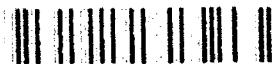




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Delayed Resuscitation with Hypertonic
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Hemorrhage in Swine

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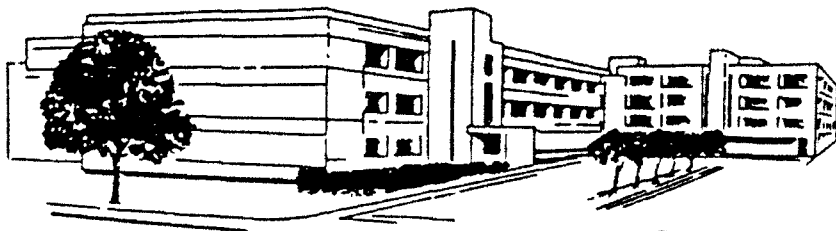
John D. O'Benar
and
Stephen P. Bruttig

Division of Military Trauma Research

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Delayed resuscitation with hypertonic saline/dextran from uncontrolled aortotomy hemorrhage in swine -- J.D. O'Benar and S.P. Bruttig

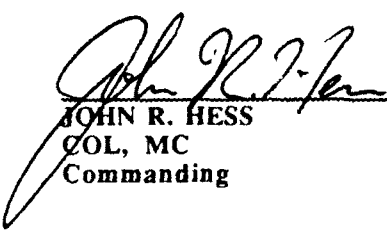
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Immediate resuscitation from hemorrhage, a common therapy in clinical practice, is associated with high mortality in laboratory models of uncontrolled hemorrhage. We hypothesized that a delayed resuscitation might improve survival, and that gradual repletion of vascular volume might be the most beneficial treatment. To investigate delayed resuscitation, we subjected anesthetized swine weighing 35 to 45 kg to wire suture abdominal aortotomy which resulted in an uncontrolled hemorrhage. After a 30 min delay, they were injected with 4 ml/kg intravenous hypertonic saline dextran solution (7.5% saline in 6% Dextran 70) administered either as a bolus over 1 minute or as a slow infusion over 12 minutes. Survival was enhanced to 63%, 5/8, in the bolus groups and 78%, 7/9, in the slow infusion group over a survival rate of 57%, 8/14, in the untreated controls. These differences in survival were not statistically significant. However there was a tendency for treatment to increase blood loss (817 $\pm$ 95 ml in the bolus group, 645 $\pm$ 86 ml in the slow infusion group versus 520 $\pm$ 42 ml in the control group). Hypertonic saline/dextran increased cardiac output to 4.7 $\pm$ 0.37 L/min in the slow infusion group and 3.4 $\pm$ 0.33 L/min in the bolus group at 30 min after treatment over 2.4 $\pm$ 0.20 L/min in the control group. Mean arterial pressure was sustained at 63 $\pm$ 5 mmHg in the slow infusion group, 43 $\pm$ 3 mmHg					
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in the bolus group, versus 49 ± 4 mmHg in the control group. These results are consistent with the hypothesis that hypertonic saline dextran is an effective resuscitation solution for uncontrolled hemorrhage when administered 30 minutes after the insult, especially as a slow infusion.

ABSTRACT

Immediate resuscitation from hemorrhage, a common therapy in clinical practice, is associated with high mortality in laboratory models of uncontrolled hemorrhage. We hypothesized that a delayed resuscitation might improve survival, and that gradual repletion of vascular volume might be the most beneficial treatment. To investigate delayed resuscitation, we subjected anesthetized swine weighing 35 to 45 kg to wire suture abdominal aortotomy which resulted in an uncontrolled hemorrhage. After a 30 min delay, they were injected with 4 ml/kg intravenous hypertonic saline/dextran solution (7.5% saline in 6% Dextran 70) administered either as a bolus over 1 minute or as a slow infusion over 12 minutes. Survival was enhanced to 63%, 5/8, in the bolus groups and 78%, 7/9, in the slow infusion group over a survival rate of 57%, 8/14, in the untreated controls. These differences in survival were not statistically significant based on the chi-square test. However there was a tendency for treatment to increase blood loss (817 ± 95 ml in the bolus group, 645 ± 86 ml in the slow infusion group versus 520 ± 42 ml in the control group). Hypertonic saline/dextran significantly increased cardiac output to 4.7 ± 0.37 L/min in the slow infusion group and 3.4 ± 0.33 L/min in the bolus group at 30 min after treatment over 2.4 ± 0.20 L/min in the control group. Mean arterial pressure was sustained at 63 ± 5 mmHg in the slow infusion group, significantly different from 43 ± 3 mmHg in the bolus group, versus 49 ± 4 mmHg in the control group. These results are consistent with the hypothesis that hypertonic saline/dextran is an effective resuscitation solution for uncontrolled hemorrhage when administered 30 minutes after the insult, especially as a slow infusion.

Key Words: Hemorrhage, hypertonic saline/dextran, pigs, aortotomy, resuscitation

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**Delayed Resuscitation with Hypertonic Saline/Dextran
From Uncontrolled Aortotomy Hemorrhage in Swine -- John
D. O'Benar, Ph.D. & Stephen P. Bruttig, Ph.D.**

For the past five years, we have investigated the use of hypertonic saline/dextran (HSD 7.5% NaCl in 6% Dextran 70) as a resuscitation fluid to treat hemorrhagic shock. Maningas et al. (1) found that in controlled blood loss (46 ml/kg over 15 min) in pigs, HSD in a dose of 11.5 ml/kg was capable of producing 100% survival in a model which was 100% lethal if left untreated. Subsequent studies by this group have shown that 4 ml/kg of HSD is the minimal effective dose of this resuscitation fluid. Bickell et al., by contrast, studied pigs in which an uncontrolled blood loss was produced by aortotomy (2). In this model, which was 100% survivable if left untreated, HSD (at 4 ml/kg) was lethal if administered within 5 min following hemorrhage. These authors attributed lethality to the increased systemic blood pressure and hemodilution produced by HSD. The increased systemic blood pressure disrupted the developing thrombus at the aortotomy site and re-initiated the hemorrhage which, coupled with hemodilution, prevented reformation of the mural thrombus. This explanation is further supported by experiments in rats in which early hypertonic saline infusion in a model of "uncontrolled" hemorrhagic shock led to an increased blood loss from injured vessels, a fall in mean arterial pressure and early mortality (3,4). The question remains: What would be the effect of HSD in the uncontrolled hemorrhage if HSD were administered more gradually and at a more clinically realistic time, i.e., 30 min post injury?

This study was designed to investigate this question by determining the efficacy of HSD in a model in which resuscitation was delayed and gradual. We thus sought to determine whether delay and gradual HSD administration would improve hemodynamics and survival. Preliminary experiments in rabbits have shown successful resuscitation if the HSD treatment is delayed 30 min after aortotomy (5). Therefore, we proposed to resolve these differences in administration, and more importantly, outcome, by determining the effect of delayed administration of HSD on survival and function following an uncontrolled (aortotomy) hemorrhage. Bolus and gradual infusions

were compared to determine if one mode of administration is to be preferred over the other.

The logistic advantage of HSD, i.e., the small volume required to resuscitate and the short time required to administer HSD, coupled with the potential enhancement of survival from massive hemorrhage, make HSD administration a particularly attractive therapy in combat casualty care. However, questions remain concerning its efficacy after traumatic injury, especially that involving uncontrolled truncal vascular hemorrhage. Consequently, the present experiments evaluated the effects of time delay (30 min) and type of administration (gradual vs. bolus) in improving the effectiveness of HSD as a potential resuscitation solution.

Materials and Methods

Forty-four female swine weighing 35-45 kg were entered into the study. After an overnight fast, they were premedicated with an intramuscular injection of 2.2 mg/kg ketamine, 2.2 mg/kg xylazine and 0.08 mg/kg atropine, followed by halothane anesthesia via a face mask. After endotracheal intubation, anesthesia was maintained with oxygen, 12% nitrous oxide and 1-2% halothane via respirator. A neck incision was performed and a Swan-Ganz cannula was placed via the internal jugular vein for measurement of cardiac output, central venous and pulmonary artery pressure. An external jugular catheter was inserted for sampling and injection and a carotid catheter for sampling and systemic arterial pressure measurement. Next, splenectomy was performed through a midline laparotomy with ligation of all vascular pedicles. The abdominal aorta was exposed, using warm saline-soaked towels to retract the viscera. The aorta was marked with two points 5 mm apart approximately 10 cm proximal to the iliac artery bifurcation. A 4-0 surgical wire was threaded through the ventral aortic wall, into the lumen and back out again at these points using a curved 27 gauge needle as a guide. The free ends of the surgical wire were then exteriorized through a small hole in the abdominal wall and the abdominal incision

was sewn closed. The nitrous oxide was discontinued and the animal spontaneously breathed a mixture of oxygen and 1.0 - 1.5 per cent halothane. After a ten minute stabilization period, two control samples were taken ten minutes apart. Samples consisted of hemodynamic data: phasic and mean pulmonary wedge and systemic pressures, central venous pressure, cardiac output and ECG; complete blood gases, including complete co-oximeter readings and blood chemistries, including lactate, albumin, total protein, and blood glucose measurements. Arterial and venous hematocrits were also determined. If the hemodynamic readings were unstable (did not agree within 10%) an additional ten minute period was allowed and measurements were retaken.

Aortotomy (hemorrhage) was then accomplished by pulling out the wire suture through the abdominal wall. This caused a 5 mm slit-like tear in the long axis of the ventral abdominal aortic wall. Hemodynamic variables were measured and samples were taken at 5, 15, 30, 42, 60, 90 and 120 min post aortotomy. Animals were alternately assigned to one of four treatment groups and treatment was begun immediately after the 30 min sample. In Group A (the control group, N=14), no fluid was given. In Group B (slow infusion group, N=9), hypertonic saline/dextran (7.5% NaCl in 6% Dextran-70, HSD) was administered slowly, at 4 ml/kg, over a period of 12 min. In Group C (bolus infusion group, N=8), the same dose of HSD was administered in approximately 1 min. Group D (N=4), which served as non-hemorrhage controls, consisted of sham-operated time controls in which the aortotomy suture was placed but never pulled. After the last sample at two hours post-aortotomy, humane euthanasia was performed on surviving animals with an overdose of barbiturate. The abdominal incision was then reopened and the total blood loss into the abdominal cavity was estimated by volumetric measurement of all available free blood and clot.

The data were evaluated using an analysis of covariance with the 30 min post-aortotomy sample (pre-treatment) as the covariate. When the F ratio was significant, the Newman-Keuls test was used to identify

the specific group and time differences. Reported values are expressed as means $\pm$ standard error of the mean. Differences in survival were analyzed using a chi-square test. Differences were considered significant at $p < 0.05$.

Results

Most clear-cut were the survival data from these experiments. Survival was 57% (8/14) in untreated controls, and was enhanced to 63% (5/8) in the bolus group and 78% (7/9) in the slow infusion group. These differences were not statistically significant by a chi-squared test. This increased survival was despite a tendency for treatment to increase blood loss (520 ± 42 ml in control, 817 ± 95 ml in bolus versus 645 ± 86 ml in slow infusion).

As expected, mean arterial pressure decreased markedly with aortotomy. (Fig.1) In the unresuscitated hemorrhage group, for example, mean arterial pressure decreased from 95 ± 5 mmHg to 28 ± 2 mmHg in 5 minutes. Other aortotomy groups showed similar declines. With resuscitation, the bolus group showed no discernable increase in arterial pressure with infusion. The slow infusion group, on the other hand, did show an increase in arterial pressure greater than that of the other groups to nearly 60 mmHg, and this increase was sustained in survivors throughout the 90 min recovery period.

Cardiac output decreased predictably with hemorrhage with no difference between groups. (Fig. 2) Administration of HSD, either by the slow infusion or the bolus effected improvement in cardiac output. Improvements from slow infusion were both faster and greater, increasing to 4.7 ± 0.37 L/min, a value greater than that of the time control group. Bolus resuscitation was adequate, however, and in both bolus and slow infusion groups, improvement was more or less sustained throughout the observation period. The mean pulmonary artery pressure (MPAP) decreased with aortotomy and increased again with resuscitation (Fig. 3). The slow infusion produced better recovery in MPAP

than the bolus, the latter remaining below control values for most of the recovery period. The superiority of the slow infusion method of resuscitation was maintained throughout the observation period. Figure 4 shows data for total peripheral resistance. For the most part, this variable decreased with aortotomy and decreased again with resuscitation. This latter decrease in peripheral resistance is consistent with a vasodilator or rheologic effect of hypertonic saline/dextran (6). Except for an unexplained spike at 60 minutes, (slow infusion), these low resistance values were maintained until the termination of the experiment.

Figure 5 shows oxygen delivery per kg body weight data. Resuscitation after aortotomy produced a sudden decline and negligible recovery in this variable. Perhaps this lack of recovery can be attributed to a lack of oxygen-carrying capacity due to the hemodilution caused by HSD infusion.

Discussion

Bickell, et al. (2) showed that significant bleeding was likely to be re-initiated with immediate resuscitation of aortotomy hemorrhage and that with the sudden increase in pressure, the thrombus would likely be eroded and blown off. The present study, on the other hand, allowed a 30 min delay for the thrombus to stabilize and thus be secure under the increase in pressure initiated by HSD. These studies are realistic in the sense that most resuscitation is begun only after the delays incurred during response by health care providers. We would estimate these delays to be minimally 30 minutes. Measurements of blood loss support this hypothesis. In the Bickell experiment the volume of hemorrhage in the hypertonic saline/dextran group was $1,340 \pm 230$ ml versus 783 ± 85 ml in the control. In our study, which added HSD, the hemorrhage volumes were also greater in the treatment groups than control group; volumes still did not approach those of the Bickell study and were apparently compatible with increased survival.

Also noteworthy is the fact that the slow-infusion group, with greater survival and greater hemodynamic effectiveness, lost less blood than the bolus group, in which blood loss was more severe and cardiac output and arterial pressures were less affected by treatment. It is possible that the bolus increased the pressure transiently and partially eroded the clotting at the site of aortotomy. Recently, a trial of delayed resuscitation in human trauma victims has been reported (7). This study produced a trend (non-significant) toward increased survival for patients given fluids at a delayed time, about 90 minutes longer than in the control group.

It should be pointed out that not all studies have been successful in treating uncontrolled hemorrhage with hypertonic solutions. Using a rat model in which the ileocolic arteries were severed, Gross et al. (4) injected 5 ml/kg hypertonic saline at various times up to 2 hours after insult. They reported further decreases in mean arterial pressure and mortality rates that exceeded those of untreated controls. One difference between their study and ours was the exclusion of colloid and this may account for the difference in results. Also, if the walls of the vessels had simply been incised -- like those of the aorta in the present study -- instead of the vessels being completely transected, it is possible that more stable clots could have formed and the results might have been more similar to those of the present study.

To summarize the current study, the results are compatible with the hypothesis that hypertonic saline/dextran is an effective resuscitation solution in the treatment of uncontrolled hemorrhage when administered 30 minutes after the insult, especially as a slow infusion. Evidently hemodilution did not represent a lethal threat in these studies, as this was compensated for by oxygen extraction. These studies offer great promise for the use of HSD in the treatment of traumatic injury, especially that involving uncontrolled hemorrhage.

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However, further investigation is indicated in the area of delayed resuscitation with HSD slow infusions.

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MEAN ARTERIAL PRESSURE

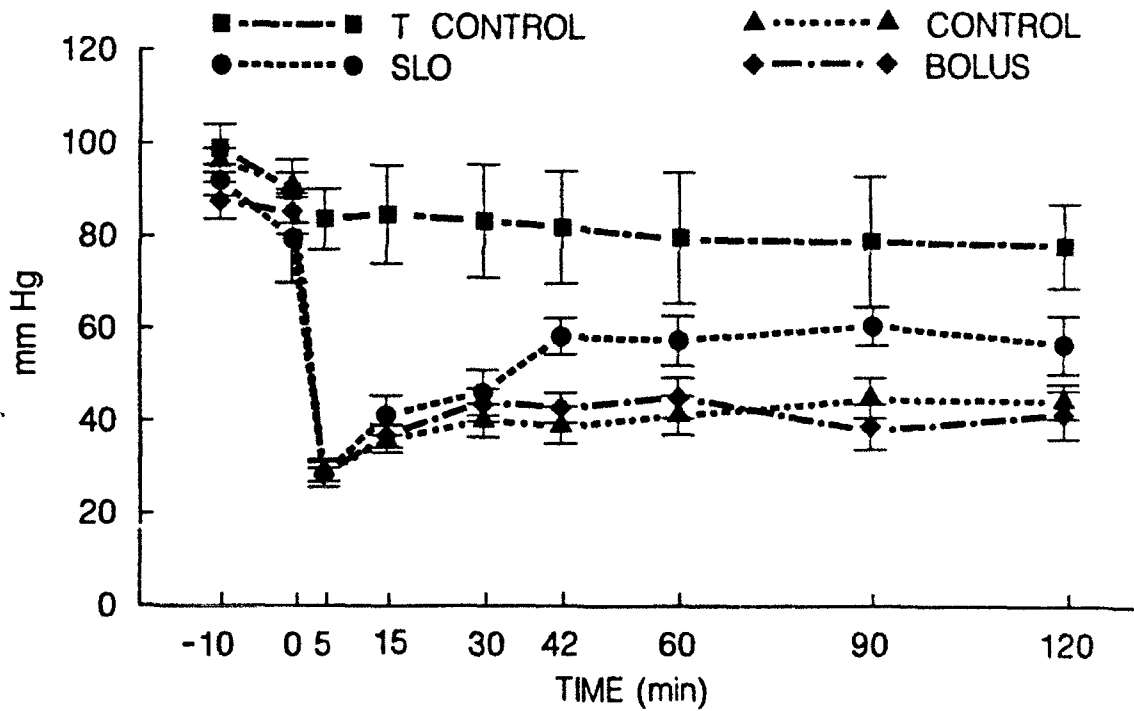


Figure 1. Mean arterial pressure versus time during the course of the experiment.

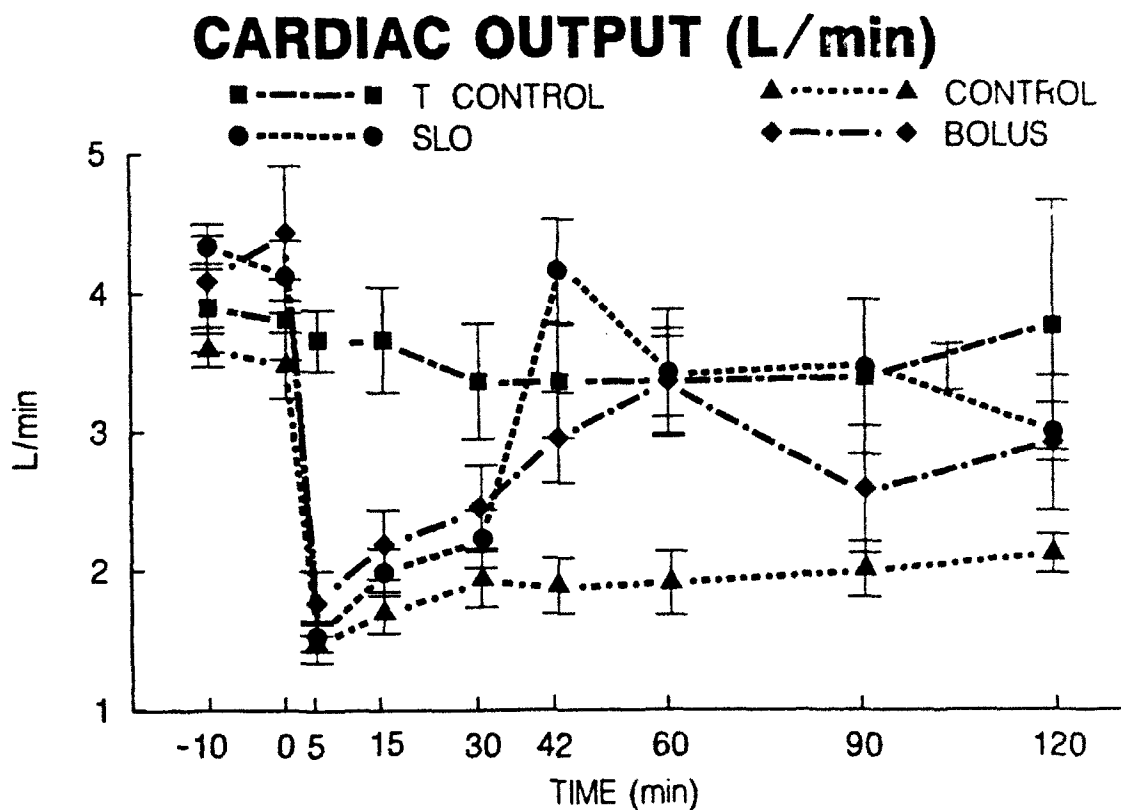


Figure 2. Cardiac output versus time during the course of the experiment.

MEAN PULMONARY ARTERY PRESSURE

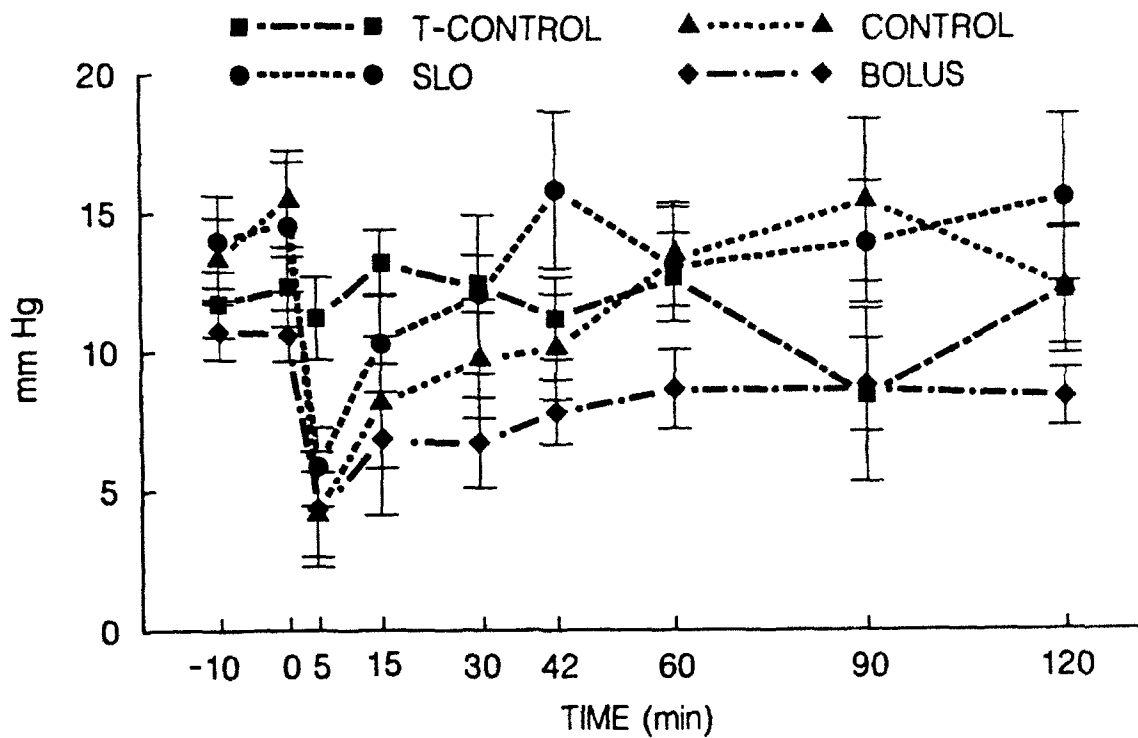


Figure 3. Mean pulmonary artery pressure versus time during the course of the experiment.

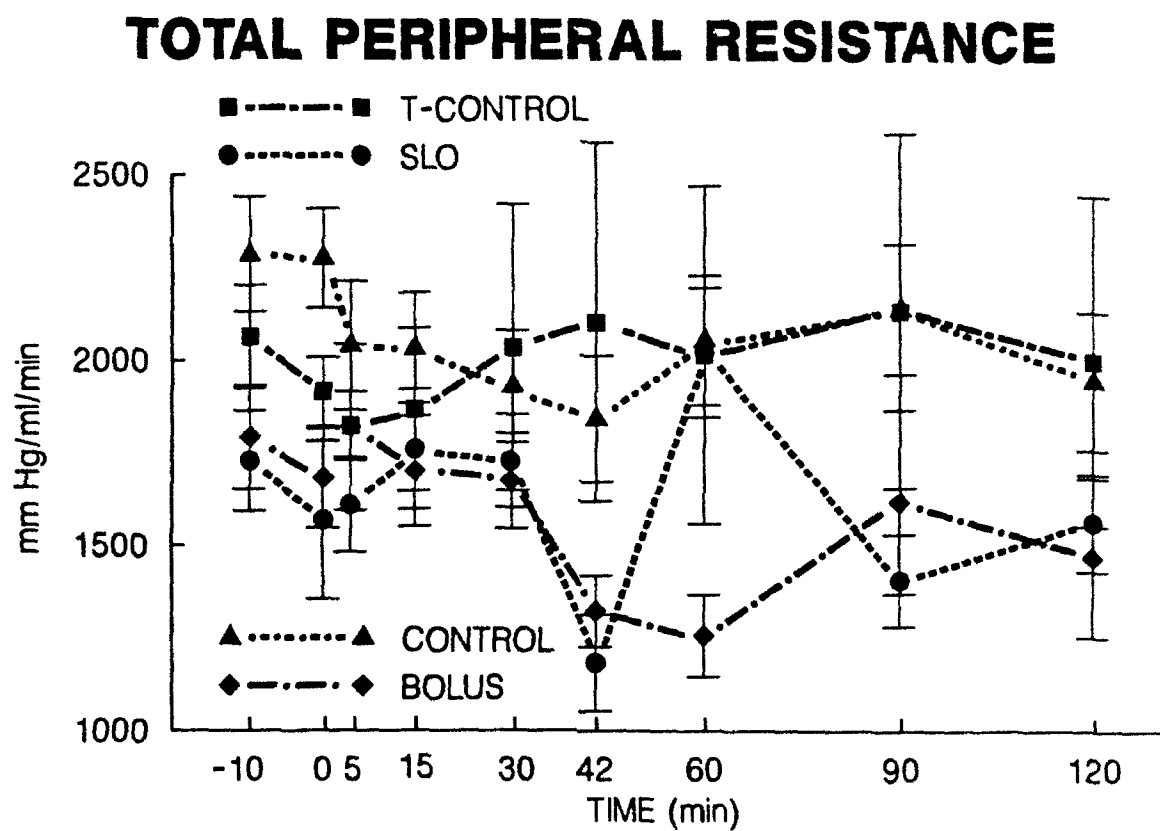


Figure 4. Total peripheral resistance versus time during the course of the experiment.

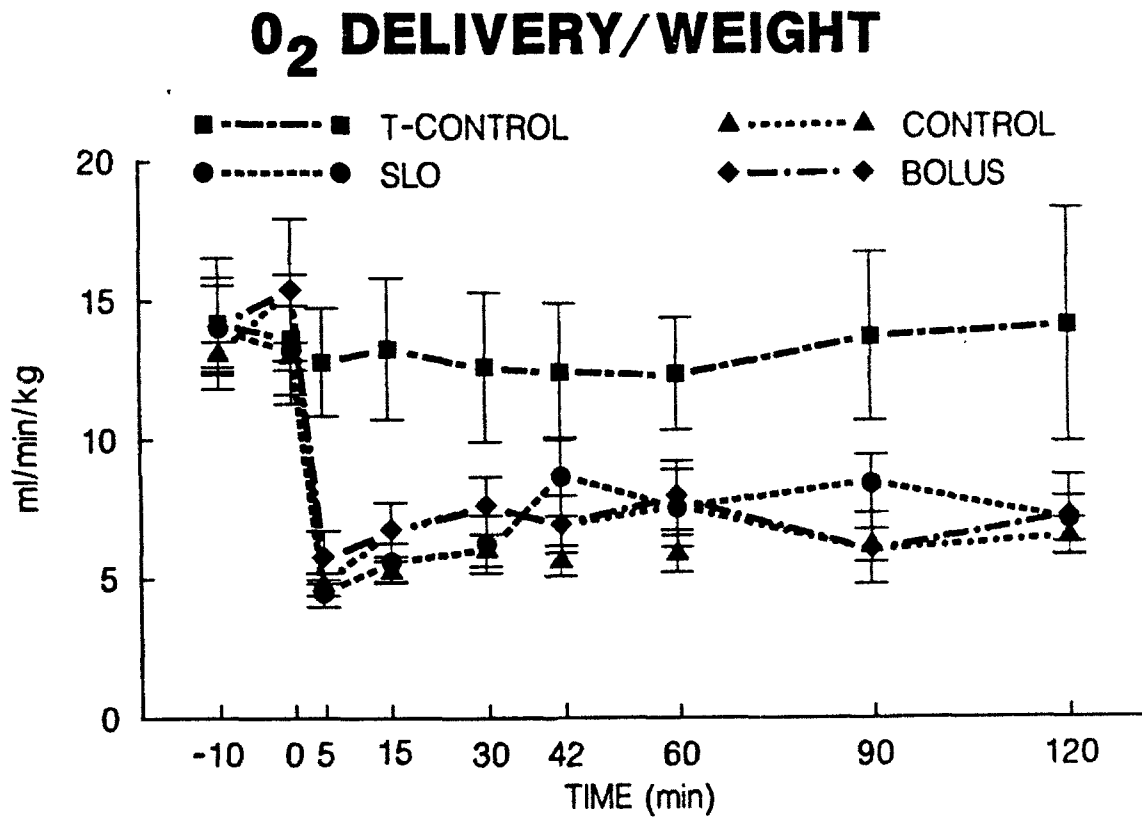


Figure 5. O₂ delivery/body weight versus time during the course of the experiment.

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