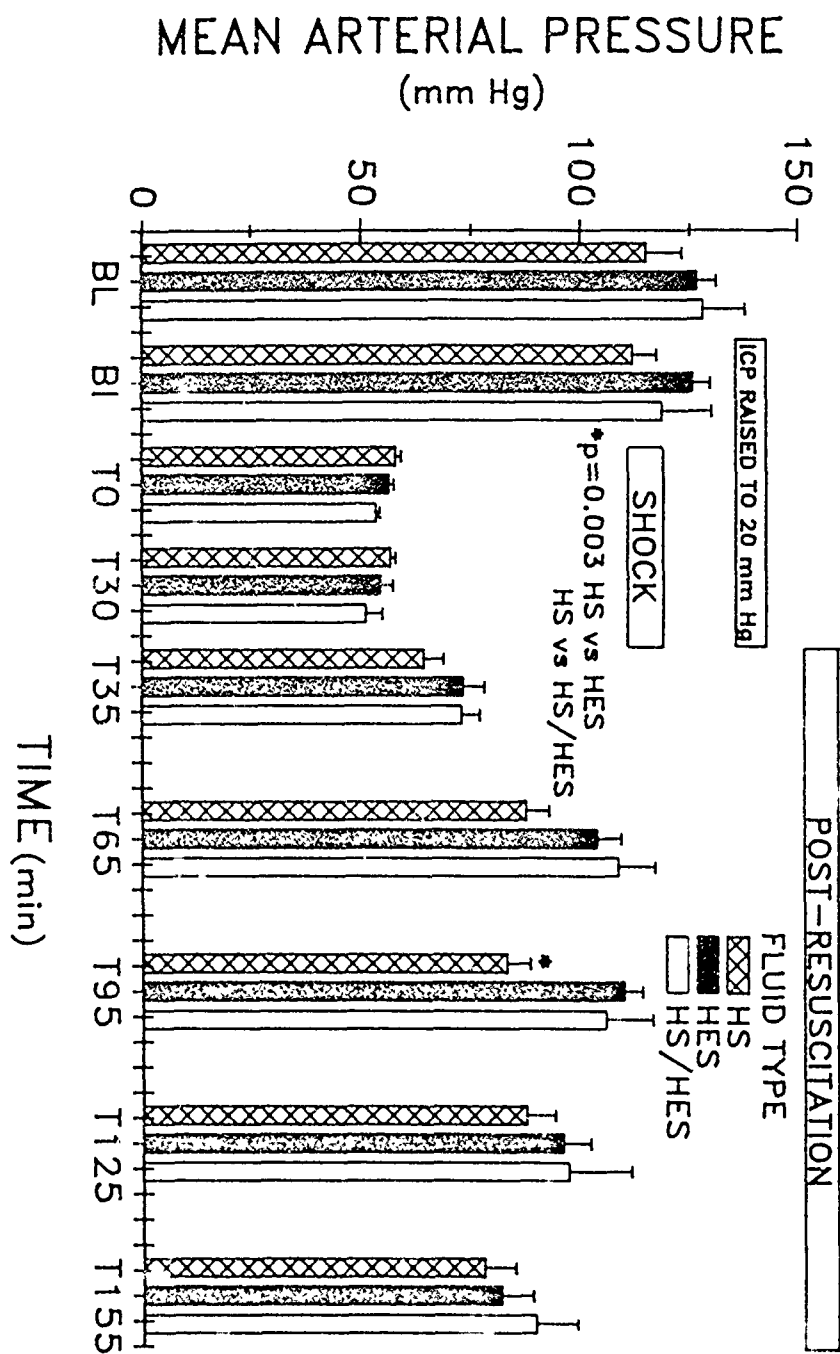
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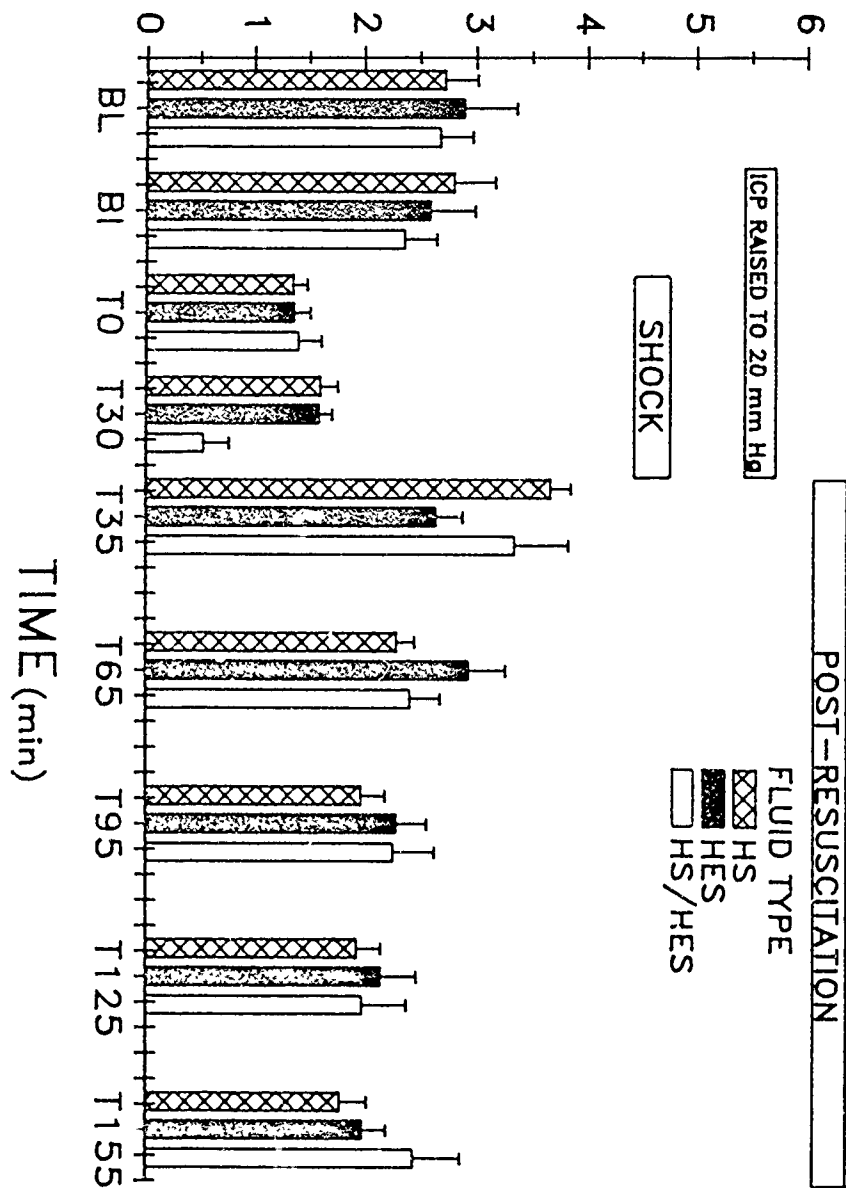
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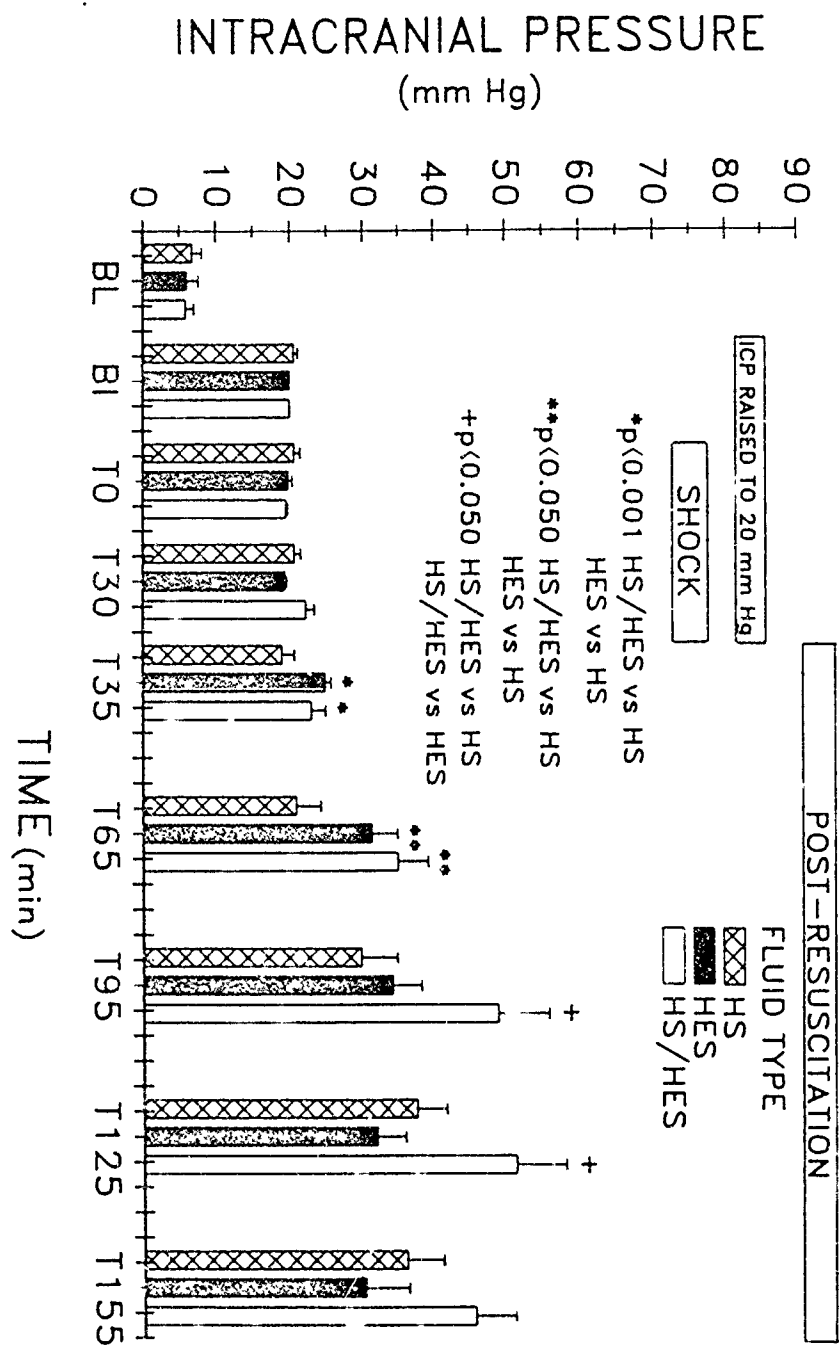


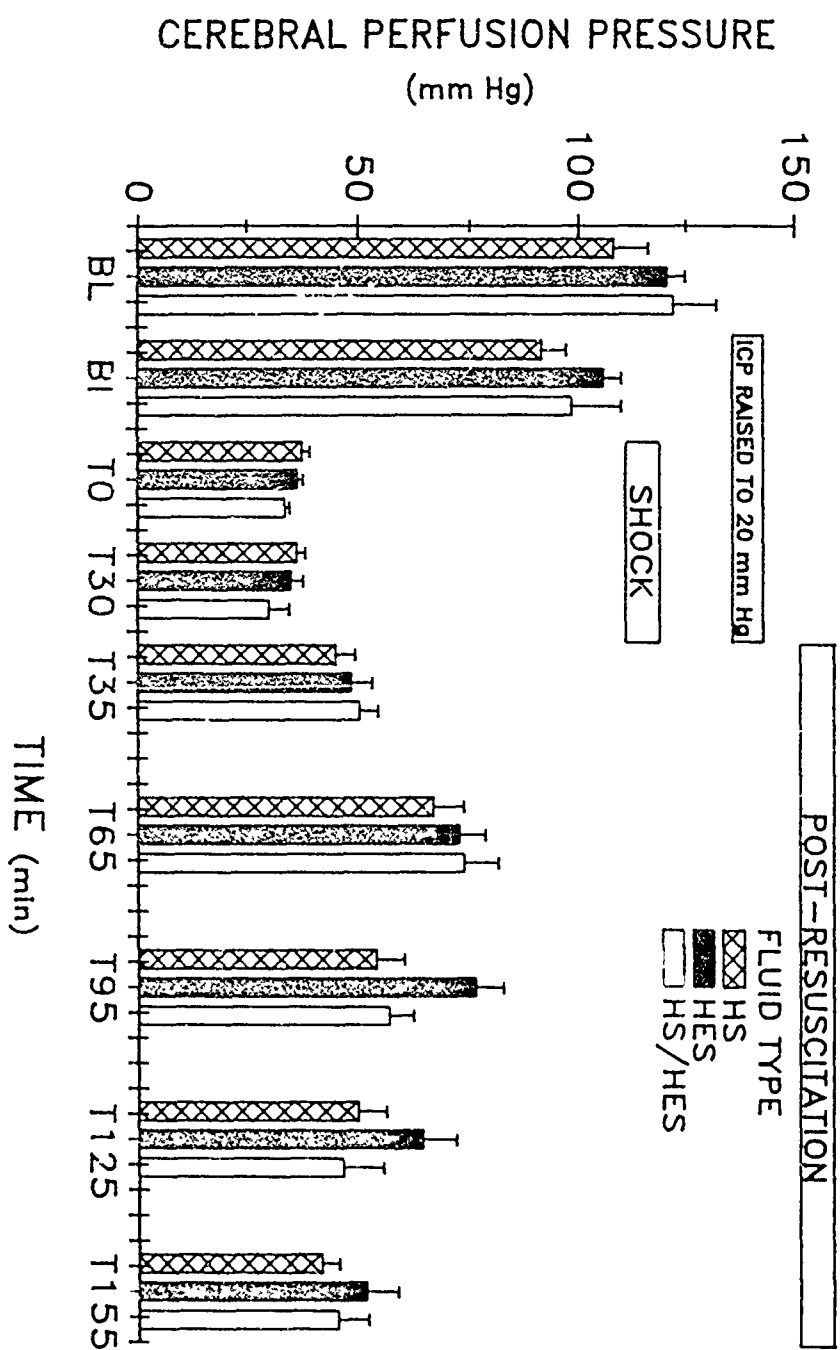


CARDIAC OUTPUT

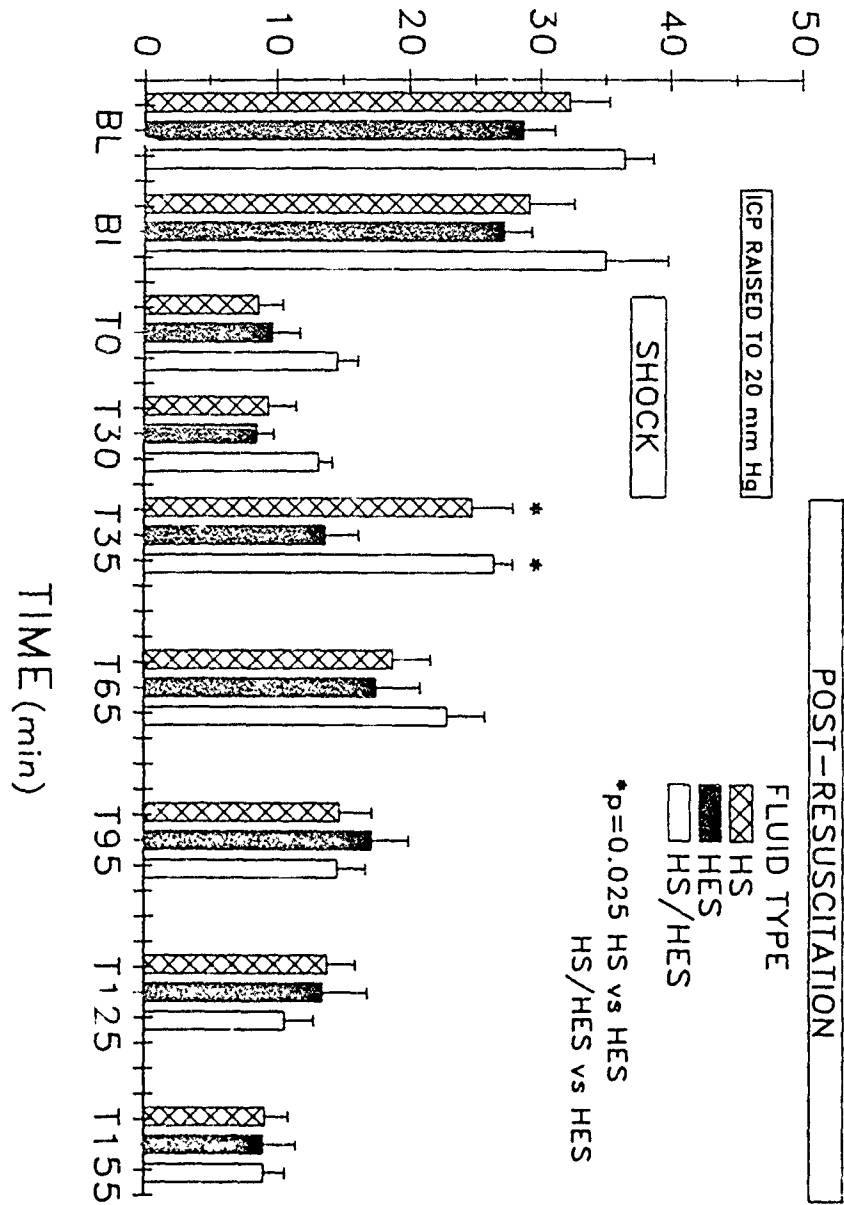
(ml · min⁻¹)







CEREBRAL BLOOD FLOW (ml · min⁻¹)



Running title: Small-volume resuscitation

CEREBROVASCULAR EFFECTS OF SMALL VOLUME RESUSCITATION
FROM HEMORRHAGIC SHOCK:
COMPARISON OF HYPERTONIC SALINE AND CONCENTRATED
HYDROXYETHYL STARCH IN DOGS

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ABSTRACT

To determine if hypertonic and hyperoncotic resuscitation solutions exerted comparable effects on cerebral hemodynamics following hemorrhagic shock, we compared randomly assigned, equal volumes ($6.0 \text{ ml} \cdot \text{kg}^{-1}$) of hypertonic (7.2%) saline (HS) and hyperoncotic (20%) hydroxyethyl starch (HES) for resuscitation from acute experimental hemorrhage in 12 anesthetized dogs. Regional cerebral blood flow (radiolabelled microspheres), intracranial pressure (cisternal catheter), and systemic hemodynamics were recorded. Rapid hemorrhage reduced mean arterial pressure to 45 mm Hg for 30 minutes. Resuscitation fluids were infused over 5 minutes. Both fluids restored mean arterial pressure and cardiac output equally. Cardiac output rapidly declined, however, in the HS group in comparison to the HES group ($p < 0.05$ 60 minutes following resuscitation). Intracranial pressure and cerebral perfusion pressure were similar at all intervals. Regional cerebral blood flow was similar following both fluids. Neither fluid restored cerebral oxygen transport to baseline values. Following severe hemorrhagic shock of brief duration, systemic and cerebral hemodynamic values are restored equally well by highly concentrated colloid or by hypertonic saline, although hypertonic saline only transiently improves cardiac output.

INTRODUCTION

Following acute trauma or hemorrhage, prompt restoration of systemic hemodynamics is essential. An ideal fluid for acute resuscitation should restore systemic hemodynamics when administered in a volume constituting only a fraction of shed blood volume. Recently, small-volume resuscitation with hypertonic salt solutions has proven effectively to restore systemic hemodynamics. Following initial reports by Velasco and colleagues (32,13,26), numerous investigators have studied hypertonic saline, in a variety of concentrations, with and without added colloid (25,7,24,31,11,28,15,6,5). Based upon these reports, it is apparent that small volumes of hypertonic salt solutions improve survival in severe, experimental hemorrhagic shock (32,26,31,11,28,15), that they are associated with lower intracranial pressure (ICP) following resuscitation than are isotonic salt solutions (25,7,24,5), and that the systemic hemodynamic effects of hypertonic saline alone are relatively short-lived (25,28,15). Addition of colloid, usually 6.0% dextran, produces more sustained hemodynamic effects than hypertonic saline solutions alone (28,15,16).

However, rapid infusion of hypertonic solutions containing sodium in concentrations substantially in excess of normal serum concentrations produces hyponatremia and hypertonicity. Although moderate hypertonicity appears to be well tolerated when it develops during the resuscitation of burned patients or during replacement of perioperative fluid losses with hypertonic solutions (19,27), unanswered questions remain regarding presumably rare, but potentially lethal, complications of rapid increases in serum sodium concentration, such as subdural hemorrhage or central pontine myelinolysis (20,12,21).

We performed a study to determine whether rapid resuscitation with a highly concentrated solution of the synthetic colloid hydroxyethyl starch (HES) would produce improvements in systemic and cerebral hemodynamics comparable to those produced by

equal volumes of 7.2% saline.

METHODS

Twelve mongrel dogs of either sex, weighing 18-24 kg, were managed according to guidelines established by the institution's Animal Care and Use Committee.

Anesthesia

Following an overnight fast, dogs were anesthetized with intravenous thiopental sodium ($8.0 \text{ mg} \cdot \text{kg}^{-1}$), paralyzed with pancuronium ($0.2 \text{ mg} \cdot \text{kg}^{-1}$), endotracheally intubated, then anesthetized with halothane 0.5% in nitrous oxide and oxygen (60:40). Animals were ventilated, using an Edco Model 822 large animal ventilator (Edco Scientific, Inc., Chapel Hill, NC), at a tidal volume of $15 \text{ ml} \cdot \text{kg}^{-1}$ and a rate sufficient to maintain PaCO_2 35-45 mm Hg. Additional pancuronium, given as needed, prevented respiratory movement.

Hemodynamic Monitoring

Two brachial artery catheters were placed, the right for continuous monitoring of systemic arterial blood pressure and the left as a reference organ for cerebral blood flow (CBF) determinations using radioactive microspheres. A 7-Fr pigtail catheter was inserted into the left ventricle through the left femoral artery for injection of radioactive microspheres. The right femoral artery was cannulated and used as a second reference organ. A flow-directed, pulmonary artery catheter was placed percutaneously via the right external jugular vein for cardiac output (CO), pulmonary artery pressure and pulmonary artery occlusion pressure (PAOP) measurements. Pressure recording utilized a Grass Model 79D polygraph (Grass Instrument Co., Quincy, MA) with Gould Statham P23 transducers (Gould, Inc., Oxnard, CA). Core temperature, monitored continuously using the thermistor on the pulmonary artery catheter, was maintained using a 37°C heating pad applied to the trunk and extremities. CO was measured using an American Edwards 9520A CO computer (American Edwards, Santa Ana, CA). All transducers were intermittently

zeroed and calibrated at the level of the left atrium. To facilitate rapid hemorrhage, all animals underwent splenectomy. Animals were then turned to the prone, "sphinx" position and the occipital musculature dissected from the underlying bone. The superior sagittal sinus was cannulated using a 3-Fr double-lumen O₂ saturation catheter (American Edwards Lab., Santa Ana, CA) for continuous cerebral venous oxygen O₂ saturation and sagittal sinus pressure monitoring and for rapid sampling of cerebral venous blood. An 18-ga catheter inserted into the cisterna magna and zeroed at the level of the external auditory meatus (7 cm above the left atrium) provided continuous monitoring of ICP.

Regional Cerebral Blood Flow Measurement

Regional cerebral blood flow (rCBF) was measured with radioactive microspheres (15 μ m), using the organ reference sample method (17,8). Radioactive microspheres were labelled with ¹⁵³Gd, ⁹⁵Nb, ¹¹³Sn, ⁸⁵Sr, and ⁴⁶Sc. Paired reference organ blood samples (ROBS) were withdrawn simultaneously from the right femoral and left brachial arteries using an Edco Model 843 Infusion-Withdrawal Syringe Pump (Edco Scientific, Inc., Chapel Hill, NC). Prior to injection, microspheres were vortexed for 4 minutes to insure adequate mixing. Each microsphere dose was calculated to yield greater than 400 microspheres per tissue segment and a minimum of 15,000 counts per ROBS. Injection of each microsphere type was carried out over a 15-second period. The ROBS were taken beginning 30 seconds prior to microsphere injection and continued for 60 seconds post-injection, at a withdrawal rate of 2.06 ml•min⁻¹. Counts per minute (CPM) in ROBS pairs differed by no more than 5%. After sacrificing, brains were sectioned into right cerebral hemisphere, left cerebral hemisphere, and brainstem, and counted along with the arterial reference samples in a well-type gamma counter (Auto-Gamma 5000, Packard Instruments, Downers Grove, IL). Aliquots of microspheres labelled with each radionuclide were counted along with the blood

and tissue samples, and curve stripping to correct for isotope overlap was performed using a microcomputer connected to the gamma counter.

Experimental Sequence

The experimental sequence is summarized in Fig. 1. After instrumentation, all animals were stabilized for 30 minutes and baseline (BL) data recorded. Recorded data consisted of rCBF, ICP, systolic and diastolic arterial pressures (SAP and DAP), CO, PAOP, pulmonary artery systolic and diastolic pressures (PAS and PAD), heart rate, body temperature, arterial and cerebral venous pH, PCO₂, PO₂, O₂ saturation, hemoglobin concentration (IL 282, Instrumentation Laboratory, Lexington, MA), serum osmolality (5500 vapor pressure osmometer, Wescor, Inc., Logan, UT) and colloid oncotic pressure (4100 colloid osmometer, Wescor, Inc.). The following calculations were made:

1. mean arterial pressure (MAP) = $DAP + 1/3 (SAP - DAP)$
2. cerebral perfusion pressure (CPP) = $MAP - ICP$
3. cerebral metabolic rate for oxygen (CMRO₂) = $CBF / 100 \times \text{cerebral A-VDO}_2$
4. cerebrovascular resistance (CVR) = CPP / CBF
5. CBF was derived from the formula:

$$CBF = \frac{C_t \times \text{withdrawal rate} \times 100}{C_r \times wt}$$

where C_t = CPM in the tissue sample, C_r = CPM in the reference sample
and wt = weight of the tissue sample.

After anticoagulation with heparin (500 IU•kg⁻¹ intravenously), blood was rapidly withdrawn through the right brachial artery catheter to reduce MAP to 45 mm Hg; MAP was maintained at that level for 30 minutes by removing or reinfusing shed blood.

The second set of cerebral and hemodynamic data was obtained at the mid-shock time interval, designated as T15, indicating the number of minutes from the onset of shock. Following the shock interval, animals were randomized to one of two fluid groups, based upon the type of resuscitation fluid: Group HS received $6.0 \text{ ml} \cdot \text{kg}^{-1}$ of 7.2% saline ($1232 \text{ mEq} \cdot \text{L}^{-1} \text{ Na}^+$), and group HES received $6.0 \text{ ml} \cdot \text{kg}^{-1}$ of 20% hydroxyethyl starch dissolved in 0.8% saline ($137 \text{ mEq} \cdot \text{L}^{-1} \text{ Na}^+$). Additional data were collected immediately after fluid infusion (T35) and thereafter at hourly intervals for two hours (T95, T155).

Statistical Analysis

All statistical analyses were performed using SAS (SAS Institute, Cary, NC). The Kruskal-Wallis test confirmed similarity at baseline and during shock. A multivariate repeated measures of analysis of variance (ANOVA) was performed to determine if interactions between groups and time existed at subsequent post-resuscitation intervals (2). Interactions were analyzed further with the Holm's sequentially rejective multiple test procedure using a significance level of 0.05 (9). To assess time and group differences when an interaction was not present, a multivariate repeated measures of ANOVA and an analysis of covariance were performed on the dependent variables. Statistically significant group effects were further evaluated using Holm's sequentially rejective multiple test procedure.

RESULTS

Systemic Variables

All values in the text, tables, and figures are expressed as means $\pm$ SEM.

Mean Arterial Pressure

Shed blood volume was similar in the two groups (Table I). Baseline MAP in the two experimental fluid groups was comparable, then was maintained experimentally near 45 mm Hg for 30 minutes prior to fluid resuscitation (Figure 2A). Immediately following acute fluid resuscitation (T35), MAP increased similarly in the HS and HES groups, to 82 ± 3.8 (mean $\pm$ SEM) and 78 ± 3.5 mm Hg, respectively. At T95 (one hour post-resuscitation), MAP continued to increase in the HES group to 97 ± 1.8 mm Hg. There were no statistically significant differences in MAP.

Cardiac Output

Baseline CO was similar (3.2 ± 0.4 L $\cdot$ min $^{-1}$ in HS and 3.9 ± 0.2 L $\cdot$ min $^{-1}$ in HES) (Figure 2B). Hemorrhage significantly decreased CO to approximately 50% of baseline in both groups. Following resuscitation, CO approached baseline levels in both groups. CO then decreased rapidly in the HS group; CO in the HES group remained similar to the T35 level for the duration of the experimental period ($p < 0.05$ between groups at T95).

Other Systemic Variables

PaCO $_2$, Hgb, PaO $_2$, pH, blood temperature, and PAOP were similar at all intervals (Table II). Serum osmolality was greatest at T155 in the HS group compared to HES. Colloid oncotic pressure (as % of baseline) increased significantly following resuscitation in the HES group compared to HS ($p < 0.05$) (Table III).

Cerebral Hemodynamics

Intracranial Pressure

Prior to initiation of shock, there were no differences in ICP (7.2 ± 2.0 and 4.6 ± 1.9 mm Hg in the HS and HES groups, respectively) (Figure 3A). Resuscitation (T35) increased ICP slightly in both groups. Throughout the post-resuscitation period, ICP in both the HS and HES groups remained below baseline without significant difference.

Cerebral Perfusion Pressure

Cerebral perfusion pressure (CPP) (Figure 3B) followed the same general pattern as MAP. CPP was not restored to baseline by either fluid following resuscitation. CPP continued to increase following resuscitation in the HES group, reaching a maximum at T95. No differences in CPP were detected between groups at any time period.

Regional Cerebral Blood Flow

Regional cerebral blood flow (rCBF) was similar between right and left cerebral hemispheres and brainstem in both groups at baseline (Figure 4). Induction of hemorrhage resulted in only small ($\sim 20\%$) reductions in rCBF compared to baseline ($p = \text{NS}$). Fluid resuscitation increased rCBF transiently in the HS group, exceeding baseline ($p = \text{NS}$). Regional CBF in both groups after T35 was similar throughout the remainder of the experiment. Because arterial content (CaO_2) declined as Hgb declined (Table II), cerebral oxygen transport ($\text{CBF} \times \text{CaO}_2$) remained below baseline values after resuscitation in both groups (Table IV). CMRO_2 did not change significantly over the course of the study; in general, declines in CBF were balanced by increases in cerebral A-V DO_2 .

DISCUSSION

These data demonstrate that hyperoncotic 20% HES and hypertonic 7.2% saline produce comparable systemic hemodynamic and cerebral hemodynamic improvement when administered in equal volumes, approximating 15% of shed blood volume, following hemorrhagic shock. Although most variables remained similar throughout the two hours following resuscitation, CO declined more rapidly in animals that received HS. Presumably, continued movement of interstitial fluid into the plasma volume along an oncotic pressure gradient explains the more persistent effects of the hyperoncotic solution. If these data can be confirmed in additional animal studies and in clinical trials, highly concentrated colloid solutions may prove as practical as hypertonic solutions for the initial resuscitation and stabilization of victims of trauma, including those with intracranial injuries.

Interest in the applicability of small-volume resuscitation for trauma patients was stimulated by studies performed by Velasco and colleagues in the early 1980's. They first demonstrated that dogs subjected to a hemorrhage equal to approximately one-half estimated blood volume could be effectively resuscitated using 7.5% saline in a dose of $4.0 \text{ ml} \cdot \text{kg}^{-1}$, a volume that was only about one tenth of the initial shed blood volume (32). They subsequently demonstrated that hypertonic saline improved systemic hemodynamics only if a vagally mediated reflex arc were intact (13). Subsequent investigators demonstrated that hypertonic resuscitation fluid might be particularly appropriate if hemorrhage accompanied head injury, because hypertonic saline produced lower post-resuscitation ICP than did conventional crystalloid solutions (25,7,24,6,5). Colloid-containing solutions also were associated with lower ICP following resuscitation than conventional crystalloid solutions, although the advantage over conventional fluids was less prominent and consistent than the advantages of hypertonic solutions (7,6,5,22,23).

However, hypertonic solutions carry several major liabilities in comparison to resuscitation with either crystalloid or colloid solutions. First, the systemic effects of acute administration of hypertonic solutions on CO tend to be transient (25,28,15). The present data confirm those previous observations. Although MAP remained reasonably stable in the HS group from T35 to T155, CO declined precipitously from T35 to T95. In contrast, concentrated HES maintained stable levels of CO throughout the post-resuscitation interval. Numerous investigators have attempted to increase the duration of the desirable hemodynamic effects of hypertonic solutions by adding colloid (11,28,15,33). However, previous studies have not defined a concentration of colloid alone that produced comparable early hemodynamic effects.

One consequence of hemorrhage followed by resuscitation without red blood cells is the production of post-resuscitation hemodilution. Changes in Hgb, serum osmolality, and colloid oncotic pressure depend upon the type of fluid infused. The cerebral effects of hemodilution and of changes in osmolality and oncotic pressure have been extensively investigated in animals that have not been subjected to hemorrhagic shock. Tommasino and colleagues isovolemically hemodiluted anesthetized rabbits with lactated Ringer's solution to reduce hematocrit from approximately 40% to 19% (30). Following initial hemodilution, sufficient additional fluid was given to maintain stable arterial blood pressure and central venous pressure. Lactated Ringer's solution, which is slightly hypotonic relative to plasma, produced early increases in ICP and brain water that rapidly resolved. Six percent HES did not alter ICP or brain water. Hemodilution with either fluid was associated with an increase in CBF of approximately 50%. Todd and colleagues induced acute isovolemic hemodilution using a hypertonic solution (Na^+ 252 mEq·l⁻¹) and compared

it to 0.9% NaCl after reduction of hematocrit from 40 to 20% (29). Both solutions produced comparable dilution-related increases of at least 50% in CBF.

However, hemodilution following shock appears to exert different cerebrovascular effects than isovolemic hemodilution occurring without intervening shock. In most studies, hemodilutional resuscitation fails to improve CBF sufficiently to offset the decline in CaO_2 produced by a reduction in hemoglobin (25,22,23). During resuscitation following a 30-minute shock interval in dogs, Prough and colleagues reduced hemoglobin from 13.1 ± 0.6 to $7.0 \pm 0.6 \text{ g}\cdot\text{dl}^{-1}$ with lactated Ringer's solution and from 13.5 ± 0.4 to $8.4 \pm 0.4 \text{ g}\cdot\text{dl}^{-1}$ with 7.5% saline and found no increase in CBF above shock values (25). CBF similarly failed to increase following hemodilutional resuscitation with 6.0% hydroxyethyl starch in animals both with and without intracranial mass lesions (22,23). Emerson and colleagues induced hemorrhagic shock of three hours duration in pentobarbital-anesthetized dogs (3). Resuscitation with shed blood alone failed to restore CBF to baseline values. Cerebrovascular resistance actually increased during resuscitation. Infusion of dextran after three hours of hemorrhagic hypotension restored CBF nearly to baseline but failed to increase CBF as would be expected as a consequence of hemodilution (3). Gunnar and colleagues (6) also restored CBF to baseline by returning 50% of shed blood, then infusing low molecular weight dextran, 3.0% saline, or 0.9% saline in a volume equal to shed blood volume, after which they continued a rapid infusion of 0.9% saline. Although CBF returned to baseline, Hgb and CaO_2 , which presumably declined as a consequence of hemodilution, were not reported.

The slight decline in CBF produced by a MAP of 45 mm Hg in this study is consistent with that produced by hemorrhagic hypotension in baboons (4), cats (14), and dogs (25,1). Although restoration of MAP in the presence of intact autoregulation should

restore CBF, shocked animals may also require more aggressive expansion of intravascular volume to increase CBF. Following more aggressive volume administration, CBF may exceed baseline (4,18). After two hours of hemorrhagic shock in baboons, McNamara and colleagues returned shed blood, then infused additional lactated Ringer's solution as necessary to restore either baseline left atrial pressure or baseline MAP (18). Using either regimen, they were able to increase CBF to values exceeding baseline. However, they did not report hemoglobin or hematocrit values in those animals.

In the present study, immediately following resuscitation, CBF increased only to baseline values in the HES group. Although the HS group demonstrated an increase in CBF sufficient to offset partially the reduction in hemoglobin, the increase in CBF, like the increase in CO, was transient. Although, by definition, these animals were not normovolemic following small-volume resuscitation, MAP throughout the post-resuscitation interval was well in excess of the experimental autoregulatory threshold for dogs (1).

One possible mechanism explaining the difference between hemodilution following shock and isovolemic hemodilution without antecedent shock is the magnitude of sympathetic stimulation. Fitch and colleagues demonstrated that alpha blockade, an intervention that does not alter resting CBF, increases CBF in hypotensive animals (4). Perhaps the greater volume expansion produced by McNamara and colleagues or Gunnar and colleagues (6) reduced the level of circulating catecholamines.

The effects of fluid administration, with or without brain injury, on brain water and ICP have been studied experimentally. Zornow and colleagues used hollow-fiber plasmapheresis to acutely alter plasma osmolality or colloid oncotic pressure in rabbits and demonstrated that acute reductions of $13 \pm 6 \text{ mOsm} \cdot \text{kg}^{-1}$ in plasma osmolality significantly increased cortical water content, but that a 65% reduction in oncotic pressure

from 20 ± 2 mm Hg to 7 ± 1 mm Hg produced no change (36). Acute hypo-osmolality also increased ICP significantly. Todd and colleagues demonstrated that isovolemic hemodilution with hypertonic salt solutions reduced both ICP and brain water in comparison to 0.9% saline (29). Zornow and colleagues induced isovolemic hemodilution with 0.9% saline, 6.0% HES, and 5.0% albumin in rabbits that had received a cryogenic brain lesion and demonstrated that the cryogenic lesion increased ICP and brain water but that these effects were independent of the type of fluid infused (35). Kaieda and colleagues performed plasmapheresis in rabbits to produce sustained reductions in colloid oncotic pressure following cryogenic brain injury (10). There were no significant differences in ICP or brain water despite 8 hours of reduced oncotic pressure. Warner and Boehland measured the effects on brain water of infusion of blood or isovolemic hemodilution with 0.9% NaCl or 6.0% HES following 10 minutes of near-complete forebrain ischemia (34) in rats. The ischemic insult was followed by increases in brain water regardless of the fluid that was infused. In a single brain region, the caudoputamen, HES was associated with increased water content at 24 hours after ischemia (34).

In the present study, the effects on ICP of fluid resuscitation following shock (rather than isovolemic hemodilution without shock) are consistent with those in other studies of shock and resuscitation. Prough and colleagues administered $6.0 \text{ ml} \cdot \text{kg}^{-1}$ of 7.5% saline to dogs after 30 minutes after hemorrhagic shock and noted that ICP remained low in those animals that received hypertonic saline in comparison to lactated Ringer's solution (25). In dogs with and without intracranial mass lesions, $20 \text{ ml} \cdot \text{kg}^{-1}$ of 6.0% HES produced lower ICP post-resuscitation than did lactated Ringer's solution (22,23). Gunnar and colleagues induced hemorrhagic shock in barbiturate-anesthetized dogs to a MAP of approximately 40 mm Hg for 1 hour. At the end of the shock interval, 50% of the shed blood (approximately

20% of estimated blood volume) was transfused over 15 minutes followed by a volume equal to shed blood volume of 0.9% saline, 3.0% hypertonic saline, or 10% low molecular weight dextran in 0.9% saline. All animals were then given 1500 ml of additional 0.9% saline over the following 75 minutes (7,6,5). MAP and CO were similarly restored by all three fluid resuscitation regimens. The animals that received dextran had higher right atrial and pulmonary artery occlusion pressures. ICP was lowest in the animals that had received hypertonic saline and remained lowest throughout most of the resuscitation interval. In the two groups of animals that had received 0.9% saline or dextran, ICP was equal (7,6,5). Because of the complexity of the fluid resuscitation regimen in that study, it is difficult to directly compare it with the single bolus of fluid employed in the present study. However, the animals in the earlier study would certainly have had a higher blood volume throughout the post-resuscitation interval than the animals reported here. More importantly, the higher right atrial pressure in the group that received dextran would tend to increase volume in the cerebral capacitance vessels and thereby potentially increase ICP.

Based upon the data presented here, we conclude that highly concentrated HES solutions may represent an appropriate alternative to hypertonic saline for acute, small-volume resuscitation of civilian and military casualties. These data should be interpreted with caution because these animals had no experimental intracranial pathology. Further studies are necessary to define the effects of highly concentrated colloid solutions and hypertonic solutions in animals with intracranial pathology.

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Table I. Comparison of Weight, Shed Blood Volume, and Resuscitation Volume
(means $\pm$ SEM)

Group	N	Body Weight (kg)	Shed Blood Volume (ml•kg ⁻¹)	Resuscitation Volume (ml•kg ⁻¹)
HS	6	20 $\pm$ 1.6	35 $\pm$ 3.7	6.0
HES	6	22 $\pm$ 0.7	32 $\pm$ 4.7	6.0

Table II. Major Systemic Variables (Means $\pm$ SEM)

Variable	Group	Time Interval				
		BL	T15	T35	T95	T155
PaCO ₂	HES	40.9 $\pm$ 0.3	40.6 $\pm$ 0.4	41.3 $\pm$ 0.4	39.9 $\pm$ 1.0	40.7 $\pm$ 0.5
(mm Hg)	HS	39.5 $\pm$ 0.6	40.2 $\pm$ 1.7	40.4 $\pm$ 0.9	41.8 $\pm$ 2.4	38.9 $\pm$ 0.5
Hgb	HES	12.9 $\pm$ 0.9	10.8 $\pm$ 0.8	8.6 $\pm$ 0.7	9.1 $\pm$ 0.6	9.5 $\pm$ 0.8
(g $\cdot$ dl ⁻¹)	HS	13.8 $\pm$ 1.0	11.3 $\pm$ 1.0	8.4 $\pm$ 0.7	10.7 $\pm$ 0.7	10.2 $\pm$ 1.3
PaO ₂	HES	170 $\pm$ 13	154 $\pm$ 11	167 $\pm$ 14	176 $\pm$ 12	183 $\pm$ 13
(mm Hg)	HS	191 $\pm$ 13	188 $\pm$ 9	197 $\pm$ 9	176 $\pm$ 5	183 $\pm$ 14
pH	HES	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0
	HS	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0
Temp	HES	37.5 $\pm$ 0.2	38.0 $\pm$ 0.2	37.9 $\pm$ 0.2	37.9 $\pm$ 0.4	38.3 $\pm$ 0.4
(°C)	HS	37.4 $\pm$ 0.4	38.1 $\pm$ 0.4	37.8 $\pm$ 0.2	38.3 $\pm$ 0.5	38.9 $\pm$ 0.4
PAOP	HES	5.4 $\pm$ 1.4	1.3 $\pm$ 0.5	0.9 $\pm$ 1.3	2.1 $\pm$ 0.8	3.0 $\pm$ 1.3
(mm Hg)	HS	3.8 $\pm$ 2.1	0.1 $\pm$ 1.2	3.1 $\pm$ 1.7	3.1 $\pm$ 0.6	2.4 $\pm$ 0.7

PaCO₂ = partial pressure of carbon dioxide in arterial blood; Hgb = hemoglobin; PaO₂ = partial pressure of oxygen in arterial blood, Temp = blood temperature measured using the thermistor on the pulmonary artery catheter; PAOP = pulmonary artery occlusion ("wedge") pressure

Table III. Serum Osmolality and Colloid Oncotic Pressure (Means $\pm$ SEM)

Variable	Group	Time Interval	
		BL	T155
Serum Osmolality (mOsm $\cdot$ L $^{-1}$)	HS	292 $\pm$ 12	324 $\pm$ 4
	HES	291 $\pm$ 8	307 $\pm$ 6
Colloid Oncotic Pressure (% baseline)	HS	100 $\pm$ 0	70 $\pm$ 4
	HES	100 $\pm$ 0	110 $\pm$ 1*

* $p < 0.05$ HES vs HS.

Table IV. Cerebral Hemodynamic Variables (Means $\pm$ SEM)

Variable	Group	Time Interval				
		BL	T15	T35	T95	T155
CO ₂ T (ml•100g ⁻¹ •min ⁻¹)	HES	10.9 $\pm$ 1.1	7.1 $\pm$ 0.4	7.2 $\pm$ 0.5	6.7 $\pm$ 0.4	5.9 $\pm$ 0.8
	HS	10.6 $\pm$ 1.2	6.9 $\pm$ 0.8	9.9 $\pm$ 1.8	7.8 $\pm$ 1.0	6.7 $\pm$ 1.0
CMRO ₂ (ml•100g ⁻¹ •min ⁻¹)	HES	3.5 $\pm$ 0.4	3.5 $\pm$ 0.2	3.3 $\pm$ 0.4	3.3 $\pm$ 0.2	3.0 $\pm$ 0.2
	HS	2.8 $\pm$ 0.4	3.2 $\pm$ 0.4	3.5 $\pm$ 0.6	3.4 $\pm$ 0.4	3.3 $\pm$ 0.3
Cerebral	HES	5.5 $\pm$ 0.2	7.2 $\pm$ 0.7	5.5 $\pm$ 0.6	6.2 $\pm$ 0.4	7.4 $\pm$ 0.9
A-VDO ₂ (ml•100ml ⁻¹)	HS	5.3 $\pm$ 0.9	7.6 $\pm$ 1.2	4.2 $\pm$ 0.4	6.7 $\pm$ 0.9	7.4 $\pm$ 0.9

CO₂T = cerebral oxygen delivery (CBF $\times$ CaO₂); CMRO₂ = cerebral metabolic oxygen consumption (cerebral blood flow $\times$ arterial oxygen content; Cerebral A-VDO₂ = difference in oxygen content between arterial and sagittal sinus blood

FIGURE LEGENDS

- Figure 1. Experimental sequence.
- Figure 2. Response of mean arterial pressure (A) and cardiac output (B) following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS) or 20% hydroxyethyl starch (HES).
- Figure 3. Response of intracranial pressure (A) and cerebral perfusion pressure (B) following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS) or 20% hydroxyethyl starch (HES).
- Figure 4. Response of cerebral blood flow following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS) or 20% hydroxyethyl starch (HES).

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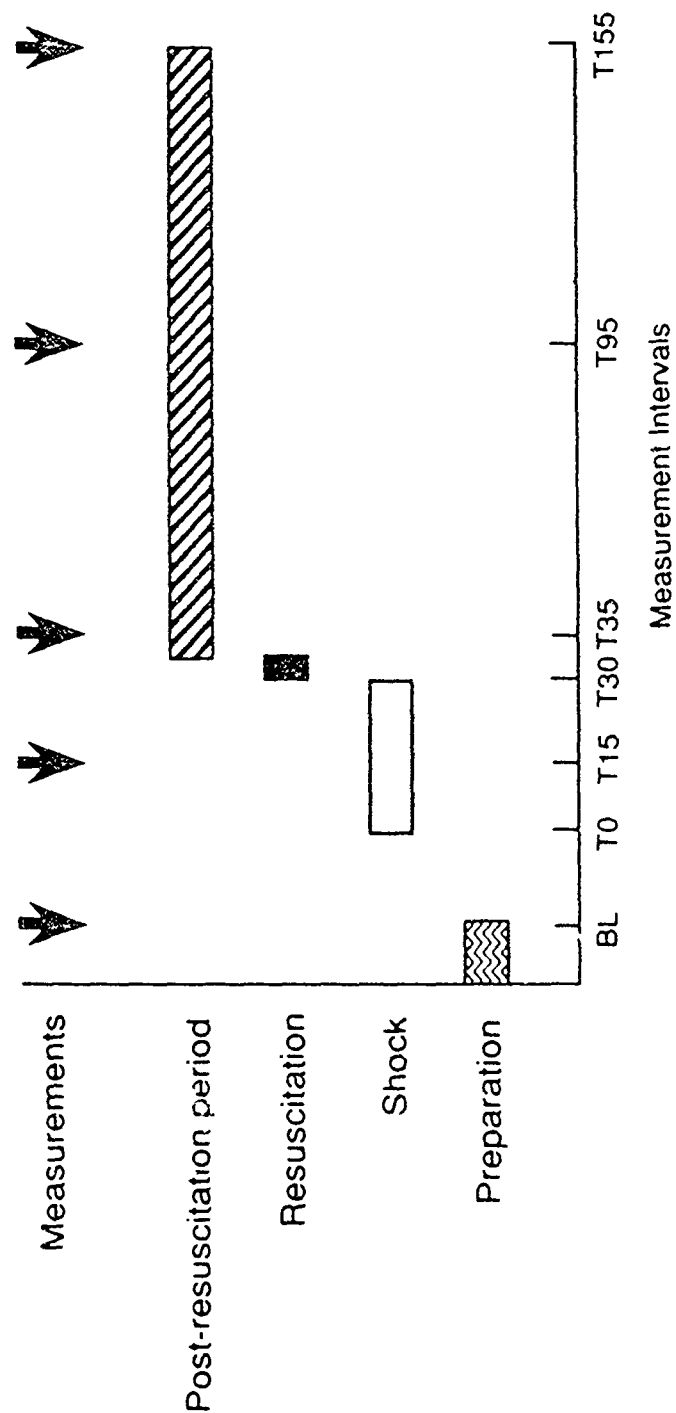
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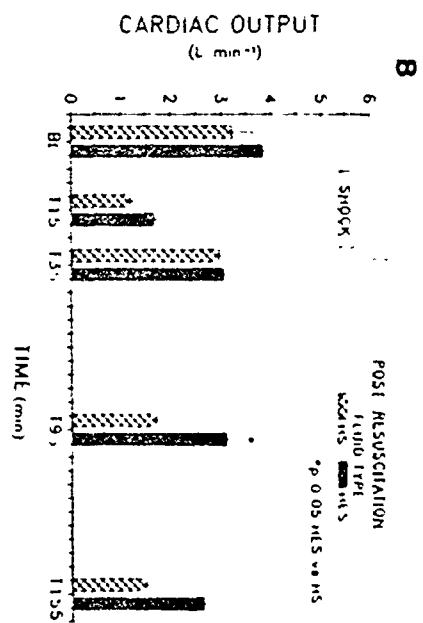
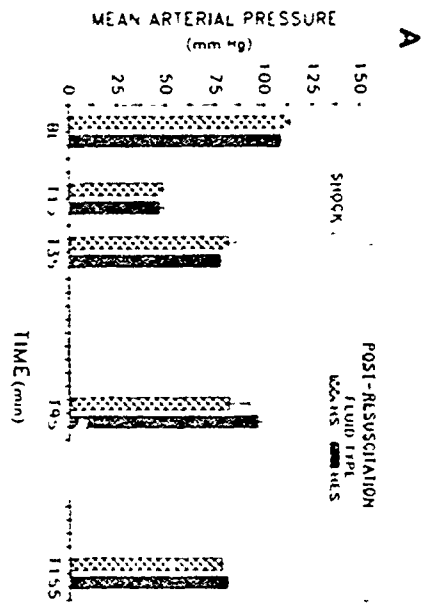
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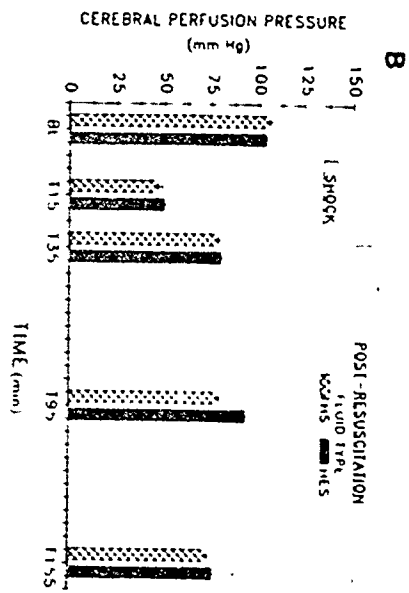
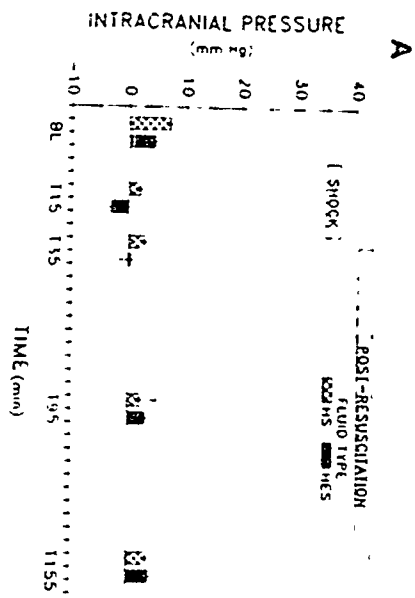
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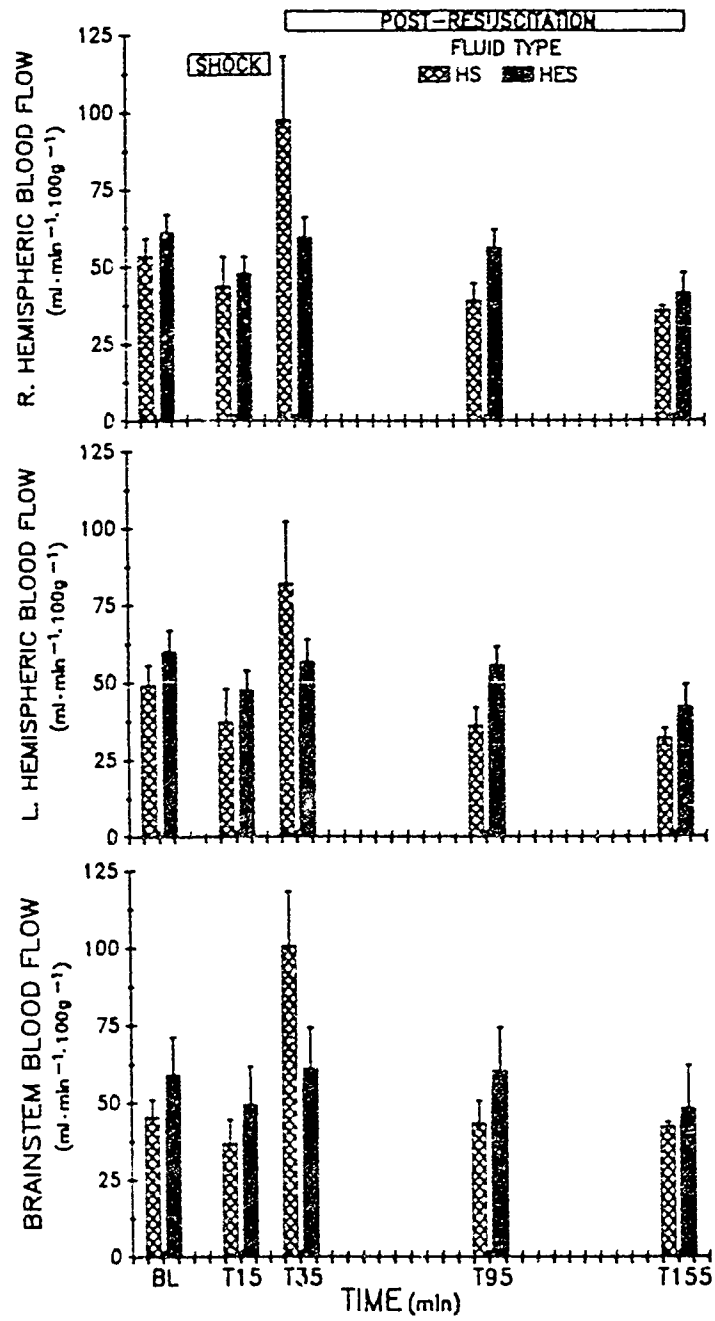
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Experimental Sequence









HEMORRHAGE AND INTRACRANIAL HYPERTENSION IN COMBINATION
INCREASE CEREBRAL PRODUCTION OF THROMBOXANE A₂

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ABSTRACT

Global cerebral ischemia and head trauma are associated with the production and release of thromboxane A₂ (TxA₂) metabolites within brain tissue and into the cerebral venous circulation. The effects of reduced cerebral perfusion pressures produced by hemorrhage alone or in combination with intracranial hypertension on TxA₂ production have not been reported. In this study, 38 anesthetized, mongrel dogs were subjected to 30 minutes of hemorrhagic shock with normal (Group I) or elevated (Group II) intracranial pressure (ICP). Cerebral and systemic hemodynamics including cerebral blood flow (CBF) (sagittal sinus outflow method); ICP; cerebral perfusion pressure (CPP); and arterial and cerebral venous concentrations of TxB₂, the major metabolite of TxA₂, were measured. Following the placement of arterial, pulmonary artery and cisterna magna catheters and cannulation of the sagittal sinus for sampling cerebral venous blood flow for TxB₂ levels (double-antibody radioimmunoassay technique), Group I animals (n = 22) were hemorrhaged to reduce CPP to 40 mm Hg for 30 minutes. In Group II, (n = 16) CPP was reduced by the combination of less severe hypotension and intracranial hypertension (20 mm Hg). Data were obtained at baseline (BL) and at the beginning and end of the 30-minute shock period, designated T0 and T30, respectively. Hemorrhagic shock significantly decreased CBF in both groups ($p < 0.05$). At T0, CBF was higher in Group I than Group II ($p < 0.05$). At T0, venoarterial differences in TxB₂ increased significantly in Group II ($p < 0.05$) but not in Group I. At T30, venoarterial levels of TxB₂ remained significantly higher in Group II ($p < 0.05$). Increased cerebral production of TxA₂ during hypotension accompanied by intracranial hypertension may contribute to the severity of neural damage produced by the combination of head trauma and shock.

INTRODUCTION

Hemorrhage from skeletal, abdominal, and thoracic injuries commonly occurs in combination with head injury in multiple-trauma patients (1). The combination of hypotension and head injury is associated with an increase in mortality and morbidity over that produced by head injury alone (2,3). The early stress responses to both trauma and severe hemorrhage are characterized by a prominent increase in sympathetic neural activity (4,5), accompanied by increased heart rate and myocardial contractility. The duration and magnitude of these cardiovascular alterations depend upon multiple systemic and local factors, including central and peripheral metabolic, circulatory, and neurohumoral changes.

Hemorrhagic hypotension and intracranial hypertension, which commonly accompany acute head injury, may decrease cerebral blood flow (CBF) (6-8). Increased intracranial pressure (ICP), due either to cerebral edema or to expansion of an intracranial mass lesion, may compress brain tissue, shifting brain away from an expanding lesion and generating regional cerebral ischemia in areas that are subjected to sufficient increases in tissue hydrostatic pressure. Increases in tissue pressure inhibit blood flow through the smaller, pressure-sensitive, arteriolar microcirculation (9). Herniation of brainstem or other central nervous system structures due to increased intracranial pressure also produce cerebral ischemia.

Regardless of etiology, cerebral ischemia stimulates the synthesis, activation, and release of potent vasoactive and immunologically active substances (10-13). Complete global cerebral ischemia causes marked release into the cerebral venous circulation of thromboxane B₂ (TxB₂) (14), the major metabolite of thromboxane A₂ (TxA₂), an endogenous eicosanoid with potent platelet aggregatory and vasoconstrictive properties (14,15). This increase in cerebral venous TxB₂, which persists for at least two hours after

reperfusion, is temporally associated with cerebral hypoperfusion (14). Pretreatment with the cyclo-oxygenase inhibitor ibuprofen decreases cerebral venous TxB_2 levels and improves total CBF after global cerebral ischemia (15). Therefore, TxA_2 appears to be an active mediator of pathological changes observed in ischemic neural injury. Studies of traumatic and ischemic cerebral injury in cats (16), rats (17), piglets (13), humans (18), and dogs (14,15) demonstrate increased eicosanoid levels in brain tissue (17), cerebrospinal fluid (18), and cerebral venous effluent (14,15).

The present study was designed to compare the effects of hemorrhagic hypotension alone, and hemorrhage accompanied by intracranial hypertension, on cerebral vascular and systemic hemodynamic parameters and on cerebral generation of TxB_2 .

MATERIALS AND METHODS

Animals used in this study were handled according to the guidelines established by the institutional Animal Care and Use Committee. Thirty-eight mongrel dogs of either sex, weighing 18-22 kg, were randomly divided into two groups. Due to greater surgical mortality in Group II, unequal numbers of animals completed the protocol. Group I (n = 22) was subjected to hemorrhage alone, while Group II (n = 16) was subjected to hemorrhage and expansion of a subdural mass lesion (detailed below). All dogs were fasted overnight, then anesthetized with thiopental sodium $8.0 \text{ mg} \cdot \text{kg}^{-1}$ iv, paralyzed with succinylcholine $4.0 \text{ mg} \cdot \text{kg}^{-1}$ iv, endotracheally intubated, maintained anesthetized with 0.5% halothane in nitrous oxide: oxygen (60:40), and ventilated using an Edco model 822 Large Animal Ventilator (Edco Scientific, Inc., Chapel Hill, NC) at a tidal volume of $15.0 \text{ ml} \cdot \text{kg}^{-1}$ and a rate sufficient to maintain normocarbica (PaCO_2 35-45 mm Hg). Additional succinylcholine given as needed, prevented respiratory movement.

HEMODYNAMIC MEASUREMENTS

Bilateral femoral artery catheters were inserted via cutdown for monitoring of arterial blood pressure and for induction of rapid hemorrhage. A flow-directed, pulmonary artery catheter was placed percutaneously via the right external jugular vein. Systemic and pulmonary pressures were recorded continuously on a Grass 79-D polygraph (Grass Instruments, Quincy, MA) with saline-filled Gould Statham P-23D transducers (Gould Inc., Oxnard, CA). Pulmonary artery occlusion pressure (PAOP) was recorded intermittently throughout the experimental period. Cardiac output (CO) was measured using an American Edwards Sat-1 cardiac output computer (Baxter Edwards Corp., Santa Ana, CA). All transducers were calibrated with the zero level established at the left atrium prior to all hemodynamic measurements except for ICP, which was zeroed at the level of the external

auditory canal (7 cm above left atrial level). Body temperature was monitored by a thermistor on the tip of the pulmonary artery catheter, and temperature was maintained with the use of a heating pad.

CEREBRAL BLOOD FLOW MEASUREMENT

Following placement of indwelling catheters, animals were placed in the left lateral decubitus position and a splenectomy performed. Animals were then turned to the "sphinx" position and the temporalis and occipital musculature was dissected from the underlying bone prior to systemic heparinization ($500 \text{ IU} \cdot \text{kg}^{-1}$). CBF was measured directly in $\text{ml} \cdot \text{min}^{-1}$ using a modification of the technique originally described by Rapela and Green (19), in which the confluence of the lateral and sagittal sinuses was cannulated and timed samples of cerebral venous outflow were collected, measured and reinfused. An 18-ga catheter inserted into the cisterna magna provided continuous ICP measurements. In the group to be subjected to intracranial hypertension, the dura was incised through a right temporo-parietal burr hole, and the balloon tip of a 7-Fr Foley catheter was inserted subdurally.

After instrumentation and surgical preparation, animals were allowed to stabilize for 30 minutes, at which time baseline (BL) data were recorded. In Group II, immediately following baseline measurements, ICP was increased to 20 mm Hg by inflation of the subdural balloon with saline; ICP was maintained at 20 mm Hg with further inflation as necessary throughout the shock period. In both Groups I and II, arterial blood was rapidly removed via an arterial cannula to reduce cerebral perfusion pressure (CPP) and to maintain CPP at a fixed level for 30 minutes by removing or reinfusing blood. Data were collected at the beginning of shock (designated T0) and at the end of the 30-minute shock period (designated T30).

DATA COLLECTED

The following data were collected at BL, T0, and T30: CBF, ICP, systolic and diastolic blood pressures (SAP and DAP, respectively), CO, pulmonary artery systolic and diastolic pressures (PAS and PAD), pulmonary artery occlusion pressure (PAOP), central venous pressure (CVP), and arterial and cerebral venous pH, PaCO₂, PaO₂, and hemoglobin (Hgb). Mean arterial pressure (MAP) and CPP were calculated from the equations:

$$\text{MAP} = \text{DAP} + 1/3 (\text{SAP} - \text{DAP}) \quad \text{Eq. 1}$$

$$\text{CPP} = \text{MAP} - \text{ICP} \quad \text{Eq. 2}$$

RADIOIMMUNOASSAY TECHNIQUES

Simultaneous blood samples were collected from the systemic arterial catheter and the sagittal sinus outflow cannula for the measurement of TxB₂ at BL, T0, and T30. Prior to each blood sample, catheter dead-space volume was discarded (1-2 ml). Simultaneous 4.0 ml blood samples were withdrawn from the systemic arterial and sagittal sinus cannulae into sterile disposable syringes and immediately transferred to blood collection tubes containing 0.5% EDTA and indomethacin (25 mcg•ml⁻¹ whole blood) and maintained on ice until centrifuged at 1500 x G at 4°C for 15 minutes. The plasma was bulb-aspirated, avoiding the white cell buffy coat layer, and placed into 3.5 ml polypropylene test tubes (Sarstedt, Inc., Rahway, NJ). All tubes were labeled and stored (-70°C) prior to analysis. Immunoreactive TxB₂ was assayed directly in plasma by previously described, double-antibody radioimmunoassay techniques (20,21). Cross-reactivities and sensitivity limits of the antibodies and reagent sources have been published (20).

STATISTICAL METHODS

A Kruskal-Wallis test was used to detect significant differences between groups at baseline using the SAS statistical program (SAS Institute, Cary, NC). A repeated measures analysis of variance (ANOVA) was used to test for differences between Groups I and II (22). A repeated measures ANOVA was used to test for time differences (Baseline, T0, and T30). When a time difference was noted, Holm's sequentially rejective multiple comparison test was used to assess when the time differences occurred to maintain an alpha level of 0.05 (23). If an interaction between group and time occurred, time differences were assessed within each group and group differences were assessed at each time point using Holm's multiple comparison procedure.

RESULTS

All values in the text, tables, and figures are expressed as means $\pm$ SEM. Table 1 lists body weight and shed blood volume for both experimental groups. Hemodynamic data are presented in Table 2. Due to experimental design, Hgb, pH, MAP, and CO were lower in Group I at T30, reflecting more severe hemorrhage. PaCO_2 , PaO_2 , and body temperature were comparable among groups at all time intervals.

HEMORRHAGE ALONE (Group I)

The induction of hemorrhage decreased MAP from 135 ± 3 mm Hg at BL to 39 ± 1 mm Hg and 37 ± 1 mm Hg at T0 and T30, respectively (Fig. 1). CO was decreased by 70% at both T0 and T30 ($p < 0.05$) (Table 2). Hgb decreased significantly at T0 ($p < 0.05$), and continued to decrease, albeit minimally, until T30 (Table 2). ICP, allowed to fluctuate freely throughout the shock period, was significantly decreased from BL ($p < 0.05$) (Fig. 2). CPP decreased from 131 ± 3 mm Hg at BL to 41 ± 1 mm Hg and 40 ± 1 mm Hg at T0 and T30, respectively ($p < 0.05$) (Fig. 3). CBF decreased significantly from 38 ± 2 $\text{ml} \cdot \text{min}^{-1}$ at BL to 22 ± 2 $\text{ml} \cdot \text{min}^{-1}$ at T0 ($p < 0.05$), where it remained (Fig. 4).

Immunoreactive TxB_2 plasma measurements at all time points were unchanged in arterial and sagittal sinus venous plasma (Table 3), although a small, statistically insignificant increase in the venoarterial difference of the TxB_2 concentration developed during the shock period (Fig. 5).

HEMORRHAGIC PLUS INTRACRANIAL MASS LESION (Group II)

Baseline MAP, 119 ± 6 mm Hg, decreased to 59 ± 3 mm Hg and 54 ± 2 mm Hg at T0 and T30 ($p < 0.05$), respectively (Fig. 1). As a result of ICP manipulation, less hemorrhage was required in Group II to reduce CPP to the target level, resulting in a significantly higher MAP at T0 and T30 compared to Group I ($p < 0.05$, intergroup comparison at T0 and T30). CO was decreased at T0 and T30 by 50% of baseline ($p < 0.05$) (Table 2). Hgb levels, 13.96 ± 0.5 g•dl⁻¹ at baseline, decreased at T0 ($p < 0.05$), but showed no further decline at T30 (Table 2). ICP, 5.5 ± 0.7 mm Hg at baseline, was experimentally maintained at 20 mm Hg throughout the 30-minute shock period (Fig. 2). CPP decreased at T0 and T30 to 40 ± 3 mm Hg and 34 ± 2 mm Hg, respectively ($p < 0.05$) (Fig. 3). CBF decreased from 31 ± 2 ml•min⁻¹ at BL to 12 ± 1 ml•min⁻¹ at T0 where it remained ($p < 0.05$) (Fig. 4).

Immunoreactive TxB₂ in Group II was similar to Group I in arterial and sagittal sinus samples at BL (Table 3). However, at T0 and T30, sagittal sinus TxB₂ levels increased significantly to $1,724 \pm 140$ pg•ml⁻¹ and $1,894 \pm 188$ pg•ml⁻¹, respectively, while arterial TxB₂ remained similar to Group I. At T0 and T30, sagittal sinus TxB₂ and the venoarterial difference in TxB₂ (Fig. 5) were significantly greater in Group II than in Group I ($p < 0.05$).

DISCUSSION

Hemorrhagic hypotension accompanied by intracranial hypertension (20 mm Hg), produced by a subdurally placed, expanding mass lesion, causes a significant and sustained release of immunoreactive TxB_2 into the cerebral venous circulation in association with a severe decline in CBF. Hemorrhage alone, sufficient to reduce CPP to a similar level, does not increase cerebral venous TxB_2 . These data suggest that incomplete cerebral ischemia, like complete cerebral ischemia, is associated with intracerebral generation of TxA_2 , although they do not clarify whether the increase in TxA_2 is a secondary phenomenon or whether, through its cerebral vasoconstrictor effects, TxA_2 produces cerebral ischemia.

The decline in CBF associated with severe hemorrhagic hypotension or acutely increased ICP has been extensively investigated (6-8,24). The cerebral vasculature has the unique ability to autoregulate CBF in response to mild reductions in CPP and to preferentially redistribute arterial perfusion within the brain. As hypotension becomes more severe, CBF is better preserved in critical areas of the brain, primarily the cardiovascular and respiratory centers in the brainstem (6,25). The primary mechanism for flow redistribution is thought to be local cerebral arteriolar vasodilation. Endogenous release of vasoactive substances and neurotransmitters such as adenosine (26) and eicosanoids (13,27) modulates changes in CBF. During profound hypotension, α -adrenergic blockade, which exerts no effect on resting CBF, increases CBF, suggesting that sympathetic activation during shock may increase cerebrovascular resistance (28). If CBF is sufficiently reduced by hemorrhagic hypotension or intracranial hypertension, cerebral ischemia ensues.

Global cerebral ischemia results in the release of TxB_2 into the cerebral venous circulation (14,15). Head trauma also stimulates eicosanoid production in brain tissue (17,18).

The intergroup differences found during the shock interval were not due to baseline differences in the measured variables between groups, since baseline differences were adjusted using multivariate repeated measures ANOVA. In the present experiment, Group I and Group II had similar CPP during early hemorrhage and only a small difference after 30 minutes of shock. CBF in Group I averaged $10 \text{ ml} \cdot \text{min}^{-1}$ more than in Group II throughout the shock interval. Because TxB_2 is produced in ischemic vascular beds (10,14,15,20), the appearance of a positive veno-arterial gradient of plasma TxB_2 implies ischemia proximal to the venous sampling site. In Group I, the total CBF of $23\text{-}24 \text{ ml} \cdot \text{min}^{-1}$ may have been sufficient to prevent cerebral ischemia. Although we cannot exclude the possibility that hemorrhagic hypotension produced regional cerebral ischemia in Group I, we can conclude that the less profound decrease in CBF produced by hemorrhage alone did not result in increased release of TxB_2 into the cerebral venous circulation.

In Group II, total CBF decreased to $11 \pm 1.0 \text{ ml} \cdot \text{min}^{-1}$ by the conclusion of the shock interval, less than half that measured in Group I. Because cerebral ischemia stimulates the release of TxB_2 (10,14,15), the additional decrement in CBF may have precipitated global cerebral ischemia. Another possible explanation for the increase in cerebral venous TxB_2 in Group II is that local distortion of the brain parenchyma and vasculature by balloon inflation may have produced sufficient mechanical and hydrostatic pressure to impair regional cerebral blood flow. Alternatively, mechanical disruption of the brain microvasculature by balloon inflation could have initiated the intravascular release of arachidonic acid and subsequent synthesis of TxA_2 . However, the data in Group II are also consistent with the possibility that generation of TxA_2 further reduces CBF, a possibility that requires further study.

In summary, the combination of intracranial hypertension and systemic hypotension results in a prominent increase in the release of TxB_2 , a potent cerebral vasoconstrictor and promoter of platelet aggregation, into cerebral venous effluent. Despite comparable levels of CPP, CBF tended to be lower in animals with a combined injury than in those that underwent hemorrhage alone. If these data can be extrapolated to human multiple trauma, it is possible that the release of TxB_2 in response to the combination of intracranial hypertension and systemic hypotension could contribute to increased mortality and morbidity following head injury combined with shock. Further animal studies are necessary to define the effects of resuscitation from profound shock on cerebral release of TxB_2 and to determine the effects of inhibitors of TxA_2 synthesis or action on cerebral vascular physiology and neurologic outcome.

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Table 1. Body Weight and Shed Blood Volume (Means $\pm$ SEM)

	N	Weight (kg)	Shed Blood Volume (ml $\cdot$ kg ⁻¹)
Group I	22	21.2 $\pm$ 1.1	32.0 $\pm$ 3.1
Group II	16	21.0 $\pm$ 1.3	22.2 $\pm$ 4.0

Table 2. Systemic and Cerebral Variables (Means $\pm$ SEM)

		BL	T0	T30
PaCO ₂ (mm Hg)	Group I	40.0 $\pm$ 0.5	31.3 $\pm$ 0.9	41.1 $\pm$ 1.6
	Group II	38.5 $\pm$ 0.6	34.5 $\pm$ 0.8	44.3 $\pm$ 1.1
PaO ₂ (mm Hg)	Group I	226 $\pm$ 6	216 $\pm$ 5	229 $\pm$ 17
	Group II	271 $\pm$ 14	254 $\pm$ 15	253 $\pm$ 14
Temp (°C)	Group I	37.1 $\pm$ 0.3	37.1 $\pm$ 0.4	37.6 $\pm$ 0.2
	Group II	37.2 $\pm$ 0.3	37.3 $\pm$ 0.3	37.9 $\pm$ 0.3
pH	Group I	7.37 $\pm$ 0.00	7.40 $\pm$ 0.01	7.19 $\pm$ 0.01*
	Group II	7.39 $\pm$ 0.08	7.40 $\pm$ 0.01	7.29 $\pm$ 0.01
MAP (mm Hg)	Group I	135 $\pm$ 3*	40 $\pm$ 1*	38 $\pm$ 1*
	Group II	119 $\pm$ 6	59 $\pm$ 3*	54 $\pm$ 2*
CO (L $\cdot$ min ⁻¹)	Group I	2.7 $\pm$ 0.2	0.7 $\pm$ 0.0*	0.8 $\pm$ 0.0*
	Group II	3.5 $\pm$ 0.4	1.7 $\pm$ 0.2*	2.0 $\pm$ 0.3*
Hgb (g $\cdot$ dl ⁻¹)	Group I	11.8 $\pm$ 0.4*	10.5 $\pm$ 0.3*	10.1 $\pm$ 0.3*
	Group II	13.9 $\pm$ 0.5	12.6 $\pm$ 0.4*	12.7 $\pm$ 0.3*
ICP (mm Hg)	Group I	4.2 $\pm$ 0.8	-1.6 $\pm$ 1.0*	-2.5 $\pm$ 0.6*
	Group II	5.5 $\pm$ 0.7	19.6 $\pm$ 0.2*	20.4 $\pm$ 0.7*
CPP (mm Hg)	Group I	131 $\pm$ 3*	41 $\pm$ 1*	40 $\pm$ 1*
	Group II	114 $\pm$ 6	40 $\pm$ 3*	34 $\pm$ 2*
CBF (ml $\cdot$ min ⁻¹)	Group I	38 $\pm$ 2*	23 $\pm$ 2*	24 $\pm$ 1*
	Group II	31 $\pm$ 2	12 $\pm$ 1*	11 $\pm$ 1*

PaCO₂ = arterial carbon dioxide tension; PaO₂ = arterial oxygen tension; Temp = blood temperature; MAP = mean arterial pressure; CO = cardiac output; Hgb = hemoglobin; ICP = intracranial pressure; CPP = cerebral perfusion pressure; CBF = cerebral blood flow.

* = $p < 0.05$ Group I and Group II Intergroup Comparison

* = $p < 0.05$ Group I and Group II Intragroup Comparison (BL - T0, BL - T30)

Table 3. Plasma Arterial and Cerebral Venous TxB₂ Levels (Means ± SEM)

		BL	T0	T30
Arterial TxB ₂ (pg•ml ⁻¹)	Group I	647±69	469±43	707±58
	Group II	726±171	618±106	613±126
Sagittal Sinus TxB ₂ (pg•ml ⁻¹)	Group I	682±71	557±50	862±104
	Group II	961±188	1724±178 ⁺	1894±238 ⁺
Venoarterial TxB ₂ (pg•ml ⁻¹)	Group I	35±40	87±45	154±78
	Group II	235±139	1106±134 ⁺	1281±196 ⁺

^{*} = p<0.05, Group I & Group II Intergroup Comparison

⁺ = p<0.05, Group II Intragroup Comparison (BL - T0, BL - T30)

LEGENDS

- Figure 1. Mean arterial pressure in Groups I and II at BL (just prior to balloon inflation), immediately following acute hemorrhage (T0) and after 30 minutes of hemorrhagic shock (T30).
- Figure 2. Intracranial pressure in Groups I and II at BL (just prior to balloon inflation), immediately following acute hemorrhage (T0) and after 30 minutes of hemorrhagic shock (T30).
- Figure 3. Cerebral perfusion pressure in Groups I and II at BL (just prior to balloon inflation), immediately following acute hemorrhage (T0) and after 30 minutes of hemorrhagic shock (T30).
- Figure 4. Cerebral blood flow (measured in $\text{ml} \cdot \text{min}^{-1}$) by the cerebral venous outflow technique at BL, immediately following hemorrhage (T0) and after 30 minutes of hemorrhagic shock (T30).
- Figure 5. Cerebral venoarterial difference of thromboxane A_2 (measured as its stable metabolite, thromboxane B_2) at BL, immediately following induction of hemorrhage (T0), and after 30 minutes of shock (T30).

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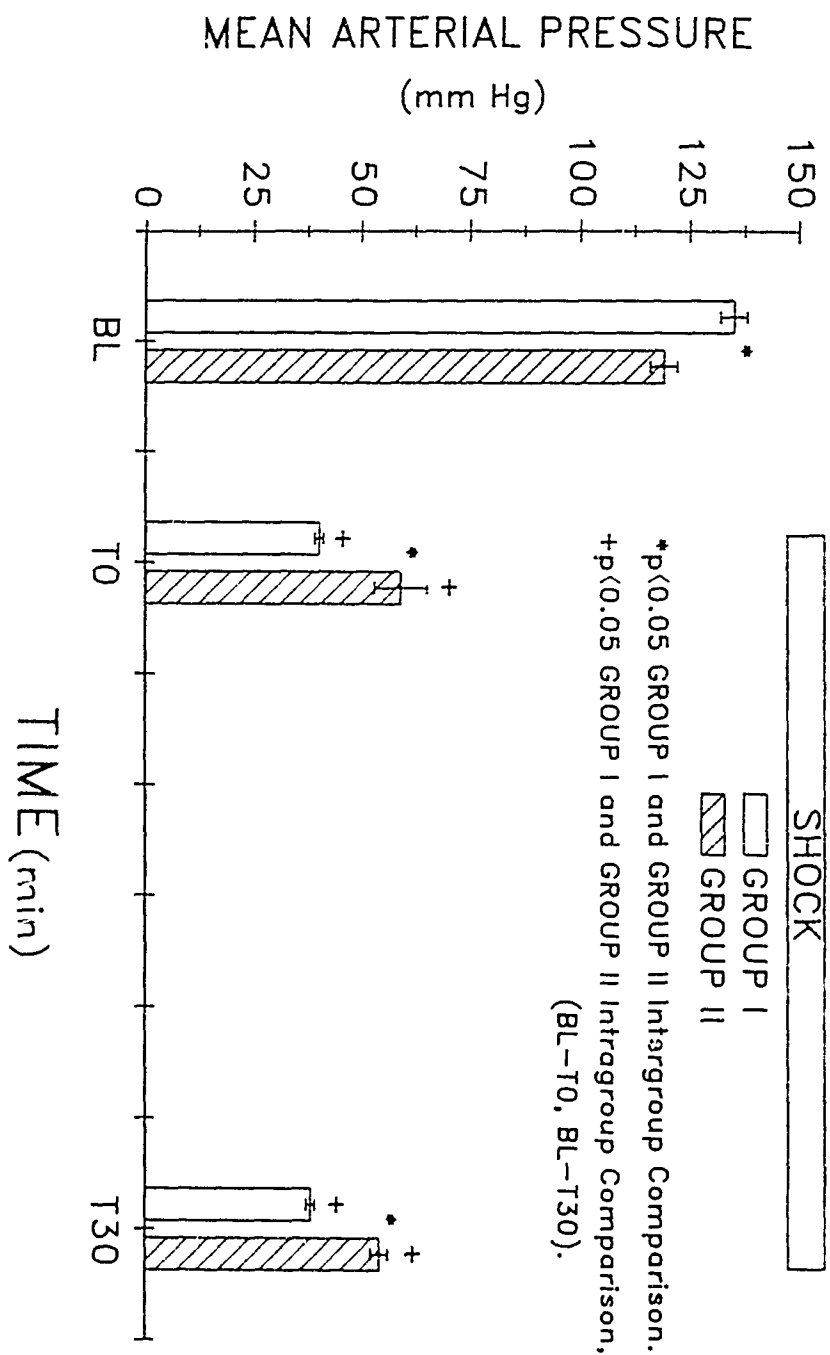
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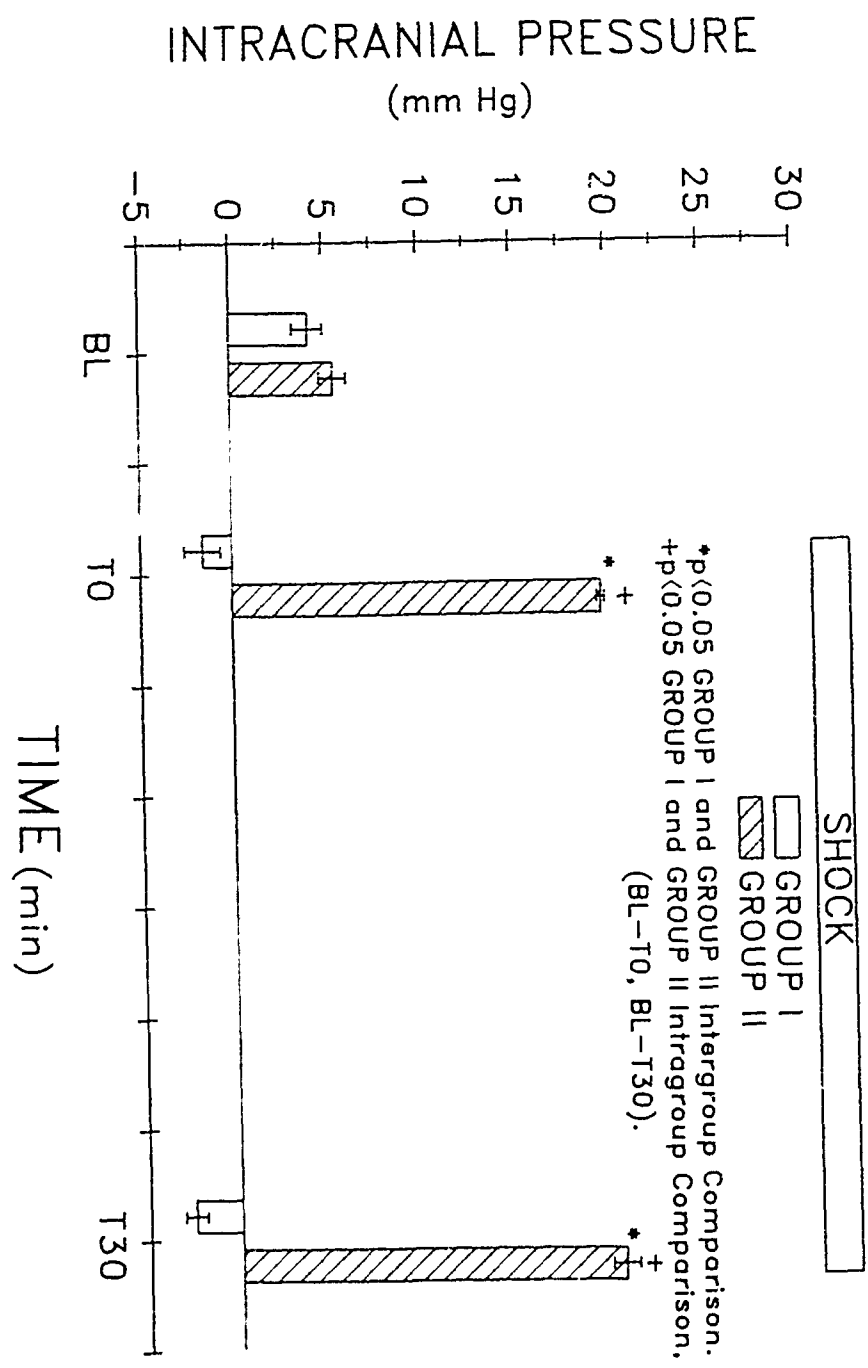
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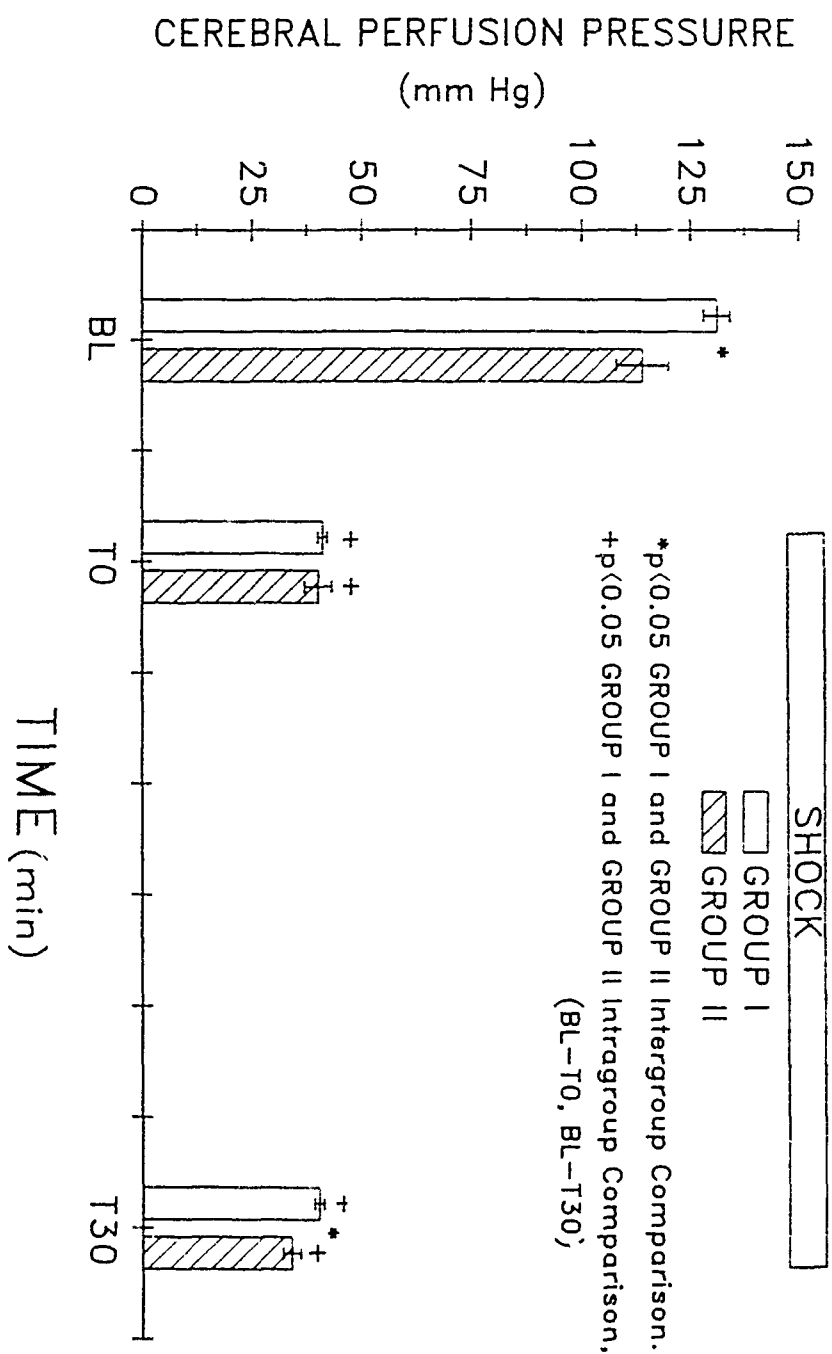
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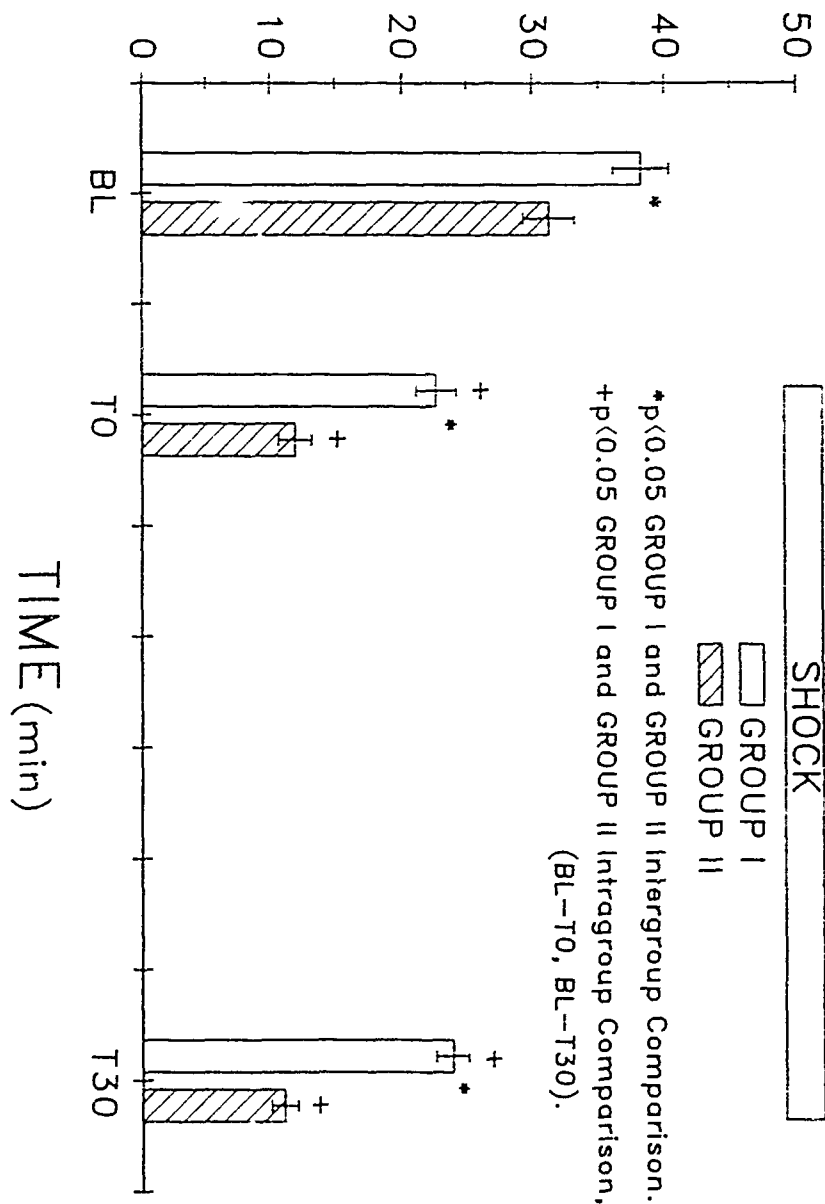
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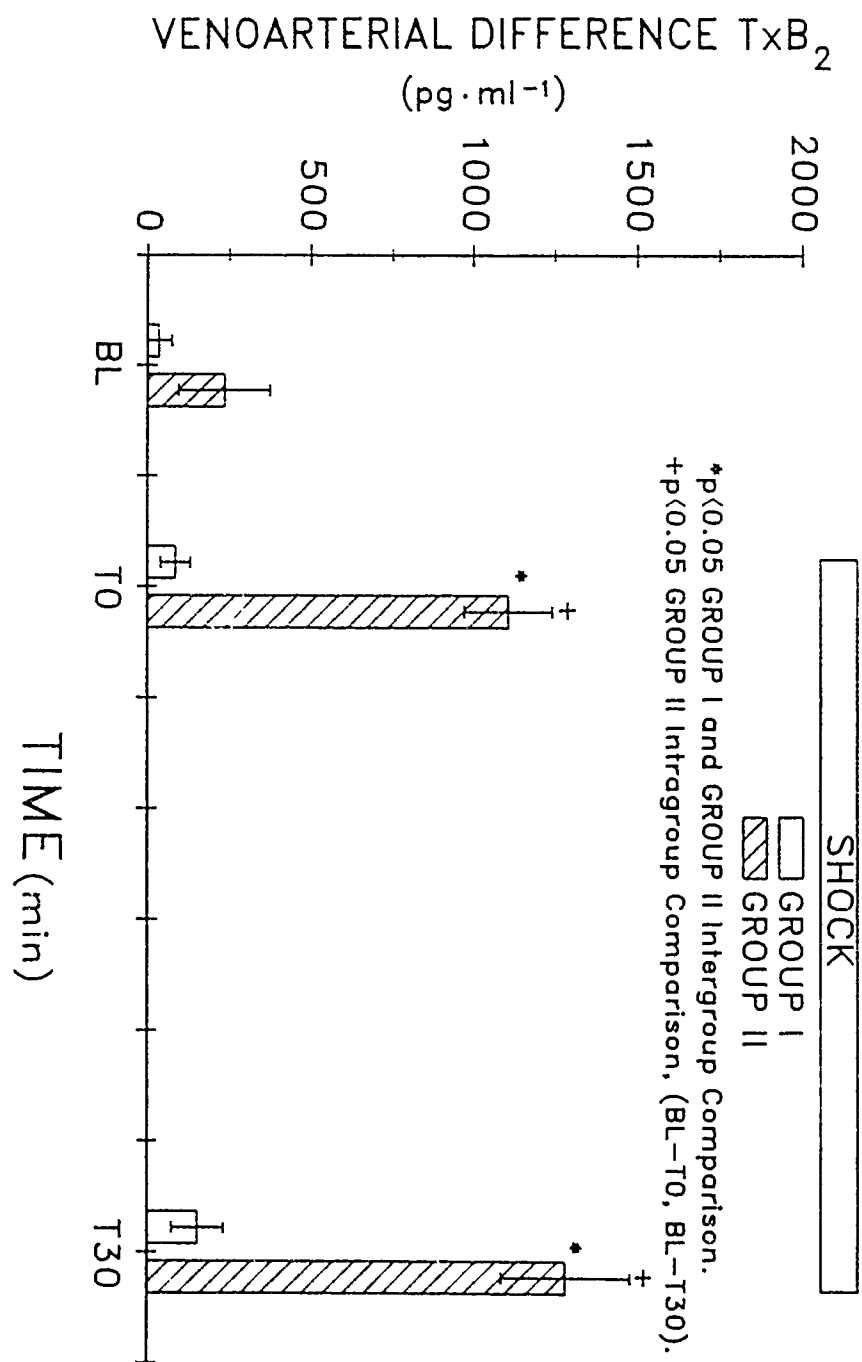






CEREBRAL BLOOD FLOW (ml · min⁻¹)





RESUSCITATION FROM HEMORRHAGIC SHOCK WITH HYPERTONIC SALINE
IN THE PRESENCE OF A SUBDURAL MASS

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ABSTRACT

We compared canine cerebrovascular and systemic hemodynamics following fluid resuscitation with $6.0 \text{ ml} \cdot \text{kg}^{-1}$ of 7.2% saline to $54 \text{ ml} \cdot \text{kg}^{-1}$ of 0.8% saline (providing an equal sodium load) in a model of intracranial hypertension (produced by inflation of a subdural balloon) and hemorrhagic shock. Twelve anesthetized, intubated mongrel dogs were ventilated with 0.5% halothane in nitrous oxide and oxygen (60:40) to maintain normocarbida. While intracranial pressure (ICP) was maintained at 20 mm Hg by inflation of a right-hemispheric, subdural balloon, rapid hemorrhage reduced mean arterial pressure to 55 mm Hg and maintained it at that level for 30 minutes. Subsequently, over five minutes, one of two randomly assigned resuscitation fluids was infused: (1) 7.2% hypertonic saline, $6 \text{ ml} \cdot \text{kg}^{-1}$ (HS; 1232 mEq/L sodium) or 0.8% saline $54 \text{ ml} \cdot \text{kg}^{-1}$ (SAL; 135 mEq/L sodium). As fluid infusion began, ICP was permitted to vary without further manipulation. Data were collected at baseline (BL), after balloon inflation (BI), at the beginning of the shock interval (T0), at the end of the shock interval (T30), immediately following fluid infusion (T35), and at thirty-minute intervals thereafter for two hours (T65, T95, T125, T155). ICP and cerebral blood flow were compared among groups using repeated measures ANOVA. Although SAL produced a slightly more rapid increase in mean arterial pressure, the levels were comparable from T65 to T155. At T35 and T65, ICP in the SAL group increased significantly compared to HS which decreased slightly ($p < 0.05$ at both intervals). By T95, ICP in group HS had increased to $30 \pm 5 \text{ mm Hg}$, comparable to SAL ($32 \pm 3 \text{ mm Hg}$). Despite the differences in ICP at T35 and T65, CBF was comparable at all intervals after resuscitation. Neither fluid restored CBF to baseline values. Following a severe

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reduction in cerebral perfusion pressure, resuscitation with hypertonic saline fails to sustain a lower ICP than conventional crystalloid resuscitation fluid therapy and does not improve forebrain CBF.

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Key words: Hemorrhagic shock
Intracranial pressure
Subdural mass
Hypertonic saline
Resuscitation
Cerebral blood flow

Running title: Hypertonic resuscitation following hemorrhage.

INTRODUCTION

Traumatic hypotension is associated with increased mortality in patients who have suffered closed head injury.¹³ In patients with a Glasgow Coma Score ≤ 8 on admission to the hospital, a systolic blood pressure less than 90 mm Hg is associated with a risk of poor neurologic outcome that is 13 times greater than the risk in those patients in whom systolic arterial pressure exceeds 90 mm Hg.³ This may in part be due to impaired cerebral autoregulation following head injury, a phenomenon that has been demonstrated in animals {Llewellyn} and man {Muizelaar, Bruce 75}. Head-injured patients are particularly likely to demonstrate impaired autoregulation if they have sustained extra-axial hematomas {Bruce 75}. However, despite increased vulnerability to hypotension, little is known about cerebral circulatory responses to fluid resuscitation in situations in which both an intracranial mass lesion and hemorrhage are present.

Hemorrhagic shock reduces ICP in animals without intracranial pathology²¹ and reduces ICP to an even greater extent if an intracranial mass lesion exists.^{6,19} Subsequent restoration of blood pressure rapidly increase ICP, the magnitude of increase depending upon the type of resuscitation fluid used.^{6,19} Small volumes (4.0-6.0 ml•kg⁻¹) of hypertonic resuscitation solutions produce a minimal increase in ICP in comparison to the large increase associated with conventional crystalloid solutions,^{5,20,21} yet produce substantial improvements in blood pressure, cardiac output, and survival after otherwise lethal hemorrhage.^{5,15,23,26,29} Hypertonic solutions are associated with lower post-resuscitation ICP even when infused in a volume sufficient to produce hyperdynamic cardiac output values.⁶⁻⁸ However, previous models that combine hemorrhagic shock and an intracranial mass lesion have not experimentally maintained

intracranial hypertension during hemorrhage.^{6,7,19} Therefore, they may not replicate the effect on ICP of an expanding intracranial mass lesion, in a multiply injured patient.

The present study combines hemorrhagic shock and decreased intracranial compliance, produced by a subdural mass lesion that is progressively expanded during hemorrhage, to compare the cerebrovascular and systemic hemodynamic effects of resuscitation with equal quantities of sodium, either highly concentrated in a small volume (7.2% saline; $6.0 \text{ ml} \cdot \text{kg}^{-1}$) or less concentrated in a larger volume (0.8% saline; $54 \text{ ml} \cdot \text{kg}^{-1}$).

METHODS

Twelve mongrel dogs weighing 18-24 kg were handled according to guidelines established by the institutional Animal Care and Use Committee. Dogs were fasted overnight, anesthetized with intravenous thiopental sodium ($8.0 \text{ mg} \cdot \text{kg}^{-1}$), paralyzed with intravenous vecuronium ($0.2 \text{ mg} \cdot \text{kg}^{-1}$), endotracheally intubated, and maintained under anesthesia with halothane 0.5% in nitrous oxide and oxygen (60:40). Animals were mechanically ventilated at a rate and tidal volume ($15 \text{ ml} \cdot \text{kg}^{-1}$) necessary to maintain normocarbida.

Bilateral femoral arterial catheters were placed to monitor arterial blood pressure and to induce rapid hemorrhage. A pulmonary artery catheter was inserted percutaneously via the right external jugular vein. Systemic and pulmonary pressures were recorded continuously on a Grass model 79D polygraph (Grass Instrument Co., Quincy, MA) with saline-filled Gould-Statham P23 transducers (Gould, Inc., Oxnard, CA). Pulmonary artery occlusion pressure (PAOP) was recorded intermittently. Cardiac output (CO) was recorded intermittently using an American Edwards Sat-1 CO computer (American Edwards, Corp., Santa Ana, CA). All transducers were intermittently calibrated with the zero level established at the level of the left atrium. Blood temperature was monitored by a thermistor on the tip of the pulmonary artery catheter. Body temperature was maintained using a heating pad applied to the trunk and extremities.

Following splenectomy, animals were turned to the prone "sphinx" position, and the temporalis and occipital musculature dissected from the skull. After heparinization ($500 \text{ IU} \cdot \text{kg}^{-1}$), the confluence of the sagittal and lateral sinuses was cannulated.

Cerebral blood flow (CBF) was measured in $\text{ml} \cdot \text{min}^{-1}$ using timed samples of cerebral venous outflow, a technique originally described by Rapela and Green.²² An 18-ga catheter inserted into the cisterna magna, zeroed to the level of the external auditory canal (7 cm above the left atrium), provided continuous ICP monitoring. The dura was incised through a right temporoparietal burr hole and the balloon tip of a 7-Fr Foley catheter was inserted subdurally. Animals were subjected to no further manipulation during the subsequent 30 minutes.

Baseline (BL) measurements included: CBF, ICP, systolic and diastolic arterial pressure (SAP and DAP), systolic and diastolic pulmonary artery pressure (PAS and PAD), PAOP, CO, and serum osmolality (5500 Vapor Pressure Osmometer, Wescor, Inc., Logan, UT). Arterial and cerebral venous pH, PCO_2 , and PO_2 were measured with an IL 1306 blood gas analyzer and arterial and cerebral oxygen saturation and hemoglobin (Hgb) were analyzed in an Il 282 CO-Oximeter (Instrumentation Laboratory, Lexington, MA). From the collected data we calculated mean arterial pressure ($\text{MAP} = \text{DAP} + 1/3 [\text{SAP} - \text{DAP}]$), cerebral perfusion pressure ($\text{CPP} = \text{MAP} - \text{ICP}$), cerebral arteriovenous oxygen content difference (cerebral A-V DO_2), and estimated cerebral oxygen consumption (CMRO_2) in $\text{ml} \cdot \text{min}^{-1}$ as $\text{CBF} \times \text{the cerebral A-VDO}_2$ and cerebral oxygen transport (CO_2T) in $\text{ml} \cdot \text{min}^{-1}$ as $\text{CBF} \times \text{arterial O}_2 \text{ content (CaO}_2\text{)}$.

Immediately following baseline (BL) measurements, ICP was increased to 20 mm Hg by inflation of the subdural balloon with saline and was maintained at that level throughout shock. Following balloon inflation (BI), a second data set was obtained. Arterial blood withdrawal then rapidly reduced MAP to 55 mm Hg and maintained it at

that level for 30 minutes. Data were recorded at the beginning and end of the 30-minute shock interval at measurement intervals designated T0 and T30 where T = time and the subsequent number denotes the minutes elapsed since the beginning of the shock interval. Animals were then randomly assigned to receive one of two resuscitation fluids over a five-minute interval: Group HS received $6 \text{ ml} \cdot \text{kg}^{-1}$ of 7.2% NaCl ($1232 \text{ mEq} \cdot \text{L}^{-1} \text{ Na}^+$), and group SAL received $54 \text{ ml} \cdot \text{kg}^{-1}$ of 0.8% saline ($137 \text{ mEq} \cdot \text{L}^{-1} \text{ Na}^+$). As resuscitation began, ICP was allowed to vary independently. Data were collected immediately following fluid infusion (T35) and at thirty minute intervals thereafter for two hours, designated as T65, T95, T125, and T155. Figure 1 summarizes the experimental preparation.

Statistical Analysis

The Kruskal-Wallis test was employed to detect differences between the three fluid groups at BL and BI. A multivariate repeated measures analysis of variance (ANOVA) was performed to determine if interactions between groups and time existed.⁴ Interactions were analyzed further with the Holm's sequentially rejective multiple test procedure using a significant level of 0.05.⁹ To assess time or group differences when an interaction was not present, a multivariate repeated measures ANOVA and an analysis of covariance were performed on the dependent variables.

RESULTS

Mean body weights and volumes of shed blood during hemorrhage for Group HS and SAL are listed in Table 1. In this and all subsequent tables and figures, the data are reported as means $\pm$ SEM. Body weight and shed blood volume were comparable between groups.

Mean Arterial Pressure

Both fluid groups exhibited comparable MAP at BL, BI, T0, and T30 (Figure 2). Fluid resuscitation (T35) rapidly increased MAP in the SAL group to 80 ± 6 mm Hg where it remained throughout the experimental period. Infusion of HS produced a gradual increase in MAP over the first thirty minutes to a maximum pressure of 88 ± 5 mm Hg at T65. At no time did either of the two resuscitation fluids restore MAP to baseline. There were no significant post-resuscitation differences in MAP.

Cardiac Output

Cardiac output (CO) declined during hemorrhage to approximately 50% of baseline (Figure 3). CO increased following resuscitation in both groups with SAL resulting in significant increases in CO compared to HS at T35 ($p < 0.05$). By T65, CO had declined in both groups. There were no subsequent significant differences.

Other Systemic Variables

PaCO₂, hemoglobin (Hgb), PaO₂, pH, blood temperature, and PAOP were similar among groups at all time intervals (Table 2). After resuscitation, serum osmolality was greater in the HS group ($p < 0.05$ HS vs SAL at T95 and T155).

Cerebral Hemodynamic Data

Intracranial Pressure

ICP (Fig. 4) was similar before balloon inflation in the both groups and was maintained at 20 mm Hg throughout the shock interval (T0-T30). Resuscitation (T35) resulted in initial increases in ICP in the SAL group in comparison to T30 values in the SAL group ($p < 0.05$) and in comparison to the HS group which remained at shock levels ($p < 0.05$ SAL vs HS at T35). By T65, ICP in the SAL group remained significantly greater than during shock ($p < 0.05$ T30 vs T65). ICP in the HS group remained significantly lower at 20 ± 3 mm Hg ($p < 0.05$ SAL vs HS at T65). ICP in the HS group increased gradually between T65 and T95 to 30 ± 5 mm Hg, comparable to ICP in the SAL group. Fluid resuscitation with either fluid increased ICP significantly over the duration of the post-resuscitation interval ($p < 0.05$, T30 vs T95, T125 and T155 within both groups).

Cerebral Perfusion Pressure

CPP (Fig. 5) followed the same general pattern as MAP and was statistically similar between groups throughout the post-resuscitation interval.

Cerebral Blood Flow

During shock, CBF declined significantly in both groups compared to baseline CBF (Fig. 6) ($p < 0.05$ within each group). Resuscitation (T35) was associated with an increase in CBF in both groups with HS resulting in greater, though not statistically different increases. After T35, CBF declined gradually in both groups.

Table 4 lists interval changes in cerebral A-VDO₂, CMRO₂, and CO₂T. Note that the units for the later two measurements are ml•min⁻¹ to correspond to the units of CBF

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measurements. There were no significant differences in these variables.

DISCUSSION

Trauma is the leading cause of death in the United States for persons under the age of 45 (1-3; Wisner paper) with head injury accounting for approximately 50 to 60% of the trauma deaths (2,4,5; Wisner paper). While a majority of these deaths occur at the scene, many also occur during patient transport (4,6; Wisner paper). Seventy percent of victims of motor vehicle trauma, the largest single group of civilian trauma victims, have accompanying head injury (7,8; Wisner paper). Patients with multiple injuries often require vigorous fluid resuscitation at the scene and during transport to replace deficits as well as ongoing blood loss (9,10,11; Wisner paper). Conventional fluid resuscitation usually consists of large volumes of isotonic crystalloid solutions. The rapid infusion of large volumes of isotonic crystalloid increases ICP and may promote the formation of cerebral edema by decreasing colloid oncotic pressure, although recent data discounts decreased oncotic pressure as a mechanism producing increased ICP in non-injured brain following crystalloid administration {1599,1142}. To avoid resuscitation-induced increases in ICP, as well as to develop more rapidly effective resuscitation regimens, investigators have evaluated small volumes of hyperosmolar saline as a substitute for larger volumes of isotonic or slightly hypotonic fluids. To date, a number of studies have reported effective, acute resuscitation with hyperosmolar saline solutions in a fraction of the required volume of isotonic crystalloid {1986,1898,1078,1135,1112,1127,1087,1070, 1303,1987,1299,1069,1119, Whitley, Prough}. Hypertonic saline solutions also appear to increase myocardial efficiency {1303}, lower pulmonary artery pressures, reduce systemic vascular resistance (Gazitua, Rowe, Norlich and Rocha E Silva), enhance central venoconstriction (new Lopes '86) and preferentially

redistribute blood volume centrally by precapillary vasoconstriction of muscle and skin vascular beds (Rocha E Silva '86, Lundvall '69). The added benefits of low cost and long shelf life make hyperosmolar saline solutions especially attractive for use following civilian and military trauma.

In addition to rapidly improving blood pressure and cardiac output, hypertonic saline resuscitation lowers ICP, improves cerebral perfusion pressure, and sometimes enhances CBF in comparison to isotonic saline solutions (3,5,11,12; Prough paper, Whitley). Prough et al compared a single bolus of 7.5% saline ($6.0 \text{ ml} \cdot \text{kg}^{-1}$) to lactated Ringer's solution ($60 \text{ ml} \cdot \text{kg}^{-1}$) following a 30 minute interval of hemorrhagic shock, produced by rapid blood loss approximating 50% of canine blood volume ($40 \text{ ml} \cdot \text{kg}^{-1}$) (3). Administration of 7.5% saline was associated with a significantly lower post-resuscitation ICP but a similar, reduced level of CBF ($^{133}\text{Xenon}$ clearance method) and cerebral oxygen transport. Subsequently, Whitley et al, using a model that combined using a hemorrhagic shock decreased intracranial compliance (produced by inflation of a subdural balloon), reported that 7.2% saline significantly improved regional CBF (radioactive microsphere technique) in comparison to 0.8% saline in dogs (Whitley, ASA abstract).

In 1988, Gunnar et al compared the systemic and cerebral hemodynamic effects of resuscitation with 3.0% saline, 0.9% saline, and 10% dextran-40 (11). Following a one hour interval of hemorrhagic shock, (shed blood volume approximating $32 \text{ ml} \cdot \text{kg}^{-1}$; MAP 51-74 mm Hg), one-half of the original shed blood was reinfused followed by infusion of one of the test fluids in a volume equal to the initial shed blood volume. The investigators subsequently infused 1500 ml of 0.9% saline over the ensuing 1.25 hours,

then reinfused the remaining one-half of the shed blood (11). ICP in animals that had received 10% dextran-40 or 0.9% saline significantly exceeded that in the 3% saline group. In a subsequent study, Gunnar et al compared the effects on ICP of the same three fluid choices in a similar hemorrhagic shock model in which intracranial compliance was limited by the inflation of an epidural balloon (5). Systemic hemodynamics and ICP were compared after balloon inflation (following a 15-minute stabilization period at the conclusion of which ICP averaged 18.6 ± 0.8 mm Hg), during shock, and following resuscitation. ICP decreased during the shock interval approximately 10 mm Hg in all groups. After resuscitation, maximal mean ICP values for the 0.9% saline and 10% dextran-40 groups were 46 ± 12.1 mm Hg and 45.3 ± 24 mm Hg, respectively, compared to approximately 4 mm Hg in the 3% saline group.

The present study, attempted as did those of Gunnar et al, to duplicate the specific features of acute, pre-hospital resuscitation. The primary distinguishing characteristics of the present study were more severely reduced intracranial compliance and a more clinically pertinent type of initial resuscitation. In addition, the cerebral venous outflow technique facilitates greater temporal resolution of changes in CBF. These data support previous observations that small volume resuscitation with HS produces comparable, yet transient, systemic hemodynamic improvement to that produced by larger volumes of slightly hypotonic crystalloid (Prough, JNS). These data also confirm the ability of HS to limit resuscitation induced increases in ICP, a complication of the infusion of large volumes of isotonic crystalloid (Wilson '51, Gunnar '86, Prough, JNS). Despite lower ICP in the HS group immediately following fluid resuscitation, CBF did not significantly improve during the post-resuscitation period

when compared to pre-shock levels, and was only slightly (not significantly) superior to the saline control group.

Gunnar et al reported, as described above, that ICP remained at or below baseline levels throughout the post-resuscitation period in animals resuscitated with hypertonic saline despite the presence of an epidural mass with a volume approximating 2.8 ± 0.32 ml. In contrast, 0.9% saline-resuscitated animals had a marked increase in ICP. We also found minimal increases in ICP immediately following resuscitation with HS. At the same interval, ICP increased markedly in the 0.8% saline group. However, in contrast to the observations of Gunnar et al, starting at about one hour into the two hour observation period (T95), ICP began to increase gradually to a level comparable to that of 0.8% saline. In the present study, systemic variables MAP and CO changed in a fashion that should not have increased CBF, cerebral blood volume, or ICP. MAP remained stable in both the HS and the SAL groups from T65-T155. CO decreased from T35 forward in both groups. Nevertheless, ICP increased from 20 ± 3 mm Hg at T65 to 30 ± 5 mm Hg at T95, effectively eliminating any advantage of hypertonic saline over 0.8% saline in terms of ICP.

The difference in ICP trends following resuscitation with HS between these two studies may be explained by differences in experimental design. First, Gunnar et al resuscitated animals with $32 \text{ ml} \cdot \text{kg}^{-1}$ of 3% saline or 0.9% saline after returning one-half of the shed blood volume. Therefore, the total osmolar load of 3% saline considerably exceeded that provided by $6.0 \text{ ml} \cdot \text{kg}^{-1}$ of 7.2% saline in our present study. Two hours post-resuscitation, serum osmolality was 334 ± 7.5 mOsm/L in the 3% saline group (Gunnar et al) and 321 ± 6 mOsm/L in the 7.2% saline group (present study). Gunnar and colleagues reported that wet brain weight in the HS-resuscitated animals

was significantly less than in those resuscitated with isotonic saline or dextran-40 (69.8 ± 0.3 gm to 74.5 ± 1.9 and 74.3 ± 1.8 gm, respectively), suggesting less brain water in the HS-resuscitated animals. Second, resuscitation was carried out initially with one-half of the previously shed blood volume prior to test fluid infusion. Infusion of one-half the shed blood alone increased cardiac index to control values and markedly improved MAP, PAWP and other systemic parameters, after which a much larger volume of hypertonic saline was administered. In contrast, we resuscitated animals only with a small volume of blood-free solution. Therefore, total body sodium at the end of resuscitation was certainly greater in the study by Gunnar et al than in the present study. More effective resuscitation may have restored cell membrane potentials and more effectively restored cellular function, perhaps including the function of sodium-potassium pumps. Third, Gunnar et al permitted ICP to decline during shock. Therefore cerebral ischemia should have been less profound during shock. Cerebral perfusion pressure increased from a low of approximately 40 mm Hg at the beginning of shock to approximately 65 mm Hg by the end of the shock interval due to a spontaneous increase in MAP. This was significantly greater than the 40 mm Hg that was maintained during shock in the present study. Comparison of intracranial balloon volumes revealed an epidural balloon volume of 2.8 ± 0.32 (ml) and a subdural balloon volume of 4.8 ± 0.9 (ml) in the two hypertonic saline groups. Gunnar and colleagues have since reported, using their previously reported hemorrhagic shock-epidural mass resuscitation model, that 3% saline produced no significant increase in cerebral blood flow compared to 0.9% saline or 10% dextran-40 despite a higher CPP and lower ICP compared to the current study (12).

In these experiments, the failure of an adequate post-resuscitation CPP, to maintain CBF in the post-resuscitation period indicated a reduced ability of the cerebral microvasculature to compensate (i.e. autoregulate), a condition predisposing the brain parenchyma to ischemic damage and disruption of the blood-brain barrier. Gunnar et al demonstrated blood-brain barrier breakdown on the side of the epidural balloon, adjacent to the epidural balloon in all animals, including those receiving 3% saline. If the blood-brain barrier were more severely damaged, as seems likely, following more profoundly reduced cerebral perfusion pressure during shock in the present study, enhanced movement of sodium into brain tissue could explain the late increase in ICP.

In summary, these data confirm the concept that hypertonic saline solutions produce superior effects on ICP immediately after resuscitation if hemorrhage is accompanied by an intracranial mass lesion. However, viewed in relation to the work of Gunnar et al., these data emphasize that the superiority of hypertonic solutions is highly dependent upon the severity of the cerebral ischemic insult and may be critically affected by the extent to which systemic perfusion is restored and maintained.

5 June 1990
Subdural.mas

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LEGENDS

Figure 1. Summary of experimental preparation.

Figure 2. Response of mean arterial pressure following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS) or 0.8% saline (SAL).

Figure 3. Changes in cardiac output following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS) or 0.8% saline (SAL).

Figure 4. Response of intracranial pressure following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS) or 0.8% saline (SAL). Intracranial hypertension induced by inflation of an subdural balloon accompanied hemorrhage.

Figure 5. Changes in cerebral perfusion pressure following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS) or 0.8% saline (SAL). Intracranial hypertension induced by inflation of an subdural balloon accompanied hemorrhage.

Figure 6. Response of cerebral blood flow following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS) or 0.8% saline (SAL). Intracranial hypertension induced by inflation of an subdural balloon accompanied hemorrhage.

Table 1. Body Weight, Shed Blood Volume, Resuscitation Volume and Balloon Volume
(means $\pm$ SEM)

Group	N	Weight (kg)	Blood Loss (ml•kg ⁻¹)	Resus. Volume (ml•kg ⁻¹)	Balloon Volume* (ml)
HS	6	18.6 $\pm$ 2.7	21.5 $\pm$ 2	6.0	4.8 $\pm$ 0.9
SAL	6	20.4 $\pm$ 1.0	20.9 $\pm$ 2	54	5.4 $\pm$ 0.7

* Balloon volume describes the volume of saline that could be withdrawn from the balloon at the termination of the experiment.

Table 2. Major Systemic Variables (Means $\pm$ SEM)

Group		BL	Balloon Inflation	TO	T30	T35	T65	T95	T125	T155
PaCO ₂ (mm Hg)	HS	38 $\pm$ 0.9	40 $\pm$ 1.2	32 $\pm$ 1.7	42 $\pm$ 0	52 $\pm$ 2.5	38 $\pm$ 0.7	40 $\pm$ 0.9	38 $\pm$ 0.8	38 $\pm$ 1.2
	SAL	37 $\pm$ 0.9	36 $\pm$ 1.0	34 $\pm$ 1.8	43 $\pm$ 1.4	39 $\pm$ 1.0	36 $\pm$ 1.0	40 $\pm$ 1.6	37 $\pm$ 1.5	39 $\pm$ 1.5
Hgb (g $\cdot$ dl ⁻¹)	HS	14.2 $\pm$ 0.6	14.3 $\pm$ 0.6	12.2 $\pm$ 0.8	12.5 $\pm$ 0.7	9.7 $\pm$ 0.8	11.4 $\pm$ 0.8	12.4 $\pm$ 0.5	12.1 $\pm$ 0.6	12.2 $\pm$ 0.6
	SAL	11.8 $\pm$ 1.1	12.6 $\pm$ 1.0	11.0 $\pm$ 0.9	11.4 $\pm$ 1.0	8.3 $\pm$ 0.9	9.6 $\pm$ 0.9	10.4 $\pm$ 1.0	10.7 $\pm$ 1.1	11.5 $\pm$ 0.6
PaO ₂ (mm Hg)	HS	255 $\pm$ 33	276 $\pm$ 31	209 $\pm$ 27	211 $\pm$ 29	242 $\pm$ 27	232 $\pm$ 28	246 $\pm$ 31	241 $\pm$ 27	231 $\pm$ 24
	SAL	295 $\pm$ 34	291 $\pm$ 38	289 $\pm$ 39	258 $\pm$ 33	301 $\pm$ 35	292 $\pm$ 35	289 $\pm$ 36	272 $\pm$ 36	253 $\pm$ 35
pH	HS	7.4 $\pm$ 0.0	7.4 $\pm$ 0.0	7.4 $\pm$ 0.0	7.2 $\pm$ 0.0	7.1 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0
	SAL	7.4 $\pm$ 0.0	7.4 $\pm$ 0.0	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0
Temp (°C)	HS	38.2 $\pm$ 0.2	38.2 $\pm$ 0.4	38.3 $\pm$ 0.4	39.1 $\pm$ 0.3	38.7 $\pm$ 0.2	38.9 $\pm$ 0.2	39.2 $\pm$ 0.2	39.4 $\pm$ 0.2	39.3 $\pm$ 0.4
	SAL	37.0 $\pm$ 0.5	37.1 $\pm$ 0.6	37.1 $\pm$ 0.6	37.5 $\pm$ 0.7	36.8 $\pm$ 0.6	36.9 $\pm$ 0.6	37.2 $\pm$ 0.7	37.8 $\pm$ 0.6	37.9 $\pm$ 0.9
PAOP (mm Hg)	HS	3.6 $\pm$ 1.8	2.6 $\pm$ 1.9	1.3 $\pm$ 1.6	1.1 $\pm$ 1.5	3.3 $\pm$ 1.9	2.1 $\pm$ 1.8	2.1 $\pm$ 1.7	2.5 $\pm$ 1.8	2.2 $\pm$ 1.9
	SAL	2.7 $\pm$ 1.2	1.5 $\pm$ 1.0	0.0 $\pm$ 0.7	-0.4 $\pm$ 0.7	7.1 $\pm$ 0.9	0.9 $\pm$ 0.6	0.4 $\pm$ 1.0	0.8 $\pm$ 1.3	0.3 $\pm$ 1.2

Table 3. Serum Osmolality (Means $\pm$ SEM)

	Group	BL	T95	T155
Serum Osmolality (mOsm•L ⁻¹)	HS	287±3	337±13*	321±6*
	SAL	291±4	309±4	308±4

* p<0.05, HS vs SAL

Table 4. Major Cerebral Variables (Means $\pm$ SEM)

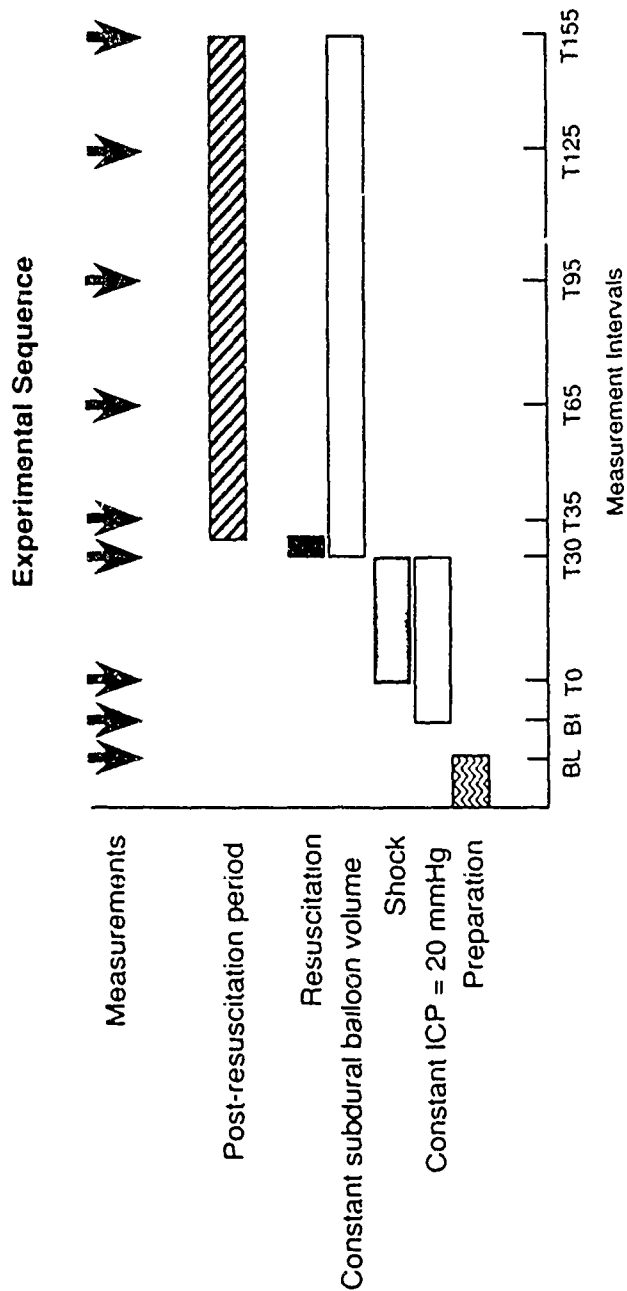
Group	BL	Balloon Inflation	TO	T30	T35	T65	T95	T125	T155
Cerebral A-VDO ₂ (ml $\times$ 100 $\times$ ml ⁻¹)									
HS	6.0 $\pm$ 0.7	7.2 $\pm$ 0.9	9.6 $\pm$ 0.9	7.8 $\pm$ 1.1	5.0 $\pm$ 0.3	6.3 $\pm$ 1.0	7.6 $\pm$ 0.7	8.7 $\pm$ 1.0	8.1 $\pm$ 1.3
SAL	6.0 $\pm$ 0.6	6.5 $\pm$ 0.8	10.5 $\pm$ 0.9	8.4 $\pm$ 0.5	5.6 $\pm$ 0.5	6.7 $\pm$ 0.4	7.4 $\pm$ 0.9	6.5 $\pm$ 1.3	6.2 $\pm$ 1.5
CMRO ₂ (ml $\times$ min ⁻¹)									
HS	1.6 $\pm$ 0.4	1.7 $\pm$ 0.3	0.7 $\pm$ 0.2	0.7 $\pm$ 0.3	1.3 $\pm$ 0.3	1.1 $\pm$ 0.3	1.1 $\pm$ 0.3	1.1 $\pm$ 0.3	0.8 $\pm$ 0.2
SAL	1.9 $\pm$ 0.1	2.0 $\pm$ 0.2	1.3 $\pm$ 0.2	0.7 $\pm$ 0.2	1.1 $\pm$ 0.2	0.9 $\pm$ 0.1	0.8 $\pm$ 0.1	0.7 $\pm$ 0.2	0.7 $\pm$ 0.3
CO $\bar{V}$ (ml $\times$ min ⁻¹)									
HS	5.7 $\pm$ 1.1	5.3 $\pm$ 0.8	1.4 $\pm$ 0.3	1.5 $\pm$ 0.5	3.1 $\pm$ 0.7	2.8 $\pm$ 0.7	2.3 $\pm$ 0.7	2.1 $\pm$ 0.4	1.4 $\pm$ 0.4
SAL	5.8 $\pm$ 0.6	5.7 $\pm$ 0.6	2.1 $\pm$ 0.3	1.6 $\pm$ 0.4	2.7 $\pm$ 0.4	1.9 $\pm$ 0.3	1.9 $\pm$ 0.4	1.8 $\pm$ 0.4	1.6 $\pm$ 0.5

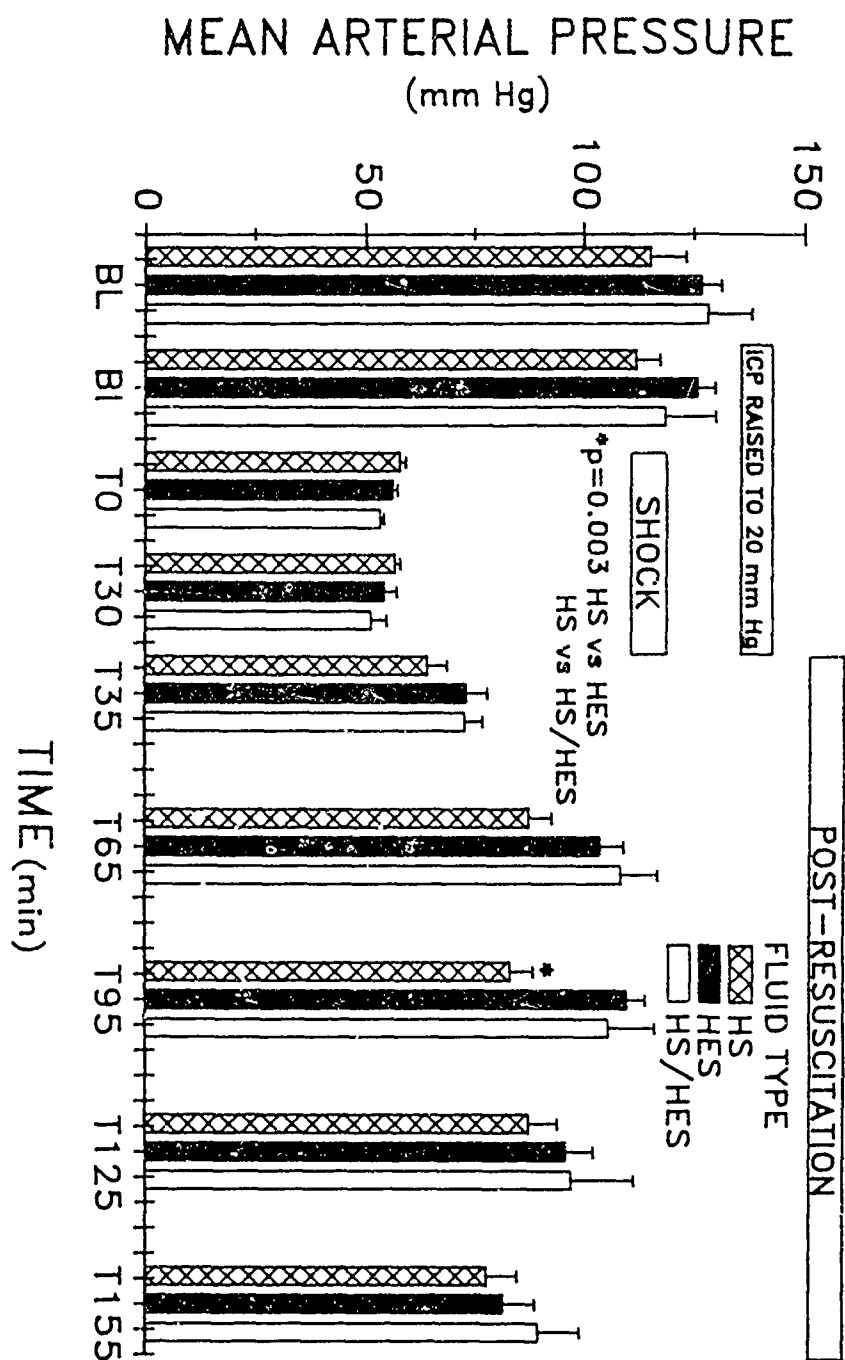
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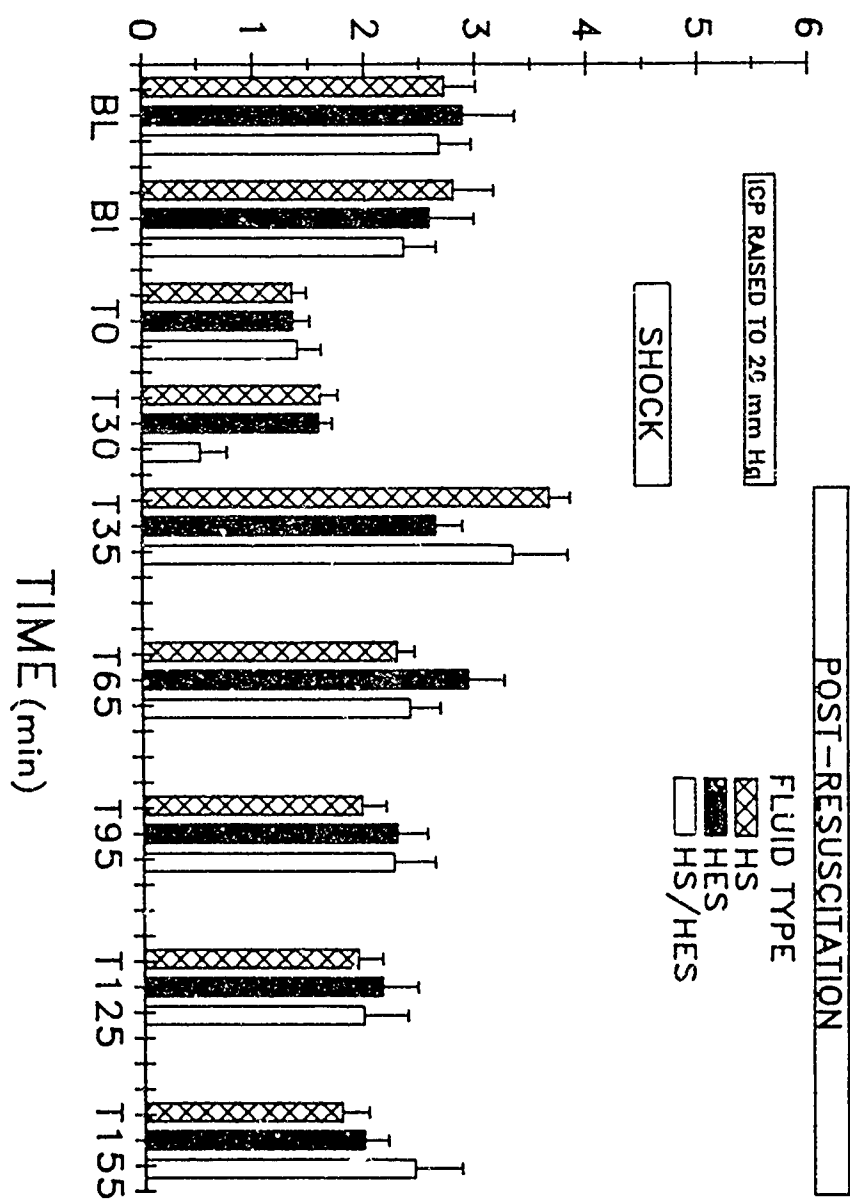
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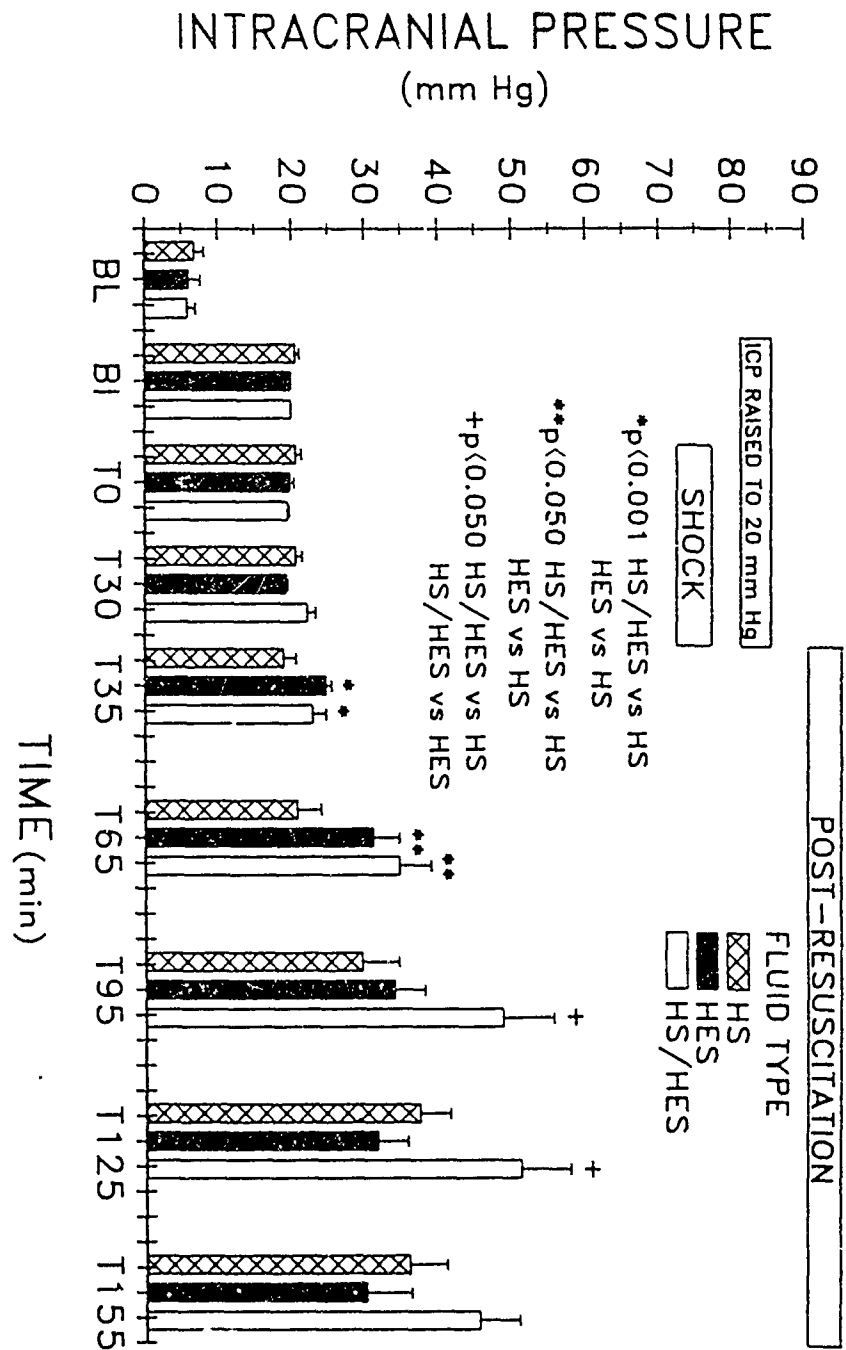
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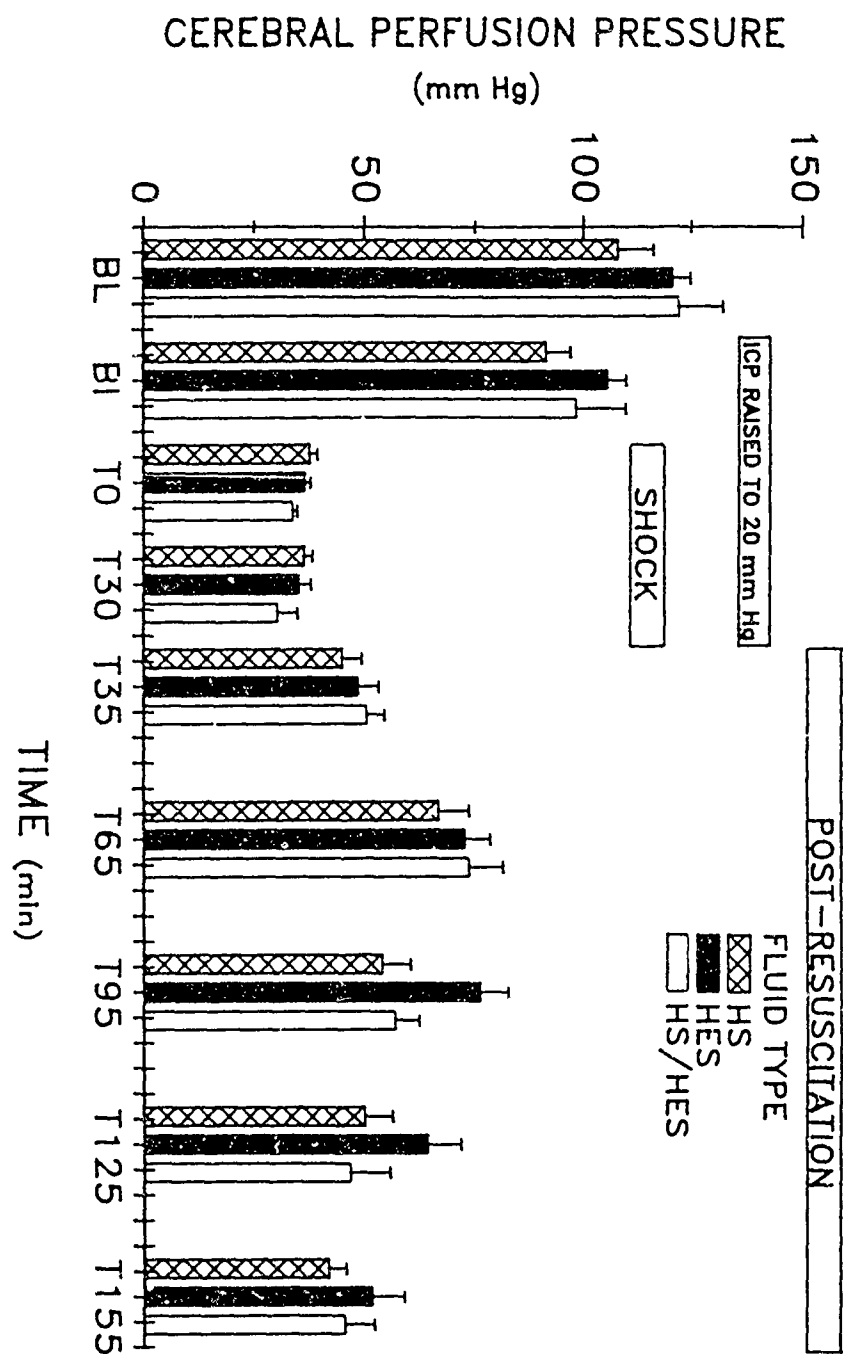


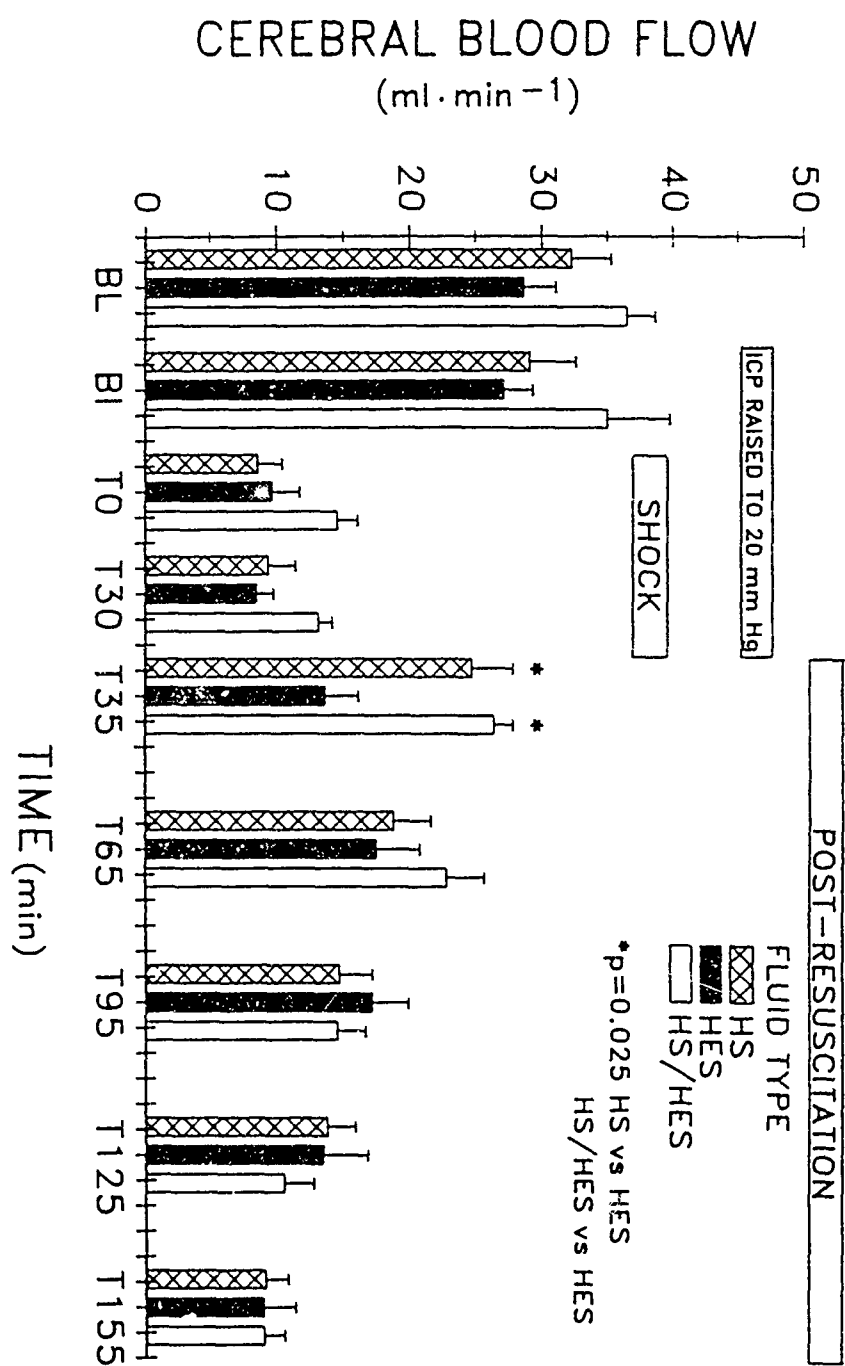


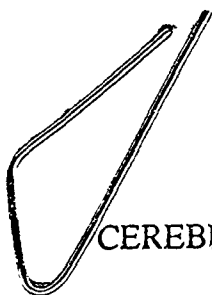
CARDIAC OUTPUT (ml · min⁻¹)











CEREBROVASCULAR EFFECTS OF SMALL VOLUME RESUSCITATION

FROM HEMORRHAGIC SHOCK:

COMPARISON OF HYPERTONIC SALINE AND CONCENTRATED

HYDROXYETHYL STARCH IN DOGS

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Presented in part at the 1989 Twelfth Annual Conference on Shock, Marco Island, FL

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Wake Forest University Medical Center, Winston-Salem, N

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whole paper

Running title: Small-volume resuscitation

REPLACES: WHITLEY, et al - SMALL VOLUME RESUSCITATION WITH 7.2% SALINE WITH AND WITHOUT HYDROXYETHYL STARCH IN A MODEL OF HEMORRHAGIC SHOCK AND INTRACRANIAL HYPERTENSION

CEREBROVASCULAR EFFECTS OF SMALL VOLUME RESUSCITATION
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ABSTRACT

To determine if hypertonic and hyperoncotic resuscitation solutions exerted comparable effects on cerebral hemodynamics following hemorrhagic shock, we compared randomly assigned, equal volumes ($6.0 \text{ ml} \cdot \text{kg}^{-1}$) of hypertonic (7.2%) saline (HS) and hyperoncotic (20%) hydroxyethyl starch (HES) for resuscitation from acute experimental hemorrhage in 12 anesthetized dogs. Regional cerebral blood flow (radiolabelled microspheres), intracranial pressure (cisternal catheter), and systemic hemodynamics were recorded. Rapid hemorrhage reduced mean arterial pressure to 45 mm Hg for 30 minutes. Resuscitation fluids were infused over 5 minutes. Both fluids restored mean arterial pressure and cardiac output equally. Cardiac output rapidly declined, however, in the HS group in comparison to the HES group ($p < 0.05$, 60 minutes following resuscitation). Intracranial pressure and cerebral perfusion pressure were similar at all intervals. Regional cerebral blood flow was similar following both fluids. Neither fluid restored cerebral oxygen transport to baseline values. Following severe hemorrhagic shock of brief duration, systemic and cerebral hemodynamic values are restored equally well by highly concentrated colloid or by hypertonic saline, although hypertonic saline only transiently improves cardiac output.

Key Words: Shock, hemorrhagic

Intracranial pressure

Cerebral blood flow

Hypertonic saline

Hydroxyethyl starch

Intravenous fluids

INTRODUCTION

Following acute trauma or hemorrhage, an ideal fluid for acute resuscitation should promptly restore systemic hemodynamics when administered in a volume constituting only a fraction of shed blood volume. Small volumes of hypertonic salt solutions, administered in a dose equal to a fraction of the shed blood, effectively restore blood pressure and cardiac output in experimental hemorrhagic shock (1-3). Small volumes of hypertonic salt solutions also improve survival in severe, experimental hemorrhagic shock (1,2,4-7) and are associated with lower intracranial pressure (ICP) following resuscitation than are isotonic salt solutions (8-12). However, because the systemic hemodynamic effects of hypertonic saline alone are relatively short-lived (6-8), the addition of colloid, usually 6.0% dextran, produces more sustained hemodynamic effects than hypertonic saline solutions alone (7,8).

However, rapid infusion of hypertonic solutions containing sodium in concentrations substantially in excess of normal serum concentrations produces hypernatremia and hypertonicity. Although moderate hypertonicity appears to be well tolerated when it develops during the resuscitation of burned patients or during replacement of perioperative fluid losses with hypertonic solutions (13,14), unanswered questions remain regarding presumably rare, but potentially lethal, complications of rapid increases in serum sodium concentration, such as subdural hemorrhage or central pontine myelinolysis (15-17).

We performed a study to determine whether rapid resuscitation with a highly concentrated solution of the synthetic colloid hydroxyethyl starch (HES) would produce improvements in systemic and cerebral hemodynamics comparable to those produced by equal volumes of 7.2% saline.

METHODS

Twelve mongrel dogs of either sex, weighing 18-24 kg, were managed according to guidelines established by the institution's Animal Care and Use Committee.

Anesthesia

Following an overnight fast, dogs were anesthetized with intravenous thiopental sodium ($8.0 \text{ mg} \cdot \text{kg}^{-1}$), paralyzed with pancuronium ($0.2 \text{ mg} \cdot \text{kg}^{-1}$), endotracheally intubated, then anesthetized with halothane 0.5% in nitrous oxide and oxygen (60:40). Animals were ventilated, using an Edco Model 822 large animal ventilator (Edco Scientific, Inc., Chapel Hill, NC), at a tidal volume of $15 \text{ ml} \cdot \text{kg}^{-1}$ and a rate sufficient to maintain normocarbida. Additional pancuronium, given as needed, prevented respiratory movement.

Hemodynamic Monitoring

Arterial catheters were placed in the right femoral and both brachial arteries for continuous monitoring of systemic arterial blood pressure and for use as reference organs for cerebral blood flow (CBF) determinations using radioactive microspheres (left brachial and right femoral arteries). A 7-Fr pigtail catheter was inserted into the left ventricle through the left femoral artery for injection of radioactive microspheres. A flow-directed, pulmonary artery catheter was placed percutaneously via the right external jugular vein for cardiac output, pulmonary artery pressure and pulmonary artery occlusion pressure (PAOP) measurements. Pressure recording utilized a polygraph (Model 79D, Grass Instrument Co., Quincy, MA) and transducers (Model P23, Gould, Inc., Oxnard, CA). Core temperature, monitored continuously using the thermistor on the pulmonary artery catheter, was maintained using a 37°C heating pad applied to the trunk and extremities. Cardiac output

was measured using thermodilution (Model 9520A, American Edwards, Santa Ana, CA). All transducers were intermittently zeroed and calibrated. To facilitate rapid hemorrhage and reduce autotransfusion from the splenic reservoir, all animals underwent splenectomy. Animals were then turned to the prone, "sphinx" position and the occipital musculature dissected from the underlying bone. The superior sagittal sinus was cannulated for sagittal sinus pressure monitoring and for rapid sampling of cerebral venous blood. An 18-ga catheter inserted into the cisterna magna and zeroed at the level of the external auditory meatus (7 cm above the left atrium) provided continuous monitoring of ICP.

Regional Cerebral Blood Flow Measurement

Regional cerebral blood flow (rCBF) was measured with 15 μ m radiolabelled microspheres (^{153}Gd , ^{95}Nb , ^{113}Sn , ^{85}Sr , and ^{46}Sc), using the organ reference sample method (18,19). Paired reference organ blood samples (ROBS) were withdrawn simultaneously (Model 843 Infusion Withdrawal Syringe Pump, Edco Scientific, Inc., Chapel Hill, NC). Prior to injection, microspheres were vortexed for 4 minutes. Each microsphere dose was calculated to yield greater than 400 microspheres per tissue segment and a minimum of 15,000 counts per ROBS. Injection of each microsphere type was carried out over a 15-second period. The ROBS were taken beginning 30 seconds prior to microsphere injection and continued for 60 seconds post-injection, at a withdrawal rate of $2.06 \text{ ml} \cdot \text{min}^{-1}$. Counts per minute (CPM) in ROBS pairs differed by no more than 5%. After sacrificing, brains were sectioned into right cerebral hemisphere, left cerebral hemisphere, and brainstem, and counted along with the arterial reference samples in a well-type gamma counter (Auto-Gamma 5000, Packard Instruments, Downers Grove, IL). Aliquots of microspheres labelled

with each radionuclide were counted along with the blood and tissue samples, and curve stripping to correct for isotope overlap was performed using a microcomputer.

Experimental Sequence

The experimental sequence is summarized in Fig. 1. After instrumentation, all animals were stabilized for 30 minutes and baseline (BL) data recorded. Recorded data included hemodynamic data plus serum osmolality (5500 vapor pressure osmometer, Wescor, Inc., Logan, UT), colloid oncotic pressure (4100 colloid osmometer, Wescor, Inc.), and arterial and cerebral venous pH, PCO₂, PO₂, O₂ saturation, and hemoglobin concentration (IL813 and IL282, Instrumentation Laboratory, Lexington, MA). Mean arterial pressure (MAP), cerebral perfusion pressure (CPP), cerebral metabolic rate for oxygen (CMRO₂), and cerebrovascular resistance (CVR) were calculated from standard formulae. CBF was derived from the formula:

$$CBF = \frac{C_t \times \text{withdrawal rate} \times 100}{C_r \times \text{wt}}$$

where C_t = CPM in the tissue sample, C_r = CPM in the reference sample
and wt = weight of the tissue sample.

After anticoagulation with heparin (500 IU•kg⁻¹ intravenously), blood was rapidly withdrawn through the right brachial artery catheter to reduce MAP to 45 mm Hg; MAP was maintained at that level for 30 minutes by removing or reinfusing shed blood.

The second set of cerebral and hemodynamic data was obtained at the mid-shock time interval, designated as T15, indicating the number of minutes from the onset of shock. Following the shock interval, animals were randomized to one of two fluid groups, based upon the type of resuscitation fluid: Group HS received 6.0 ml•kg⁻¹ of 7.2% saline (1232

mEq•L⁻¹ Na⁺), and group HES received 6.0 ml•kg⁻¹ of 20% hydroxyethyl starch dissolved in 0.8% saline (137 mEq•L⁻¹ Na⁺). Previous studies had demonstrated the acute efficacy of a similar volume and concentration of hypertonic saline (8); the concentration of hydroxyethyl starch was selected to provide the maximum dose of colloid that could be effectively infused in a volume equal to that of the hypertonic fluid. Additional data were collected immediately after fluid infusion (T35) and thereafter at hourly intervals for two hours (T95, T155).

Statistical Analysis

All statistical analyses were performed using SAS (SAS Institute, Cary, NC). The Kruskal-Wallis test confirmed similarity at baseline and during shock. A multivariate repeated measures of analysis of variance (ANOVA) was performed to determine if interactions between groups and time existed at subsequent post-resuscitation intervals (20). Interactions were analyzed further with the Holm's sequentially rejective multiple test procedure using a significance level of 0.05 (21). To assess time and group differences when an interaction was not present, a multivariate repeated measures ANOVA and an analysis of covariance were performed on the dependent variables. Statistically significant group effects were further evaluated using Holm's sequentially rejective multiple test procedure.

RESULTS

Systemic Variables

All values in the text, tables, and figures are expressed as means $\pm$ SEM.

Mean Arterial Pressure

Body weight and shed blood volume were similar in the two groups (Table 1). Baseline MAP in the two experimental fluid groups was comparable, then was maintained experimentally near 45 mm Hg for 30 minutes prior to fluid resuscitation (Figure 2A). Immediately following acute fluid resuscitation (T35), MAP increased similarly in the HS and HES groups, to 82 ± 3.8 (mean $\pm$ SEM) and 78 ± 3.5 mm Hg, respectively. There were no statistically significant differences in MAP at T95 or T155.

Cardiac Output

Baseline cardiac output was similar (3.2 ± 0.4 L $\cdot$ min⁻¹ in HS and 3.9 ± 0.2 L $\cdot$ min⁻¹ in HES) (Figure 2B). Hemorrhage significantly decreased cardiac output to approximately 50% of baseline in both groups. After resuscitation, cardiac output approached baseline levels in both groups, then decreased rapidly in the HS group ($p < 0.05$ between groups at T95); cardiac output in the HES group remained similar to the T35 level for the duration of the experimental period.

Other Systemic Variables

PaCO₂, Hemoglobin (Hgb), PaO₂, pH, blood temperature, and PAOP were similar at all intervals (Table 2). Serum osmolality was greatest at T155 in the HS group compared to HES. Colloid oncotic pressure (as % of baseline) increased significantly following resuscitation in the HES group compared to HS ($p < 0.05$) (Table 3).

Cerebral Hemodynamics

Intracranial Pressure

Prior to initiation of shock, there were no differences in ICP (7.2 ± 2.0 and 4.6 ± 1.9 mm Hg in the HS and HES groups, respectively) (Figure 3A). ICP declined, though not significantly, during shock. Resuscitation (T35) increased ICP slightly in both groups. Throughout the post-resuscitation period, ICP in both the HS and HES groups remained below baseline levels without significant difference between groups.

Cerebral Perfusion Pressure

CPP (Figure 3B) followed the same general pattern as MAP. CPP was not restored to baseline by either fluid following resuscitation, but CPP continued to increase following resuscitation in the HES group, reaching a maximum at T95. No differences in CPP were detected between groups at any time period.

Regional Cerebral Blood Flow

Regional cerebral blood flow (rCBF) was similar between right and left cerebral hemispheres and brainstem in both groups at baseline (Figure 4). Induction of hemorrhage resulted in small (~20%) reductions in rCBF compared to baseline ($p=NS$). Fluid resuscitation increased rCBF transiently in the HS group, exceeding baseline ($p=NS$). Regional CBF in both groups after T35 was similar throughout the remainder of the experiment. Because arterial content (CaO_2) declined as Hgb declined (Table 2), cerebral oxygen transport ($CBF \times CaO_2$) remained below baseline values after resuscitation in both

groups (Table 4). CMRO_2 did not change significantly over the course of the study; declines in CBF and CaO_2 were balanced by increased cerebral oxygen extraction.

DISCUSSION

These data demonstrate that hyperoncotic 20% HES and hypertonic 7.2% saline produce comparable systemic hemodynamic and cerebral hemodynamic improvement when administered in equal volumes, approximating 15% of shed blood volume, following hemorrhagic shock. Although most variables remained similar throughout the two hours following resuscitation, cardiac output declined more rapidly in animals that received HS. Presumably, this represents a rapid decline in the acute expansion of intravascular volume associated with the hypertonic infusion. This conclusion is supported by the more rapid increase in Hgb in the HS group following resuscitation. If these data can be confirmed in additional animal studies and in clinical trials, highly concentrated colloid solutions may prove as practical as hypertonic solutions for the initial resuscitation and stabilization of victims of trauma, including those with intracranial injuries.

Interest in the applicability of small-volume resuscitation for trauma patients was stimulated by studies performed by Velasco and colleagues in the early 1980's. They first demonstrated that dogs subjected to a hemorrhage equal to approximately one-half estimated blood volume could be effectively resuscitated using 7.5% saline in a dose of $4.0 \text{ ml} \cdot \text{kg}^{-1}$, a volume that was only about one tenth of the initial shed blood volume (1). They subsequently demonstrated that hypertonic saline improved systemic hemodynamics only if a vagally mediated reflex arc were intact (2). Subsequent investigators demonstrated that hypertonic resuscitation fluid might be particularly appropriate if hemorrhage accompanied head injury, because hypertonic saline produced lower post-resuscitation ICP than did conventional crystalloid solutions (8-12). Colloid-containing solutions also were associated

with lower ICP following resuscitation than conventional crystalloid solutions, although the advantage over conventional fluids was less prominent and consistent than the advantages of hypertonic solutions (9,11,12,22,23).

However, hypertonic solutions carry several major liabilities in comparison to resuscitation with either crystalloid or colloid solutions. First, the systemic effects of acute administration of hypertonic solutions on cardiac output tend to be transient (6-8). The present data confirm those previous observations. Although MAP declined little in the HS group from T35 to T155, cardiac output declined precipitously. In contrast, concentrated HES maintained stable levels of cardiac output throughout the post-resuscitation interval. Numerous investigators have attempted to increase the duration of the desirable hemodynamic effects of hypertonic solutions by adding colloid (5-7,24). However, previous studies have not defined a concentration of colloid alone that produced comparable early hemodynamic effects when infused in a small volume.

One consequence of hemorrhage followed by resuscitation without red blood cells is the production of post-resuscitation hemodilution. The cerebral effects of hemodilution and of changes in osmolality and oncotic pressure have been extensively investigated in animals that have not been subjected to hemorrhagic shock. Tommasino and colleagues isovolemically hemodiluted anesthetized rabbits with lactated Ringer's solution to reduce hematocrit from approximately 40% to 19% (25). Lactated Ringer's solution, which is slightly hypotonic relative to plasma, produced early increases in ICP and brain water that rapidly resolved. Six percent HES did not alter ICP or brain water. Hemodilution with either fluid was associated with an increase in CBF of approximately 50%. Isovolemic

hemodilution using a hypertonic solution (Na^+ 252 $\text{mEq}\cdot\text{l}^{-1}$) reduced ICP and brain water and increased CBF 50% (26).

Zornow and colleagues used hollow-fiber plasmapheresis to acutely alter plasma osmolality or colloid oncotic pressure in rabbits and demonstrated that acute reductions of $13 \pm 6 \text{ mOsm}\cdot\text{kg}^{-1}$ in plasma osmolality significantly decreased ICP and increased cortical water content, but that a 65% reduction in oncotic pressure from $20 \pm 2 \text{ mm Hg}$ to $7 \pm 1 \text{ mm Hg}$ produced no change (27). Following cryogenic brain injury, sustained reductions in colloid oncotic pressure also produced no significant differences in ICP or brain water (28). Warner and Boehland showed that brain water increased after infusion of blood or isovolemic hemodilution with 0.9% NaCl or 6.0% HES following 10 minutes of near-complete forebrain ischemia (29) in rats. Brain water increased regardless of the fluid that was infused (29).

However, hemodilution following shock appears to exert different cerebrovascular effects than isovolemic hemodilution occurring without intervening shock. In most studies, hemodilutional resuscitation fails to improve CBF sufficiently to offset the decline in CaO_2 produced by a reduction in Hgb (8,22,23). During resuscitation following a 30-minute shock interval in dogs, Prough and colleagues reduced Hgb from 13.1 ± 0.6 to $7.0 \pm 0.6 \text{ g}\cdot\text{dl}^{-1}$ with lactated Ringer's solution and from 13.5 ± 0.4 to $8.4 \pm 0.4 \text{ g}\cdot\text{dl}^{-1}$ with 7.5% saline and found that neither increased CBF above shock values (10). CBF similarly failed to increase following hemodilutional resuscitation with 6.0% hydroxyethyl starch in animals both with and without intracranial mass lesions (22,23). The immediate post-resuscitation increase in the present study may reflect the shorter interval required to measure rCBF using

microspheres in comparison to the ^{133}Xe clearance technique in the previous studies (22,23,8). Following hemorrhagic shock of three hours duration in pentobarbital-anesthetized dogs (30), resuscitation with dextran restored CBF nearly to baseline but failed to increase CBF as would be expected as a consequence of hemodilution (30).

The slight decline in CBF produced by a MAP of 45 mm Hg in this study is consistent with that produced by hemorrhagic hypotension in baboons (31), cats (32), and dogs (8,33). Although restoration of MAP in the presence of intact autoregulation should restore CBF, shocked animals may also require more aggressive expansion of intravascular volume to increase CBF. After two hours of hemorrhagic shock in baboons, McNamara and colleagues returned shed blood, then infused additional lactated Ringer's solution as necessary to restore either baseline left atrial pressure or baseline MAP (34). Using either regimen, they were able to increase CBF to values exceeding baseline. However, they did not report Hgb or hematocrit values in those animals.

In the present study, immediately following resuscitation, CBF increased only to baseline values in the HES group. Although the HS group demonstrated an increase in CBF sufficient to offset partially the reduction in hemoglobin, the increase in CBF, like the increase in cardiac output, was transient. Although, by definition, these animals were not normovolemic following small-volume resuscitation, MAP throughout the post-resuscitation interval was well in excess of the experimental autoregulatory threshold for dogs (33).

One possible mechanism explaining the difference between hemodilution following shock and isovolemic hemodilution without antecedent shock is the magnitude of sympathetic stimulation. Fitch and colleagues demonstrated that alpha blockade, an

intervention that does not alter resting CBF, increases CBF in hypotensive animals (31). Perhaps the greater volume expansion produced by McNamara (34) and colleagues or Gunnar and colleagues (12) reduced the level of circulating catecholamines.

In the present study, the effects on ICP of fluid resuscitation following shock (rather than isovolemic hemodilution without shock) are consistent with those in other studies of shock and resuscitation. Prough and colleagues administered $6.0 \text{ ml} \cdot \text{kg}^{-1}$ of 7.5% saline to dogs after 30 minutes of hemorrhagic shock and noted that ICP declined during shock and remained low in those animals that received hypertonic saline but increased in those that received lactated Ringer's solution (8). In dogs with and without intracranial mass lesions, $20 \text{ ml} \cdot \text{kg}^{-1}$ of 6.0% HES produced lower ICP post-resuscitation than did lactated Ringer's solution (22,23). Gunnar and colleagues induced hemorrhagic shock ($\text{MAP} \approx 40 \text{ mm Hg}$ for one hour) in barbiturate-anesthetized dogs, then reinfused 50% of the shed blood followed by a volume equal to shed blood volume of 0.9% saline, 3.0% hypertonic saline, or 10% low molecular weight dextran in 0.9% saline (9,11,12). MAP and cardiac output were similarly restored by all three fluid resuscitation regimens. ICP was lowest in the animals that had received hypertonic saline and remained lowest throughout most of the resuscitation interval. In the two groups of animals that had received 0.9% saline or dextran, ICP was equal (9,11,12). Because of the complexity of the fluid resuscitation regimen in that study, it is difficult to directly compare it with the single bolus of fluid employed in the present study. However, the animals in the earlier study would certainly have had a higher blood volume throughout the post-resuscitation interval than the animals reported here.

Based upon the data presented here, we conclude that highly concentrated HES solutions may represent an appropriate alternative to hypertonic saline for acute, small-volume resuscitation of trauma victims. These data should be interpreted with caution because these animals had no experimental intracranial pathology. Further studies are necessary to define the effects of highly concentrated colloid solutions and hypertonic solutions in animals with intracranial pathology.

Table 1. Comparison of Weight, Shed Blood Volume, and Resuscitation Volume

(means $\pm$ SEM)

Group	N	Body Weight (kg)	Shed Blood Volume (ml $\cdot$ kg $^{-1}$)	Resuscitation Volume (ml $\cdot$ kg $^{-1}$)
HS	6	20 $\pm$ 1.6	35 $\pm$ 3.7	6.0
HES	6	22 $\pm$ 0.7	32 $\pm$ 4.7	6.0

Table 2. Major Systemic Variables (Means $\pm$ SEM)

Variable	Group	Time Interval				
		BL	T15	T35	T95	T155
PaCO ₂	HES	40.9 $\pm$ 0.3	40.6 $\pm$ 0.4	41.3 $\pm$ 0.4	39.9 $\pm$ 1.0	40.7 $\pm$ 0.5
(mm Hg)	HS	39.5 $\pm$ 0.6	40.2 $\pm$ 1.7	40.4 $\pm$ 0.9	41.8 $\pm$ 2.4	38.9 $\pm$ 0.5
Hgb	HES	12.9 $\pm$ 0.9	10.8 $\pm$ 0.8	8.6 $\pm$ 0.7	9.1 $\pm$ 0.6	9.5 $\pm$ 0.8
(g $\cdot$ dl ⁻¹)	HS	13.8 $\pm$ 1.0	11.3 $\pm$ 1.0	8.4 $\pm$ 0.7	10.7 $\pm$ 0.7	10.2 $\pm$ 1.3
PaO ₂	HES	170 $\pm$ 13	154 $\pm$ 11	167 $\pm$ 14	176 $\pm$ 12	183 $\pm$ 13
(mm Hg)	HS	191 $\pm$ 13	188 $\pm$ 9	197 $\pm$ 9	176 $\pm$ 5	183 $\pm$ 14
pH	HES	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0
	HS	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0
Temp	HES	37.5 $\pm$ 0.2	38.0 $\pm$ 0.2	37.9 $\pm$ 0.2	37.9 $\pm$ 0.4	38.3 $\pm$ 0.4
(°C)	HS	37.4 $\pm$ 0.4	38.1 $\pm$ 0.4	37.8 $\pm$ 0.2	38.3 $\pm$ 0.5	38.9 $\pm$ 0.4
PAOP	HES	5.4 $\pm$ 1.4	1.3 $\pm$ 0.5	0.9 $\pm$ 1.3	2.1 $\pm$ 0.8	3.0 $\pm$ 1.3
(mm Hg)	HS	3.8 $\pm$ 2.1	0.1 $\pm$ 1.2	3.1 $\pm$ 1.7	3.1 $\pm$ 0.6	2.4 $\pm$ 0.7

PaCO₂ = partial pressure of carbon dioxide in arterial blood, Hgb = hemoglobin; PaO₂ = partial pressure of oxygen in arterial blood; Temp = blood temperature measured using the thermistor on the pulmonary artery catheter; PAOP = pulmonary artery occlusion ("wedge") pressure

Table 3. Serum Osmolality and Colloid Oncotic Pressure (Means $\pm$ SEM)

Variable	Group	Time Interval	
		BL	T155
Serum Osmolality (mOsm $\cdot$ L ⁻¹)	HS	292 $\pm$ 12	324 $\pm$ 4
	HES	291 $\pm$ 8	307 $\pm$ 6
Colloid Oncotic Pressure (% baseline)	HS	100 $\pm$ 0	70 $\pm$ 4
	HES	100 $\pm$ 0	110 $\pm$ 1*

* $p < 0.05$ HES vs HS.

Table 4. Cerebral Hemodynamic Variables (Means $\pm$ SEM)

Variable	Group	Time Interval				
		BL	T15	T35	T95	T155
CO ₂ T (ml•100g ⁻¹ •min ⁻¹)	HES	10.9 $\pm$ 1.1	7.1 $\pm$ 0.4	7.2 $\pm$ 0.5	6.7 $\pm$ 0.4	59 $\pm$ 08
	HS	10.6 $\pm$ 1.2	6.9 $\pm$ 0.8	9.9 $\pm$ 1.8	7.8 $\pm$ 1.0	67 $\pm$ 10
CMRO ₂ (ml•100g ⁻¹ •min ⁻¹)	HES	3.5 $\pm$ 0.4	3.5 $\pm$ 0.2	3.3 $\pm$ 0.4	3.3 $\pm$ 0.2	30 $\pm$ 02
	HS	2.8 $\pm$ 0.4	3.2 $\pm$ 0.4	3.5 $\pm$ 0.6	3.4 $\pm$ 0.4	33 $\pm$ 03
Cerebral	HES	5.5 $\pm$ 0.2	7.2 $\pm$ 0.7	5.5 $\pm$ 0.6	6.2 $\pm$ 0.4	74 $\pm$ 09
A-VDO ₂ (ml•100ml ⁻¹)	HS	5.3 $\pm$ 0.9	7.6 $\pm$ 1.2	4.2 $\pm$ 0.4	6.7 $\pm$ 0.9	74 $\pm$ 09

CO₂T = cerebral oxygen delivery (CBF x CaO₂); CMRO₂ = cerebral metabolic oxygen consumption (cerebral blood flow x arterial oxygen content); Cerebral A-VDO₂ = difference in oxygen content between arterial and sagittal sinus blood

FIGURE LEGENDS

- Figure 1. Experimental sequence.
- Figure 2. Response of mean arterial pressure (A) and cardiac output (B) following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS) or 20% hydroxyethyl starch (HES).
- Figure 3. Response of intracranial pressure (A) and cerebral perfusion pressure (B) following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS) or 20% hydroxyethyl starch (HES).
- Figure 4. Response of cerebral blood flow following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS) or 20% hydroxyethyl starch (HES).

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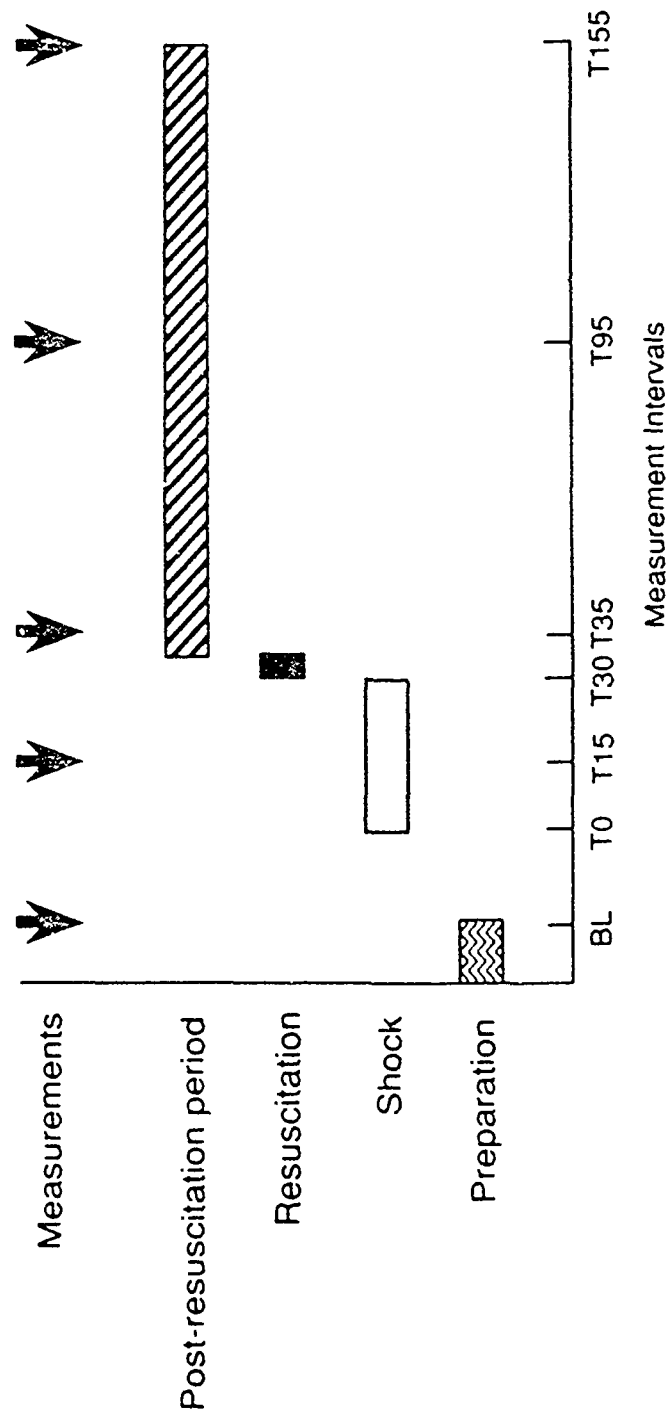
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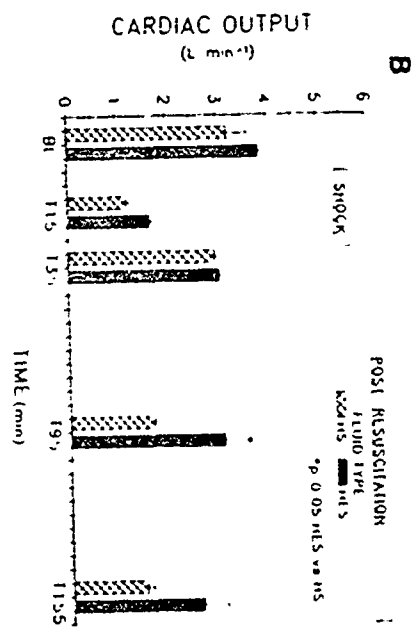
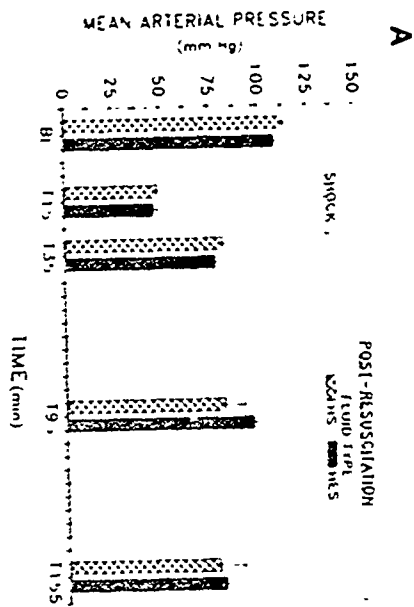
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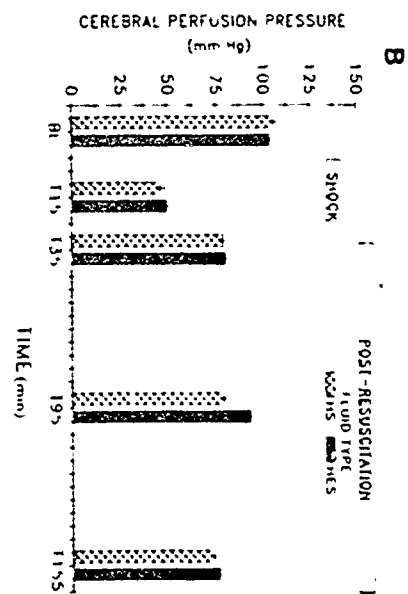
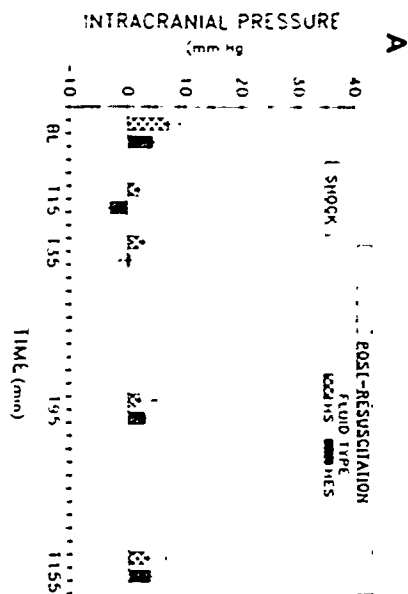
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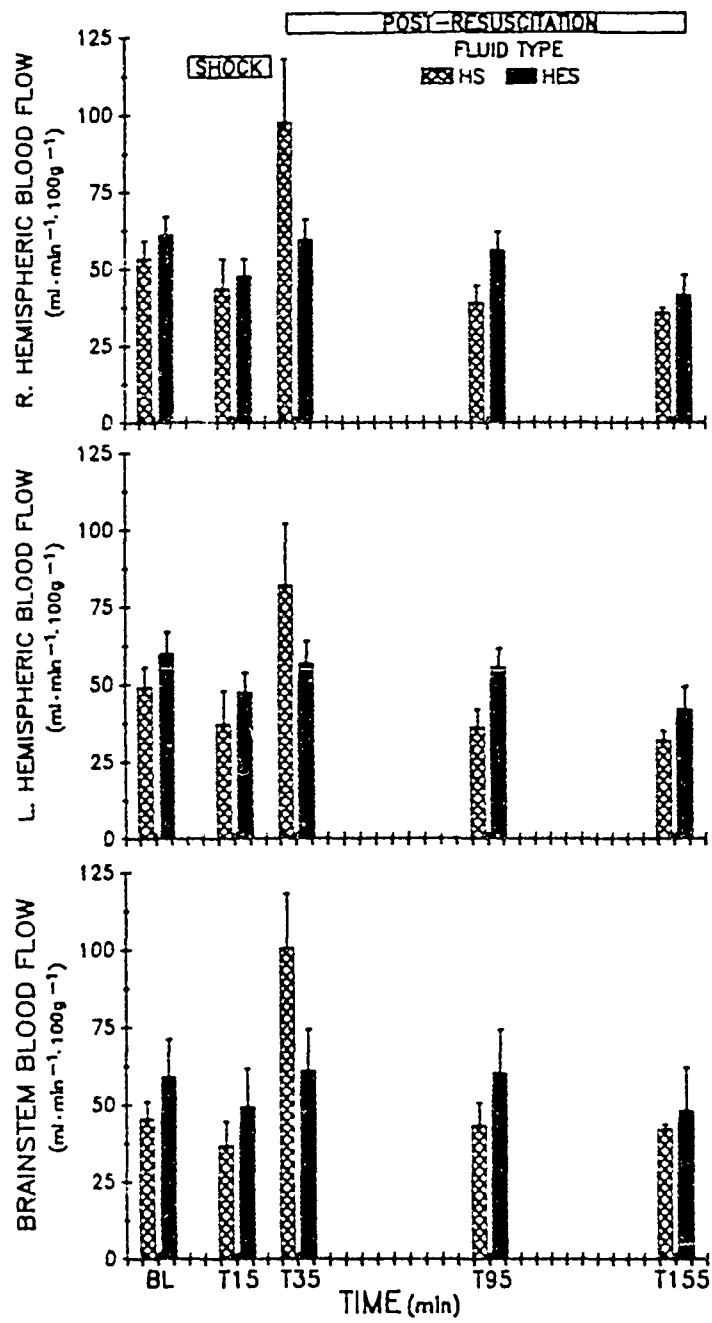
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Experimental Sequence









REGIONAL CEREBRAL BLOOD FLOW FOLLOWING RESUSCITATION FROM
HEMORRHAGIC SHOCK WITH HYPERTONIC SALINE:
INFLUENCE OF A SUBDURAL MASS

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Subdural mass

ABSTRACT

After severe hemorrhage, hypertonic saline restores systemic hemodynamics and lowers intracranial pressure (ICP), but its effects on regional cerebral blood flow (rCBF) when used for resuscitation of experimental animals with combined shock and intracranial hypertension have not been reported. We compared rCBF changes (radiolabeled microsphere technique) following resuscitation from hemorrhage with either 0.8% or 7.2% saline in animals with and without a subdural mass. We studied 24 mongrel dogs anesthetized with 0.5% halothane and 60% nitrous oxide. In Group I (n=12), hemorrhage reduced mean arterial pressure (MAP) to 45 mm Hg for 30 minutes. In Group II (n=12), ICP was increased and maintained constant at 15 mm Hg while hemorrhage reduced MAP to 55 mm Hg for 30 minutes (cerebral perfusion pressure $\approx$ 40 mm Hg in each group). After the 30-minute shock period, 6 animals in each group received one of 2 randomly assigned resuscitation fluids over a 5-minute interval: (1) 7.2% hypertonic saline (HS; sodium 1232 mEq $\cdot$ L $^{-1}$; volume 6.0 ml $\cdot$ kg $^{-1}$); or (2) 0.8% isotonic saline (SAL; sodium 137 mEq $\cdot$ L $^{-1}$; volume 54 ml $\cdot$ kg $^{-1}$). Once fluid resuscitation began, ICP was permitted to vary independently in both groups. Data were collected at baseline (before subdural balloon inflation in Group II), midway through the shock interval (T15), immediately after fluid infusion (T35), and 60 and 90 minutes later (T95, T155). In both Groups I and II, ICP was significantly lower in animals resuscitated with HS compared to SAL ($p < 0.05$). In Group I, CBF was higher at T35 following resuscitation with HS ($p < 0.05$). In Group II, rCBF was significantly higher in HS-treated than in SAL-treated dogs in the affected hemisphere ($p < 0.05$). We conclude that, when used for resuscitation from hemorrhagic shock with associated intracranial hypertension, 7.2% hypertonic saline reduces ICP and increases rCBF.

INTRODUCTION

Hypotension is associated with increased mortality in patients who have suffered closed head injury.¹ For those with a Glasgow Coma Score ≤ 8 on admission to the hospital, a systolic blood pressure < 90 mm Hg is associated with a risk of poor neurologic outcome that is 13 times greater than the risk of those in whom systolic arterial pressure exceeds 90 mm Hg.² Although inadequate cerebral perfusion during shock or subsequent resuscitation might contribute to increased mortality and morbidity, cerebral circulatory changes during acute hemorrhage and resuscitation have not been described in man. Animal models must provide basic information about changes in intracranial pressure (ICP), cerebral blood flow (CBF), and cerebral metabolism during shock and resuscitation.

Hemorrhagic shock reduces ICP in animals without intracranial pathology³ and reduces ICP to an even greater extent if an intracranial mass lesion exists.^{4,5} Subsequent restoration of blood pressure produces a rapid increase in ICP, the magnitude of increase depending upon the type of resuscitation fluid used.^{4,5} Small volumes ($4.0\text{--}6.0$ ml $\cdot$ kg⁻¹) of hypertonic resuscitation solutions produce a minimal increase in ICP in comparison to the large increase associated with conventional crystalloid solutions,^{3,6} yet produce substantial improvements in blood pressure, cardiac output, and survival after otherwise lethal hemorrhage.⁷⁻¹⁰ Hypertonic solutions are associated with lower ICP than isotonic fluids even when employed for resuscitation in a volume sufficient to produce hyperdynamic cardiac output values.^{5,11,12}

Resuscitation with highly hypertonic solutions ($\geq 7.0\%$ saline) does not improve global CBF in animals with normal ICP;³ however, the effects on regional (r)CBF and ICP have not been reported in animals with hemorrhagic shock and associated

intracranial hypertension. The following study was designed to evaluate and compare the effects on ICP and rCBF of resuscitation from hemorrhage with 7.2% saline versus 0.8% saline in animals with and without intracranial hypertension.

METHODS

Twenty-four mongrel dogs weighing 18-24 kg were handled according to guidelines established by our institution's Animal Care and Use Committee. Dogs were fasted overnight, anesthetized with intravenous thiopental sodium ($8.0 \text{ mg} \cdot \text{kg}^{-1}$), paralyzed with intravenous vecuronium ($0.2 \text{ mg} \cdot \text{kg}^{-1}$), endotracheally intubated, and maintained under anesthesia with halothane 0.5% in nitrous oxide and oxygen (60:40). Animals were mechanically ventilated at a rate and tidal volume ($15 \text{ ml} \cdot \text{kg}^{-1}$) necessary to maintain normocarbida.

Bilateral brachial artery catheters were placed, the right for continuous monitoring of systemic arterial blood pressure and the left as a reference organ for CBF determinations using radioactive microspheres. A 7-Fr pigtail catheter was inserted into the left ventricle through the left femoral artery for injection of radioactive microspheres. The right femoral artery was cannulated and used as a second reference organ. A flow-directed, pulmonary artery catheter was placed via the right external jugular vein to measure cardiac output (CO) and pulmonary artery occlusion pressure (PAOP). Hemodynamic pressure monitoring utilized a Grass 79D polygraph (Grass Instrument Co., Quincy, MA) with Gould-Statham P23 transducers (Gould, Inc., Oxnard, CA). Systemic and pulmonary artery pressures were recorded continuously; PAOP was measured intermittently. Core temperature was monitored continuously by a thermistor on the tip of the pulmonary artery catheter and normothermia was maintained with the use of a heating pad applied to the trunk and extremities. CO was recorded intermittently using an American Edwards 9520A CO computer (American Edwards Laboratories, Santa Ana, CA). All transducers were intermittently calibrated at the level of the left atrium.

Following splenectomy, animals were turned to the prone "sphinx" position, and the temporalis and occipital musculature dissected from the skull. After heparinization ($500 \text{ IU} \cdot \text{kg}^{-1}$), the confluence of the sagittal and lateral sinuses was cannulated using a 3-Fr, double-lumen, O_2 saturation catheter (American Edwards Laboratories, Santa Ana, CA) for continuous monitoring of cerebral venous O_2 saturation and for cerebral venous sampling. An 18-ga catheter inserted into the cisterna magna and zeroed at the level of the external auditory meatus (7 cm above left atrial level) provided continuous ICP monitoring. In Group II animals, the dura was incised through a right temporoparietal burr hole and the balloon tip of a 7-Fr Foley balloon catheter was inserted subdurally for manipulation of ICP during the shock interval.

CEREBRAL BLOOD FLOW MEASUREMENT

Cerebral blood flow measurements were obtained using radioactive microspheres ($15 \mu\text{m}$) labelled with Gd 153, Nb 95, Sn 113, Sr 85, and Sc 46 using the organ reference-sample method.¹³ Paired reference organ blood samples (ROBS) were withdrawn simultaneously from the right femoral and left brachial arteries using an Edco Model 843 Infusion-Withdrawal Syringe Pump (Edco Scientific, Inc., Chapel Hill, NC). Prior to injection, microspheres were vortexed for 4 minutes to insure adequate mixing. The dose of each microsphere type was calculated to yield ≥ 400 microspheres per tissue segment and a minimum of 15,000 counts per ROBS. Injection of each microsphere type was carried out over 15 seconds. Each ROBS was taken beginning 30 seconds prior to microsphere injection and continuing for 60 seconds post-injection, at a withdrawal rate of $2.06 \text{ ml} \cdot \text{min}^{-1}$. At the conclusion of the experiment the animals were sacrificed,

the brains were removed, dissected, and counted along with the arterial reference samples in a well-type gamma counter (Auto-Gamma 5000, Packard Instruments, Downers Grove, IL). Aliquots of microspheres labelled with each radionuclide were counted along with the blood and tissue samples. Curve stripping, to correct for isotope overlap, was performed using a microcomputer connected to the gamma counter.

Cerebral blood flow was derived from the formula:

$$\text{Blood flow} = \frac{C_t \times \text{withdrawal rate} \times 100}{C_r \times Wt} \quad \text{Eq. 1}$$

where C_t = counts per minute in the tissue sample, C_r = counts per minute in the reference sample, and Wt = weight of the tissue sample. rCBF was determined for the right cerebral hemisphere (RCH), left cerebral hemisphere (LCH), and brainstem (BBF). Global CBF was calculated as a weighted mean of rCBF from all samples.

Baseline (BL) measurements included: CBF, ICP, systolic and diastolic arterial pressures (SAP and DAP), systolic and diastolic pulmonary arterial pressures (PAS and PAD), PAOP, CO, and serum osmolality (5500 vapor pressure osmometer, Wescor, Inc., Logan, UT). Arterial and cerebral venous pH, PCO_2 , and PO_2 were measured with an IL 1306 blood gas analyzer, and arterial and cerebral oxygen saturation and hemoglobin (Hgb) were analyzed in an Il 282 CO-Oximeter (Instrumentation Laboratory, Lexington, MA). From the collected data, we calculated mean arterial pressure ($MAP = DAP + 1/3 [SAP - DAP]$), cerebral perfusion pressure ($CPP = MAP - ICP$), cerebral arteriovenous oxygen content difference ($A-VD_{cere}O_2$), and the cerebral metabolic rate for O_2 ($CMRO_2 = CBF \times A-VD_{cere}O_2$).

Method of Hemorrhage

Figure 1 summarizes the measurement intervals and interventions. After instrumentation, animals were stabilized for 30 minutes and baseline (BL) data were collected. Immediately following baseline data collection and just prior to the initiation of hemorrhagic shock, ICP in animals prepared with subdural balloons (Group II) was increased to 15 mm Hg by balloon inflation (BI) with saline and maintained at that level with additional inflation volume as necessary throughout the 30-minute hemorrhagic shock interval. All animals were then rapidly hemorrhaged via the right brachial artery, Group I to a MAP of 45 mm Hg and Group II to a MAP of 55 mm Hg (target cerebral perfusion pressure = 40 mm Hg in both groups), and maintained by further removal or re-infusion of shed blood. Cerebral and hemodynamic data were obtained halfway through the shock interval, designated as T15 (fifteen minutes from the onset of shock). At T30, animals were resuscitated as follows (Table 1): Group I animals, (ICP normal; $n=12$), were randomly assigned to resuscitation with either 7.2% saline (HS; $6.0 \text{ ml} \cdot \text{kg}^{-1}$) or 0.8% saline (SAL, $54 \text{ ml} \cdot \text{kg}^{-1}$). The volumes were chosen to provide equal sodium loads. Animals with subdural mass lesions (Group II) were also randomly assigned to the alternative resuscitation fluids as described above. In Group II, just prior to resuscitation, the subdural balloon was clamped and ICP was allowed to vary spontaneously during and following resuscitation. Resuscitation fluids were infused intravenously over a 5-minute period in both groups. At the conclusion of infusion (T35), a third data set was obtained. Animals were then followed for two hours with data collection at 60-minute intervals, designated as T95 and T155, while lactated

Ringer's solution was infused only at a rate sufficient to maintain patency of intravenous catheters.

Statistical Analysis

The Kruskal-Wallis test was used to assess differences between groups at baseline and during shock. A multivariate repeated measures analysis of variance (ANOVA) was performed to determine if interactions between HS and SAL within groups existed at subsequent post-resuscitation intervals.¹⁴ Interactions were analyzed further with the Holm's sequentially rejective multiple test procedure using a significance level of 0.05.¹⁵ To assess time and fluid differences within groups when an interaction was not present, a multivariate repeated measures ANOVA and an analysis of covariance was performed on the dependent variables. When a statistically significant fluid effect was evident, Holm's sequentially rejective multiple test procedure was used to determine significance.

RESULTS

All values in the text, tables, and figures are expressed as means $\pm$ SEM.

Mean body weights and volumes of shed blood during hemorrhage for Groups I (HS and SAL) and II (HS and SAL) are listed in Table 1. Body weights and shed blood volumes were comparable within Group I and within Group II. Animals in Group II required less blood loss because the target MAP exceeded that in Group I.

Systemic Data

Both subgroups in each group exhibited comparable MAP at baseline and during shock (Figure 2). In response to fluid resuscitation (T35), MAP increased similarly with HS and SAL in both groups but was not restored to baseline. SAP was better restored than DAP (Table 2).

CO (Table 2) declined during hemorrhage to approximately 50% of baseline. CO increased following resuscitation in all groups; in both Groups I and II, CO was better restored by SAL ($p < 0.05$). No significant difference between HS and SAL in either group remained at T95 or T155. PAOP was similar among subgroups at all time intervals.

Blood temperature, PaCO_2 , pH, PaO_2 , Hgb, and arterial O_2 content (CaO_2) were similar among subgroups at all time intervals (Table 3). Serum osmolality in the HS subgroup of Group I increased significantly with fluid resuscitation and continued to increase throughout the post-resuscitation period ($p < 0.05$). Serum osmolality in the HS subgroup in Group II increased, but not significantly, following resuscitation (Table 4).

Cerebral Hemodynamic Data

Intracranial Pressure

ICP (Figure 3) was similar before balloon inflation in all four subgroups and was maintained at 15 mm Hg throughout the shock interval in Group II. Following resuscitation with SAL, ICP increased markedly in both groups (T35). In contrast, ICP did not rise following resuscitation in the two HS subgroups. Analysis of covariance confirmed a difference between HS and SAL both in Group I ($p < 0.05$) and in Group II ($p = 0.001$) at T35. During the 2-hr observation period, ICP in Group I-SAL decreased over time to nearly that in Group I-HS, which remained less than baseline pre-shock values. By T95, ICP had increased slightly in Group II-HS but remained below 20 mm Hg, whereas ICP in Group II-SAL decreased only slightly from a maximal pressure of 34 ± 3 mm Hg at T35 to 28 ± 3 mm Hg. There were no significant differences between HS and SAL in Group II at later time periods, although HS did maintain lower ICP throughout the experimental period.

Cerebral Perfusion Pressure

CPP (Figure 4) followed the same general pattern as MAP. CPP was not restored to baseline in either group by HS or SAL following resuscitation. No statistical differences in CPP were detected between HS and SAL in Group I or II at any time period.

Global CBF and Cerebral Oxygen Transport

Kruskal-Wallis testing excluded significant differences in global CBF and cerebral oxygen transport (CO_2T) at baseline and during shock (Table 5). Induction of hemorrhage decreased CBF and CO_2T in all subgroups. Fluid resuscitation increased CBF in both fluid subgroups of Group I to baseline or greater at T35 with significantly greater blood flows measured in the HS subgroup compared to SAL ($p < 0.05$). CO_2T in the HS subgroup of Group I increased to baseline with resuscitation, then decreased over time. The increase of CBF at T35 was sufficient to offset the acute decline in CaO_2 produced by hemodilution. In contrast, CO_2T in the SAL subgroup of Group I decreased immediately following resuscitation; the small increase in CBF failed to offset the decline in CaO_2 .

In Group II, neither fluid restored CBF to baseline following resuscitation. Because the increase in CBF slightly exceeded the hemodilution-induced decline in CaO_2 , CO_2T increased slightly at T35 in the HS subgroup of Group II, then declined. The SAL subgroup of Group II showed progressive deterioration in CO_2T after resuscitation ($p < 0.05$ vs HS at T35, T95, and T155). In Group II (subdural mass), HS animals had significantly better cerebral blood flow compared to SAL throughout the experimental period ($p < 0.05$ at T35, T65, and T155).

Regional CBF

rCBF changes are illustrated in Figure 5. There were no differences in hemispheric rCBF between HS or SAL in either Group I or II at baseline or during shock (Figure 5). In Group I, fluid resuscitation increased rCBF in the right cerebral hemisphere at T35 above baseline with HS and to baseline with SAL ($p < 0.05$ HS vs

SAL). By T95, RCH blood flow in Group I (no mass lesion) had stabilized at shock levels with no further changes observed.

Induction of hemorrhage resulted in marked reductions in rCBF in the right cerebral hemisphere in Group II (subdural mass) animals. In Group II, rCBF in the right cerebral hemisphere remained lower than baseline after administration of either fluid. HS did increase rCBF in the right cerebral hemisphere somewhat, in contrast to SAL, which did not improve blood flow to the right hemisphere. RCH blood flow in Group II animals resuscitated with SAL continued to decline during the observation period to $< 10 \pm 4 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$. By analysis of covariance, a significant difference ($p < 0.05$) existed between RCH blood flow in HS and SAL resuscitated animals in Groups at T35. In the SAL subgroup of Group II, RCH blood flow decreased further to flows less than those measured during the shock period. A significant difference between HS and SAL in Group II was still present at T95 and T155 ($p < 0.05$).

LCH blood flow (Figure 5) in Group I mirrored the pattern found in RCH. In Group II, LCH blood flow was restored to baseline by HS; SAL produced minimal improvement. The difference in Group II LCH blood flow between HS and SAL at T35 and T95 approached significance ($p = 0.06$).

BBF (Figure 5) was similar between HS and SAL in Groups I and II at baseline and during shock, with insignificant changes in BBF due to hemorrhage in either group. Resuscitation increased BBF immediately following infusion of HS and SAL in both groups, to baseline or greater. BBF in both groups stabilized at baseline levels and did not significantly decline throughout the experimental period.

Cerebral Metabolic Rate of Oxygen

CMRO₂ in Group I increased slightly during hemorrhage and remained similar for the remainder of the experiment (Table 5). CMRO₂ gradually declined in both Group II subgroups following resuscitation. Although not statistically different, HS appeared to be associated with greater utilization of oxygen in Group II animals following resuscitation.

DISCUSSION

There is currently a growing interest in the use of hypernatremic/hypertonic crystalloid solutions for intravascular volume replacement following hemorrhage. Such solutions can (1) effectively restore circulatory homeostasis in smaller total fluid volumes as compared to isotonic crystalloid solutions,^{3,7,8,11,16} (2) improve myocardial contractility,¹⁷ and (3) lower pulmonary artery pressures and systemic resistance.¹⁸⁻²⁰ Their low cost and long shelf life make hypertonic solutions attractive for acute resuscitation following major trauma either in the hospital or at the scene of the injury.

The major potential physiologic advantage of hypertonic resuscitation solutions is that ICP is not increased as it is by conventional resuscitation solutions such as lactated Ringer's solution, a slightly hypotonic fluid. However, lower ICP alone is not a sufficient justification for hypertonic resuscitation. CBF is dependent on CPP which in turn is more powerfully influenced by MAP than ICP because the magnitude of ICP is so much less.³ Therefore, before employing hypertonic solutions for resuscitation, it is essential to determine if CBF is improved, particularly under circumstances where reduced intracranial compliance amplifies the cerebral physiologic difference between hypertonic and slightly hypotonic fluids.

These data further clarify the cerebral physiologic effects of hypertonic resuscitation solutions when compared to comparable sodium loads administered as slightly hypotonic solutions. At comparable levels of CPP in both groups immediately following resuscitation, the hypertonic solution was associated with higher CBF than the slightly hypotonic crystalloid solution, although that tendency rapidly disappeared in animals without intracranial hypertension. However, in animals with intracranial mass lesions, the difference in rCBF persisted throughout the 120 minute post-resuscitation

interval, despite comparable increases in CPP. In fact, in both subgroups of Group II, CPP was restored to a level associated with preserved autoregulation in animals without intracranial pathology.²¹

These data also expand existing information regarding the effects of hypertonic resuscitation solutions on ICP. The intact blood-brain barrier is poorly permeable to sodium. Therefore, changes in serum sodium and associated changes in osmolality cause rapid changes in ICP and in brain water. Isovolemic hemodilution with hypertonic lactated saline ($252 \text{ mEq} \cdot \text{L}^{-1} \text{ Na}^+$) decreases ICP and brain water in comparison to 0.9% saline.²² Zornow and colleagues used plasmapheresis to acutely reduce serum osmolality or oncotic pressure in rabbits and demonstrated that small decreases in serum osmolality increased both ICP and brain water.²³

The major objective of the present study was to characterize further the cerebral hemodynamic changes that occur following resuscitation with HS after severe hemorrhage associated with reduced intracranial compliance. In this model, $6 \text{ ml} \cdot \text{kg}^{-1}$ of 7.2% saline replaced 17% of the shed blood volume, in marked contrast to conventional crystalloid replacement therapy which requires replacement of 2-3 times blood loss. The potential value of hypertonic saline as a resuscitation fluid after hemorrhagic shock with severe CNS injury is evident from the reduction in ICP seen immediately following resuscitation, since it is well established that increases in ICP commonly occur following conventional crystalloid resuscitation as confirmed in this present series of experiments. The effect of HS on ICP was apparent throughout the post-resuscitation period in Group II-HS; at no time did ICP exceed 20 mm Hg as it did consistently in Group II-SAL. Because inflation of a subdural balloon, unlike clinical or experimental head injury, is not associated with acceleration-deceleration trauma, it is possible that the

ability of the intracranial contents to compensate for an increase in intracranial volume was greater in these animals than could be expected following a concussive injury. Nonetheless, it is readily apparent that HS is superior to isotonic crystalloid solutions in minimizing ICP increases due to rapid fluid infusion following hemorrhage.

Hypertonic saline has been associated with a lower ICP than isotonic salt solutions when used for resuscitation from hemorrhagic shock.^{3,5,11,12} Prough and colleagues compared a single bolus of 7.5% hypertonic saline ($6.0 \text{ ml} \cdot \text{kg}^{-1}$) to lactated Ringer's solution ($60 \text{ ml} \cdot \text{kg}^{-1}$) following a 30-minute shock interval produced by blood loss of approximately $40 \text{ ml} \cdot \text{kg}^{-1}$ in mongrel dogs.³ Hypertonic saline was associated with a significantly lower post-resuscitation ICP than lactated Ringer's solution, but a similar, reduced level of CBF and cerebral oxygen transport. The superior rCBF achieved with HS in the present study may reflect the greater precision of measurements of CBF using radiolabelled microspheres in comparison to the $^{133}\text{Xenon}$ clearance technique employed in the earlier study. In addition, microsphere measurements require less time to perform and therefore may have more accurately identified an early transient peak in CBF.

Gunnar and colleagues compared 3.0% saline, 0.9% saline, and a 10% solution of dextran-40.¹¹ Following a one-hour interval of hemorrhagic shock, the investigators returned one-half of the shed blood, infused one of the test fluids in a volume equal to shed blood, then infused 1500 ml of 0.9% saline over the ensuing 1.25 hours.¹¹ In that study, ICP in the group that had received 0.9% saline consistently exceeded ICP in the group that had received 3.0% saline.¹¹ Subsequently, in animals that had been subjected to hemorrhagic shock combined with epidural balloon inflation, Gunnar and colleagues compared systemic hemodynamics and ICP after balloon inflation, during shock, and

following resuscitation.⁵ Following resuscitation, ICP increased dramatically in a group that had received 0.9% saline and increased little in a group that had received 3.0% saline.

Several important differences in experimental design require comment. First, Gunnar and colleagues chose to resuscitate animals with equal volumes of the test solutions. Because the osmolar load administered to the animals receiving 3.0% saline greatly exceeded that associated with a smaller volume of 7.5% saline in the present study, the effects of hypertonicity on ICP should have been greater. Second, resuscitation was initiated with one-half of the previously shed blood. Infusion of blood alone increased cardiac index to control values. In contrast, in our present study, resuscitation was initiated with blood-free solutions, as usually occurs in clinical resuscitation. Third, although Gunnar and colleagues inflated the epidural balloon prior to shock, they then permitted ICP to decline as a consequence of shock.⁵ Because ICP was permitted to decline during the shock interval, the magnitude of associated cerebral ischemia may well have been less. Cerebral perfusion pressure increased from a low of approximately 40 mm Hg at the beginning of shock to approximately 65 mm Hg by the end of the shock interval. Gunnar and colleagues subsequently reported preliminary data suggesting that a resuscitation regimen equivalent to the one they had previously reported produced no differences in CBF.¹² However, as before, ICP was permitted to decline during hemorrhage, resulting in a higher CPP during the shock interval.

In the current study, right hemispheric CBF was better restored in Group II-HS, but this effect did not appear to be due to improved CPP alone, since CPP was similar between both subgroups at all time periods. In these experiments, the failure of an adequate CPP to maintain CBF suggests a reduced ability of the brain vessels to

compensate (i.e., autoregulate). Several explanations may account for improved right hemispheric CBF following hypertonic solutions. First, hypertonic saline, by decreasing brain water, could limit local brain tissue pressure increases in a manner analogous to mannitol.^{24,25} A second possible mechanism is direct cerebral vasodilatation by hypertonic saline. Originally suggested by Harbedo,²⁶ that mechanism is supported by Wahl,²⁷ who reported a direct vasodilatory action of hypertonic saline when applied topically to pial vessels. While the mechanism explaining the vasodilation is unknown, it has been suggested that the hyperosmolarity may induce local ionic changes that affect cerebrovascular tone.

As noted by Todd et al,²² many trauma patients suffer major neurological injuries in addition to severe systemic injury and hemorrhage. Intracranial injury complicates fluid resuscitation because of the potential for adverse cerebral hemodynamic effects. Although hypertonic solutions appear to reduce ICP and improve CBF, severe hypernatremia may be associated with confusion, coma,²⁸ blood-brain barrier disruption,²⁹ and cerebral dehydration leading to possible intracranial hemorrhage. These effects appear to represent a negligible risk if hypertonicity develops in association with hypertonic resuscitation, in contrast to hypertonicity developing as a consequence of pathologic loss of free water.

We conclude that hypertonic saline solutions offer advantages over conventional slightly hypotonic and isotonic solutions in resuscitation following hemorrhage with superimposed neurological injury (e.g., subdural or epidural hematoma). We have shown improvement in global and regional CBF and also demonstrated that systemic hemodynamics are sufficiently improved to maintain adequate tissue perfusion until more definitive therapy of shock can be instituted. Further studies are necessary to

determine if acute resuscitation with hypertonic saline limits neurological impairment in severely traumatized patients with CNS injury.

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Table 1. Comparison of Body Weight, Shed Blood and Resuscitation Volume
(Means $\pm$ SEM)

Group	N	Body Weight (kg)	Blood Loss (ml•kg ⁻¹)	Volume Infused (ml•kg ⁻¹)
Group I HS	6	20 $\pm$ 1.2	35 $\pm$ 2.0	6.0
SAL	6	22 $\pm$ 1.2	37 $\pm$ 2.0	54.0
Group II HS	6	22 $\pm$ 0.8	30 $\pm$ 2.5	6.0
SAL	6	22 $\pm$ 0.8	33 $\pm$ 3.0	54.0

Table 2. Major Systemic Variables (Means $\pm$ SEM)

Group		BL	T15	T35	T95	T155
MAP (mm Hg)	I HS	113.2 $\pm$ 4.4	48.6 $\pm$ 3.5 ⁺⁺	81.7 $\pm$ 3.8	81.7 $\pm$ 10.4	77.7 $\pm$ 12.8
	I SAL	118.2 $\pm$ 9.0	44.8 $\pm$ 2.4 ⁺⁺	86.2 $\pm$ 5.0	86.8 $\pm$ 2.8	80.8 $\pm$ 8.7
	II HS	108.3 $\pm$ 5.8	55.0 $\pm$ 1.5 ⁺⁺	78.5 $\pm$ 8.0	91.7 $\pm$ 4.2	73.3 $\pm$ 12.4
	II SAL	110.5 $\pm$ 9.4	53.7 $\pm$ 0.9 ⁺⁺	86.7 $\pm$ 9.1	94.5 $\pm$ 9.3	73.8 $\pm$ 13.6
SAP (mm Hg)	I HS	142 $\pm$ 6.4	77 $\pm$ 6.4	133 $\pm$ 9.6	128 $\pm$ 9.3	114 $\pm$ 11.3
	I SAL	147 $\pm$ 6.8	68 $\pm$ 5.8	127 $\pm$ 4.1	119 $\pm$ 3.4	115 $\pm$ 8.2
	II HS	138 $\pm$ 7.8	*	116 $\pm$ 7.4	120 $\pm$ 5.7	103 $\pm$ 12.6
	II SAL	139 $\pm$ 7.9	*	120 $\pm$ 7.5	123 $\pm$ 5.7	94 $\pm$ 12.3
DAP (mm Hg)	I HS	99 $\pm$ 4.6	34 $\pm$ 2.8	56 $\pm$ 4.0	58 $\pm$ 13.3	50 $\pm$ 13.1
	I SAL	103 $\pm$ 8.9	30 $\pm$ 1.2	66 $\pm$ 5.8	71 $\pm$ 3.4	65 $\pm$ 7.6
	II HS	95 $\pm$ 5.9	*	60 $\pm$ 7.8	78 $\pm$ 3.9	58 $\pm$ 10.9
	II SAL	96 $\pm$ 6.0	*	71 $\pm$ 8.0	80 $\pm$ 4.0	53 $\pm$ 10.3
CO (L $\cdot$ min ⁻¹)	I HS	3.2 $\pm$ 0.4	1.2 $\pm$ 0.1	2.9 $\pm$ 0.3	1.7 $\pm$ 0.1	1.5 $\pm$ 0.1
	I SAL	3.9 $\pm$ 0.2	1.4 $\pm$ 0.2	4.9 $\pm$ 0.5 ⁺	2.7 $\pm$ 0.3	2.2 $\pm$ 0.4
	II HS	4.1 $\pm$ 0.2	1.8 $\pm$ 0.1	3.7 $\pm$ 0.2	2.2 $\pm$ 0.2	2.0 $\pm$ 0.3
	II SAL	3.8 $\pm$ 0.3	1.6 $\pm$ 0.1	5.3 $\pm$ 0.6 ⁺	2.5 $\pm$ 0.3	1.7 $\pm$ 0.3
PAOP (mm Hg)	I HS	4 $\pm$ 2	0 $\pm$ 1	3 $\pm$ 2	3 $\pm$ 1	2 $\pm$ 1
	I SAL	5 $\pm$ 1	3 $\pm$ 1	9 $\pm$ 1	4 $\pm$ 1	3 $\pm$ 1
	II HS	5 $\pm$ 2	1 $\pm$ 1	1 $\pm$ 1	1 $\pm$ 1	1 $\pm$ 2
	II SAL	5 $\pm$ 2	3 $\pm$ 1	8 $\pm$ 3	3 $\pm$ 1	3 $\pm$ 1

* only MAP recorded @ T15 in Group II
⁺ p<0.05 SAL vs HS, Group I and Group II
⁺⁺ p<0.05 BL vs T15, Group I and Group II

Table 3. Major Systemic Variables (Means $\pm$ SEM)

	Group	BL	T15	T35	T95	T155
Temp (°C)	I HS	37.4 $\pm$ 0.4	38.1 $\pm$ 0.4	37.8 $\pm$ 0.2	38.3 $\pm$ 0.5	38.9 $\pm$ 0.4
	I SAL	37.3 $\pm$ 0.4	38.1 $\pm$ 0.5	36.6 $\pm$ 0.3	37.9 $\pm$ 0.3	38.7 $\pm$ 0.2
	II HS	36.7 $\pm$ 0.3	37.4 $\pm$ 0.3	37.3 $\pm$ 0.3	37.8 $\pm$ 0.4	38.2 $\pm$ 0.4
	II SAL	38.0 $\pm$ 0.3	38.6 $\pm$ 0.4	37.3 $\pm$ 0.2	38.0 $\pm$ 0.4	38.6 $\pm$ 0.6
PaCO ₂ (mm Hg)	I HS	39.5 $\pm$ 0.6	40.2 $\pm$ 1.7	40.4 $\pm$ 0.9	41.8 $\pm$ 2.4	38.9 $\pm$ 0.5
	I SAL	41.2 $\pm$ 0.6	41.2 $\pm$ 0.4	39.5 $\pm$ 0.5	40.8 $\pm$ 1.3	41.2 $\pm$ 1.4
	II HS	37.1 $\pm$ 0.8	38.4 $\pm$ 1.3	36.9 $\pm$ 0.8	36.0 $\pm$ 0.8	36.7 $\pm$ 0.8
	II SAL	38.4 $\pm$ 2.3	38.8 $\pm$ 1.0	40.0 $\pm$ 0.8	39.3 $\pm$ 0.6	39.3 $\pm$ 1.6
pH	I HS	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0
	I SAL	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.0
	II HS	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.0
	II SAL	7.4 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.0	7.3 $\pm$ 0.0	7.2 $\pm$ 0.0
PaO ₂ (mm Hg)	I HS	191 $\pm$ 13	188 $\pm$ 9	197 $\pm$ 9	176 $\pm$ 5	183 $\pm$ 14
	I SAL	170 $\pm$ 8	155 $\pm$ 10	186 $\pm$ 6	168 $\pm$ 7	163 $\pm$ 6
	II HS	231 $\pm$ 15	214 $\pm$ 12	214 $\pm$ 18	232 $\pm$ 9	221 $\pm$ 9
	II SAL	208 $\pm$ 19	212 $\pm$ 19	255 $\pm$ 20	246 $\pm$ 23	207 $\pm$ 32
Hgb (g·dl ⁻¹)	I HS	13.8 $\pm$ 1.0	11.3 $\pm$ 1.0	8.4 $\pm$ 0.7	10.7 $\pm$ 0.7	10.2 $\pm$ 1.3
	I SAL	14.1 $\pm$ 0.8	11.3 $\pm$ 0.7	7.3 $\pm$ 0.5	9.7 $\pm$ 0.7	10.8 $\pm$ 0.9
	II HS	11.3 $\pm$ 0.7	10.1 $\pm$ 0.6	7.9 $\pm$ 0.4	9.3 $\pm$ 0.3	9.6 $\pm$ 0.4
	II SAL	10.7 $\pm$ 0.6	9.4 $\pm$ 0.6	6.3 $\pm$ 0.6	8.3 $\pm$ 0.8	8.7 $\pm$ 1.1
CaO ₂ (ml·100ml ⁻¹)	I HS	18.8 $\pm$ 1.2	15.6 $\pm$ 1.2	11.8 $\pm$ 0.9	14.9 $\pm$ 0.9	14.3 $\pm$ 1.7
	I SAL	19.5 $\pm$ 1.1	15.7 $\pm$ 0.9	10.3 $\pm$ 0.6	13.5 $\pm$ 0.9	14.9 $\pm$ 1.2
	II HS	14.7 $\pm$ 0.7	13.3 $\pm$ 0.6	10.8 $\pm$ 0.7	12.5 $\pm$ 0.3	12.5 $\pm$ 0.4
	II SAL	14.7 $\pm$ 1.1	12.9 $\pm$ 0.9	9.0 $\pm$ 0.9	11.6 $\pm$ 1.2	12.0 $\pm$ 1.6

Table 4. Serum Osmolality (mosm·L⁻¹) (Means ± SEM)

		BL	T95	T155
Group I No Mass				
	7.2% HS	292±12	318±6**	324±4**
	0.8% SAL	292±7	281±14	299±0
Group II With Mass				
	7.2% HS	292±13	303±4	309±2
	0.8% SAL	289±9	290±5	292±7

* p<0.05 HS vs SAL, Group I
+ p<0.05 BL vs T95, BL vs T155, Group I

Table 5. Major Cerebral Variables (Means $\pm$ SEM)

	Group	BL	T15	T35	T95	T155
Global CBF (ml $\cdot$ 100g $^{-1}\cdot$ min $^{-1}$)	I HS	56 $\pm$ 6	46 $\pm$ 8	86 $\pm$ 16+	53 $\pm$ 8	47 $\pm$ 5
	I SAL	46 $\pm$ 3	38 $\pm$ 3	53 $\pm$ 6	49 $\pm$ 6	44 $\pm$ 4
	II HS	64 $\pm$ 14	38 $\pm$ 10	59 $\pm$ 11++	44 $\pm$ 10++	32 $\pm$ 8++
	II SAL	62 $\pm$ 8	30 $\pm$ 46	37 $\pm$ 7	19 $\pm$ 5	13 $\pm$ 5
CO $_2$ T (ml $\cdot$ 100g $^{-1}\cdot$ min $^{-1}$)	I HS	10.6 $\pm$ 1.2	6.9 $\pm$ 0.8	9.9 $\pm$ 1.8	7.8 $\pm$ 1.0	6.7 $\pm$ 1.0
	I SAL	9.0 $\pm$ 0.7	5.9 $\pm$ 0.3	5.4 $\pm$ 0.4	6.5 $\pm$ 0.8	6.4 $\pm$ 0.4
	II HS	9.2 $\pm$ 2.0	5.0 $\pm$ 1.4	5.7 $\pm$ 1.0	4.6 $\pm$ 1.1	3.3 $\pm$ 1.0
	II SAL	9.2 $\pm$ 1.7	3.9 $\pm$ 0.9	3.2 $\pm$ 0.9**	2.1 $\pm$ 0.7**	1.1 $\pm$ 0.6**
CMRO $_2$ (ml $\cdot$ 100g $^{-1}\cdot$ min $^{-1}$)	I HS	2.8 $\pm$ 0.4	3.2 $\pm$ 0.4	3.5 $\pm$ 0.6	3.4 $\pm$ 0.4	3.3 $\pm$ 0.3
	I SAL	2.6 $\pm$ 0.3	3.2 $\pm$ 0.2	2.6 $\pm$ 0.3	3.2 $\pm$ 0.3	3.3 $\pm$ 0.3
	II HS	3.1 $\pm$ 0.9	2.5 $\pm$ 0.5	2.6 $\pm$ 0.5	2.2 $\pm$ 0.4	1.7 $\pm$ 0.3
	II SAL	2.9 $\pm$ 0.2	2.1 $\pm$ 0.4	1.6 $\pm$ 0.5	1.0 $\pm$ 0.3	0.7 $\pm$ 0.5
Cerebral A-VDO $_2$ (ml $\cdot$ 100ml $^{-1}$)	I HS	5.3 $\pm$ 0.9	7.6 $\pm$ 1.2	4.2 $\pm$ 0.4	6.7 $\pm$ 0.9	7.4 $\pm$ 0.9
	I SAL	5.6 $\pm$ 0.5	8.1 $\pm$ 0.4	5.0 $\pm$ 0.6	6.7 $\pm$ 0.6	7.8 $\pm$ 1.1
	II HS	4.9 $\pm$ 0.7	7.0 $\pm$ 0.6	4.9 $\pm$ 0.4	6.3 $\pm$ 0.6	7.0 $\pm$ 0.9
	II SAL	4.9 $\pm$ 0.6	7.2 $\pm$ 0.5	4.4 $\pm$ 0.4	5.7 $\pm$ 0.4	7.1 $\pm$ 1.2

+ p<0.05 HS vs SAL for CBF in Group I

++ p<0.05 HS vs SAL for CBF in Group II

** p<0.05 SAL vs HS for CO $_2$ T in Group II

LEGENDS

- Figure 1. Summary of experimental sequence.
- Figure 2. Response of mean arterial pressure following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS), or 0.8% saline (SAL) in animals without (Group I) and with (Group II) an intracranial mass.
- Figure 3. Response of intracranial pressure following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS), or 0.8% saline (SAL) in animals without (Group I) and with (Group II) an intracranial mass. Intracranial hypertension induced by inflation of a subdural balloon accompanied hemorrhage in Group II.
- Figure 4. Changes in cerebral perfusion pressure following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS), or 0.8% saline (SAL) in animals without (Group I) and with (Group II) an intracranial mass.

Figure 5. Response of regional cerebral blood flow (right and left cerebral hemisphere and brainstem), following resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS), or 0.8% saline (SAL) in animals without (Group I) and with (Group II) an intracranial mass.

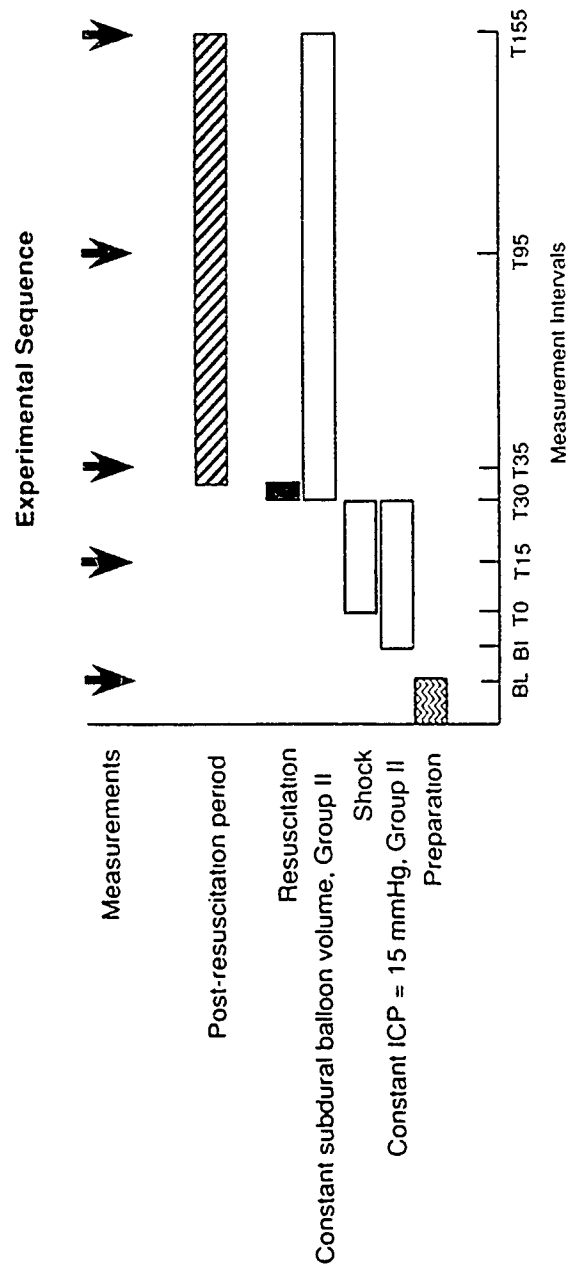
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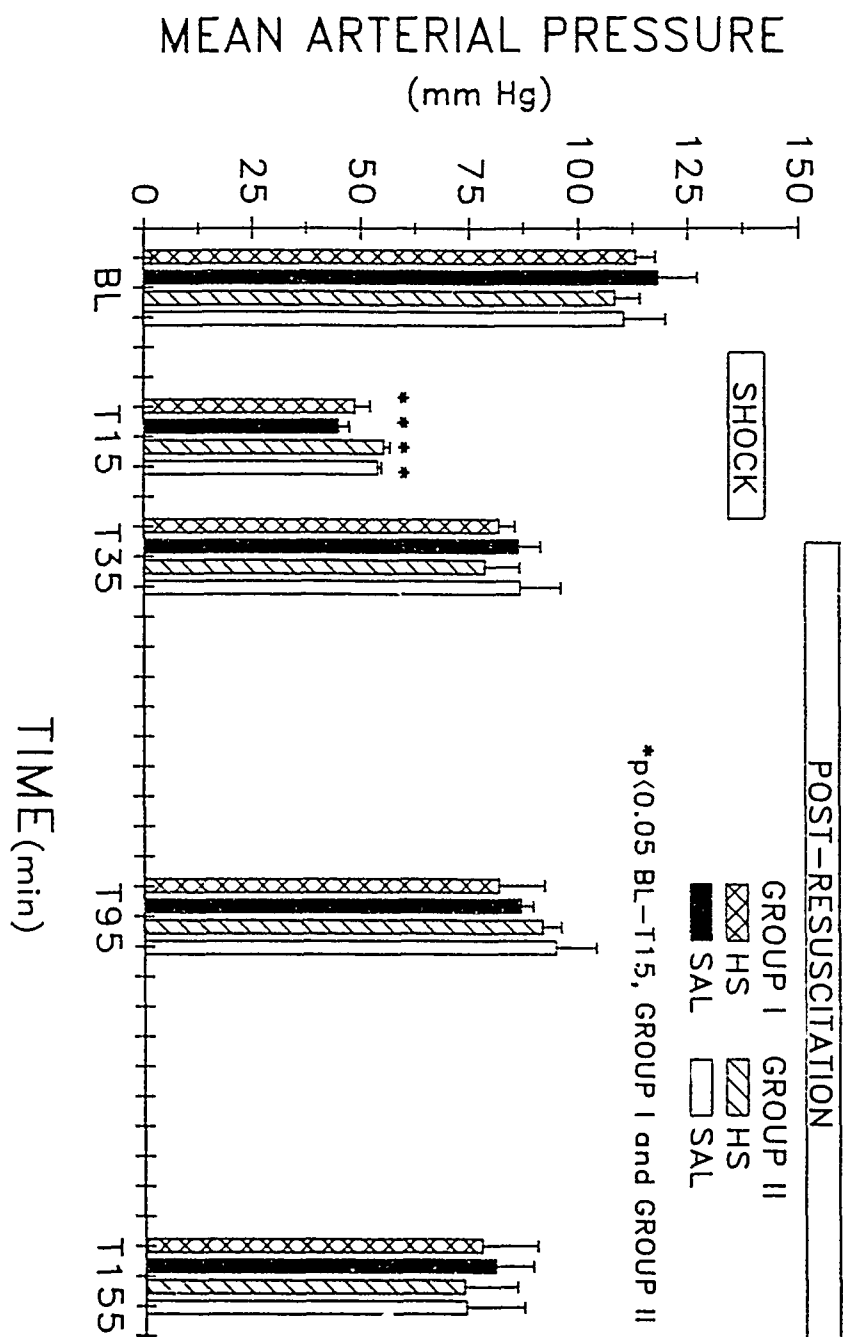
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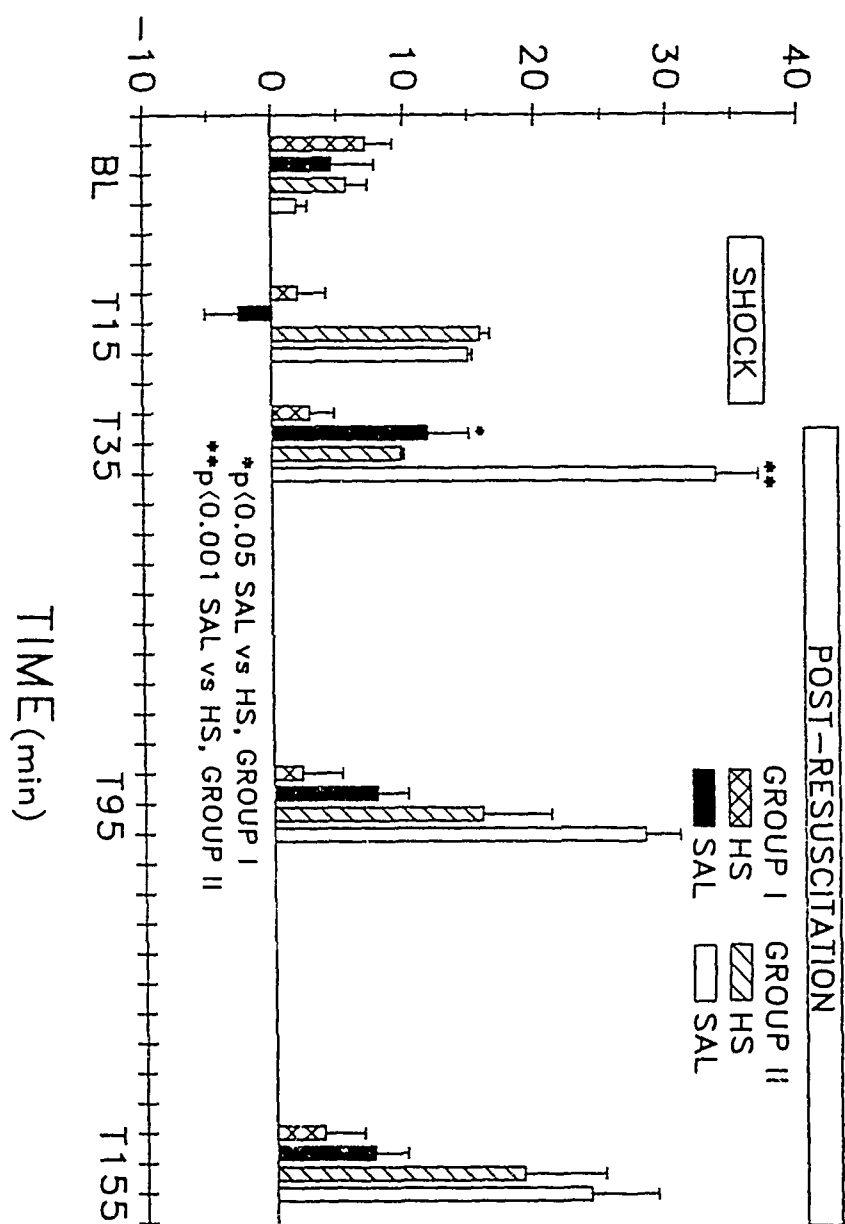
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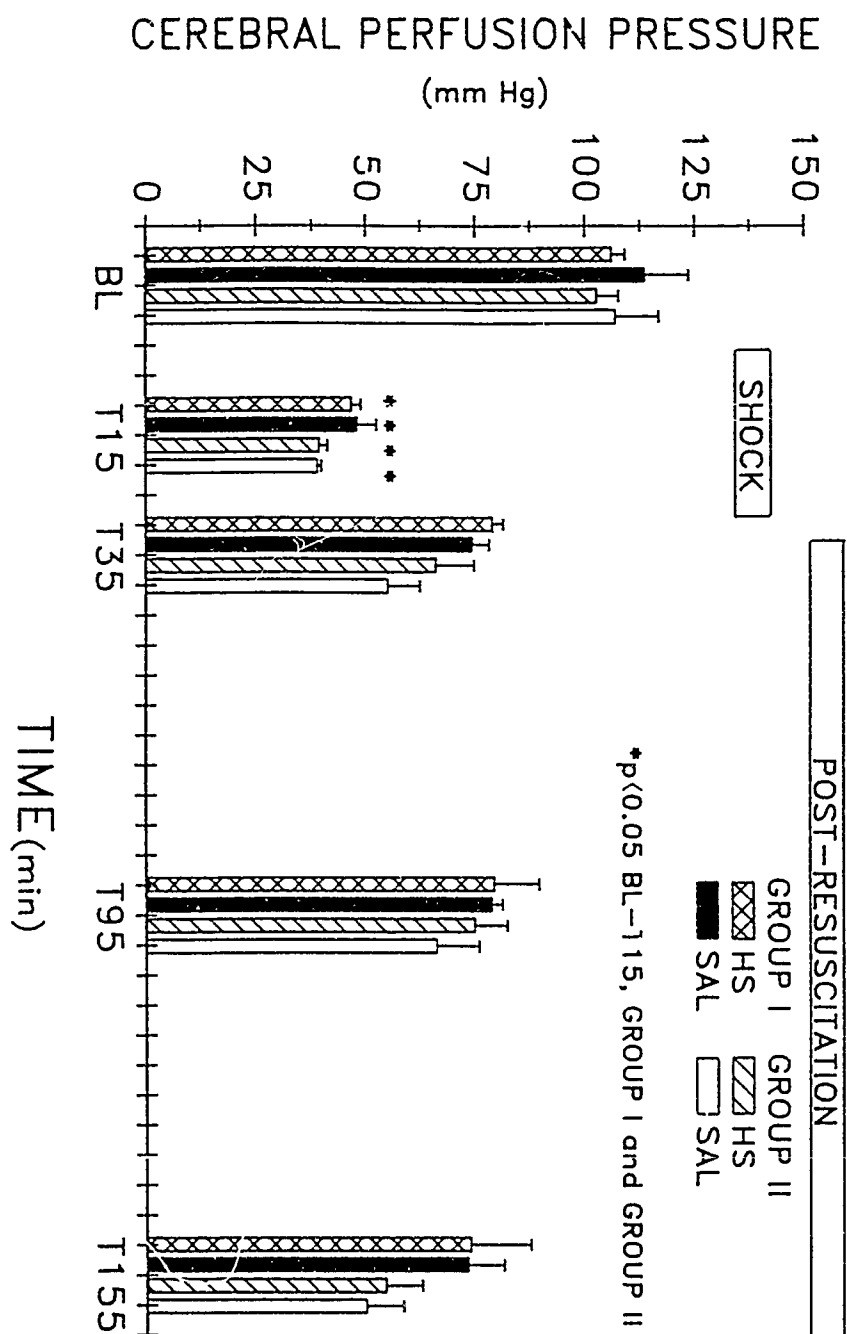


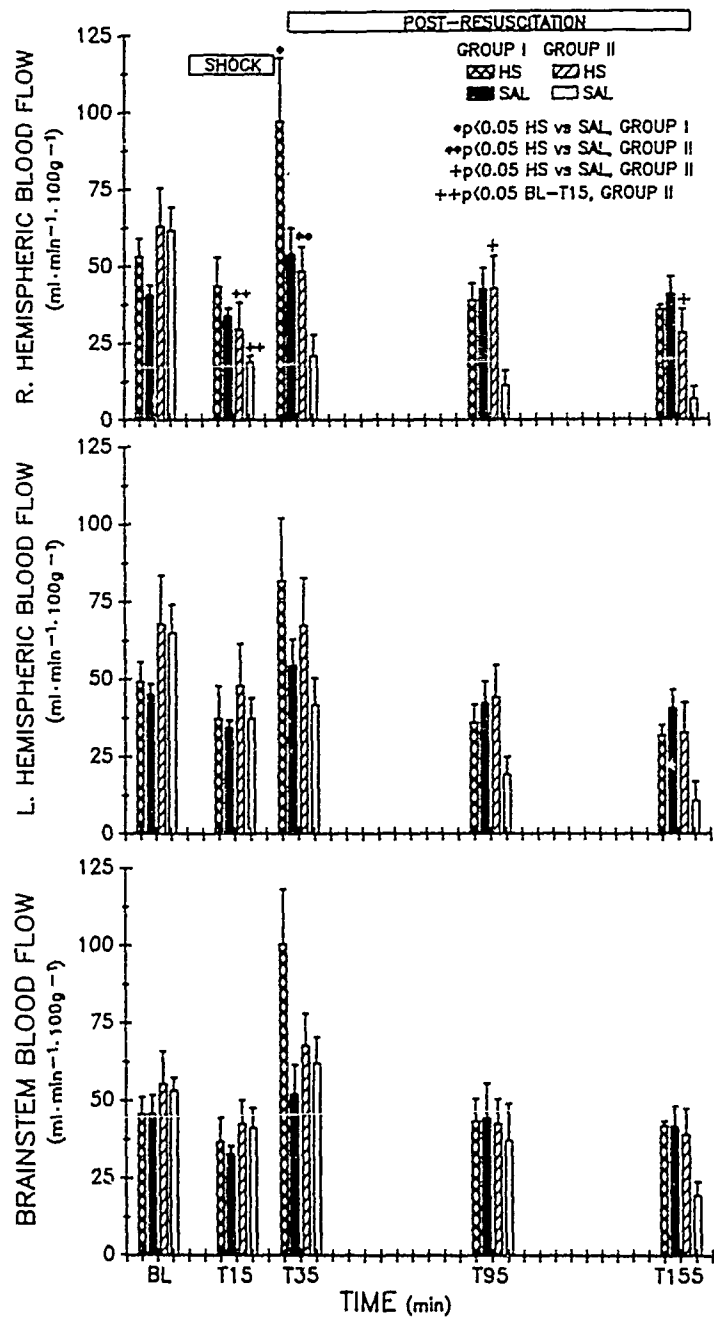


INTRACRANIAL PRESSURE

(mm Hg)







HYPERTONIC/HYPERONCOTIC FLUID RESUSCITATION
FOLLOWING HEMORRHAGIC SHOCK

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Running Head: Hypertonic/Hyperoncotic Resuscitation

ABSTRACT

We compared canine systemic and cerebral hemodynamics following small volume resuscitation from hemorrhagic shock with 7.2% saline (HS; 1233 mEq/L sodium), 20% hydroxyethyl starch (HES) in 0.8% saline, or a combination fluid consisting of 20% hydroxyethyl starch in 7.2% saline (HS/HES), each in a volume approximating 12% of shed blood volume ($4 \text{ ml} \cdot \text{kg}^{-1}$). Eighteen endotracheally intubated mongrel dogs (18-24 kg) were ventilated to maintain normocarbica with 0.5% halothane in nitrous oxide and oxygen (60:40). Following a 30-minute period of hemorrhagic shock (mean arterial pressure = 40 mm Hg), extending from time (T) 0 to T30, animals received one of three randomly assigned intravenous resuscitation fluids: HS, HES or HS/HES. Data were collected at baseline (BL), at the beginning of the shock period (T30), immediately after fluid infusion (T35), and at 60-minute intervals for two hours (T95, T155). Mean arterial pressure (MAP) declined during shock and was maintained at 40 mm Hg. Following resuscitation, MAP increased similarly in all groups, but baseline MAP was not restored. Cardiac output (CO) also increased after resuscitation in all groups, but failed to return to baseline. ICP decreased during shock and increased slightly immediately following resuscitation in all groups. Cerebral blood flow (CBF) declined in all groups during shock. Following resuscitation, CBF increased and exceeded baseline in the HS and HS/HES groups compared to HES which resulted in only a slight increase in CBF ($p < 0.05$ HS vs HES at T35). These results indicate that small volume resuscitation with a combination of HS/HES is equal to or superior to HS or HES in its overall effects on systemic and cerebral hemodynamics; however, infused in a volume of $4 \text{ ml} \cdot \text{kg}^{-1}$, neither HS/HES, HS, or HES were able to restore or

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sustain systemic arterial pressure.

INTRODUCTION

Prompt restoration of blood pressure and cardiac output is essential in the acute resuscitation of trauma victims. Ideally, the fluid infused should rapidly restore systemic perfusion. Fluids that are effective when infused in small volumes are particularly attractive for resuscitation at the trauma scene or during emergency transport. Recently, small volumes of hypertonic salt solutions have been used to effectively restore systemic hemodynamics. Velasco and colleagues initially reported that as little as $4.0 \text{ ml} \cdot \text{kg}^{-1}$ of 7.5% saline could effectively restore systolic blood pressure and cardiac output and produce 100% survival in dogs subjected to hemorrhage approximating half of estimated canine blood volume, or about $40 \text{ ml} \cdot \text{kg}^{-1}$ {1986,1101,1088}. Subsequent investigators have demonstrated that hypertonic saline, in a variety of concentrations, with and without added colloid, produces acute stabilization when administered in a volume much smaller than the original shed blood volume {1087,1300,1092,1112,1299,1968,1995,1996,1291}. In addition to restoring systemic hemodynamic status, hypertonic solutions also tend to reduce intracranial pressure (ICP) {Prough, CCM 1985; Prough, JNS 1986}, an effect that may be advantageous in patients in whom cranial trauma complicates hemorrhagic shock. Colloid, usually 6.0% low-molecular weight dextran, has been added to hypertonic solutions to extend the relatively short-lived hemodynamic effects {1087,1968,1944}. Although dextran solutions are commonly used for resuscitation in Europe, the more commonly employed synthetic colloid in this country is hydroxyethyl starch. Few data are available to characterize the cerebrovascular effects of concentrated solutions of hydroxyethyl starch when added to either isotonic or hypertonic saline solutions.

Therefore, we performed the following study to compare the effects on systemic and cerebral hemodynamics of acute resuscitation with $4.0 \text{ ml} \cdot \text{kg}^{-1}$ of 7.2% saline, 20% hydroxyethyl starch in 0.8% saline, or 20% hydroxyethyl starch in 7.2% saline.

METHODS

Animals were handled according to guidelines established by the institution's Animal Care and Use Committee. Eighteen mongrel dogs of either sex, weighing 18-24 kg, were anesthetized with thiopental sodium ($8.0 \text{ mg} \cdot \text{kg}^{-1}$ iv), paralyzed with pancuronium ($0.2 \text{ mg} \cdot \text{kg}^{-1}$ iv), and endotracheally intubated. Halothane 0.5% in nitrous oxide and oxygen (60:40) maintained anesthesia. Animals were ventilated using an Edco Model 822 large-animal ventilator (Edco Scientific, Inc., Chapel Hill, NC), at a tidal volume of $15 \text{ ml} \cdot \text{kg}^{-1}$ and a rate sufficient to maintain normocarbida (PaCO_2 35-45 mm Hg). Additional pancuronium, given as needed, prevented respiratory movement.

Two femoral artery catheters were placed for monitoring of arterial blood pressure and for induction of rapid hemorrhage, respectively. A flow-directed, pulmonary artery catheter was placed via the right external jugular vein to measure cardiac output (CO) and pulmonary artery occlusion pressure (PAOP). Hemodynamic pressure monitoring utilized a Grass 79D polygraph (Grass Instrument Co., Quincy, MA) with Gould-Statham P23 transducers (Gould, Inc., Oxnard, CA). Systemic and pulmonary artery pressures were recorded continuously; PAOP was measured intermittently. Body temperature was monitored continuously by a thermistor on the tip of the pulmonary artery catheter and was maintained near baseline values by applying a heating pad applied to the trunk and extremities. CO was recorded intermittently using an American Edwards 9520A CO computer (American Edwards, Santa Ana, CA). All transducers, except for ICP, were intermittently calibrated at the level of the left atrium.

Cerebral Blood Flow Measurement

Following splenectomy, animals were turned to the prone "sphinx" position and the occipital musculature was dissected from the underlying cranial vault. Cerebral blood flow (CBF) was measured using a modification of the technique originally described by Rapela and Green {1934}, where the confluence of the sagittal sinus was cannulated and timed samples of cerebral venous outflow measured. A 18 G catheter inserted into the cisterna magna and zeroed to the level of the external auditory meatus (7 cm above left atrial level) provided continuous ICP monitoring.

Method of Hemorrhage

After instrumentation, all animals were left undisturbed for 30 minutes, after which baseline (BL) data were recorded. Recorded data consisted of organ blood flow, systolic and diastolic arterial pressures (SAP and DAP), CO, PAOP, pulmonary arterial systemic and diastolic pressure (PAS and PAD), body temperature, arterial pH, PaCO₂, PaO₂ (IL 1306 Instrumentation Laboratory, Lexington, MA), and hemoglobin (Hgb) (IL 282; Instrumentation Laboratory, Lexington, MA). Mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) were calculated from the following formulas:

$$\text{MAP} = \text{DAP} + 1/3 (\text{SAP} - \text{DAP}) \quad \text{Eq. 1}$$

$$\text{CPP} = \text{MAP} - \text{ICP} \quad \text{Eq. 2}$$

After anti-coagulation with heparin (500 IU•kg⁻¹ iv), blood was rapidly withdrawn through the right femoral artery catheter to reduce MAP to 40 mm Hg; MAP was maintained at that level for 30 minutes by removing or reinfusing shed blood. Hemodynamic data were obtained at the beginning of the shock period (T0) and at the

end of the 30 minute shock period (T30), a notation in which T stands for time and the number following T indicates the number of minutes elapsed from the onset of shock. Following the shock interval, animals were randomly assigned to one of three groups, based upon the composition of resuscitation fluid: Group HS (n=6) received $4.0 \text{ ml} \cdot \text{kg}^{-1}$ of 7.2% hypertonic saline ($1233 \text{ mEq} \cdot \text{L}^{-1}$ sodium), Group HES (n=6) received $4.0 \text{ ml} \cdot \text{kg}^{-1}$ of 20% hydroxyethyl starch dissolved in 0.8% saline, and Group HS/HES (n=6) received $4.0 \text{ ml} \cdot \text{kg}^{-1}$ of 20% hydroxyethyl starch dissolved in 7.2% saline. Additional data were collected immediately after infusion of the resuscitation fluid over 5 minutes (T35) and thereafter at hourly intervals for two hours (T95, T155). Figure 1 summarizes the experimental preparation. Following the completion of the experimental period, all brains were examined for evidence of subarachnoid, subdural or epidural hemorrhage.

Statistical Analysis

The Kruskal-Wallis test was employed to assess differences among the groups at baseline and during shock. A multivariate repeated measures analysis of variance (ANOVA) was performed to determine if interactions between groups and time existed at subsequent post-resuscitation intervals {2039}. Interactions were analyzed further with the Holm's sequentially rejective multiple test procedure using a significance level of 0.05 {143}. To assess time and group differences when an interaction was not present, a multivariate repeated measures ANOVA and an analysis of covariance were performed on the dependent variables. When a statistically significant group effect was evident, Holm's sequentially rejective multiple test procedure was used to determine which groups differed.

RESULTS

Mean body weight, shed blood volume, and resuscitation volume for the HS, HES, and HS/HES groups are listed in Table 1. The body weights and volumes of shed blood were similar among groups. All subsequent values in the text, tables, and figures are expressed as means $\pm$ SEM.

SYSTEMIC VARIABLES

Kruskal-Wallis testing detected no difference in MAP at baseline or during shock among the three groups (Table 2). Immediately following resuscitation, MAP increased similarly in all groups but remained well below baseline. By 120 minutes following resuscitation (T155) MAP had decreased in all groups to values similar to those present during shock (Figure 2A). Systolic (SAP) and diastolic arterial pressures (DAP) were comparable among groups after resuscitation but tended to be higher in the HS/HES group (Table 2). There were no statistical differences in MAP, SAP or DAP among fluid groups detected during the post-resuscitation period.

Cardiac output (CO) decreased by approximately 70% with induction of shock ($p < 0.05$ TO compared to BL). Following resuscitation, CO increased approximately twofold in each of the three fluid groups (Figure 2B) but did not attain baseline values. This increase in CO at T35 was followed by a gradual decrease which continued throughout the post-resuscitation period in all groups.

PAOP, although decreased during shock, was comparable to baseline throughout the post-resuscitation period (Table 2). Hemoglobin (Hgb) decreased in all three groups following resuscitation. Hgb increased in the HS group from T35 to T155 but

continued to decline in the HES and HS/HES groups (Table 2). Other variables including pH, PaCO₂, PaO₂, and body temperature were similar among groups at all time intervals (Table 3).

Cerebral Variables

Cerebral blood flow (CBF) at baseline was comparable among groups. Kruskal-Wallis testing failed to detect a difference at baseline or during shock among groups. CBF following resuscitation (T35) differed significantly among groups. Resuscitation with HS increased CBF to greater than baseline values compared to HS/HES which restored CBF to baseline and HES which produced only a slight increase in CBF (Figure 3). ANOVA demonstrated a group difference at T35 between HS and HES ($p < 0.05$). While HS and HS/HES initially increased CBF, the increase was transient; CBF declined gradually from T35 to T95 to a level that approximated CBF levels during shock. CBF in all three groups was comparable at T95 and T155.

ICP was comparable among groups at baseline. Induction of shock decreased ICP significantly from baseline in all groups ($p < 0.05$). Following resuscitation, ICP increased in all groups, but was not restored to baseline (Figure 4A). ICP, like CBF, decreased gradually over time in all groups.

Cerebral perfusion pressure (CPP) followed the same general pattern as MAP (Figure 4B).

DISCUSSION

In the 1980's Velasco and colleagues stimulated considerable interest in the applicability of small-volume resuscitation in hemorrhagic shock {1986}. They first demonstrated that dogs, subjected to hemorrhage equal to approximately one-half of estimated canine blood volume, could be effectively resuscitated using 7.5% saline in a dose of $4 \text{ ml} \cdot \text{kg}^{-1}$, a volume that was equal to about one-tenth of the initial shed blood volume {1986, new Lopes}. They further demonstrated that hypertonic saline failed to improve systemic hemodynamics if a vagally mediated reflex arc were abolished or if hypertonic saline was infused into the aorta rather than into the inferior vena cava {1101, new Lopes [1986]}. Other investigators, using similar hemorrhagic shock preparations, have been unable to reproduce sustained improvements in blood pressure and cardiac output {1087,1291,1968,1299,1984,1898, Whitley, Prough} and the associated long term survival. As a result of the transient response to hypertonic saline alone, subsequent investigators added a colloid component, usually 6.0% low-molecular weight dextran, in order to extend the effect of hypertonic saline {1291,1303,1968,1984}.

While several investigators have studied the effects of hypertonic saline in combination with 6% dextran, they have not investigated the systemic or cerebral effects of highly concentrated (20%) hydroxyethyl starch in combination with hypertonic resuscitation solutions {1303}. The present study suggests that this combination, like the combination of hypertonic saline with 6.0% low-molecular dextran, somewhat prolongs the duration of systemic hemodynamic improvement without interfering with the immediate hemodynamic responses {1984,1303}. In a recent study, Kramer and colleagues bled unanesthetized adult sheep to a $\text{MAP} = 50 \text{ mm Hg}$ for three hours

(shed blood volume = 42 ± 7 ml•kg⁻¹) and then resuscitated the animals with 200 ml of either 0.9% saline or 7.2% saline with 6% dextran-70 {1984}. Only the combination fluid restored blood pressure and CO. Lactated Ringer's solution was then administered as necessary to both groups thirty minutes following the initial fluid bolus to restore or maintain CO at baseline levels. The group that had received the combination fluid required only one-sixth the quantity of lactated Ringer's solution required by the isotonic saline group. In a subsequent study, Smith and colleagues compared the hemodynamic effects in sheep following resuscitation with 4 ml•kg⁻¹ of hypertonic saline with sodium acetate, hypertonic saline alone or a combination of 7.2% saline with 6.0% dextran-70 who had been bled to a MAP = 50 mm Hg for two hours {1291}. They demonstrated that the combination fluid sustained a significantly higher CO over the three hour, post-resuscitation observation period than did hypertonic saline alone or hypertonic saline to which sodium acetate had been added {1291}.

Two more recent studies have demonstrated that hypertonic saline in combination with colloid is superior to 0.9% saline or 7.5% saline in similar volumes. Maningas and colleagues studied the effects of 0.9% saline, 7.5% saline, 6.0% dextran-70, or 7.5% saline in 6.0% dextran-70 following potentially lethal hemorrhage in swine {1303}. Each fluid was given in a volume equal to 25% of the shed blood volume. The combination fluid was associated with 100% survival for 96 hours in comparison to significantly poorer survival in the groups that received 0.9% saline or 7.5% saline. Velasco and colleagues demonstrated that the combination of 7.5% saline and 6.0% dextran-70 was associated with somewhat higher survival and more sustained improvement in plasma volume than similar volumes of 6.0% dextran-70 or 7.5% saline alone {1898}.

Our data demonstrate that each of the three, small volume resuscitation fluids produced comparable, short-term systemic and cerebral hemodynamic improvement. However, when administered in equal volumes of $4.0 \text{ ml} \cdot \text{kg}^{-1}$ all failed to restore and maintain MAP, CO or to improve cerebral blood flow beyond the immediate post-resuscitation interval. These data differ significantly from those reported by Velasco {1986} and Kramer {1984}. Velasco et al successfully resuscitated 100% of dogs bled to 50% of estimated blood volume using $4 \text{ ml} \cdot \text{kg}^{-1}$ of 7.5% saline {1986}. Following a more severe hemorrhage, (i.e., MAP = 35 mm Hg for 30 or 60 minutes) resuscitation with $6 \text{ ml} \cdot \text{kg}^{-1}$ of 7.5% saline alone failed to produce 100% survival in mongrel dogs subjected to 30 or 60 minute shock periods {1898}. MAP was better maintained in animals that received $6.0 \text{ ml} \cdot \text{kg}^{-1}$ of 7.5% saline combined with 6.0% dextran despite similar expansion of plasma volume and similar increases in plasma sodium. Although either hypertonic saline alone or hypertonic saline combined with 6% dextran produced comparable short-term resuscitation, the combination fluid better sustained MAP in animals shocked for either 30 or 60 minutes.

Explanations as to why our data fail to demonstrate sustained systemic hemodynamic improvement following resuscitation with either hypertonic saline or the combination fluid may relate to differences in study design. First, we more rapidly exsanguinated animals, reducing MAP to 40 mm Hg in approximately 5 minutes, rather than the 15 minute interval employed by Velasco et al {1898}. Second, all animals in the present study were splenectomized, a procedure which limits the canine compensatory response to hemorrhage. Splenectomy, generally considered to be a necessary prelude to canine hemorrhage models, was not performed in Velasco's study.

Third, we infused fluid into a forelimb vein rather than the femoral vein, although peripheral and central infusions appear to be equivalent (Hands, new). Fourth, and most importantly, animals in the present study were paralyzed and provided controlled ventilation. The effects of mechanical ventilation on preload and cardiac output may have influenced the systemic response both to hemorrhage and the resuscitation fluids. In contrast, dogs in the study of Velasco et al. were intubated but breathed spontaneously.

Kramer and colleagues {1299} demonstrated that hypertonic/hyperoncotic fluids are superior to equal small volumes of 0.9% saline alone as resuscitation for hemorrhage. They infused $4.0 \text{ ml} \cdot \text{kg}^{-1}$ of 7.5% saline/6% dextran or 0.9% saline directly into the right atrium following 30 minutes of hemorrhage shock (MAP 45 - 55 mm Hg). Thirty minutes after initial resuscitation, additional lactated Ringer's solution was administered to maintain CO at or above baseline values. Animals that had received the combination fluid required only $6.0 \text{ ml} \cdot \text{kg}^{-1}$ of additional fluid whereas those who had received only 0.9% saline required $48 \text{ ml} \cdot \text{kg}^{-1}$ of additional lactated Ringer's solution. The initial infusion of 7.5% saline/6.0% dextran restored MAP to baseline. In contrast, in the present study, neither 7.2% saline alone, 20% HES alone, or the combination restored MAP. Methodologic differences between the two studies include choice of species (sheep vs. dogs), anesthesia (unanesthetized vs. anesthetized), and ventilatory management (spontaneous vs. controlled).

As expected, ICP decreased in all groups during shock. Resuscitation resulted in small transient increases in ICP in all groups. Cerebral perfusion pressure remained comparable among groups. Nevertheless, CBF was statistically greater in the HS group

than in the HES group immediately following resuscitation, although the difference had resolved 60 minutes later. One hour after resuscitation, CBF had declined to levels measured during shock in all groups. The initial improvement in CBF could represent a primary cerebral vasodilator effect of acute hypertonicity (John - we can use ref from LAIA paper) or it could result from lower blood viscosity. If the response could be prolonged and if similar effects could be demonstrated in patients with head injury, hypertonic resuscitation solutions might be preferable for resuscitation of patients with combined head injury and hemorrhagic shock. These data complement previous data from this laboratory, in which $6.0 \text{ ml} \cdot \text{kg}^{-1}$ of 7.2% saline and $60 \text{ ml} \cdot \text{kg}^{-1}$ of lactated Ringer's solution produced comparable restoration of CBF following hemorrhagic shock {Prough JNS}. Taken together, these studies suggest that small volumes of hypertonic fluid or large volumes of slightly hypotonic fluid produce comparable increases in CBF, although ICP is far greater after the latter fluid {Prough, JNS}. ICP is similar if small volumes of hypertonic fluid, hyperoncotic fluid, or the combination are given, but CBF is improved most by the hypertonic fluid. Adding hypertonic saline to concentrated colloid results in an intermediate improvement in CBF.

Based upon the data presented here, we conclude that highly concentrated hydroxyethyl starch solutions in combination with HS may present an alternative to hypertonic saline or HES alone for small-volume resuscitation of trauma victims. Although the volumes administered in the current study were insufficient to fully restore systemic hemodynamics, the short-term improvement, coupled with improved CBF, might be satisfactory pending definitive resuscitation.

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Table 1. Body Weight, Shed Blood, and Resuscitation Volumes (Means $\pm$ SEM)

Group	N	Weight (kg)	Blood Loss (ml•kg ⁻¹)	Resus. Volume (ml•kg ⁻¹)
HS	6	20.7 $\pm$ 0.9	29 $\pm$ 2.3	4.0
HES	6	20.9 $\pm$ 1.0	31 $\pm$ 3.2	4.0
HS/HES	6	21.9 $\pm$ 1.2	36 $\pm$ 2.9	4.0

Table 2. Major Systemic Variables (Means $\pm$ SEM)

Group		BL	T0	T30	T35	T95	T155
MAP	HS	135 $\pm$ 2	41 $\pm$ 0.4	37 $\pm$ 0.3	57 $\pm$ 2	59 $\pm$ 2	27 $\pm$ 2
	HES	140 $\pm$ 1	39 $\pm$ 0.5	37 $\pm$ 0.3	65 $\pm$ 3	60 $\pm$ 6	42 $\pm$ 4
	HS/HES	138 $\pm$ 2	40 $\pm$ 0.4	40 $\pm$ 0.3	72 $\pm$ 4	79 $\pm$ 2	44 $\pm$ 2
SAP (mm Hg)	HS	169 $\pm$ 3	65 $\pm$ 4	56 $\pm$ 1	80 $\pm$ 4	87 $\pm$ 4	52 $\pm$ 4
	HES	178 $\pm$ 3	52 $\pm$ 5	56 $\pm$ 1	86 $\pm$ 3	85 $\pm$ 6	62 $\pm$ 6
	HS/HES	148 $\pm$ 5	52 $\pm$ 1	54 $\pm$ 1	96 $\pm$ 3	105 $\pm$ 1	65 $\pm$ 3
DAP (mm Hg)	HS	118 $\pm$ 2	33 $\pm$ 1	31 $\pm$ 1	38 $\pm$ 2	39 $\pm$ 3	22 $\pm$ 2
	HES	121 $\pm$ 1	32 $\pm$ 1	28 $\pm$ 1	48 $\pm$ 3	48 $\pm$ 6	33 $\pm$ 3
	HS/HES	120 $\pm$ 2	35 $\pm$ 1	33 $\pm$ 1	49 $\pm$ 5	66 $\pm$ 2	34 $\pm$ 1
PAOP (mm Hg)	HS	4 $\pm$ 0.3	3 $\pm$ 0.5	4 $\pm$ 0.5	3 $\pm$ 0.3	5 $\pm$ 0.4	3 $\pm$ 0.5
	HES	3 $\pm$ 0.2	2 $\pm$ 0.3	3 $\pm$ 0.3	4 $\pm$ 0.3	3 $\pm$ 0.6	4 $\pm$ 0.3
	HS/HES	3 $\pm$ 0.2	1 $\pm$ 0.3	3 $\pm$ 0.3	2 $\pm$ 0.2	3 $\pm$ 0.4	3 $\pm$ 0.4
Hgb (g $\cdot$ dl $^{-1}$)	HS	12.2 $\pm$ 0.2	10.5 $\pm$ 0.2	9.7 $\pm$ 0.2	7.9 $\pm$ 0.2	7.5 $\pm$ 0.0	9.4 $\pm$ 0.2
	HES	11.8 $\pm$ 0.4	10.6 $\pm$ 0.3	10.2 $\pm$ 0.3	9.0 $\pm$ 0.2	8.4 $\pm$ 0.4	8.0 $\pm$ 0.4
	HS/HES	12.9 $\pm$ 0.3	10.9 $\pm$ 0.2	11.0 $\pm$ 0.5	8.6 $\pm$ 0.1	10.6 $\pm$ 0.1	8.1 $\pm$ 0.2

Table 3. Major Systemic Variables (Means $\pm$ SEM)

	Group	BL	T0	T30	T35	T95	T155
pH	HS	7.37 $\pm$ 0.0	7.41 $\pm$ 0.0	7.19 $\pm$ 0.0	7.05 $\pm$ 0.0	7.21 $\pm$ 0.0	7.13 $\pm$ 0.0
	HES	7.36 $\pm$ 0.0	7.40 $\pm$ 0.0	7.16 $\pm$ 0.0	7.10 $\pm$ 0.0	7.22 $\pm$ 0.0	7.19 $\pm$ 0.0
	HS/HES	7.37 $\pm$ 0.0	7.40 $\pm$ 0.0	7.21 $\pm$ 0.0	7.10 $\pm$ 0.0	7.28 $\pm$ 0.0	7.17 $\pm$ 0.0
PaCO ₂ (mm Hg)	HS	40 $\pm$ 0.2	30 $\pm$ 0.5	38 $\pm$ 0.6	51 $\pm$ 1	34 $\pm$ 0.7	33 $\pm$ 0.4
	HES	41 $\pm$ 0.5	31 $\pm$ 1	46 $\pm$ 2	49 $\pm$ 0.7	35 $\pm$ 1	34 $\pm$ 1
	HS/HES	39 $\pm$ 0.2	30 $\pm$ 0.5	39 $\pm$ 0.4	48 $\pm$ 1	33 $\pm$ 0.3	38 $\pm$ 0.8
PaO ₂ (mm Hg)	HS	231 $\pm$ 2	216 $\pm$ 3	261 $\pm$ 15	243 $\pm$ 7	226 $\pm$ 2	226 $\pm$ 2
	HES	212 $\pm$ 7	208 $\pm$ 3	209 $\pm$ 5	217 $\pm$ 4	215 $\pm$ 2	210 $\pm$ 3
	HS/HES	235 $\pm$ 4	226 $\pm$ 4	222 $\pm$ 4	202 $\pm$ 7	224 $\pm$ 2	216 $\pm$ 4
Temp (°C)	HS	38 $\pm$ 0.2	38 $\pm$ 0.2	38 $\pm$ 0.1	38 $\pm$ 0.1	38 $\pm$ 0.1	37 $\pm$ 0.2
	HES	37 $\pm$ 0.1	37 $\pm$ 0.1	37 $\pm$ 0.2	37 $\pm$ 0.2	37 $\pm$ 0.2	38 $\pm$ 0.1
	HS/HES	37 $\pm$ 0.0	37 $\pm$ 0.1	37 $\pm$ 0.1	37 $\pm$ 0.0	38 $\pm$ 0.0	38 $\pm$ 0.1

LEGENDS

- Figure 1. Summary of experimental procedure.
- Figure 2. Changes in mean arterial pressure (A) and cardiac output (B) following resuscitation from hemorrhagic shock with 7.2% saline (HS), 20% hydroxyethyl starch in 0.8% saline (HES), or HES dissolved in 7.2% saline (HS/HES).
- Figure 3. Changes in cerebral blood flow following resuscitation from hemorrhagic shock with 7.2% saline (HS), 20% hydroxyethyl starch in 0.8% saline (HES), or HES dissolved in 7.2% saline (HS/HES).
- Figure 4. Changes in intracranial pressure (A), and cerebral perfusion pressure (B) following resuscitation from hemorrhagic shock with 7.2% saline (HS), 20% hydroxyethyl starch in 0.8% saline (HES), or HES dissolved in 7.2% saline (HS/HES).

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Our data, however, do complement the results of numerous other investigators who reported better maintenance of systemic hemodynamics with a hypertonic saline/hyperoncotic fluid combination following resuscitation from hemorrhage compared to hypertonic saline alone or isotonic saline {1299,1303, Prough, Whitley, 1898}. In a recent study from our laboratory (in press) we compared the systemic hemodynamic effects on organ perfusion with isotonic saline, 7.2% saline, 20% hydroxyethyl starch dissolved in 0.8% saline or 20% hydroxyethyl starch dissolved in 7.2% saline. While there were no statistical differences in MAP between groups, MAP continued to increase over time only in those groups containing 20% hydroxyethyl starch compared to 0.8% saline or 7.2% saline which decreased gradually over time. In this study, animals were resuscitated with small, equal volumes (6 ml/kg), except the 0.8% saline group which received 54 ml/kg, following a 30 minute period of hemorrhagic shock with a constant MAP = 45 mm Hg. Interestingly, CO was restored to baseline in the 0.8% saline and the hypertonic-hydroxyethyl starch group. Although CO in the 0.8% saline group quickly decreased over time HS/HES maintained significantly higher CO compared to 0.8% saline or 7.2% saline which resulted in more improved organ blood flows. The primary difference between these two studies, in addition to the 45 mm Hg MAP during the shock interval, was the administered resuscitation fluid volume which was increased to 6 ml/kg.

EFFECTS OF MODERATE TRAUMATIC BRAIN INJURY,
HEMORRHAGE, AND FLUID RESUSCITATION ON CEREBRAL BLOOD FLOW
AND OXYGEN TRANSPORT

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ABBREVIATED TITLE: CBF following head trauma and shock

KEY WORDS: Brain: cerebral blood flow
 Intravenous fluid therapy
 Radioactive microspheres
 Shock: hemorrhagic
 Trauma: central nervous system

ABSTRACT

We investigated the effects of combined traumatic brain injury, hemorrhagic hypotension, and fluid resuscitation on intracranial pressure (ICP), cerebral blood flow (CBF), arterial oxygen content (CaO_2), cerebral oxygen transport ($\text{CO}_2\text{T} = \text{CBF} \times \text{CaO}_2$), and electroencephalographic activity (EEG) in cats. Adult mongrel cats were prepared for fluid-percussion traumatic brain injury and radioactive microsphere CBF measurement. Under anesthesia consisting of isoflurane 0.8% in N_2O and O_2 (70:30), cats were randomly assigned to undergo moderate trauma alone (Group T; $n=8$), hemorrhagic hypotension followed by resuscitation with 10% hetastarch (Group H; $n=8$), or the combination of trauma and hemorrhage followed by resuscitation with 10% hetastarch (Group TH; $n=8$). Trauma alone produced significant decreases in CBF ($p<0.01$) but no significant changes in other variables. Hemorrhage and resuscitation, in the absence of trauma, significantly reduced CaO_2 but produced no significant changes in CBF, ICP, or EEG score. Trauma followed by hemorrhage and resuscitation produced significant ($p<0.01$) decreases in CBF, CaO_2 , CO_2T , and EEG score. These data demonstrate that the combination of brain trauma, hemorrhagic hypotension, and fluid resuscitation is associated with more severe deficits in cerebral oxygen availability and neurological function than either insult alone.

INTRODUCTION

Multiple organ system trauma, hypovolemia, and hypotension often accompany traumatic brain injury (TBI). In a recent study involving almost seven thousand adults, Luerssen, et al.,¹ reported that over 40% of patients sustained multiple organ trauma in addition to head injury. Approximately 15-20% of severe head injuries are associated with arterial hypotension;^{1,2} the combination carries a poorer prognosis than head injury that is unaccompanied by hypotension.^{1,3} Since TBI impairs the normal cerebral vasodilation that occurs in response to hypotension⁴ and hypoxemia⁵ in experimental models, hypotension following clinical head injury would likely result in significant decreases in cerebral perfusion and oxygen transport. Although Lewelt described cerebrovascular responses to declines in arterial oxygen content (CaO_2) produced by hypoxemia in head-injured cats,⁵ no data describe the response to the reduction in CaO_2 that occurs with rapid resuscitation with asanguineous fluids.

Therefore, we have compared the effects of moderate fluid-percussion TBI alone, moderate hemorrhagic hypotension followed by resuscitation, and the combination of TBI followed by hemorrhage and resuscitation on cerebral blood flow (CBF), intracranial pressure (ICP), CaO_2 and, in these acutely anemic animals, cerebral oxygen transport (CO_2T).

METHODS AND MATERIALS

Using a protocol approved by our Institutional Animal Care and Use Committee, 24 mongrel cats (2.5 ± 0.1 kg) of either sex were fasted overnight and then anesthetized with ketamine hydrochloride ($25 \text{ mg}\cdot\text{kg}^{-1}$). All cats had tracheostomies performed, were paralyzed with pancuronium bromide ($0.3 \text{ mg}\cdot\text{kg}^{-1}$), and were mechanically ventilated with 1.6% isoflurane in $\text{N}_2\text{O}:\text{O}_2$ (70:30). A midline incision was made, the scalp was reflected, and an 11-mm midline craniotomy was drilled using a water-cooled dental drill. A stainless-steel adapter ring was glued over the intact dura and then secured to 2 skull screws using dental acrylic. Details of the preparation for fluid-percussion injury have been described elsewhere.⁶ An additional burr hole was drilled for placement of a stainless-steel bolt that was fluid-coupled to a pressure transducer to monitor ICP. Polyethylene cannulae were placed in the right brachial and left femoral arteries for microsphere reference sample withdrawal. The left brachial artery was cannulated for continuous monitoring of blood pressure. The right femoral artery was cannulated for induction of controlled hemorrhage. The left femoral vein was cannulated for drug infusion and fluid resuscitation. A polyethylene cannula with a slightly flared tip was placed in the left atrium via a left thoracotomy. At the conclusion of surgical preparation, all wound sites were infiltrated with a local anesthetic (0.5% lidocaine) and isoflurane concentration was reduced to 0.8-1.0% in $\text{N}_2\text{O}:\text{O}_2$ (70:30). During the subsequent 30-minute equilibration interval, PaO_2 , PaCO_2 , and pH were adjusted to normal limits using ventilatory rate and volume adjustments.

At the conclusion of the equilibration period, baseline (BL) CBF was measured using the radioactive microsphere technique.⁷ For each blood flow determination, approximately 1 million microspheres ($15\mu\text{m}$) labelled with ^{113}Sn , ^{85}Sr , ^{46}Sc , ^{153}Gd , or ^{95}Nb

suspended in 0.9% saline and polyoxyethylene sorbitan monooleate (Tween 80) were injected through the left atrial cannula. Prior to injection, the stock bottle of microspheres was agitated for 4 minutes using a vortex mixer. Immediately before and for 90 seconds after injection, arterial reference samples were withdrawn at a rate of $1.03 \text{ ml} \cdot \text{min}^{-1}$ using a syringe pump. Counts per minute from the reference samples were averaged and used to calculate blood flows as described below. Arterial blood pressure, ICP, PaO_2 , PaCO_2 , and pH were recorded during each blood flow determination.

Following the completion of the baseline CBF determination, all cats were prepared for brain injury, connected to the trauma device, and then randomized to one of 3 groups (Figure 1). Group T (Trauma only) cats ($n=8$) were subjected to moderate fluid-percussion TBI ($2.2 \pm 0.1 \text{ atm}$) but were not hemorrhaged or resuscitated. Group H (Hemorrhage) cats ($n=8$) were not injured but were hemorrhaged at a constant rate until approximately 30% ($18 \text{ ml} \cdot \text{kg}^{-1}$) of total blood volume was removed. At the end of the shock interval (EOS), a second CBF determination was performed. The shed blood was then replaced with an equal volume of 10% hydroxyethyl starch. CBF was determined immediately, 60, and 120 minutes after the completion of the resuscitation period at (R0, R60, and R120, respectively). In Group T cats, CBF was determined at time intervals that corresponded to those in the other groups. Group TH cats ($n=8$) were subjected to moderate TBI ($2.3 \pm 0.1 \text{ atm}$) and then hemorrhaged and resuscitated identically to group H. CBF was determined at the same intervals as in group H.

During each CBF determination, one-minute strips of biparietal EEG were recorded on a Grass 7D recording polygraph (Grass Instruments Co., Quincy, MA). These strips were later analyzed using a 5-point visual inspection scale modified from a

scale described by Prior et al.⁸ Each strip was assigned one of the following numerical scores:

- 5 Normal - indistinguishable from baseline EEG
- 4 Depressed amplitude - amplitude reduced by more than 25% of baseline;
no burst suppression
- 3 Moderate suppression - intermittent short (<3 sec) periods of burst
suppression or a decrease in amplitude of greater than 50% of baseline
amplitude
- 2 Profound burst suppression - long periods (>3 sec) of total suppression
with short, intermittent periods of activity
- 1 Isoelectric - no evidence of electrical activity

Visual analysis was performed by investigators blinded to the group and time at which the strip was recorded. Interobserver reliability of the EEG analysis score used for these studies was tested by comparing scores of two observers who analyzed the same polygraph tracings using a weighted kappa statistic.⁹

After the final (R120) CBF determination, the animals were sacrificed using sodium pentobarbital (50 mg•kg⁻¹) followed by saturated potassium chloride. The brains were removed, dissected into 23 regions bilaterally, and counted along with the arterial references samples in a well-type gamma counter (Auto-Gamma 5000, Packard Instruments, Downers Grove, IL). Aliquots of microspheres labelled with each radionuclide were counted along with the blood and tissue samples; curve stripping to correct for isotope overlap was performed using a microcomputer connected to the gamma counter. Using the reference sample method,¹⁰ CBF for individual brain regions was calculated according to the formula:

$$\text{CBF (ml}\cdot\text{100g}^{-1}\cdot\text{min}^{-1}) = \frac{C_t \times \text{RBF} \times 100}{C_r \times W_b}$$

where C_t = counts in tissue sample; C_r = counts in reference arterial sample; RBF = reference arterial withdrawal rate; W_b = weight of tissue sample. Global CBF was calculated as a weighted average of regional CBF. Cerebral O_2 transport (CO_2T) was calculated as:

$$\text{CO}_2\text{T} = \text{CaO}_2 \times \text{CBF} \times 100^{-1}$$

where $\text{CaO}_2 = \text{PaO}_2 \times 0.0031 + (\text{Hgb} \times 1.39 \times \% \text{Hgb saturation})$.

SAS[®] statistical software (SAS, Cary, NC) was used for all statistical analyses. The Kruskal-Wallis test was used to evaluate potential differences among groups at baseline. A multivariate repeated analysis of covariance, adjusting for baseline values, was used to test group effects and time*group interactions.¹¹ When a time*group interaction was present, the group effects were tested separately at each time point. Holm's sequentially rejective multiple test procedure was used to determine which groups differed when a group effect was present. The EEG scores were analyzed using an analysis of variance of ranked scores at each time point.¹² Local CBF values were analyzed only for descriptive purposes. When a time*group interaction was present, the group effects were analyzed at each time point using Holm's procedure. A significance level of 0.05 was used for all procedures.

RESULTS

Systemic Variables

All values in the text and tables are expressed as mean $\pm$ standard error of the mean.

There were no significant changes in body temperature, PaCO₂, or PaO₂ in any group at any time point (Table 1). Arterial pH declined in all groups over the duration of the experiment without intergroup differences.

Baseline mean arterial blood pressure (MAP) did not differ significantly among the three groups (Table 2, Figure 2). In Group T (trauma only), MAP declined gradually over the entire observation period. In Groups H (hemorrhage) and TH (trauma-hemorrhage), MAP declined approximately 20% during hemorrhage and then returned transiently to control levels following resuscitation. MAP fell during the post-resuscitation period, with Group TH exhibiting the greatest decrease. Left atrial pressure declined during hemorrhage in Groups H and TH. Hemoglobin concentration declined during resuscitation with hydroxyethyl starch and remained significantly lower in Groups H and TH than in Group T for the remainder of the experiments. Because PaO₂ remained above normal at all intervals in all groups, CaO₂ changed in parallel with changes in hemoglobin concentration. Cardiac output did not change significantly over time in any group.

Cerebral Variables

ICP increased slightly in Groups T and H during and after resuscitation (Figure 3; Table 3) and then returned to baseline levels by 120 minutes post-resuscitation. Group TH exhibited greater, but not statistically significantly greater increases in ICP at the R0, R60, and R120 points in comparison to Group H.

Total CBF did not change significantly during hemorrhage in Groups H and TH and during the analogous time interval in Group T (Figure 4; Table 3). Group T exhibited a significant ($p < 0.01$) decrease in CBF over time after injury. In Group H, CBF exceeded pre-hemorrhage levels during resuscitation, then returned to control levels 2 hours post-resuscitation (R120). CBF in Group TH increased only to pre-hemorrhage levels during resuscitation, then decreased markedly ($p < 0.005$) by 60 (R60) and 120 (R120) minutes after resuscitation.

Local CBF in all three groups followed the same pattern as total CBF (Figure 5). The lowest CBF levels were observed in the hippocampus of Group TH at R120, at which time CBF was $9.7 \pm 6.4 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$. The minimum CBF recorded in any other brain region was approximately $16 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$. The caudate nucleus of the trauma-hemorrhage group exhibited the greatest percent change in CBF (88%), decreasing from $159.6 \pm 21.2 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$ at baseline to $23.3 \pm 17.9 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$ at R120.

CO_2T decreased insignificantly over time in Groups T and H (Table 4). CO_2T declined significantly in Group TH, with the most marked decreases occurring 60 and 120 minutes post-resuscitation, where CO_2T was 2.3 ± 1.3 ($p < 0.01$) and 1.9 ± 1.2 ($p < 0.01$) $\text{mlO}_2 \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$, respectively.

Weighted kappa statistics indicated close agreement between the two independent raters ($k = 0.67$). Groups T and H exhibited small, gradual declines in EEG score over time (Figure 6). The EEG score in Group TH remained stable until the end of shock and then declined significantly ($p < 0.01$), demonstrating profound suppression at R120.

DISCUSSION

Feline fluid-percussion TBI, modified from a lapine model^{13,14} by Sullivan, et. al.,¹⁵ is the best characterized of current experimental models of TBI and reproduces many of the features of concussive brain injury in humans. The technique produces pressure transients (~20 msec) similar to those recorded in human cadaver skulls during sudden impact.¹⁴ Subsequent to TBI, cats demonstrate behavioral suppression resembling traumatic unconsciousness in humans.^{16,17} Fluid-percussion injury (FPI) results in a loss of pressure autoregulation⁴ similar to that reported in brain injured patients.¹⁸ FPI generates diffuse axonal injury¹⁹ and brain stem pathology¹⁵ reminiscent of that observed in human pathologic studies.^{20,21} Pathological changes in multimodality evoked potentials reported in brain-injured humans²² are also observed in cats after FPI.²³ FPI results in immediate²⁴ and delayed secondary²⁵ increases in ICP similar to those reported in humans. Catecholamine levels increase markedly after FPI in cats²⁵ and after closed head trauma in humans.²⁶

These data are the first to describe the cerebrovascular responses to hemorrhagic shock and resuscitation following TBI. Physiologic changes in the groups subjected to trauma or hemorrhage alone (Groups T and H) compare favorably to those in previous studies. In animal models, mild hemorrhage comparable to that produced in the present model usually causes no change in CBF.²⁷ Following more severe hemorrhage, resuscitation with red-cell-free fluid fails to restore CBF to pre-shock values, despite substantial reductions in Hgb and CaO_2 .^{28,29} In contrast, isovolemic hemodilution, in which blood is withdrawn and simultaneously replaced with red-cell-free fluid, is associated with an increase in CBF that offsets approximately one-half of the decrease in CaO_2 .³⁰⁻³² The acute response to hemodilution of group H following mild hemorrhage is

similar to the response to isovolemic hemodilution.

The change in CBF following trauma, hemorrhage, and resuscitation must be examined in relationship to the previously described effects of isovolemic hemodilution and of hemodilution following more profound shock. Following hemorrhagic shock of 30 minutes' duration, dogs with or without intracranial mass lesions failed to show an increase in CBF despite marked hemodilution.^{28,29,33} Following three hours of hemorrhagic shock, resuscitation with dextran increased CBF to baseline values but did not offset the effects of hemodilution.³⁴

The reason for the failure of hemodilution following profound shock, or in this model, TBI and mild shock, to offset reductions in CaO_2 is unknown. One possibility is that sympathetic nervous system stimulation alters the ability of the cerebrovasculature to respond appropriately to stimuli. Fitch and colleagues demonstrated that α -receptor blockade (phenoxybenzamine) did not change baseline CBF, but preserved CBF at baseline levels when mean arterial pressure had been reduced to values that produced marked reductions in CBF in the absence of α -blockade.³⁵ The authors concluded that sympathoadrenal discharge accompanying hemorrhage reduces CBF. Rosner et al. reported that TBI in cats increased serum norepinephrine levels 100-fold and epinephrine levels 500-fold.²⁵ Sympathetic stimulation may be responsible for the rightward shift of the lower limits of cerebral autoregulation following trauma in cats.⁴ Since both profound hemodilution and hypotension necessitate cerebral vasodilation if CO_2T is to be maintained, we speculate that sympathoadrenal responses may be responsible for the failure of CBF in Group TH to increase to the degree observed in Group H in response to hemodilution. Fluid percussion TBI produces a gradual decline in MAP and in cerebral perfusion pressure (CPP) that correlates with the magnitude of

the injury.³⁶⁻³⁸ The magnitude of change in CPP in Group T that we observed in the present study (Table 3) is consistent with a moderate level of TBI.

Although these data are the first to use microsphere methodology to measure CBF in cats, CBF values correspond well with data in other species. Boarini and colleagues studied isoflurane, 1.5 and 2.0%, in dogs and measured CBF values of 68 ± 3 to $103 \pm 18 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$.²¹ Newberg and others reported canine CBF values of $91 \pm 10 \text{ ml} \cdot 100\text{g} \cdot \text{min}^{-1}$ under 1.4% isoflurane anesthesia.²² The present data demonstrate similar baseline CBF values at 1.6% isoflurane (approximately 1 MAC) (Table 3). The flows at baseline slightly exceed those in previous studies of TBI in cats.³⁷ However, previous studies employed barbiturate anesthesia.

The increase in ICP following the sequence of fluid-percussion injury, hemorrhage, and fluid resuscitation represents an unexpected observation. In Group T, ICP increased less than 10 mm Hg, consistent with previous reports of mild to moderate experimental fluid-percussion TBI.^{36,37} However, following the combination of TBI, mild hemorrhage, and fluid resuscitation (similar to that required in the immediate stabilization of hypovolemic, head-injured patients), ICP increased nearly 600% at R0 and remained twice the level in Groups H and T even 120 minutes following resuscitation. Lewelt reported that hemorrhage following FPI was associated with an increase in ICP,⁴ the opposite of the response to hemorrhage of ICP in uninjured brain.^{28,29} Since fluid administration tends to increase ICP further, as indeed occurred in group H, the effect may have been exaggerated by trauma. As is evident from the variability in the TH Group, not all animals responded similarly. Further studies are necessary to evaluate the response of ICP to more severe hemorrhage and resuscitation.

In Group H, CBF did not differ significantly from baseline over time. In

contrast, CBF decreased significantly over time in Groups T and TH. McIntosh, et al.,³⁸ reported similar decreases in CBF after fluid-percussion TBI in cats. The decline in CBF in Group TH was greater than in either Group H or T but the difference was statistically significant only between Groups H and TH. Therefore these data support those of Lewelt and colleagues, who demonstrated that experimental brain trauma impairs the cerebral vasodilatory response to blood pressure reduction.⁴ In addition, they suggest that vasoregulation is so severely impaired that vasodilation does not accompany even the combination of declining blood pressure and acute anemia. Although the mechanism of impaired vasoregulation is unknown, experimental evidence indicates that both TBI^{39,40} and hemorrhagic shock⁴¹ result in the release of substantial quantities of vasoactive eicosanoids that may contribute to cerebral hypoperfusion.

Although the number of animals in each group is insufficient to permit statistical analysis of individual brain regions, the patterns observed in this study do suggest hypotheses that merit further study. In general, changes in regional CBF followed the same patterns as did whole-brain CBF. However, hippocampal CBF in Group TH declined to the lowest levels of any region in any group. Two hours after resuscitation (R120), hippocampal CBF in Group TH was $9.7 \pm 6.4 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$. CBF $< 10 \text{ ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$ (at normal levels of Hgb) is associated with increased extracellular potassium, presumably because of ischemia-induced ion pump failure.^{42,43} Ischemia of this magnitude produces increases in brain water content⁴⁴ and, if not reversed within 2-3 hours, cerebral infarction.⁴⁵ Because the Hgb was also reduced in the TH group, actual oxygen availability was even lower than the global and regional CBF values suggest. The profound EEG changes observed in the combination lesion animals also suggests that brain oxygen availability was reduced below acceptable levels.

The effects of trauma and hemorrhage on EEG activity were assessed using a visual inspection scale modified from a scale developed by Prior, et al.⁸ and subsequently utilized by Gregory, et al.⁴⁶ to evaluate EEG activity in cats following hemorrhagic hypotension. The scale used in the present studies was reduced from a 6-point to a 5-point scale to minimize subjectivity. As the weighted kappa statistics ($k = 0.67$) indicate, interrater reliability between the two blinded investigators was good.

Head trauma alone produced a slight, statistically insignificant decline in EEG activity. While higher levels of TBI produce significant decreases in total power of fast-Fourier transformed EEGs,³⁸ the moderate level of injury used in the present study produced no significant changes. The EEG score did not change significantly in Group H. The MAP threshold at which changes in EEG activity occur may depend on the method used to quantify EEG activity. Gregory, et al.,⁴⁶ using a similar EEG score in cats without head injury, reported that the EEG score did not change significantly until MAP reached about 25 mm Hg. In contrast, Hossmann, et al.⁴⁷ reported that total power of the fast-Fourier transformed EEG was reduced significantly when CBF decreased below 50% of baseline. MAP in Group H never fell below 80 mm Hg so changes in EEG score due to this level of hemorrhage alone would be unlikely to occur. The EEG score in Group TH deteriorated progressively and significantly, with all but one animal developing an isoelectric tracing by 120 minutes following resuscitation. In Group TH, mean EEG score was significantly reduced by R60, when CPP was 51 ± 12 mm Hg and CBF was 28 ± 16 ml•100g⁻¹•min⁻¹. Although these values are above the MAP and CBF thresholds determined by Gregory, et al.⁴⁶ for significant changes in EEG scores, McIntosh, et al.³⁸ reported significant changes in EEG power following trauma at CBF values similar to those reported in the present study. Therefore, TBI may

predispose to changes in EEG activity at levels of MAP and CBF that would not be associated with EEG changes in the untraumatized brain. We are currently investigating the relative contributions of arterial hypotension and decreasing CO_2T to changes in EEG activity.

Previous investigators have demonstrated the enhanced vulnerability of traumatized brain to secondary insults, such as hypotension or hypoxia, that would be insufficient to produce injury in untraumatized brain. Ishige and colleagues used in vivo phosphorus-31 magnetic resonance spectra to examine the effects of profound hypotension (MAP 30-40 mm Hg) on fluid-percussion brain injury.⁴⁸ Fluid-percussion brain injury alone or hypotension alone resulted in a small increase in organic phosphate, a slight decrease in phosphocreatine, and a moderate decline in brain pH. However, the combination of head injury and a decline in MAP to 30 mm Hg severely depleted high-energy phosphates, in association with a marked increase in inorganic phosphate and a precipitous decline in pH. When hypoxemia, insufficient to produce injury (about 40 mm Hg), and fluid percussion injury, also insufficient to produce consistent neurologic dysfunction, are combined in rats, severe disability or death results.⁴⁹ In cats, Anderson and colleagues demonstrated more severe brain energy depletion if hypoventilatory hypoxemia was superimposed on fluid percussion injury than if either hypoventilatory hypoxemia or fluid percussion injury were induced individually.⁵⁰ Jenkins et al. induced global cerebral ischemia following mild fluid-percussion injury in rats and demonstrated that the combined insult resulted in cellular death in hippocampal CA1 neurons that were undamaged by separate insults.^{51,52}

The present study demonstrates that conventional fluid resuscitation fails to reverse the adverse effects of combined hemorrhage and head injury. Following brain

injury and mild hemorrhage, fluid resuscitation only transiently restores cerebral perfusion pressure, is associated with prominent if variable increases in ICP, and fails to increase CBF sufficiently to offset the decline in CaO_2 . Subsequent declines in CBF are associated with a decline in cerebral oxygen transport to less than 25% of baseline values. If the traumatized human brain is similarly affected by the sequence of trauma, hemorrhage, and resuscitation, these data may explain, in part, the increased mortality and neurologic morbidity in patients who have suffered the combination of traumatic brain injury and hypotension.

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FIGURE LEGENDS

- Figure 1 Experimental protocol for Groups T (Trauma only), H (Hemorrhage and resuscitation only) and TH (Trauma and Hemorrhage). The preparation (open bar) and post-resuscitation (solid bar) periods were identical for all groups.
- Figure 2 Mean arterial pressure (MAP) in cats after hemorrhage alone (n=8), trauma alone (n=8) or trauma followed by hemorrhage (n=8).
BL = baseline (pre-injury or hemorrhage); EOS = end of shock (hemorrhage); R0 = immediately following resuscitation; R60 = 60 minutes after resuscitation; R120 = 120 minutes after resuscitation.
- Figure 3 Intracranial pressure (ICP) after hemorrhage alone, trauma alone, or trauma followed by hemorrhage.
- Figure 4 Total cerebral blood flow (CBF) after hemorrhage alone, trauma alone, or trauma followed by hemorrhage.
- Figure 5 Local cerebral blood flow (CBF) after trauma followed by hemorrhage. Caudate = caudate nucleus; Par-Occ = parietal-occipital coronal section.
- Figure 6 Electroencephalogram (EEG) scores after hemorrhage alone,

trauma alone, or trauma followed by hemorrhage.

TABLE 1. TEMPERATURE AND ARTERIAL BLOOD GASES

Variable	Group	Time Interval						
		Baseline	End of Shock	R0	R30	R60	R90	R120
Temperature (°C)	N	37.6±0.2	37.8±0.2	37.9±0.2	38.4±0.1	38.1±0.1	38.1±0.2	38.2±0.2
	T	37.8±0.2	38.2±0.2	38.2±0.2	38.1±0.1	38.4±0.2	38.5±0.2	38.2±0.1
	TM	37.7±0.2	37.7±0.2	37.8±0.2	38.4±0.1	38.0±0.1	38.0±0.2	38.4±0.2
pH	N	7.36±0.01	7.31±0.01	7.27±0.01	7.30±0.02	7.26±0.01	7.22±0.03	7.16±0.05
	T	7.33±0.01	7.32±0.01	7.31±0.01	7.29±0.1	7.27±0.2	7.23±0.04	7.23±0.03
	TM	7.35±0.01	7.30±0.01	7.26±0.02	7.27±0.02	7.31±0.6	7.19±0.04	7.12±0.05
PaCO ₂ (mm Hg)	N	30.5±0.5	30.7±0.8	31.9±0.6	30.5±0.6	30.9±0.5	30.1±0.5	31.3±0.6
	T	30.7±0.3	31.2±0.7	32.2±0.7	32.4±0.8	31.4±0.9	31.5±0.8	32.1±1.0
	TM	30.2±0.4	31.1±1.1	32.2±0.7	32.4±0.8	31.4±0.9	31.5±0.8	32.1±1.0
PaO ₂ (mm Hg)	N	124±8	126±4	136±5	125±7	123±6	130±6	123±6
	T	121±4	120±5	123±4	124±6	126±8	122±7	129±8
	TM	121±6	120±6	131±7	119±9	118±10	116±6	112±7

TABLE 2. SYSTEMIC HEMODYNAMIC VARIABLES

Variable	Group	Time Interval						
		Baseline	End of Shock	R0	R30	R60	R90	R120
Mean Arterial Pressure (mm Hg)	H	127±4	89±8	126±6	104±6	94±7*	92±8	84±14*
	T	130±5	125±11	123±11	112±12	100±17	87±18*	86±15*
	TN	117±9	88±8	140±14	88±13	74±13*	64±13	* 54±12*
Left Atrial Pressure (mm Hg)	H	3.3±0.5	-1.0±0.4	3.2±0.7	1.3±0.5	1.1±0.7*	0.6±0.4	0.6±0.6*
	T	3.0±1.2	2.6±1.2	2.4±1.3	4.3±2.4	2.0±1.5	0.4±1.2	1.1±1.3
	TN	2.1±0.4	-0.6±0.6	5.3±1.5	2.0±0.9	1.9±0.6	0.8±0.4	0.4±1.2
Cardiac Output (L·min ⁻¹)	H	0.5±0.1	0.4±0.1	0.5±0.1		0.7±0.1		0.5±0.1
	T	0.6±0.1	0.5±0.1	0.4±0.1		0.4±0.1		0.5±0.1
	TN	0.5±0.0	0.4±0.1	0.6±0.0		0.6±0.1		0.4±0.1
Hemoglobin (Gram %)	H	11.2±0.7	10.5±0.5	5.6±0.4*	5.7±0.3*	6.0±0.4*	5.8±0.4*	5.8±0.4*
	T	11.4±0.6	11.6±0.6	11.6±0.7	11.8±0.8	11.4±0.9	11.0±1.0	11.3±1.2
	TN	10.6±0.6	10.5±0.5	5.3±0.3*	5.1±0.3*	4.9±0.4*	4.5±0.3*	4.8±0.4*

* = p<.05 vs BL

TABLE 3. CEREBROVASCULAR VARIABLES

Variable	Group	Time Interval						
		Baseline	End of Shock	R0	R30	R60	R90	R120
Intracranial Pressure (mm Hg)	H	7.9±1.2	8.5±1.8	15.9±1.8	10.9±1.5	8.5±1.3	6.1±1.5	5.1±1.9
	T	5.4±1.0	12.1±4.5	14.1±6.3	30.1±16.7	14.5±5.8	10.9±3.9	7.9±3.7
	TH	5.0±1.6	8.3±2.0	35.6±18	23.2±9.1	22.1±9.9	15.4±5.6	14.4±5.3
Cerebral Perfusion Pressure (mm Hg)	H	120±5	81±9	110±7	94±7	86±8	86±7	79±13
	T	125±5	113±12	109±14	82±25	86±21	76±19	78±14
	TH	112±9	80±7	104±13	64±12	51±12	49±14	39±11
Total Cerebral Blood Flow (ml·100g ⁻¹ ·min ⁻¹)	H	94±9	94±7	122±11		99±7		70±16
	T	101±14	85±9	70±7		48±10		43±12
	TH	91±11	79±14	99±27		28±16		21±14
Brainstem Blood Flow (ml·100g ⁻¹ ·min ⁻¹)	H	59±5	57±3	74±6		63±5		46±10
	T	59±6	43±4	38±3		29±6		28±8
	TH	55±6	39±6	61±13		22±11		14±9
Cerebral Oxygen Transport (ml·100g ⁻¹ ·min ⁻¹)	H	12.8±1.2	13.3±1.5	9.1±0.9		8.0±0.6*		5.3±1.3*
	T	14.8±1.7	13.0±1.2	10.8±1.2		7.9±1.8*		7.0±1.8*
	TH	13.1±2.0	11.4±2.4	7.7±2.4		2.3±1.3*		1.9±1.2*

* = p<.05 vs BL

