Use of Near-Infrared Spectroscopy in Early Determination of Irreversible Hemorrhagic Shock

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SUMMARY

Progression to irreversible shock may not be clinically apparent until a patient has been given several liters of fluids as well as multiple units of blood and blood products. In combat situations or in situations in which fluids for resuscitation are limited, resources need to be appropriately allocated. Therefore, early differentiation between patients who will progress to irreversible shock and those who are resuscitatable is important. We investigated whether the use of near-infrared spectroscopy (NIRS) in hemorrhage and resuscitation could assist in early detection of irreversible hemorrhagic shock. An established porcine model of hemorrhagic shock was used for experimentation. Twenty animals were treated with the same protocol including sedation and mechanical ventilation followed by instrumentation with a pulmonary artery catheter, arterial catheter, inferior vena cava (IVC) cannula, and placement of NIRS probes on the liver surface (during laparotomy), stomach (via modified nasogastric tube), and hind limb surface (skeletal muscle monitoring). Hemorrhagic shock was induced by removal of 35% blood volume via the IVC cannula. Animals

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remained in shock for 90 minutes after which resuscitation was promptly initiated using lactated Ringer's solution (20 cc/kg) in a stepwise fashion of four fluid boluses. Hemodynamic and NIRS variables were measured at baseline, every 30 minutes during shock, and after each resuscitative step. NIRS measurements of tissue oxyhemoglobin saturation (StO_2) in the liver, stomach, and hind limb were compared at all time points between animals that expired during resuscitation (unresuscitatable) and animals that survived all resuscitative steps (resuscitatable). All animals were similar with regard to body weight, volume hemorrhaged, and baseline hemodynamic and NIRS variables. After the first resuscitative step, both stomach and leg StO_2 differed significantly between resuscitatable and unresuscitatable animals. Neither global oxygen measurements nor lactate distinguished resuscitatable from unresuscitatable animals. Linear regression analysis revealed that skeletal muscle (leg) StO_2 obtained after the first resuscitative step was a significant predictor of death despite resuscitation (r^2=0.45) (p=0.005). Combined, stomach and skeletal muscle StO_2 strongly predicted death despite resuscitation (r^2=0.74) (p=0.003). In conclusion, non-invasive monitoring of leg and stomach StO_2 with near-infrared spectroscopy differentiates resuscitatable from unresuscitatable animals after the initial resuscitative bolus. Use of this potentially pocket-sized, non-invasive spectrometer may help guide appropriate use of resuscitative fluids and has possible point-of-care applications.

1.0 INTRODUCTION

Death from hemorrhagic shock occurs in thousands of patients each year after civilian and military trauma. The initiating event in hemorrhagic shock includes decreased blood flow to tissues due to hypovolemia, resulting in a decrease in tissue oxygen delivery and subsequent cellular dysoxia. Optimal treatment for early hemorrhagic shock includes adequate control of bleeding followed by restoration of tissue oxygen delivery with appropriate resuscitation. Unfortunately, from a military perspective, this optimal strategy may not be available for many patients due to field situations that preclude prompt transport to the appropriate treatment facility [Holcomb 2003]. Thus, patients may reach definitive treatment in the advanced stages of shock, having passed a point beyond which restoration of oxygen delivery cannot overcome the "oxygen debt" despite appropriate resources and the best efforts of medical personnel.

Although decades have elapsed since the description of irreversible hemorrhagic shock by Wiggers [Wiggers 1950] in animal models of hemorrhagic shock, the events that occur at the cellular level are still not completely understood. Accordingly, the ability to determine which patients will progress to irreversibility is not accurate. With evaluation of laboratory measures such as base deficit and lactate, clinicians can gauge the magnitude of oxygen debt [Moomey 1999] [Abramson 1993] [Rutherford 1992] [Siegel 2003]. However, alone these laboratory measures alone do not accurately predict irreversibility and are not available to medics in the field. Therefore, determination of the magnitude of shock using a rapid, non-invasive method may be useful at the point of care in the field not only in military, but also in our urban trauma setting. Such a method would be useful to allow appropriate triage depending on availability of medical resources.

Near-infrared (NIR) spectroscopy is a technique that utilizes fiber-optic light to non-invasively determine the percentage of oxygen saturation of chromophores (e.g. hemoglobin) based on spectrophotometric principles. This technology has been utilized to experimentally determine regional tissue oxygen saturation (StO_2) [Mancini 1994] [Beilman 1999] [Beilman 2001] [Taylor 2004] [Cohn 2001] and the content / oxidation state of mitochondrial cytochrome aa_3 in tissue [Cairns 1997] [Balaban 1996] by monitoring the differential tissue optical absorbance of near-infrared light. Unlike "pulse-oximetry," NIR spectroscopy measures not only arterial, but also venous oxyhemoglobin saturation at the microcirculatory level. This measurement therefore is a reflection of both oxygen delivery (DO_2) and oxygen consumption (VO_2) of the tissue bed sampled [Rhee

1997] [Simonson 1994]. Non-invasive determination of these parameters using NIR spectroscopy has been described [Beilman 1999] [Beilman 2001] [Taylor 2004] [Cohn 2001] [Rhee 1997] [Simonson 1994].

In light of its non-invasive nature and potential for accurately determining regional tissue oxygen kinetics, we sought to evaluate the utilty of NIR spectroscopy for early determination of irreversibility in hemorrhagic shock. A porcine model of hemorrhagic shock was chosen for experimentation in order to appropriately control for hemorrhage volume and timing, amount, and type of resuscitation. We hypothesized that tissue oxyhemoglobin saturation (StO_2), as determined by NIR spectroscopy, may be able to distinguish reversible from irreversible shock early during resuscitation.

2.0 METHODS

2.1 Animal Protocol:
Twenty male Yorkshire-Landrace pigs (Fanning Farms, Howe, Indiana) weighing 13-20 kg underwent an identical hemorrhagic shock/resuscitation protocol after its approval by the University of Minnesota Animal Use Committee. Each animal was maintained without food and with free access to water for 12 hours prior to the experiment. Animals were initially sedated with a single dose of intramuscular ketamine (20 mg/kg) and 2 mL of intravenous althesin (Pitman-Moore Ltd., Middlesex, UK), a steroid anesthetic which has minimal hemodynamic effects as compared to other anesthetic agents [Davis 1984] [Faber 1989]. The animals were endotracheally intubated and then ventilated using a Siemens 900 ventilator with settings adjusted to maintain a pO_2 of 80-120 mmHg and a pCO_2 of 35-45 mmHg. Maintenance anesthesia was an intravenous infusion of althesin (10 mg/kg/hour) and 60% inhaled nitrous oxide. Following anesthesia induction, the animals were splenectomized to avoid autotransfusion. The following lines were placed: Swan-Ganz catheter in the pulmonary artery via the right jugular vein, 12 Fr venous bypass catheter in the inferior vena cava (IVC), cystostomy catheter in the bladder, and an arterial catheter in the right carotid artery.

2.2 Near-infrared spectroscopic methodology/measurements:
Near-infrared spectroscopy probes (Hutchinson Technology, Inc, Hutchinson, Minnesota) were placed directly on the liver at laparotomy, on the surface of the hind limb, and into the stomach via a modified nasogastric tube. These probes contain bundles of multiple silica core optical fibers that transmit optical energy via light emitting diodes (LEDs) to the tissue and detect reflected light from the tissue. The maximum depth of the tissue volume sampled is directly related to the distance between the illumination fibers and the detection fibers, and the mean depth is half the probe spacing [Cui 1991]. The InSpectra™ device used on the hind limb of our animals had a probe spacing of 25 mm. The nasogastric tube, which was modified to incorporate the optical fibers, and the liver probe each possessed a spacing of 3 mm. Reflected light from the tissues returns it to a photosensitive detector that quantifies light absorbance by the tissue (Figure 1). Based on spectrophotometric principles, light absorption is then correlated with the chemical concentration of chromaphores (e.g. hemoglobin) in the volume of tissue illuminated by the fiber optic, near-infrared light [Machter 1994]. Percent tissue hemoglobin oxygen saturation (StO_2) is calculated and displayed in real-time.

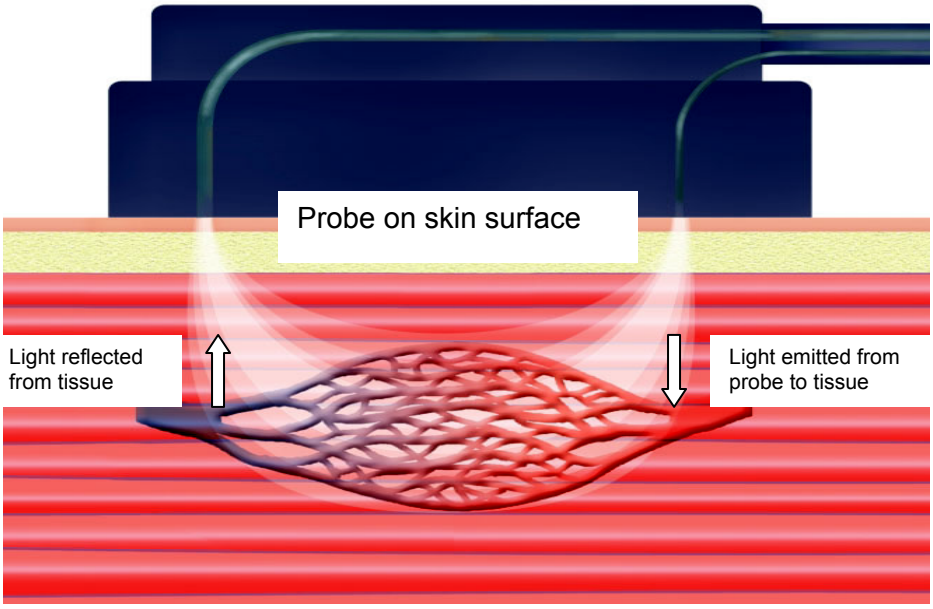


Figure 1: Cartoon of a near-infrared spectroscopy probe

2.3 Hemorrhagic shock protocol:

After baseline NIR and hemodynamic measurements were taken, hemorrhagic shock was induced by a 35% bleed (estimated by weight) into a heparinized blood collection bag via IVC cannula. The systolic blood pressure typically dropped to 40-50 mmHg with this maneuver. The animals remained in shock for 90 minutes at which time, following measurements, they received resuscitation with lactated Ringer's solution (20 cc/kg body weight) in four boluses (Figure 2). NIR and hemodynamic measurements were obtained every30 minutes during shock and then after each of the four boluses. Surviving animals were then sacrificed using a bolus of KCl (1-2mg/kg). Hemodynamic and NIR variables of animals that expired during the resuscitative process were compared to those that survived the entire resuscitative process.

2.4 Conventional Oxygen delivery and consumption measurement*:*
Pulmonary Artery (PA) catheter measurements of cardiac output (CO) were made via thermodilution and obtained at baseline and every 30 minutes during shock and after each resuscitative step in synchrony with NIR spectroscopic measurements. Arterial and mixed venous blood gases as well as lactate, hemoglobin (Instrument Laboratories, Lexington, MA) and other hemodynamic parameters (e.g. mean arterial pressure and heart rate) were obtained along with the PAC measurements. Oxygen delivery (DO_2) and oxygen consumption (VO_2) were calculated based on the conventional equations (below).

$$DO_2 = [(1.39 \times hgb \times SaO_2) + (0.003 \times PaO_2)] \times CO \times 10$$

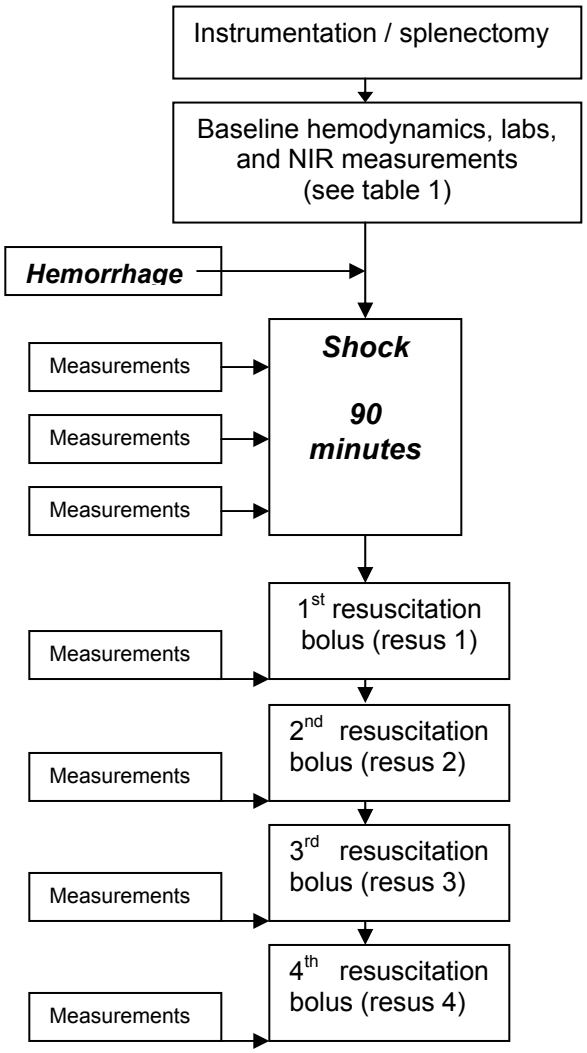
$$VO_2 = [(1.39 \times hgb \times (SaO_2 - SvO_2) + 0.003 \times (PaO_2 - PvO_2)] \times CO \times 10$$

Hemodynamic measures	Laboratory measures	NIR measures
BP, HR, temperature, PAP, PCWP, UOP, CO, DO_2, VO_2	ABG, VBG, lactate, hemoglobin	StO_2 of stomach, liver, skeletal muscle (hind limb)

Table 1 (above): Hemodynamic, laboratory, and NIR spectroscopy measures obtained at all time points. BP: blood pressure; HR: heart rate; PAP: pulmonary artery pressures; PCWP: pulmonary capillary wedge pressure; UOP: urine output; CO: cardiac output; DO_2: oxygen delivery; VO_2: oxygen consumption; ABG: arterial blood gas; VBG: venous blood gas; StO_2: tissue oxyhemoglobin saturation as measured by near-infrared spectroscopy. Significance determined by Mann-Whitney U test.

2.5 Statistical analysis of data:
Hemodynamic and NIRS variables were compared at all time points between the animals that expired during resuscitation from irreversible hemorrhagic shock and those that survived to complete the resuscitation protocol by using a one-way ANOVA and Mann-Whitney U test (SPSS for Macintosh, version 10.0). Variables recorded are shown in Table 1. Correlations between variables were performed using a Spearman correlation. Stepwise linear regression analysis was used to determine the relationship between variables and mortality using survival to the end of resuscitation (resus 4) as the dependent variable. A p value of ≤ 0.05 defined significance.

Figure 2: Hemorrhagic shock protocol timeline



3.0 RESULTS

Of the twenty animals that underwent the hemorrhagic shock / lactated Ringer's resuscitation protocol, eighteen animals survived the 90 minutes of hemorrhagic shock to reach resuscitation. Of these eighteen animals, six died from hemorrhagic shock despite receiving at least one fluid bolus. The hemodynamics and NIR spectroscopic measures of these six animals dying of "irreversible" hemorrhagic shock were compared to the other twelve animals that survived to complete all four resuscitative steps. In this study, we defined "irreversible" to indicate death after resuscitation began.

All eighteen animals were similar with respect to body weight and volume hemorrhaged as well as baseline measures of mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), DO_2, VO_2, and plasma lactate (Table 2a). Baseline StO_2 of hind limb, liver, and stomach were similar among all animals as well (Table 2b).

	Irreversible (*n=6*)	**Reversible** (*n=12*)	**P value**
Weight (kg) ± SD	16.7±1.1	16.2±2.0	0.78
Baseline HR (beats/minute) ± SD	158±27.8	178±40.6	0.22
Baseline MAP (mmHg) ± SD	86.7±10.8	84.8±13.5	0.74
Baseline CO (liters/minute) ± SD	2.63±0.8	2.68±0.7	0.93
Baseline DO_2 (mL O_2/minute)	22.2±5.8	22.7±6.7	0.84
Baseline VO_2 (mL O_2/minute)	4.2±2.1	5.7±2.4	0.30
Baseline lactate (mmol/liter)	1.7±0.7	2.9±2.6	0.48
Volume hemorrhaged (cc/kg) ± SD	507.3±101.0	468.6±108.3	0.51

Table 2a: Comparison of baseline weight, heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), oxygen delivery (DO2), oxygen consumption (VO2), lactate, and volume hemorrhaged for animals with irreversible and reversible shock. Significance determined by Mann-Whitney U test.

Baseline StO_2 values	**Irreversible** *(n=6)*	**Reversible** *(n=12)*	**p value**
Skeletal muscle (leg) StO_2 %saturation±SD	66.0%±10.6%	66.7%±16.5%	0.96
Liver StO_2 %saturation±SD	79.3%±9.1%	80.4%±11.5%	0.51
Stomach StO_2 %saturation±SD	65.0%±35.2%	79.4%±14.0%	0.99

Table 2b: Comparison of baseline NIR spectroscopic measurements of tissue oxyhemoglobin saturation in the leg, liver, and stomach for animals with irreversible versus reversible hemorrhagic shock. Significance determined by Mann-Whitney U test.

Expectedly, all animals experienced a decrease in CO (Figure 3a) and DO_2 and an increase in lactate (Figure 3b) during hemorrhagic shock. Animals also experienced a drop in StO_2 in skeletal muscle, liver, and stomach during shock (Figures 4a, 4b, 4c).

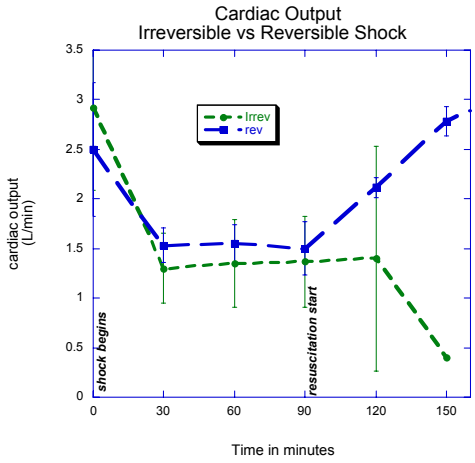


Figure 3a: Cardiac output (liters/minute) during hemorrhagic shock and resuscitation for animals with irreversible versus reversible hemorrhagic shock. No significant differences found at any time points as determined by Mann-Whitney U test and ANOVA.

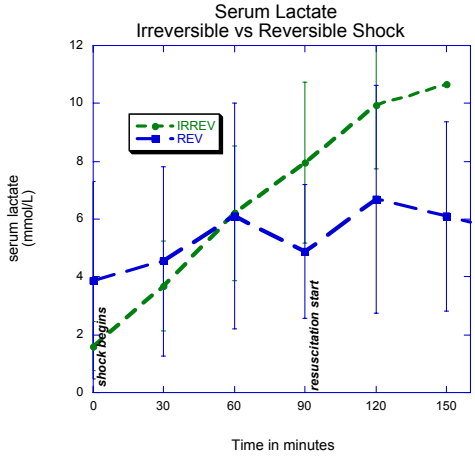


Figure 3b: Serum lactate levels (mmol/liter) during hemorrhagic shock and resuscitation for animals with irreversible versus reversible hemorrhagic shock. No significant differences found at any time points as determined by Mann-Whitney U test and ANOVA.

Time from the onset of shock to resuscitation was significantly shorter in the animals that did not survive resuscitation when compared to those surviving resuscitation (Table 3). Two animals that survived shock expired within four minutes of receiving the first resuscitative fluid bolus. Because these animals were pre-morbid at the time of resuscitation, they were excluded from analysis of NIR and hemodynamic

measurements to avoid falsely skewing the results. With exclusion of these two animals, the median time from the onset of resuscitation to death in animals dying of irreversible hemorrhagic shock was 34 minutes (range 11-59 minutes), with a mean of 34.5 ± 22 minutes. The average time for delivery of a fluid bolus was 2.6 ± 0.5 minutes. The average time between fluid boluses was 25.2 ± 6.7 minutes.

	Median time from shock to resuscitation (range)	Mean time from shock to resuscitation ± SD
Irreversible shock (*n=6*)	99.5 (92-115)	101.0±8.72*
Reversible shock (*n=12*)	112.5 (106-126)	114.3±8.21

Table 3: Times in minutes from onset of shock to onset of resuscitation. *p=0.02 when comparing means between animals with irreversible versus reversible hemorrhagic shock. SD: standard deviation.

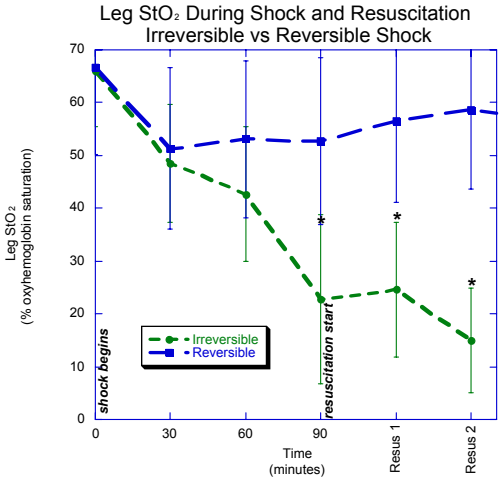


Figure 4a: Leg (skeletal muscle) StO_2 in animals with irreversible and reversible hemorrhagic shock. *p<0.05

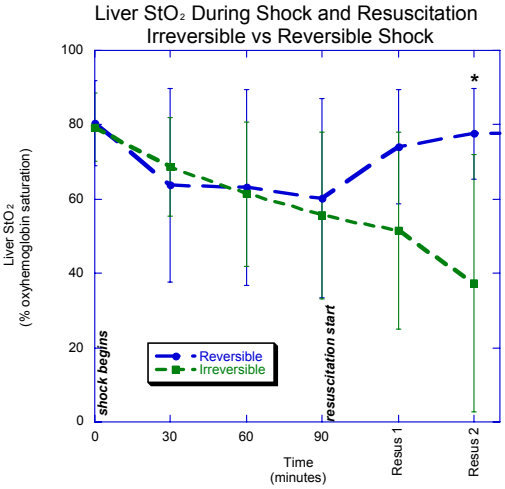


Figure 4b: Liver StO_2 in animals with irreversible and reversible hemorrhagic shock. *p=0.046

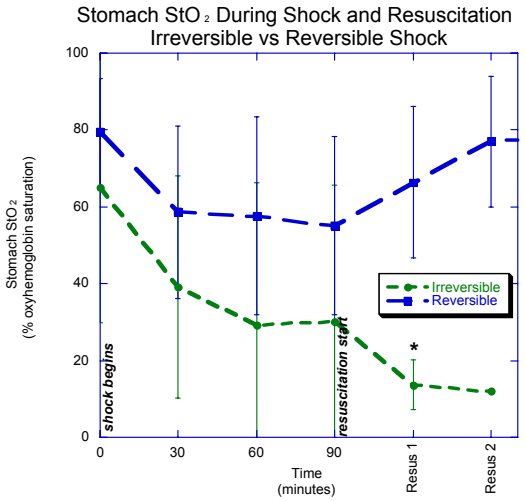


Figure 4c: Stomach StO_2 in animals with irreversible and reversible hemorrhagic shock. *p=0.034

By 90 minutes of shock, the drop in skeletal muscle StO_2 during shock was significantly greater in the four animals not surviving resuscitation when compared to those that survived to complete resuscitation (p=0.050) (Figure 4a). This disparity at 90 minutes of shock was not observed in the liver or stomach NIR measurements (Figures 4b and 4c). Skeletal muscle (leg) NIRS measurements after the first resuscitative bolus (resus 1) were significantly lower in animals dying of irreversible hemorrhagic shock than in those surviving to complete resuscitation (p=0.019). This difference persisted after the second resuscitative bolus (p=0.03). A significant difference was observed in stomach NIR measurements after resus 1 (p=0.031). However, an equipment malfunction with the modified nasogastric tube for one animal did not allow for enough stomach NIR readings to reach a statistically significant difference at the second resuscitative step. In the liver, the only NIR measurement that was significantly different between survivors and non-survivors was after the second resuscitative bolus (resus 2) (p=0.03).

There were no significant differences in cardiac output (Figure 3a), oxygen delivery, oxygen consumption, or lactate (Figure 3b) between survivors and non-survivors throughout shock or resuscitation. Pulmonary artery catheter measures of global DO_2 did not significantly correlate with regional NIRS measures of StO_2 during shock (Table 4).

Regional StO_2 (NIR)	Global DO_2 (measured with PA catheter)			
	baseline	shock 30	shock 60	shock90
Leg	-0.01(0.97)	0.097(0.71)	0.43(0.09)	0.238(0.41)
Liver	0.18(0.49)	-0.03(0.91)	0.27(0.30)	-0.08(0.78)
Stomach	0.44(0.14)	0.57(0.04)*	0.39(0.19)	-0.06(0.86)

Table 4: Correlations between global oxygen delivery (DO_2) and regional StO_2 as measured by NIR spectroscopy for all animals during shock. Results given as Spearman correlation coefficient (p value).

Stepwise linear regression analysis revealed that, by itself, the skeletal muscle (leg) NIR measurement obtained after the first resuscitative fluid bolus (resus 1) was a significant predictor of death despite resuscitation (r^2=0.45) (p=0.005). Combined, both the stomach and leg NIR measurements obtained after the first resuscitative step were particularly predictive of death despite resuscitation (r^2=0.74) (p=0.003).

4.0 DISCUSSION:

In this study, we demonstrated that non-invasive NIR spectroscopic monitoring of skeletal muscle (leg) StO_2 provides a means for early differentiation between resuscitatable and non-resuscitatable animals after a period of severe hemorrhagic shock. Despite identical shock protocols and similar baseline weights and hemodynamics, one third of animals undergoing shock were unresuscitatable. This indicates the severity of the model and underscores the basic pathophysiology of decompensated hemorrhagic shock, that a point exists beyond which resumption of oxygen delivery cannot overcome the preceding cellular energy deficit.

As expected, cardiac output and oxygen delivery decreased and lactate increased upon induction of shock in all animals. However, these global measures did not significantly differ between animals that went on to die during resuscitation and those that survived. Furthermore, these global measures were unable to predict which animals would or would not survive resuscitation. Lactate, DO_2, and base deficit have been shown to correlate with global oxygen debt [Moomey 1999] [Abramson 1993] [Rutherford 1992] and have been evaluated as potential predictors of outcome [Ivatury 1995] [Ivatury 1996] [Sauaia 1994] [Mikulaschek 1996]. Although each has its limitations, utilization of these values as markers of oxygen debt may be useful to clinicians in the hospital to determine the overall status of a patient and as measures to follow during resuscitation.

Even if such measurements are available to the clinician, a drawback of using such global values is that they provide only a general picture of the patient's oxygen debt, not the variations in oxygen debt seen at the regional tissue level. For example, the global DO_2 derived from a PA catheter may falsely indicate improvement in status despite deterioration of individual organs. Lactate traditionally "lags" due to its dependence on hepatic clearance, making it less of an accurate, dynamic marker of status. Also, it has been well-documented that epinephrine, produced abundantly during physiologic stress, stimulates lactate production by well-oxygenated skeletal muscle [Luchette 1999] [Luchette 2002]. Due to these limitations, an elevated lactate level may not translate to a DO_2 deficiency. In these experiments, lactate continued to increase upon initial resuscitation for both survivors and in non-survivors as its hepatic clearance capacity was exceeded. We also found that early in resuscitation, neither lactate, oxygen delivery, nor cardiac output could distinguish between resuscitatable and unresuscitatable animals. This dichotomy is depicted in Figures 3a, 3b and Figures 4a, 4c. Figures 3a and 3b show the non-significant differences in cardiac output and lactate for both survivors and non-survivors during shock and resuscitation. In figure 4a and 4c, however, a significant disparity in regional StO_2 was observed both late during shock and with the onset of resuscitation (resus 1) between those animals that went on to die of irreversible shock and those that survived resuscitation. These differences were not observed in the liver until late in resuscitation when death was imminent (resus 2), potentially reflecting the dual blood supply and unique metabolism of the liver.

We undertook this study to determine whether NIR-measured StO_2 could provide early differentiation between resuscitatable and unresuscitatable animals after a period of severe hemorrhagic shock. In evaluating our data, we did not wish to falsely skew our interpretation by including results from animals that were premorbid upon beginning resuscitation. Therefore, we assessed how much time elapsed between the onset of resuscitation and death in animals that received at least one fluid bolus. Two of the six animals were deemed "premorbid" as death occurred within two and four minutes of completing the first fluid bolus. We chose to eliminate the hemodynamic, laboratory and NIR measurements of these two animals in order to accurately evaluate variables in a setting of active, but futile, resuscitation. Even after elimination of these premorbid animals from analysis, a significant decrease in skeletal muscle StO_2 in unresuscitatable animals was present after 90 minutes of shock and during resuscitation. Early during resuscitation (resus 1), this value was significantly predictive of irreversible shock. Gastric StO_2 measurements early in resuscitation also

differentiated resuscitatable from non-resuscitatable animals, and, when combined, both stomach and skeletal muscle StO_2 were very significantly predictive of irreversible shock despite resuscitation.

Monitoring skeletal muscle StO_2 with NIR spectroscopy avoids the inherent limitations of following lactate and global DO_2 values. While lactate may be elevated even in well-oxygenated skeletal muscle, StO_2 may more accurately reflect oxygen delivery. Additionally, because the StO_2 value reflects a component of VO_2 ($StO_2 \sim k \bullet DO_2/VO_2$), it may represent the metabolic state of the tissue more appropriately than other oxygen indices. Finally, while global measurements of oxygen debt are inherently impractical for use in a point-of-care setting because they require equipment not routinely available to medics in the field, NIR spectroscopy has the potential to become an easily-portable and straightforward modality.

The field of NIR spectroscopy continues to branch and blossom as the technology and its interpretation improves. The probes used for skeletal muscle measurements in these experiments are applied easily, securely, and non-invasively with associated adhesive backing, similar to an EKG pad. The receiving device for these experiments was associated with a laptop computer. However, prototype hand-held devices are in development and may soon be available for future use. With these smaller devices, it is foreseeable that its use in traumatically-injured patients in the field would be appealing. Use of the skeletal muscle probe may be more feasible for use in the point-of-care setting than the modified nasogastric tube used to obtain gastric StO_2 measurements as this value may be corrupted by food particles and gastric juices in trauma patients. However, compared to other tissue beds, the potentially greater sensitivity of gastric perfusion to resuscitation adequacy [Ivatury 1995] [Ivatury 1996] warrants further research into this avenue.

Weaknesses of the study include the use of a controlled hemorrhage model. The animals used in these experiments were undergoing evaluation of the effects of resuscitation at the tissue level. Therefore we needed to be able to compare animals that were at a similar severity of shock. Additionally, our method of resuscitation using stepwise boluses differs from clinical practice during which fluid resuscitation is generally performed in a continuous fashion.

In conclusion, we have demonstrated that NIR spectroscopic measurement of skeletal muscle with or without measurement of stomach StO_2 may be useful in early determination of irreversible hemorrhagic shock. Although its limitations are incumbent, NIR spectroscopic devices have the potential to become an essential tool for the field medic in the point-of-care setting in order to appropriately allocate medical resources.

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