

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

The public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden, to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.
PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.

1. REPORT DATE (DD-MM-YYYY) 03/30/2012		2. REPORT TYPE Final Technical Report		3. DATES COVERED (From - To) Jul 2008 - Dec 2011	
4. TITLE AND SUBTITLE Decision-Assist and Closed-Loop Control of Fluid Therapy				5a. CONTRACT NUMBER CON18032	
				5b. GRANT NUMBER N00014-08-1-1056	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Kinsky, Michael P.				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The University of Texas Medical Branch at Galveston Sponsored Programs Academic 4.400J Rebecca Sealy Hospital, Galveston, TX 77555-0156				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Office of Naval Research 140 Sylvester Road Bldg, 140 Room 218 San Diego, CA 92106-3521				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT "Approved for Public Release; distribution is Unlimited".					
13. SUPPLEMENTARY NOTES 20120406388					
14. ABSTRACT Decision support (DS) and closed loop (CL) fluid therapy using a computer algorithm and high-speed fluid pump for treatment of hemorrhage has evolved from animal studies to human testing. The goals of DS and CL are to: A) effectively restore blood pressure (BP), B) efficiently reduce excessive volume e.g., edema and C) improve outcomes. We report that DS and CL can do A & B. Specifically, DS and CL reduced fluid needs by 65% and 80%, respectively when humans breath spontaneously. This effect on fluid sparing was less pronounced in positive pressure ventilation. New step will test other fluids and determine if DS and CL can improve effectiveness and efficiency in patients.					
15. SUBJECT TERMS decision assist, decision support, semi autonomous fluid resuscitation, closed loop, autonomous fluid resuscitation hemorrhage, target endpoint, fluid delivery system					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Michael Kinsky, MD
U	U	U	UU	20	19b. TELEPHONE NUMBER (Include area code) 4097721221

Final Technical Report
Decision-Assist And Closed-Loop Control Of Fluid Therapy

Michael P. Kinsky, MD

The University of Texas Medical Branch Galveston

301 University Blvd

Galveston, Texas 77555-1102

phone: (409) 772-8404 fax: (409) 772-1224 email: mkinsky@utmb.edu

Award Number: N00014-08-1-1056

<http://intranet.utmb.edu/iutmb/>

Key definitions of terminology:

'Resuscitation System' is a technology, which facilitates or performs resuscitation of circulatory shock, cardiac arrest or critical life threatening conditions, with one or more of the following components:

'Autonomous fluid resuscitation' uses a closed-Loop controller microprocessor programmed to provide automated control of fluid infusion rate or drug delivery based on a patients injury, disease and vital signs, e.g. blood pressure.

'Semi-autonomous fluid resuscitation' is a decision-assist/support recommendation that facilitate fluid resuscitation of trauma by providing specific therapeutic resuscitation directives based on guidelines and microprocessor analysis of current physiologic variables and the previous response of those variables to administered fluid therapy.

'Endpoint' variable is the variable(s) that is used to guide therapy for either Decision-Assist or Closed-Loop Control, e.g. blood pressure is an endpoint variable we will use to guide resuscitation of hemorrhage.

'Target Endpoint' is a target level or range of endpoint variable(s) that is used to guide resuscitation via algorithm derived Closed-Loop controllers or Decision-Assist recommendations.

LONG-TERM GOALS

[top-level goals]

There are several new emerging monitoring technologies for combat casualty care that can be used as platforms for decision assist (D-A) and closed loop resuscitation (CLR) algorithms. It is our goal to evaluate these and other novel technologies with algorithms for fluid resuscitation in hemorrhaged human volunteers and patient studies.

OBJECTIVES [scientific or technological objectives]

The following objectives were addressed:

Objective 1: Test the accuracy and robustness of the blood pressure monitoring and pump controllers in a clinical environment using the near term wireless vital signs monitor (WVSM) and lightweight trauma module (LTM) and other farther term technologies (*e.g.*, MiniMed, BP Guardian, BPsure, and Trauma Tablet). Intermittent cuff NIBP monitors and novel beat-to-beat NIBP will be compared to arterial catheter-transducer measurements.

1a. Test novel BP devices

1b. Test VSM integration for decision support – WVSM and eQuality.

1c. Test other novel monitors – Aesculon and Masimo

Objective 2: Evaluate the effectiveness of D-A and CLR of fluid therapy during mild hemorrhage in healthy volunteers. Volunteers will undergo a 10 mL/kg hemorrhage followed by CLR, D-A fluid therapy or standard of care fluid resuscitation, *i.e.*, fixed 3:1 bolus of lactated Ringer's (LR). Changes in blood pressure, blood volume, end-diastolic volume by echocardiography, urinary output, blood loss and total fluid, and other variables will be recorded.

2a. Anesthesia and hemorrhage + spontaneous ventilation

2b. Anesthesia and hemorrhage + positive pressure ventilation

APPROACH [technical approach, key individuals]

Note, We have re-defined the specific terminology for the terms decision assist and closed loop resuscitation in an effort towards regulatory approval. Our new nomenclature for decision assist (D-A) will be semi-automated resuscitation or decision support. The terminology for closed loop resuscitation (CLR) will now be called automated resuscitation.

Dr. Kinsky (the PI) directed the studies and administration for this project. All studies had IRB and clinical research center (CRC) approval. Informed consent was obtained prior to data collection. Dr. Kramer (CO-I on study) provided his technology and invaluable experience with autonomous systems for this project. The PI and CO-I's worked closely with industrial partners at Impact (George Beck) and Athena (Mark Darrah). The industrial partners provided requisite support for testing – below. Other key personnel included anesthesiologists (Dr. Li, Koutrouvelis and Solanki) who helped collect data and provide safety for the studies. Finally, research nurses (Nan Henkel, and other nurses from the CRC at UTMB) and Research Associate (Mike Salter) were critical to data collection and safety.

Objective 1. We have validated the accuracy and fidelity of the specific components that are essential to the integrity of the semi-automated and automated resuscitation systems. The device integrator (Trauma Tablet) was primarily tested in objective 2.

Objective 2. We demonstrated that semi-automated and automated fluid resuscitation could achieve target blood pressure (effectiveness) and reduce fluid needs (efficiency) in humans undergoing hemorrhage. A NIBP device (WVSM or eQuality) was integrated with the Trauma Tablet and Zoll power infuser to test semi-automated fluid resuscitation. The fully automated fluid resuscitation system was tested using Impact's Lightweight trauma module. Volunteers undergoing hemorrhage were randomized to semi-automated or fully automated or standard of care fluid replacement in a crossover study with experiments separated by at least six weeks. Primary endpoints included the ability to achieve and maintain blood pressure within target and total infused volume. Secondary endpoints included change in blood volume, extravascular volume changes, end-diastolic volume, and other hemodynamic and surrogate variables such as cardiac output, urinary output, pulse pressure, shock index, heart rate variability and other perfusion indices from farther term non-invasive monitors

WORK COMPLETED [tasks completed, technical accomplishments]

Overview: Expertise for guiding fluid resuscitation in patients suffering from hypovolemia for combat casualties and patients in remote locations is limited by supply and expertise often resulting in resuscitation failures. Systematic approaches that incorporate surrogate indices of vascular volume e.g., blood pressure to guide fluid resuscitation can achieve target endpoints while reducing fluid needs in experimental models of hemorrhage. During the previous funding cycle, along with our collaborative team, a semi-autonomous and autonomous system was constructed and tested. We also tested and integrated another vital signs monitor currently used in combat casualty care. We tested Criticare eQuality vital signs monitor, thereby broadening and adapting different components for our semi-autonomous system. Masimo's non-invasive hemoglobin (Rainbow Set) was also tested in an effort to determine a future role for non-invasive hemoglobin in autonomous systems. The primary components were Athena's WVSM + Zoll pump and Impact's LTM + Zoll pump for the semi-autonomous and autonomous system, respectively. A control algorithm for fluid infusion was integrated with these systems. Specifically, for the semi-autonomous system the Trauma Tablet was used and for the autonomous system, an embedded algorithm within the LTM was used. Our *In vitro*, animal & human testing demonstrated feasibility of proposed test device and resuscitation system and fidelity b/w BP and algorithm activation. Our in vivo studies demonstrated BP accuracy over a wide range of clinical BP's. We also achieved our expected outcomes, which was that by using semi-automated and automated fluid resuscitation, we could achieve target blood pressure and a reduce fluid needs > 50%. **This achievement has a high impact. First, a more precise target endpoint BP outcome could lead to less bleeding e.g., over shooting BP and a reduction in brain injury, since episodic hypotension following traumatic brain injury (TBI) dramatically increases mortality. Second, improved efficiency of fluid resuscitation could reduce the incidence of over and under-resuscitation e.g., ischemia, pulmonary edema and abdominal compartment syndrome.**

RESULTS

[Describe meaningful technical results achieved in the report fiscal year. Make the significance clear. Emphasize what was learned, not what was done. This should be a summary of significant results and conclusions, and, especially, any “new capabilities” generated.]

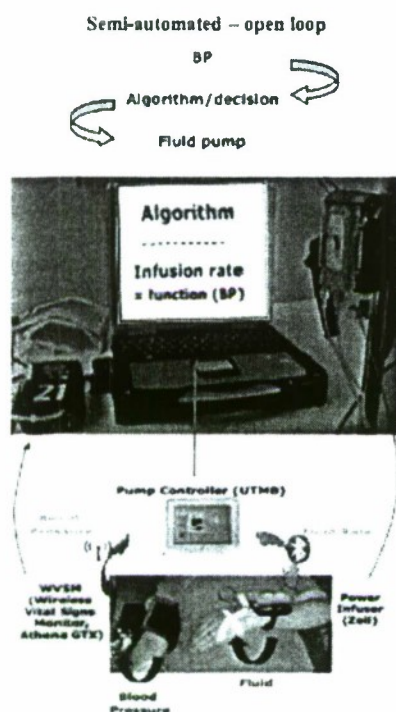


Figure 1a. Semi-autonomous Fluid Resuscitation System



Figure 1b. Autonomous Fluid Resuscitation System

We have advanced the concept of fluid resuscitation using a novel blood pressure system and fluid infusion pump coupled with expert based fluid infusion algorithms, which we term semi-automated fluid resuscitation, replacing the older nomenclature – decision assist. This is an open loop concept that incorporates a blood pressure, algorithm and infusion pump. The resuscitation platform used in our studies is the Trauma Tablet, which integrates NIBP (Athena’s WVSM), algorithm for delivering fluid based on blood pressure and iv fluid pump (figure 1a). The Trauma Tablet uses a real time operating system. The computer language that the Trauma Tablet uses to operate these systems is called QNX, which is a robust operating system often used for flight navigation. The fluid infusion pump is commercial off the shelf (COTS) product – the Zoll (Power infuser) modified for computer control. In brief, the input parameter (blood pressure via WVSM) is processed by the Trauma Tablet. The fluid rate is determined by an embedded algorithm within the Trauma Tablet to infuse a recommended fluid amount via the pump (Zoll Power infuser). The user accepts or rejects the recommendation. The fully automated fluid resuscitation system uses a similar process. However, this is an automated process in which the user does not have to accept or reject the recommendation. The fully automated system displayed (figure 1b) uses the LTM as its primary resuscitation platform. The blood pressure (arterial line) is directed connected to the system. A USB power cable is hard wired to the Power infuser. It also has the capability to connect to other IV pumps. In brief, fluid is automatically delivered based on a specified blood pressure algorithm embedded in the LTM. In this objective, we assembled the systems and performed testing to determine blood pressure accuracy, pump activation, and pump accuracy and overall fidelity. *In vitro* and *in vivo* studies were performed.

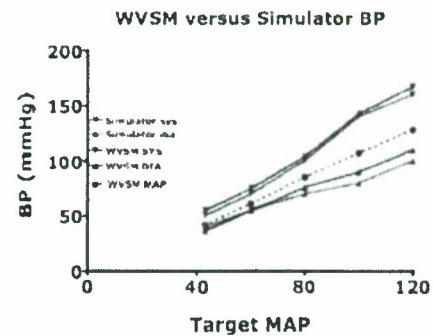
Objective 1. Device testing – BP, Algorithms & Pumps:

The fluid pump delivered fluid into a collection bag. The fluid infusion rate generated by the two systems was electronically and manually recorded and compared against simulated BP – *in vitro* studies to test the robustness of the devices and algorithms. Data collected was also used as a component of the risk management testing required for FDA approval. A blood pressure simulator (Fluke Bio Medical, BP Pump 2, Non-Invasive Blood Pressure Monitor Analyzer) was used to test and generate oscillometric BP signals at specific blood pressures. We compared systolic and diastolic BP displayed by Wireless Vital Signs Monitor (WVSM) (Athena GTX, Des Moines IA) to simulator derived systolic and diastolic BP over large range (figure 2). All studies were performed in duplicate. The average readings are displayed on the following graphs. WVSM's BP was wirelessly integrated into computer derived decision assist (D-A) algorithm that recommends a fluid infusion rate that is based on a function of blood pressure. Zoll power infuser (Zoll Medical Corporation, MA) was wirelessly connected to computer with an embedded D-A algorithm (figure 3). The flow rate was displayed and activated at specific blood pressures. Total volume over time derived from the D-A was compared to actual volume collected in a graduated cylinder. The LTM was tested using two different fluid infusion pumps using

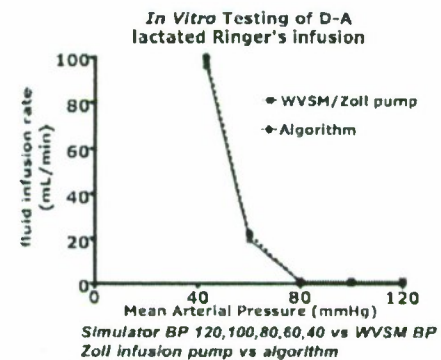
Hextend as the fluid type. Blood pressure was induced by using a hydrostatic column of water (1.3 cm = 1 mmHg) and recorded on the LTM transducer (split transducer with a HP transducer – gave identical readings). Mean pressure (MAP) was transmitted for 5 min each and recorded starting from 100 mmHg to 40 mmHg. The predicted algorithm (Hextend algorithm uses $1/3^{\text{rd}}$ the amount of fluid due to vascular volume expansion properties) was also recorded. The Delphi and Zoll pumps were activated based on specified MAP and fluid was collected into a graduated cylinder. Both pumps accurately delivered fluid based on blood pressure. The Delphi was slightly more accurate at lower blood pressure compared to the

However, the Delphi pump is no longer available and on the market. Therefore, the Zoll pump will be the candidate pump for further studies testing semi-automated and automated resuscitation systems.

In Vitro - Testing



Targeted BP testing: Simulator MAP set to 120,100,80,60,40 mmHg. Recorded WVSM (Sys) vs Sim (Sys) WVSM (Dia) vs Sim (Dia)



Integrating BP, Algorithm & Pump: D-A Testing performed by setting BP to specific pressure. WVSM BP displayed and integrated to computerized algorithm. Pump algorithm rate displayed/acknowledged. LR output recorded

Figure 2. WVSM and algorithm testing

Zoll vs Delphi Test (CLC Hextend)

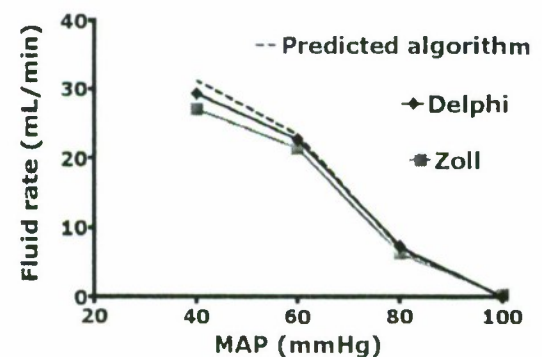


Figure 3. LTM Delphi vs Zoll based on MAP

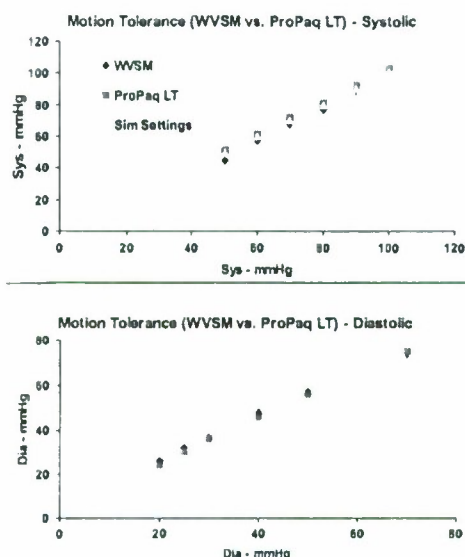


Figure 4. Motion tolerance comparison

Motion tolerance: We tested the WVSM in a motion tolerance experiment. We compared WVSM to ProPaq LT (current standard deployed monitor). Both ProPaq and WVSM gave identical readings at baseline (data not shown). Motion tolerance was induced using a blood pressure simulator (as described) with two adult blood pressure cuffs connected to the ProPaq and WVSM via PVC tubing (approx. size of adult arm) placed on a semi-stable platform. The BP simulator induced a specified blood pressure – oscillometric sound transmitted to PVC tubing, and then an observer during the each simulated blood pressure reading, rigorously shook the semi-stable platform. Figure 4 show that both ProPaq and WVSM closely approximated systolic and diastolic blood pressure over a wide range of normal and hypotensive values. This additional testing supported the use of WVSM in a rigorous environment.

In Vitro – what was learned:

- We have integrated a wireless blood pressure monitor, a computerized algorithm that administers fluid based on blood pressure to a wireless and wired pump capable of high flow rates (6L/hr).
- Excellent pump accuracy for Zoll Power infuser
- We have shown feasibility of proposed test devices with autonomous resuscitation systems
- WVSM – accurate and reliable in wide BP range and with motion

Objective 1. In Vivo testing - patient studies. The reliability and accuracy of NIBP – WVSM was compared to blood pressure measured by intra-arterial catheter during cardiac surgery to assess performance for WVSM. LTM's transducer was similarly tested. We compared intra-arterial blood pressure (IABP) (standard of care blood pressure monitor “gold standard”) in cardiac surgical patients to blood pressure recorded by the WVSM. **Rational for testing BP in CPB patients:** Patients undergoing CPB often have systolic hypertension (systolic BP > 140 mmHg) and periodic hypotension occurs with high frequency.

Inclusion criteria:

- 1) Radial intra-arterial catheter
- 2) Between 18 and 70 years of age
- 3) Male or non- pregnant female.

Exclusion Criteria:

- 1) BP difference > 10 mmHg in both arms

In Vivo – patient studies

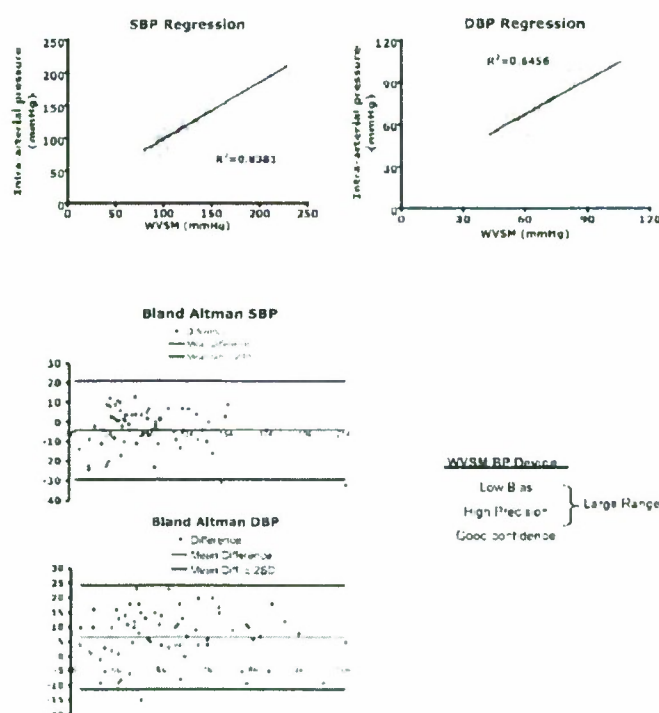


Figure 5. WVSM vs Gold standard IABP

- 2) History of neuropraxia
- 3) Refusal to consent
- 4) Failure to obtain radial artery cannulation

Ten CPB Patients were recruited. One patient refused consent and a technical failure occurred in another patient (not WVSM related). There were 71 data points collected in 8 patients from pre-induction to end of surgery. Measurements for IABP were recorded 10 seconds after WVSM deflation. A regression analysis and Bland-Altman plots were performed to compare systolic and diastolic pressure obtained from gold standard intra-arterial blood pressure (IABP) vs WVSM's NIBP (figure 5). There was a strong correlation of WVSM to IABP over a wide range of blood pressure ($r^2 = 0.84$) in patients undergoing surgery. WVSM had a low bias and high precision over this BP range. There was high fidelity between BP and algorithm activation.

In Vivo Summary – what was learned

- There was high fidelity between BP and algorithm activation. Strong correlation of WVSM to IABP over a wide range of blood pressure in patients undergoing surgery
- Low Bias / High precision for WVSM
- Positive step to determine if these components for a(n) (semi-)autonomous resuscitation systems can maintain target BP and reduce fluid during hemorrhage

Objective 2: Evaluate the effectiveness of semi-autonomous (D-A) and autonomous (CLR) fluid resuscitation of human hemorrhage.

Studies were performed at the Clinical Research Center (CRC) at UTMB after IRB and CRC approval. Initially, the proposal was designed to test autonomous fluid resuscitation in ten subjects after general anesthesia (spontaneous ventilation) and hemorrhage. However, compelling differences were observed in six subjects, therefore, an

additional study was performed in six other subjects undergoing an identical protocol, however, the subjects were intubated and supported with positive pressure ventilation. This new study was communicated with the program officer. We compared a 3:1 (standard of care) fluid resuscitation regimen for lactated Ringer's for treatment of hemorrhage to semi-autonomous the Trauma Tablet with fluid resuscitation algorithm and components (WVSM and Zoll power infuser) and arterial catheter +LTM, semi-autonomous and autonomous fluid resuscitation respectively (figure 6). **Rational for human hemorrhage with general anesthesia:** Our animal data and clinical experience is that general anesthesia blunts the compensatory response to hemorrhage and exaggerates the hemodynamic response to mild hemorrhage. *Our primary hypothesis is that semi-autonomous and autonomous care will better achieve target blood pressure and reduce fluid requirements.*

HUMAN TESTING

Figure 6. Hemorrhage study

Healthy volunteers, N=10 - 3 experiments each

Baseline hemodynamic and volumetric measurements
General anesthesia (propofol only) → 10 mL/kg hemorrhage

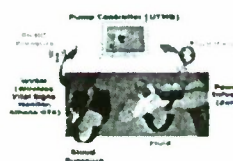
Resuscitation with LR - 3 groups or Arms

Standard of care (SOC)
3:1 LR infusion/blood



30 mL/kg bolus 20 min

Semi-autonomous



Fully Autonomous



Fluid infused based on MAP - TBI - ALGORITHM

Outcomes: 1. TARGET BP 2. TOTAL FLUID INFUSED

Experimental Protocol (Figure 7): Healthy volunteers (ASA I) were pre-screened and underwent 3 different fluid resuscitation regimens or Arms, separated by at least 4 weeks:

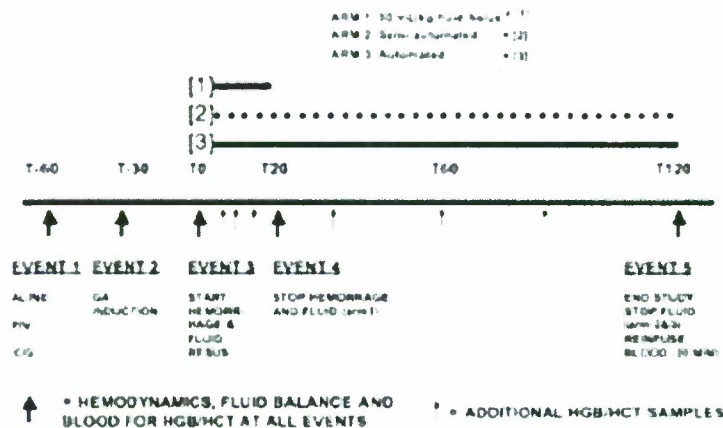
Arm 1: Standard of Care = fixed 30 mL/kg fluid bolus over 20 min (SOC)

Arm 2: Semi-automated care = Trauma Tablet - WVSM+NIBP+Zoll

Arm 3: Autonomous care = LTM - intra-arterial catheter + Zoll

Figure 7

EXPERIMENTAL PROTOCOL



SUBJECTS: 6 subjects per arm / two studies

HEMODYNAMICS

MAP – WVSM / ARTERIAL LINE

HR – ECG

CO – ECHOCARDIOGRAPHY

VOLUMETRICS (ML/KG) – Q30 MIN

TOTAL FLUID IN

BLOOD OUT

PLASMA VOLUME (PV) – ICG & HGB

URINARY OUTPUT (UO) – BLADDER SCANNER

EXTRAVASCULAR VOLUME =
 {FLUID IN/BLOOD OUT – PV – UO}

The day of the study, the subject's weight was recorded. A peripheral iv, arterial line and other monitors were placed. Baseline was defined as the 30 minute period prior to general anesthesia. Basal plasma volume determined. Subjects were induced and maintained under general anesthesia (T-30). After thirty min of general anesthesia, 10 mL/kg of blood was removed (T0). The hemorrhage occurred over 20 minutes (T20). During the hemorrhage, the fluid infusion was begun (timing, rate and amount will be dependant upon study arm and proprietary algorithm). The effects of fluid resuscitation on blood volume expansion and hemodynamics (target blood pressure) were followed for 120 minutes (T120). At T120, the blood collected during the hemorrhage from the subject was re-infused over 10-20 min. The subject was monitored during this time but no data was collected. A final body weight was recorded and the subject was discharged when CRC criteria are met. Hemodynamics, urinary output (by bladder ultrasound), echocardiography and other non-invasive data are collected throughout the protocol. Specific hemodynamic measurements included MAP (measured by arterial catheter), cardiac output (measured by echocardiography), heart rate (measured by ECG) and systemic vascular resistance (calculated from $MAP/CO \times 80$).

Primary Endpoint: The amount of time within target BP (± 5 mmHg), hemodynamics and total fluid requirements for 120 min of resuscitation was recorded and used as the primary endpoint of successful resuscitation. Secondary endpoints were cumulative time in which blood pressure is less 20 mmHg below target fluid requirements.

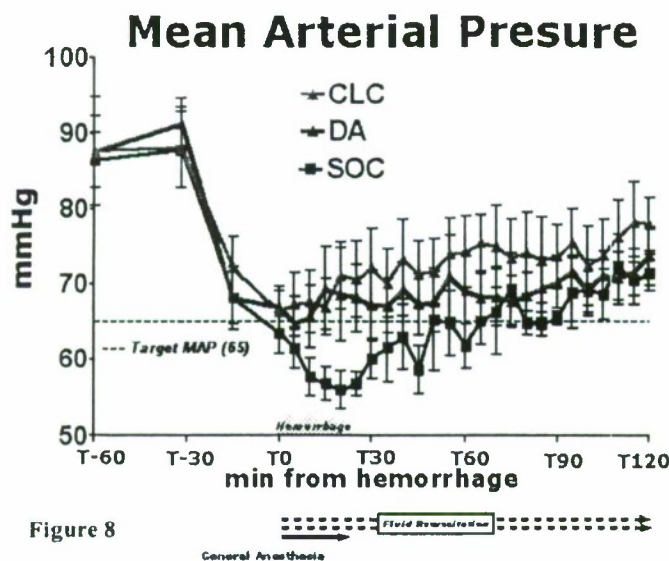


Figure 8

reduction in blood pressure and out of target for more than 30 min. There was a significant difference for blood pressure between SOC and the autonomous groups between T0 and T25.

Hemodynamics (figure 9): Heart rate increased during hemorrhage and resuscitation. There was a trend for a reduction in heart rate for the standard of care group. Cardiac output increased from baseline in all groups during hemorrhage and after resuscitation. The standard of care group was associated with the highest cardiac output (trend). Systemic vascular resistance decreased for the standard of care group and was statistically lower than autonomous group. The semi-autonomous group did not differ. End-diastolic volume increased for the standard of care group during the resuscitation period only. EDV was greater than the autonomous and semi-autonomous groups at T20. However stroke volume (EDV-ESV) did not change for the autonomous groups.

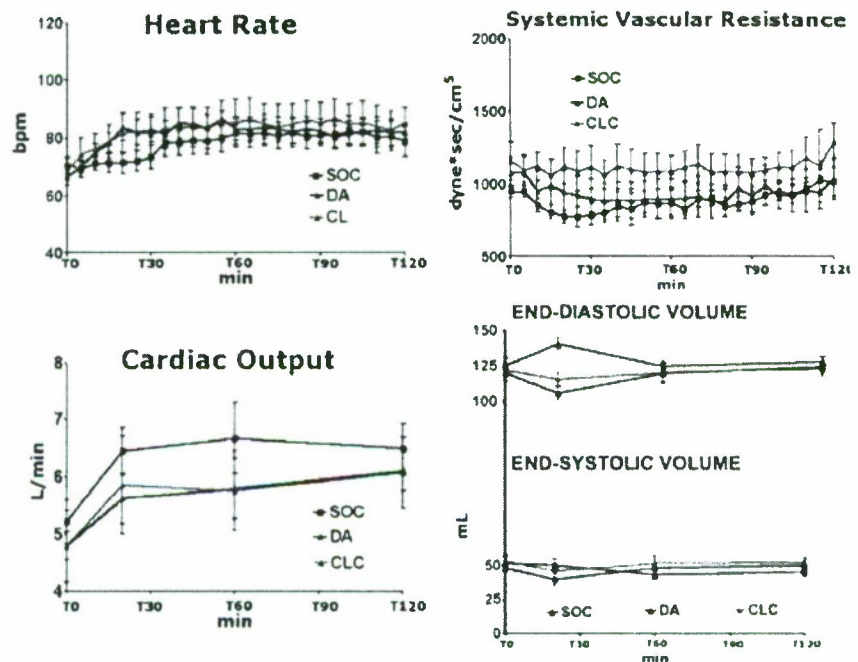


Figure 9. Hemodynamics

Objective 2a: Anesthesia and hemorrhage + spontaneous ventilation: We found significant differences between study groups with this design in six paired volunteer studies undergoing general anesthesia and hemorrhage that are spontaneously ventilating. This study is now complete and analyzed. Graphs show mean $\pm$ SEM. The semi-autonomous group is labeled as DA, the autonomous group is labeled as CLC and the standard of care 3:1 lactated Ringer's is labeled as SOC.

Blood pressure (figure 8): General anesthesia reduced blood pressure by 20-30%. Target blood pressure was best maintained in the autonomous (CLC) group. Interestingly, standard of care (SOC) was associated with a

Volumetric data (figure 10): Plasma volume was measured using indocyanine green dye. Plasma volume expansion was determined from measured hematocrit and the accounted red cell mass removal. Urinary output was measured by bladder ultrasound. A definitive urine volume was recorded at study end. Extravascular volume was calculated from total fluid administered, blood out, urinary output and plasma volume expansion. Data demonstrate a large hypervolemic response to fluid bolus in the standard of care group. The semi-autonomous care group was associated with a transient (small) decrease in plasma volume between T0-T20. The plasma volume did not change and the subjects were euvolemic in the autonomous group. A slightly greater diuresis was evident in the standard of care group. The autonomous groups had a similar urinary output. The standard of care group had a striking large positive net fluid balance and extravascular volume. The autonomous group was associated with a negative extravascular volume. Thus, the autonomous group maintained plasma volume and produce urinary output.

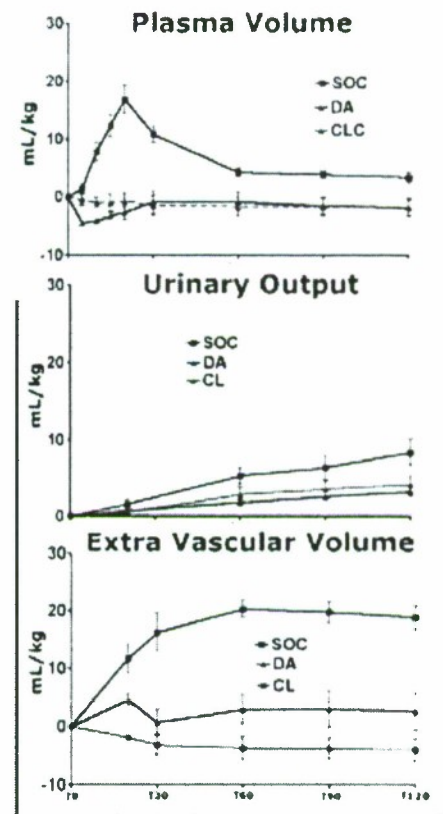


Figure 10. Volumetrics

Total fluid requirements (figure 11): The standard of care was a fixed fluid dose of 30 mL/kg over 20 min, while fluid was infused to a specific endpoint in the semi-autonomous and autonomous groups. There was a remarkable reduction in fluid needs based on the automated characteristics of the fluid infusion plan. The autonomous group reduced fluid needs by 80% compared to standard of care, while the semi-autonomous group reduced overall fluid by 60-70%. Logistically, this represents a reduced carry load for the medics. Summary: Our data demonstrate that standard of care fluid resuscitation in spontaneously hemorrhaged humans results in reduced blood pressure and hypervolemia. Autonomous and semi-autonomous fluid resuscitation can better achieve target blood pressure while logistically reducing volume needs.

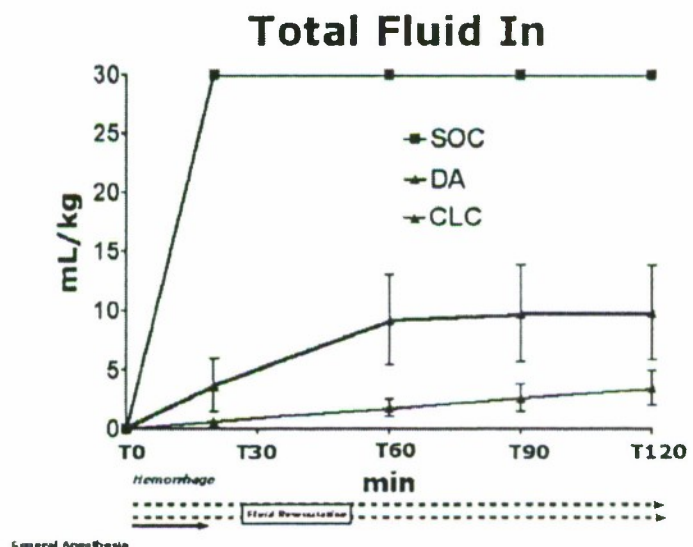


Figure 11. Total fluid requirements

Non-invasive hemoglobin testing (figure 12): Blood hemoglobin is an important determinant of oxygen delivery. Additionally, hemoglobin can be used a tracer of vascular volume. Current sampling takes time. We tested a novel monitor (Masimo Rainbow SpHb™) to determine its accuracy, precision and change during hemorrhage and resuscitation, Objectives: (1) Determine the accuracy and precision of Masimo's non-invasive hemoglobin device compared to gold standard co-ox hemoglobin samples (2) Compare the vascular volume expansion properties of a crystalloid fluid bolus in normovolemia and hemorrhage (3) Determine if non-invasive hemoglobin can be used to predict vascular volume expansion. We measured volume expansion in normovolemic human volunteers (n=5) after a 25 ml/kg - 20 min infusion of lactated Ringer's. In a second group of volunteers (n=6), subjects underwent general anesthesia and then simultaneously bled 10ml/kg and infused 30 ml/kg - 20 min of LR. Hemodynamic variables were measured, arterial pressure via catheter-transducer and cardiac output via echocardiography. Blood hemoglobin, measured by co-oximeter (Co-ox), was compared to non-invasive Masimo Rainbow SET SpHb™. Graphs show regression analysis and Bland-Altman plot for hemoglobin (co-ox) compared to Masimo (SpHb). A strong correlation was observed. Bias was small and precision was good. Additional graphs (mean $\pm$ SEM) demonstrate that hemoglobin is associated with a larger reduction with associated hemorrhage. Further, non-invasive hemoglobin can be used to discriminate this effect. Other variables, heart rate and arterial blood pressure did not change ($p > 0.05$) in either group after fluid bolus. A small increase in cardiac output and decrease in systemic vascular resistance was observed ($p < 0.05$). Hemorrhage resulted in larger decrease in hemoglobin ($p < 0.002$ -

based on AUC analysis). The 3:1 infusion of LR during a 10 ml/kg hemorrhage enhanced vascular volume efficiency and resulted in a period of hypervolemia for 40 minutes post infusion and normovolemia thereafter. Masimo's SpHb provides an effective, novel, non-invasive indicator of vascular volume expansion. SpHb monitoring could help guide fluid resuscitation during hemorrhage.

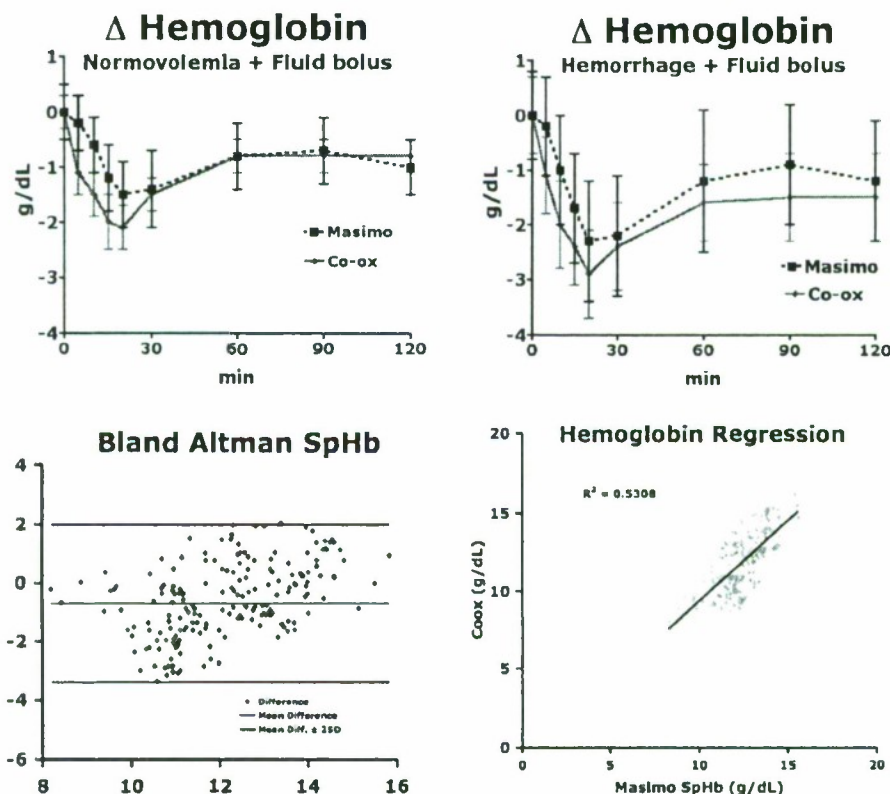
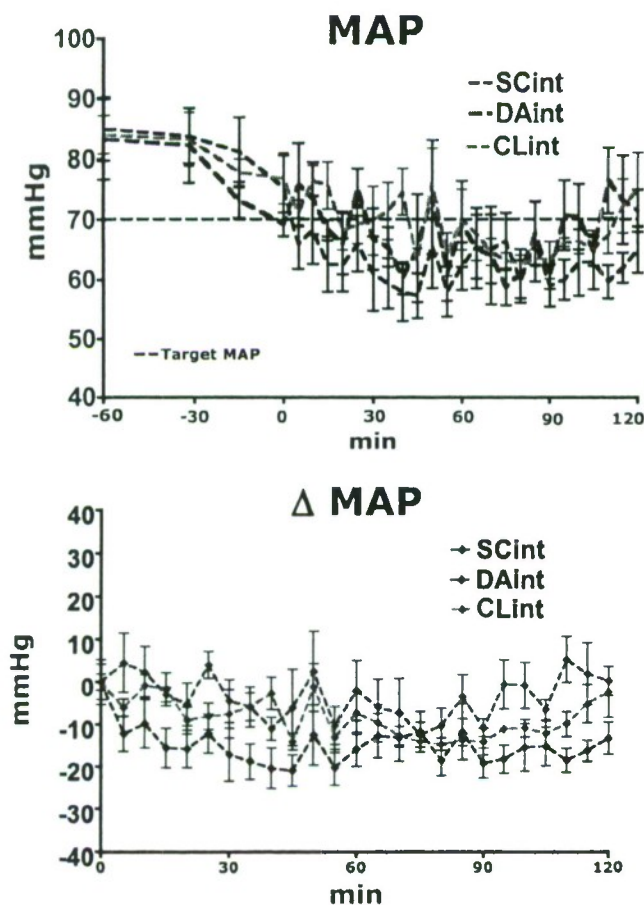


Figure 12. Precision and accuracy of non-invasive hemoglobin: normovolemia and hemorrhage

Objective 2a: Anesthesia and hemorrhage + positive pressure ventilation: In this series, subjects were intubated and mechanically ventilated. The protocol is identical otherwise to above. **Rationale for positive pressure hemorrhage studies:** Severely injured patients are often sedated and intubated. Towards this end, we studied intubated (int) subjects with supported ventilation. This is not uncommon in battlefield injuries or transported patients that may have acute controlled bleeding while sedated, intubated and paralyzed. We have screened and enrolled seven subjects. Three subjects dropped out during the study for non-safety reasons. Data displayed (mean $\pm$ SEM) were for SCint (n=7), decision assist (DAint, n=4) and closed loop (CLint, n=5). One more subject will be recruited using other funding to complete this series.

Figure 13. Target blood pressure – positive pressure

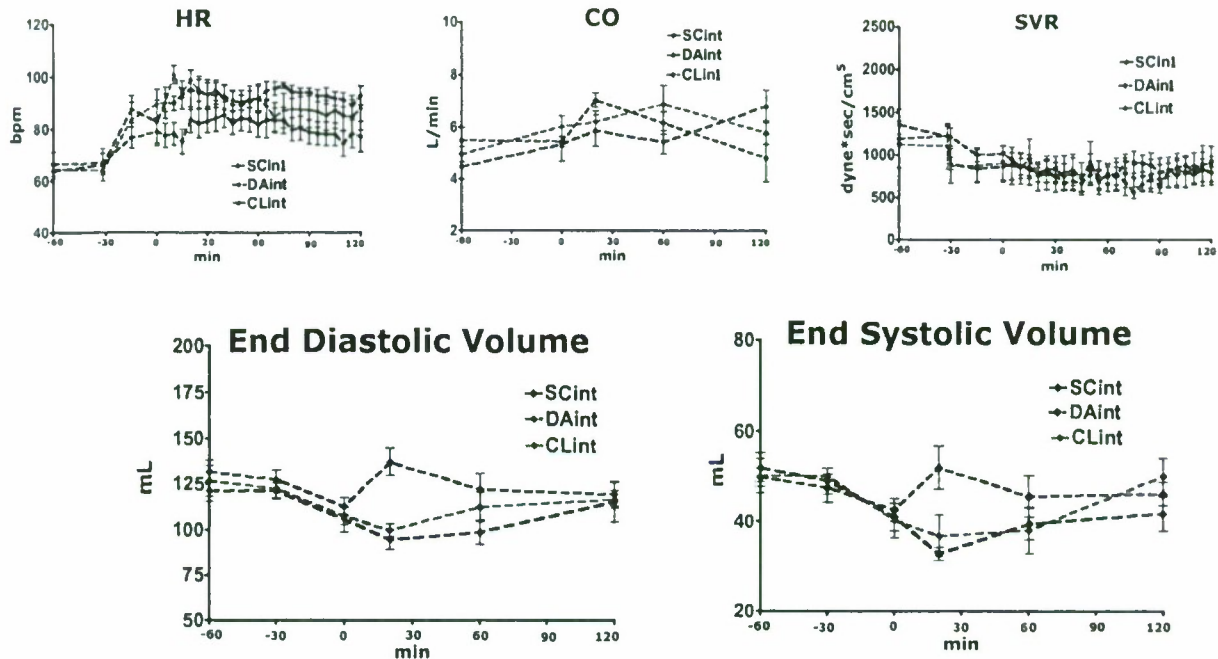


Cardiac output (CO) changed little after anesthesia and PPV. A moderate increase was observed for DAint and SCint. CO underwent little change throughout for the CLint group. Systemic vascular resistance (SVR) decreased for all groups after onset of resuscitation and remained similar to study end. There was a slight reduction in End-diastolic volume (EDV) and End-systolic volume (ESV) following GA. The EDV and ESV slowly returned to baseline for all groups. A formal statistical analysis has not been performed, however, there is a difference for EDV and ESV between the standard of care and autonomous groups at end of hemorrhage at T20 (EDV: SCint 137 ± 8 , DAint 95 ± 5 and CLint 100 ± 4 mL; ESV: SCint 52 ± 5 , DAint 33 ± 2 and CLint 37 ± 5 mL). Stroke volume (EDV-ESV) also was different at T20 (SCint 85 ± 4 , DAint 62 ± 5 and CLint 63 ± 4 mL).

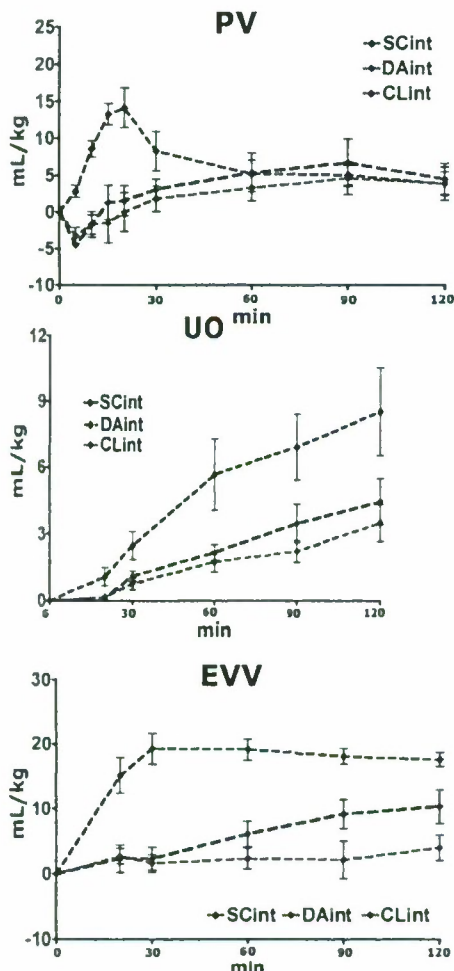
Blood pressure: Our goal was to maintain target blood pressure [we used an algorithm to maintain blood pressure target at 70 mmHg – based on a model of head injury]. This was slightly higher than that of the spontaneously ventilated group since during positive pressure intrathoracic pressure is increased. General anesthesia reduced blood pressure by 12% overall, albeit this was a smaller reduction than we observed in the spontaneous ventilation series. Target blood pressure was better maintained in the autonomous groups (DAint and CLint) during hemorrhage and early resuscitation period. Standard of care (SCint) was associated with a reduction in blood pressure below target throughout the study, while DAint and CLint had less variation. When data were compared to T0 (after general anesthesia but before hemorrhage), SCint was statistically lower than the autonomous groups during the initial resuscitation period [T0-T20]. A complete statistical analysis will be performed after the final subject is enrolled.

Hemodynamics: General anesthesia (GA) and positive pressure ventilation (PPV) was associated with an increased heart rate (HR). During hemorrhage and after resuscitation, HR was notably higher in the autonomous groups compared to SCint.

Figure 14. Hemodynamics - positive pressure ventilation



Volumetric data: Plasma volume and plasma volume expansion (PV) was measured using indocyanine green dye as we previously indicated. Urinary output was measured by bladder ultrasound. A definitive urine volume was recorded at study end. Extravascular volume was calculated from total fluid administered, blood out, urinary output and plasma volume expansion. At study end, a hypervolemic response to fluids, in all three groups was evident. However, there were key differences in the magnitude of the responses. The relationship is closely linked to fluid infusion rate and volume (see next section). Specifically, in the SCInt, the effect on PV expansion was early, large and transient. In the DAInt and CLInt, the PV was

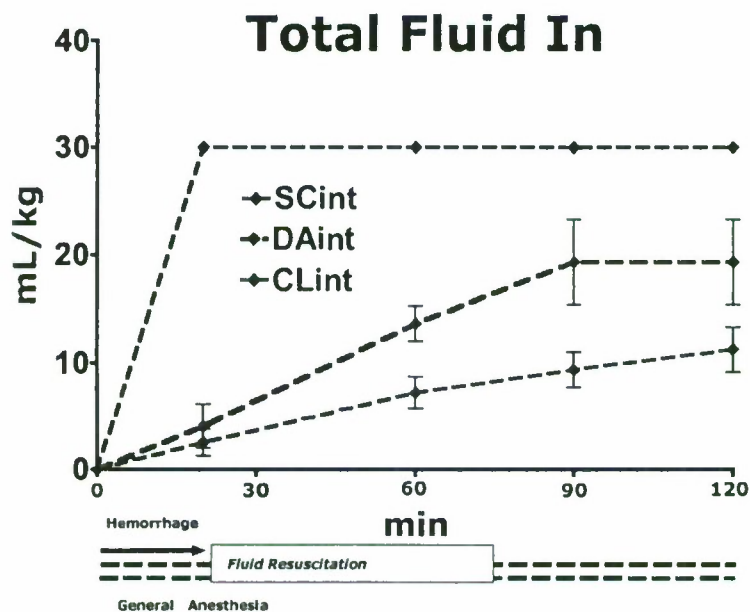


restored to basal levels within the first 30 min of hemorrhage and resuscitation and then increased slowly over the duration of the study. At T20, the change in PV was 14.1 ± 3 vs. 1.5 ± 2 and 0.0 ± 3 mL/kg for SCInt, DAInt and CLInt, respectively. Urinary output (UO) was greatest in the SCInt group. At study end, UO was 8.5 ± 2 vs. 4.4 ± 1 and 3.5 ± 1 mL/kg for SCInt, DAInt and CLInt, respectively. The amount of fluid administered minus the PV expansion and UO. The SCInt had a striking large positive net fluid balance and extravascular volume (EVV). The EVV escalated in DAInt approaching SCInt EVV. The EVV in the CLInt changed little.

Figure 15. Volumetrics - positive pressure ventilation

Total fluid requirements: The SCint group received a fixed fluid dose of 30 mL/kg over 20 min. In the semi-autonomous and autonomous groups, the fluid was infused to a specific endpoint (MAP). Overall, there was a marked reduction in fluid needs for the CLint, while the fluid infusion in the DAint group was moderately lower than SCint. The overall fluid reduction in the CLint was approximately 60-70% lower than SCint. At study end, SCint = 30.0±0, DAint =19.3±4, CLint =11.3±2 mL/kg. Most of fluid in DAint was received in the first 90 min of resuscitation. Thereafter, little fluid was infused. The autonomous groups represent a logistic benefit for medics to potentially reduce the load they must carry. There were stark differences in fluid needs as compared to subjects breathing spontaneously. Our data suggests that positive pressure reduces may reduce some of the compensatory mechanisms for maintaining blood pressure during mild hemorrhage as observed during spontaneous ventilation. Still, target endpoint - MAP is better maintained in the autonomous groups and the volume sparing effects for both these study groups (DAint and CLint) were apparent.

Figure 16. Total fluid requirements - positive pressure ventilation



(Semi)Autonomous fluid resuscitation of hemorrhage under anesthesia – what was learned:

- Large Rapid SOC fluid bolus leads to a paradoxical blood pressure decrease and evidence of over-resuscitation
- Autonomous and semi-autonomous fluid resuscitation can better achieve target blood pressure while logistically reducing volume needs. Specifically;
 - blood pressure target was maintained within baseline BP $\pm$ 5mmHg throughout the resuscitation period for the semi and autonomous groups.
 - The autonomous group reduced fluid needs by 80% compared to standard of care, while the semi-autonomous group reduced overall fluid by 60-70%. This effect is lessened when subjects were intubated and supported with positive pressure.
- We have shown feasibility of these autonomous resuscitation systems

IMPACT/APPLICATIONS [Potential future impact for science and/or systems applications]

We also achieved our expected outcomes, which was that by using semi-automated and automated fluid resuscitation, we could achieve target blood pressure and a reduce fluid needs > 50%. This achievement has a high impact:

- 1) More precise target endpoint BP outcome could lead to less bleeding e.g., over shooting BP and a reduction in brain injury, since episodic hypotension following traumatic brain injury (TBI) dramatically increases mortality
- 2) Improved efficiency of fluid resuscitation could reduce the incidence of over and under-resuscitation e.g., ischemia, pulmonary edema and abdominal compartment syndrome.

TRANSITIONS

(omit this TITLE and section if there are none)

We have completed our evaluation of the effectiveness of semi-autonomous and autonomous fluid resuscitation during mild hemorrhage in healthy volunteers that undergo general anesthesia.

We are also testing other potential input devices that could be used for the ACCS. Towards this end, we have captured data using a novel non-invasive plethysmography oximeter (Masimo Rainbow Set). This device measures and records SpO₂, SpHb, PI (perfusion index) and PVI (pleth variability index). We have discussed SpHb and we continue to analyze PI and PVI in an effort to gauge pre-load.

Specifically, this near term (already FDA approved) device could yield critical information on oxygen delivery, blood constituents (circulating blood hemoglobin levels), transfusion threshold, volume kinetics and efficiency of resuscitation efforts. Further work is needed to determine its potential for a “smart monitor” or if it can be utilized for a component of the ACCS.

Our group has also recently begun collaboration with Dr. Sandra Marshall, per suggestion of Dr. Given (program officer). Dr. Marshall is an expert on physiologic stress responses. Specifically, Dr. Marshall has developed a system to track pupil reactivity following a provocative challenge. Although her work has focused on stress fatigue, it is our hope that this same metric could be utilized to determine depth of anesthesia. These new studies will begin using a similar model in the next few months. We have IRB approval and final ONR approval is pending. A new grant (Arcos submission – Jan 2011) will utilize some of the same concepts that this grant used. Specifically, a decision support and closed-loop control platform to test colloid and blood resuscitation fluids. We additionally will be testing some of the Athena’s products for the ACCS using this grant or other funding as a sub-contract. This should be an efficient merger.

Planned clinical studies – ONR FY12-FY14

1) Testing NIBP in CLC mode*: Colloid infusion using WVSM or other NIBP device in CLC mode is begun at T30; BP is measured q2 –q5 min during and after hemorrhage for 120 min (T120). The comparison group is a 10 mL/kg colloid bolus at T30 – T50.

- a) will give untreated data
- b) will test two different colloid – lyophilized plasma* or hextend
- c) will test NIBP in CLC mode
- d) will test masimo blood volume expansion

*IRB now has final approval – transition from current ONR grant

2) Pupillary assessment for general anesthesia. We will use hemorrhage volunteers undergoing general anesthesia to test the feasibility of pupil reactivity as an index of depth of general anesthesia. This is a feasibility study. If pilot data is positive, we will see future funding with ONR. We anticipate start date – May 2012.

RELATED PROJECTS

1) The anesthesia and hemorrhage protocol, developed from this ONR proposal, is a recognized alternative to lower body negative pressure [model for hemorrhage]. The anesthesia and hemorrhage model is highly clinically relevant. Towards this end, we have secured new funding from the USAirforce to test intrathoracic pressure regulation during hemorrhage. We have now received the NOGA and will begin testing shortly.

2) STARS trial – Kramer PI. Vital signs data will be captured from point of injury throughout ICU. We are working on establishing a relationship with University of San Paulo, Brazil to perform a trial using the resuscitation system. Dr. Kramer – PI on project and CO-I on this grant, visited San Paulo Brazil September 2010. Dr. Kramer has assembled a team of clinician scientists and initial data capture will be underway after the IRB is approved. We will be testing the masimo device as well as the WVSM in Brazil. Other funding sources will be used.

REFERENCES

None

HONORS/AWARDS/PRIZES

- Patents submitted: Although other sources of funding were also used for the Trauma Tablet and Med Tablet, data from the feasibility studies outlined in this report, were used and incorporated into this patent – patent#7,857,803.