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<td>Closed-Loop Resuscitation of Hemorrhagic Shock: Novel Solutions Infused to Hypotensive and Normotensive Endpoints</td>
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<td>George C. Kramer (PI)</td>
<td>03PR04401-01</td>
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<td>University of Texas Medical Branch at Galveston 301 University Blvd Galveston, Texas 77550-2774</td>
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OBJECTIVE: To define optimal fluid resuscitation regimens for use in combat casualty care. Specific goals are to determine the infusion regimens and fluids that are most efficient (least volume) and most effective (lowest mortality with best cardiovascular and metabolic function). We tested both FDA approved fluids and novel formulations.

Our long-term goal is to develop efficient and efficacious resuscitation regimens for combat casualty care and to develop a microprocessor controlled closed-loop resuscitation system that will optimize the delivery of the solution(s) found best. Over the 3.75-year grant we completed 16 full studies, a total of 24 treatment groups with 218 individual experiments. Using our multibleed model conscious sheep hemorrhage model we studied 18 treatment groups in 124 experiments.

APPROACH: The specific objective of our project was the experimental evaluation of different fluid compositions efficacy when administered to achieve normotensive and hypotensive blood pressures using titrated fluid delivery. We tested fluids infused in large volumes to normalize blood pressure as well as limited titrated hypotensive resuscitation with a variety of other target endpoints.

Effectiveness was based on significant changes in metabolic function (lactate, base excess), and mortality suggested by trends, but not statistical significance (Rafie, 2004; Shah-abstract, 2003, Vaid, 2006; Nascimento, 2007).

SPECIFIC GAOLS:
Determine the infusion regimens and fluids that are most efficient (least volume) and most effective (lowest mortality with best cardiovascular and metabolic function). We tested both FDA approved fluids and novel formulations. FDA approved fluids tested included lactated Ringer’s (LR), Hespan, Hextend, hypertonic 3% NaCl and hypertonic 5% NaCl. We also tested non-FDA approved fluids 1) hypertonic saline dextran (HSD); 2) isotonic ketone Ringer’s; 3) Hypertonic 15% Pyruvate; 4) 8% NaCl hypertonic. Many of these solutions were tested using both normotensive and hypertensive resuscitation. Some studies used baseline cardiac output as the target variable. We used a variety of closed-loop algorithms in our prototype closed-loop system. We also evaluated drugs as adjuncts that could augment the resuscitative effects of volume expanders including isoproterenol, esmolol, norepinephrine, dobutamine, phenylephrine,
and dopamine. Studies were performed in conscious and anesthetized sheep subjected to multiple hemorrhages, and then treated using a controlled closed-loop system for resuscitation.

Overall, our research in conscious hemorrhaged animals suggests that new approaches to resuscitation using hypotensive resuscitation, monocarboxylates (isotonic ketone Ringer's or hypertonic pyruvate), or HBOCs is not as effective as the standard of care therapy designed to normalize blood pressure with large volumes of lactated Ringer's or Hextend. However, we did not study animals with uncontrolled hemorrhage models, which could change the outcomes and our conclusions.

Closed-Loop Algorithms for the Treatment of Hemorrhage: We developed and tested a variety of closed-loop algorithms based on decision tables, proportional-integral-derivative (PID) and fuzzy logic. All showed efficacy, but the PID and fuzzy logic reduced volume needs compared to the decision table. Some of the work during 2005-2007 was in preparation for our follow-on ONR Clinical Project on closed-loop and decision-assist technologies. ONR gave a high priority to this translational project, but budget award was delayed from the scheduled start date of November 2005 to April 2006. Thus, some effort on this present grant focused on transitioning from our animal studies to prototype systems with noninvasive sensors, decision-assist software, and the clinical testing of different blood pressure monitors.

Our four most important findings and accomplishments are:

1. **Normotensive resuscitation with LR was better or equivalent compared to all tested infusion regimens:** We do NOT recommend using hypotensive resuscitation to 65 mmHg in preference to attempting to restore blood pressure to near normal due to severe acidosis and death in some of the sheep in the 65-mmHg hypotensive groups. We do suggest milder regimen of hypotensive resuscitation, perhaps with a target pressure of 70-80 mmHg.

2. **We Developed a Variety of Closed-Loop Algorithms for Titrated Resuscitation of hemorrhagic shock:** All algorithms reduced fluid volumes 3:1 compared to ATLS guidelines, or versus simply turning infusion on or off depending, on whether blood pressure was below or above target. Hypotensive resuscitation greatly reduced volume requirements since target values were lower as did the use of colloids versus crystalloids. However, there was only modest additional volume sparing when colloids were combined with hypotensive resuscitation.

3. **Pharmacological Modulation of fluid Therapy:** We have shown that fluid expansion is modulated by catecholamines suggesting that low dose additives to fluids can improve volume expansion efficiency. We reported that beta-receptor activation augments and beta-agonist decreases volume expansion (Vane, 2004, Ewaldson, 2005).

4. **Closed-Loop Control with Urinary Output as Feedback:** We designed and tested a closed-loop resuscitation system in sheep, and we have started clinical trials of monitoring in burn patients. These studies were funded in part by Shriners Burns Hospitals (Hoskins, 2006).
Other Finding and Accomplishments:

5. **Hypertonic 3% NaCl**: Hypertonic 3% saline should not be used ad lib or in a dose that exceeds 10 ml/kg as it caused excessive diuresis and acidosis based on the base excess and increased lactate (Vaid 2006).

6. **Hextend**: Hextend used in doses of 10-20 ml/kg had no untoward effects and was volume sparing, but it provided no apparent benefit over LR other than volume sparing (Rafie 2004).

7. **Hypertonic 15% in Pyruvate**: Impairs cardiac output compared to isotonic LR or an 8% hypertonic saline control group (Nascimento, 2007).

8. **An HBOC (Oxyglobin)**: Did not offer benefit in our closed-loop model because dose was greatly limited by induced vasoconstriction causing rapid achievement of target pressure. Oxyglobin depressed cardiac output compared to Hespan (not published).

9. **Ketone Ringer’s**: Offered no systemic hemodynamic or metabolic advantage compared to LR, and will likely make little difference in most trauma patients (Shah-abstracts, 2003).

10. **Hypertonic 7.5% NaCl 6% Dextran 20 (HSD)**: HSD was used as an initial 4 ml/kg infusion and provided superior volume expansion properties and safety profile compared to using 3% NaCl ad lib (Vaid, 2005) and Anesth Analg 2001;93:823-31. This is somewhat surprising, since the dose of sodium with 4 ml/kg of HSD is similar to 10 ml/kg of 3% NaCl (HSD study is in preparation).

11. **Microbubbles Oxygen Carriers**: In three pilot studies, performed at the request of Col Vandre and with Dr. Given’s approval, we found no beneficial impact of perfluorocarbon microbubbles of oxygen delivery, consumption or hemodynamics.

12. **Fixed Dose 6 ml/kg (5)% NaCl Followed by Titrated Hextend**: this two-solution regimen was highly effective at reducing volume while providing equivalent hemodynamics and oxygenation (Taylor W, 2005).

13. **Review Articles**: A review article on mass casualty care using oral and GI delivery of fluid (Cancio, 2006). A book chapter reviewing blood substitutes for trauma, and combat casualty care were published (Kramer 2006). A book chapter on the physiology of the volume expansion properties of blood substance was published (Kramer, 2006).

14. **New Methods**: Developed during the award period include: Our multi-bleed conscious sheep model (Rafie, 2004)
CONCLUSIONS: Titrated closed-loop resuscitation is feasible, and our data suggests that volume sparing has equal or increased efficacy.

SIGNIFICANCE: Our closed-loop technology studies may lead to a new paradigm in trauma care. Smart resuscitation systems composed of integrated IV pumps and monitors will assist physicians in decision-making and automatically perform titrated fluid therapy.

PATENTS: The PI, a UTMB colleague and one private colleague invented a novel IV infusion pump and a fluid balance monitor. This pump could be a component of a Resuscitation System or a standalone device. UT exerted its rights, and a provisional patent was submitted to the US patent and Trademark Office, "Fluid Balance Monitoring System with Fluid Infusion Pump for Medical Treatment", Filed December 2006.


Invention Disclosure: We have collaborated with the US Army’s Institute of Surgical Research on a broad range. Cooperative Research and Development Agreement with (CRADA) focused on improving the means to treat circulatory shock. The CRADA has resulted in one invention disclosure, "Closed-Loop Resuscitation Systems for Treatment of Circulatory Shock". Inventors: Kramer, Drew, Salinas, and Cancio. The Invention Disclosure was submitted to the technology transfer offices of UTMB and ISR. A patenting strategy remains under discussion. The invention was based on our collaborative (UTMB and ISR) basic science, engineering and clinical research. This invention lead to the production of four prototype fluid balance monitors, and two prototype decision-assist devices using copyrighted algorithms embedded in a handheld PDA and tablet PC that provides Decision-Assist recommendations based on the model of patient burn records at ISR and UTMB. A commercialization plan is being developed.

UTMB and the PI have signed confidential disclosure agreements (CDA), and have begun collaborations for the development of different components of our Closed-Loop Resuscitation Systems. These include: QRS Diagnostic, Impact Instrumentation and Athena GTX, Wylie laboratories, InfoDat, Inc., Bard Medical, Abbott, and Welch Allyn.

Disclosure: The PI has no conflict of financial interest at present, however one is anticipated. The PI is the founder and a principal shareholder of Resuscitation Solutions, Inc., which plans to apply for licensure of some of the UTMB/ISR technologies described above, and the UTMB pump technology, and will seek commercialization in partnership with RSI’s strategic partners.

AWARD INFORMATION: N/A
REFEREEED PUBLICATIONS (for total award period):

**Manuscripts:**


BOOK CHAPTERS, SUBMISSIONS, ABSTRACTS AND OTHER PUBLICATIONS (for total award period).

Book Chapters:

Abstracts:


**NATO Reports:**


**Software (copyrighted):**

1. “Automated Fluid Balance Monitors” ABR version 3.1
   Drew, Salinas, Cancio and Kramer.

2. “Decision LabView Executable Assist for Burn Resuscitation”
   Salinas, Drew, Cancio, Wolf and Kramer, (Software platforms: LabVIEW Executable, C#, •Net, JAVA).