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14. ABSTRACT The long term objective is to develop and evaluate new monitoring strategies in clinically-relevant laboratory models of civilian and military trauma then translate the laboratory findings to the bedside. The short term primary objective was to assess the value of a new portable, noninvasive, continuous monitoring device (near- infrared spectroscopy, NIRS) in establishing the adequacy of resuscitation after trauma in an experimental model. That objective was achieved earlier than expected and is now being tested in patients. We are now evaluating proof of concept of other non-invasive monitoring strategies in both animals and patients. Some of these novel strategies could permit minimally-trained medics or other EMS personnel to provide care of trauma patients in the combat or civilian prehospital setting; others provide new perspectives on the diagnosis of injury severity.						
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Project Title: Use of Near-Infrared Spectroscopy to Assess the Adequacy of
Resuscitation in Trauma

ONR Award No: N00014-02-1-0035

Reporting Period: June 1, 2004 - May 31, 2005

Award Period: January 1, 1995 - December 31, 2005

Scientific and Technical Objectives

The long term objective is to develop and evaluate new monitoring strategies in clinically-relevant laboratory models of civilian and military trauma then translate the laboratory findings to the bedside. The short term primary objective was to assess the value of a new portable, noninvasive, continuous monitoring device (near- infrared spectroscopy, NIRS) in establishing the adequacy of resuscitation after trauma in an experimental model. That objective was achieved earlier than expected and is now being tested in patients. We are now evaluating proof of concept of other non-invasive monitoring strategies in both animals and patients. Some of these novel strategies could permit minimally-trained medics or other EMS personnel to provide care of trauma patients in the combat or civilian prehospital setting; others provide new perspectives on the diagnosis of injury severity.

Approach

Anesthetized, instrumented swine receive a traumatic injury to the head, chest, abdomen, or extremity. After a 10-60 min shock period, the animal receives initial resuscitation with crystalloid, colloid, or novel test fluid, supplemented with various pharmacologic agents to mimic pre-hospital care. This is followed by resuscitation with standard of care cardiopulmonary support. After a 2-72 hr post trauma observation period, the outcome is graded on the basis of mortality, physiologic changes, neurologic function, biochemical/metabolic changes, and/or histologic changes. Similar observations are then made in trauma patients.

Concise Accomplishments

Three fundamentally different monitoring strategies were developed to monitor the status of trauma patients.

1. Near infrared spectroscopy can be used to non-invasively monitor changes in the peripheral circulation and the severity of shock in both animals and patients
2. Heart rate variability can be used to non-invasively monitor changes in the activity of the autonomic nervous system and the severity of traumatic brain injury in patients
3. Systemic catheter placement was found to produce a hypercoagulable state in both animals and patients

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Expanded Accomplishments

1. Three different experimental protocols tested the hypothesis that hindlimb muscle tissue O₂ saturation (StO₂), measured non-invasively with NIRS is as reliable as invasive systemic oxygenation indices to guide fluid resuscitation. In Series 1, StO₂ tracked mixed venous O₂ saturation (SvO₂), but discriminated between three survivor groups better than SvO₂, arterial lactate, or arterial base excess. In Series 2, StO₂ tracked SvO₂ but discriminated between two survivor groups better than SvO₂, arterial lactate, or arterial base excess. In series 3, animals survived to extubation when resuscitated to an StO₂ target. Therefore, NIRS-determined muscle StO₂ was more reliable than invasive oxygenation variables as an index of shock. Since muscle StO₂ can be easily monitored in emergency situations, it may represent an improved method to gauge the severity of shock or the adequacy of fluid resuscitation after trauma. To determine clinical relevance, NIRS was used to establish: 1) the normal range of thenar StO₂ in humans, and 2) the relationship between shock state and StO₂ in trauma patients. This was a prospective, non-randomized, observational, descriptive, study in normal human volunteers (n=707) and patients admitted to the resuscitation area (n=150) of our Level I trauma center. Thenar StO₂ was as follows: Normals, $87 \pm 6\%$, Mild Shock $83 \pm 10\%$, Moderate Shock $80 \pm 12\%$, and Severe Shock $45 \pm 26\%$. Therefore, decreased StO₂ reflects the presence of severe hypoperfusion and 2) NIRS may be a novel method for rapidly and non-invasively assessing changes in tissue dysoxia.

2. Heart rate is neither periodic nor stationary in physiological conditions. Instead, there are neurogenically regulated beat-to-beat variations. Changes in heart rate variability (HRV) reflect autonomic dysfunction in patients in several pathologic states, including traumatic brain injury (TBI). Nevertheless, the clinical utility has been limited by data acquisition, off-line algorithms, and interpretation of complex statistical results. We report the design and first test of a versatile, user friendly portable system that provides an on-line HRV index. The module interfaces with a bedside monitor or uses a built-in amplifier to acquire/digitize the ECG signal at 250Hz via 12 bit conversion. Electrical/motion artifacts are filtered before real time sinus beats are detected with a QRS algorithm. Instantaneous heart rate (HR), variation in RR intervals (SDNN), and other derivatives of HRV over a user defined timescale are displayed and dynamically updated. The user can adjust the sampling frequency, digital filtering and the QRS detection parameters. The data showed that this novel HRV monitoring strategy is safe, easy to use, continuous, and non-invasive; 2) HRV index was reduced >90% in sedated TBI patients; 3) Further work is needed but HRV monitoring might improve outcome after TBI by allowing early detection of intracranial pathology and/or treatment effectiveness.

3. A higher rate of pulmonary embolism has been associated with pulmonary artery (PA) catheters, however no mechanism has been described. Conventional coagulation monitoring reveal no changes related to PA catheterization. The purpose of this study was to determine whether PA catheterization resulted in a hypercoagulable state detectable by thrombelastography (TEG). The data from healthy swine, and critically-ill patients, showed that 3 hrs after PA catheter placement, clotting time was reduced by half, which suggests that systemic catheters may enhance thrombin formation and fibrin polymerization. This may explain why PA catheters are associated with an increased risk of pulmonary emboli.

Work Plan

1. Determine the accuracy, specificity, and precision of heart rate variability monitoring as a non-invasive index for the severity of traumatic brain injury.
2. Determine whether catheters placed in site other than the pulmonary artery evoke a systemic hypercoagulable condition.

Problems/Issues

No problems are anticipated.

Peer-Reviewed Journal Articles

Status Text

In Press

6) King DR, Cohn SM, Feinstein AJ, Majetschak M, Proctor KG: Systemic coagulation changes caused by pulmonary artery catheters: laboratory findings and clinical correlation. J Trauma (in press)

In Press

5) King DR, Cohn SM, Proctor KG: Resuscitation with a hemoglobin-based oxygen carrier after traumatic brain injury. J Trauma (in press)

In Press

4) Feinstein AJ, Cohn SM, Sanui M, King DR, Proctor KG: Early vasopressin improves short term survival after pulmonary contusion. J Trauma (in press)

In Press

3) Earle SA, Proctor KG, Patel MB, Majetschak M: Ubiquitin reduces fluid shifts after traumatic brain injury Surgery (in press)

In Press

2) Feinstein AJ, Patel MB, Sanui M, Cohn SM, Majetschak M, Proctor KG: Resuscitation with pressors after traumatic brain injury. J Am Coll Surg (in press)

In Press

1) Sanui M, King DR, Feinstein AJ, Varon AJ, Cohn SM, Proctor KG: Effects of Arginine Vasopressin During Resuscitation from Hemorrhagic Hypotension after Traumatic Brain Injury. Crit Care Med (in press)

Published

15) Majetschak M, Cohn SM, Nelson JA, Burton EH, Obertacke U, Proctor KG: Effects of exogenous ubiquitin in lethal endotoxemia Surgery 2004:May;135(5):536-543

Published

14) Majetschak M, Cohn SM, Obertacke U, Proctor KG: Therapeutic potential of exogenous ubiquitin during resuscitation from severe trauma J Trauma 2004:May;56(5):991-1000

Published

13) Malhotra AK, Schweitzer JB, Fox JL, Fabian TC, Proctor KG: Cerebral perfusion pressure elevation with oxygen carrying pressor after traumatic brain injury and hypotension in swine; J Trauma 2004:May;56(5):1049-1057

Published

12) Crookes BA, Cohn SM, Burton EA, Nelson J, Proctor KG: Noninvasive muscle oxygenation to guide fluid resuscitation after traumatic shock. Surgery 2004:Jun;135(6):662-670

Published

11) King DR, Cohn SM, Proctor KG: Intracranial pressure, coagulation changes, and neurologic outcome after resuscitation from experimental traumatic brain injury with Hetastarch. Surgery 2004:Aug;136(2):355-363

Published

10) Crookes BA, Cohn SM, Bonet H, Majetschak M, Burton EA, Nelson J, Varon AJ, Linden J, Proctor KG: Building a better fluid for emergency resuscitation of traumatic brain injury. J Trauma 2004 Sep;57(3):547-554.

Published

9) King DR, Cohn SM, Proctor KG; Miami Clinical Trials Group. Modified rapid deployment hemostat bandage terminates bleeding in coagulopathic patients with severe visceral injuries. J Trauma. 2004 Oct;57(4):756-9.

Published

8) Crookes BA, Cohn SM, Bloch S, Amortegui J, Manning R, Li P, Proctor MS, Hallal A, Blackbourne LH, Benjamin R, Soffer D, Habib F, Schulman CI, Duncan R, Proctor KG: Can Near Infrared Spectroscopy identify the severity of shock in trauma patients? J Trauma. 2005 Apr;58(4):806-816.

Published

7) Majetschak M, King DR, Krehmeier U, Busby L, Thome L, Muench E, Proctor KG: Ubiquitin immunoreactivity in cerebrospinal fluid after traumatic brain injury: Clinical and experimental findings Crit Care Med. 2005 Jul;33(7):1589-1594

Books or Book Chapters**Status Text****Published**

Sanui M, Cohn SM, King DR, Feinstein AJ, Varon AJ, Proctor KG: "A Role for vasopressin during resuscitation of Traumatic shock" Chapter #11 in Combat Casualty Care in Ground-Based Tactical Situations: Trauma Technology and Emergency Medical Procedures, published Sept 2004 by North Atlantic Treaty Organization Research and Technology Office Human Factors and Medicine Panel, Ref # RTO-MP-HFM-109 <http://www.rta.nato.int/Main.asp?topic=hfm.htm>

Published

Proctor KG, Cohn SM: Background and initial pre-clinical results with novel second generation blood substitute. Proceedings of the 17th Annual Bodensee Symposium. Messmer K, Burhop KE, Hutter J (eds) Microcirculatory Effects of Hemoglobin Solutions. Prog Appl Microcirc, Basel, Karger 2004 25:95-102

Technical Reports (Non-refereed Publications)

No technical reports reported.

Abstracts/Presentations/Posters/Conference Proceedings

Patel MB, King DR, Feinstein AJ, Earle SA, Zucarelli JE, Topp RF, Armstrong JH, Proctor KG: Situational training exercise for mass casualty event. Submitted to 19th Annual Meeting of the Eastern Association for the Surgery of Trauma, Orlando, FL Jan 2006

Patel MB, Feinstein AJ, Majetschak M, Norenberg MD, Proctor KG: Hemoglobinbased oxygen carrier (HBOC) use in neurotrauma care. Submitted to 19th Annual Meeting of the Eastern Association for the Surgery of Trauma, Orlando, FL Jan 2006

Patel MB, Busby L, Proctor KG, Majetschak M: Assessment of 26S proteasome activity in skeletal muscle after trauma. Accepted for presentation at 60th Annual Surgical Forum, American College of Surgeons, San Francisco, CA Oct 2005

Feinstein AJ, Patel MB, Earle SA, Majetschak M, Proctor KG: Resuscitation with pressors after traumatic brain injury.

- a. Presented at American College of Surgeons Florida Committee on Trauma Resident Paper Competition, Miami Beach, FL Nov 2004 (* First place Research Award)
- b. Presented at American College of Surgeons Region IV Committee on Trauma Resident Paper Competition, Lexington, KY Nov 2004 (* First place Research Award)
- c. Presented at American College of Surgeons National Committee on Trauma

Resident Paper Competition Washington DC Mar 2005

Earle SA, Proctor KG, Patel MB, Majetschak M: Ubiquitin reduces fluid shifts after traumatic brain injury.

- a. Presented at American College of Surgeons Florida Committee on Trauma Resident Paper Competition, Miami Beach, FL Nov 2004
- b. Presented at The Society of University Surgeons 66th Annual Meeting, Resident

Paper Competition Nashville, TN Feb 2005

Feinstein AJ, Cohn SM, Sanui M, King DR, Proctor KG: Vasopressin prevents cardiopulmonary collapse after severe chest trauma.

- a. J Trauma 2004 Dec; 57(6):1377. Presented at 18th Annual Scientific Assembly Eastern Assoc. for the Surgery of Trauma, Fort Lauderdale, FL, Jan 2005.
- b. Presented at ATACCC2004, Advanced Technology Applications to Combat

Casualty Care, St. Pete Beach, FL Aug, 2004.

Atapattu S, Cohn SM, Feinstein AJ, Ferrada M, Manning R, Cook K, Proctor KG Novel method for quantifying heart rate variability in patients with traumatic brain injury. J Trauma 2004 Dec; 57(6):1388. Presented at 18th Annual Scientific Assembly Eastern Assoc. for the Surgery of Trauma, Fort Lauderdale, FL, Jan 2005.

King DR, Cohn SM, Lopez PP, deMoya MA, O'Keefe T, Feinstein AJ, Majetschak M, Proctor KG: Systemic coagulation changes caused by pulmonary artery catheters: laboratory findings and clinical correlation. J Trauma 2004 Dec; 57(6):1379. Presented at 18th Annual Scientific Assembly Eastern Assoc. for the Surgery of Trauma, Fort Lauderdale, FL, Jan 2005 (* Alexander Research Award)

Sanui M, Cohn SM, Feinstein AJ, Varon AJ, Proctor KG: Vasopressin during resuscitation from traumatic brain injury. Anesthesiology 2004; 101: A414 Presented at American Society of Anesthesiologists 2004 Annual Meeting Las Vegas, NV Oct, 2004

King DR, Cohn SM, Proctor KG: Resuscitation with a hemoglobin-based oxygen carrier after severe brain trauma.

- a. J Trauma 2004 Aug; 57(2):443. Presented at 64th Annual Meeting of American Assoc. for the Surgery of Trauma, Maui, HI Sept 2004
- b. Presented at Surgical Forum, 90h Clinical Congress, American College of Surgeons, New Orleans, LA Oct 2004.
- c. Presented at ATACCC 2004, Advanced Technology Applications to Combat Casualty Care, St. Pete Beach, FL Aug, 2004.

Feinstein AJ, Beck G, Cohn SM, LeCroy DE, King DR, Proctor KG: Portable emergency ventilator that servo-controls inspired oxygen concentration;

- a. Presented at 64th Annual Meeting of American Assoc. for the Surgery of Trauma, Maui, HI Sep 2004
- b. Presented at ATACCC2004, Advanced Technology Applications to Combat

Casualty Care, St. Pete Beach, FL Aug, 2004.

Majetschak M, Proctor KG: Ubiquitin and ubiquitin-related molecules for treatment and prevention of harmful activation of the immune system.

- a. Presented at First Annual Florida Tech Transfer Conference, St. Petersburg, FL, May 2004
- b. Presented at Seventh Annual BioFlorida Conference, Boca Raton, FL Oct, 2004
- c. Presented at ATACCC2004, Advanced Technology Applications to Combat

Casualty Care, St. Pete Beach, FL Aug, 2004.

Sanui M, Cohn SM, King DR, Feinstein AJ, Varon AJ, Proctor KG: Vasopressin supplements and Resuscitation from trauma.

- a. Presented at 30th Annual Gulf Atlantic Anesthesia Residents' Conference, Miami Beach, FL, Mar 2004.
- b. Presented at Florida Society of Anesthesiologists, Miami, FL, Jul, 2004 (* First place Research Award)
- c. Presented at the Research and Technology Organisation (RTO) Human Factors and Medicine (HFM) symposium on "Combat Casualty Care in Ground Based Tactical Situations: Trauma Technology and Emergency Medical Procedures", held in St. Pete Beach, FL Aug 2004

King DR, Cohn SM, Nelson JA, Proctor KG: Hetastarch solution should replace mannitol during resuscitation of traumatic brain injury. Presented at Society of University Surgeons 65th Annual Meeting Resident Paper Competition, St. Louis, MO, Feb 2004

Crookes BA, Cohn SM, Bloch S, Proctor M, Amortegui J, Manning R, Li P, Blackbourne L, Schulman C, Habib F, Benjamin R, Soffer D, Proctor KG: Can near infrared spectroscopy (NIR) identify the severity of shock in trauma patients? J Trauma 2004 Jan; 56(1):228. Presented at 17th annual scientific meeting of the Eastern Assoc. for the Surgery of Trauma, Amelia Island, FL, Jan 2004 (* Alexander Research Award)

King DR, Cohn SM, Blackbourne LH, Benjamin RE, Proctor KG: Novel hemostatic dressing in coagulopathic patients with visceral injuries: preliminary findings.

- a. J Trauma 2004 Jan; 56(1):231. Presented at 17th annual scientific meeting of the Eastern Assoc. for the Surgery of Trauma, Amelia Island, FL, Jan 2004
- b. Presented at American College of Surgeons Florida Committee on Trauma Resident Paper Competition, Jacksonville, FL Nov 2003
- c. Presented at ATACCC2004, Advanced Technology Applications to Combat Casualty Care, St. Pete Beach, FL Aug, 2004.

Awards/Honors/Invention Disclosure

Heart rate variability index to predict severity in patients with traumatic brain injury; KG Proctor and SA Atapattu; invention disclosure to Univ of Miami Miller School of Medicine;
<http://www.miami.edu/techtransfer>

Ara J. Feinstein, MD won the American College of Surgeons Committee on Trauma 2004 Florida Resident Paper Competition, and 2004 Region IV Resident Paper Competition for a study on the beneficial effects of vasopressin during resuscitation from trauma

Masamitsu Sanui, MD won the 2004 Florida Society of Anesthesiologists Resident Paper Competition for a study on the actions of vasopressin after traumatic brain injury

David R. King, MD won the 2005 Alexander Award from the Eastern Association for the Surgery of Trauma for the best paper by a resident or fellow for his study on coagulation changes caused by PA catheters

Bruce A. Crookes, MD won the 2004 Alexander Award from the Eastern Association for the Surgery of Trauma for the best paper by a resident or fellow for his study on near infrared spectroscopy in trauma patients.

Patents Submitted

Heart rate variability index to predict severity in patients with traumatic brain injury; KG Proctor and SA Atapattu; US patent application filed Jan 2005 by Univ of Miami; <http://www.miami.edu/techtransfer>

Patents Issued

No patents issued reported.

Technology Transfer

During the past several years of ONR funding, we have evaluated several compounds that were being developed by bio-pharmaceutical companies for possible use in combat casualty care or civilian trauma. Many of these products are, or have been, used by other DOD-funded investigators, including:

- polynitroxylated dextran & hemoglobin from Synzyme Technologies, LLC, Irvine, CA.
- 6% hetastarch in balanced electrolyte solution from BioTime Inc, Berkely, CA
- HBOCs from Baxter Hemoglobin Therapeutics, Boulder, CO and Biopure Corp, Cambridge, MA
- ATL-146e from Adenosine Therapeutics, Charlottesville, VA
- RDH bandage from Marine Polymer Technologies, Cambridge MA

In addition, we have evaluated several different monitoring devices that have potential usefulness in emergency or field situations:

- bispectral EEG analysis from Aspect Medical Systems, Inc., Newton, MA
- non-invasive cardiac output monitoring from Novamatrix NICO, Wallingford, CT
- heart rate variability from Medical Automation Systems, Charlottesville, VA
- Near infrared (NIR) spectroscopy by Hutchinson Technologies (Hutchinson, MN)
- thromboelastograph from Haemoscope, Inc Niles, IL
- sub-lingual CO2 sensor, Nellcor, Ballwin, MO
- portable, automatic ventilator, Impact Instrumentation, West Caldwell, NJ

Several companies provided us with their products at no cost, or reduced cost, because they are interested in the results of the experiments. Several other critical care manufacturers provide us with supplies for our studies, including:

- cerebral oximeter, Somanetics, Troy, MI
- mechanical ventilators from Impact Instrumentation, West Caldwell, NJ
- cardiac output computers and fiberoptic catheters from Edwards Critical-Care Division, Irvine, CA
- IV catheters and introducers from Arrow International, Inc., Reading, PA
- instruments and reagents from Nova Biomedical (Waltham, MA)
- Monitors, probes and fiberoptic catheters from Camino Neurocare Group (Pleasant Prarie, WI)

Several DOD-funded investigators visited our lab in the last grant period to learn or to compare techniques. In addition, the U.S. Army trains Forward Surgical Teams (FST) at the Ryder Trauma Center. During a one month rotation, these individuals receive intensive training on the latest techniques. As part of the training, U.S. Army conducts mass casualty drills and skills tests in our lab each month with each new FST. These individuals are then deployed throughout the world.