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Near-Infrared Spectroscopy for Determination of Cardiac Output Augmentation in a Swine Model of Ischemia-Reperfusion Injury

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CONTEXT: Near infrared spectroscopy (NIRS) is a noninvasive tool for assessing local oxygen balance. In circulatory shock, the microcirculatory environment as measured by NIRS during resuscitation may provide additional diagnostic tools of value to the critical care physician.

HYPOTHESIS: To assess whether a relative increase in peripheral NIRS was correlated with a clinically relevant increase in cardiac output following a fluid bolus in a swine model of shock.

METHODS AND MODELS: Nine healthy young adult swine with median weight 80 kg (interquartile range, 75–83 kg) were anesthetized and surgically instrumented. They underwent a controlled hemorrhage of 20% of their blood volume followed by partial or complete aortic occlusion to create a variable ischemia-reperfusion injury. Next, the animals underwent four 500-mL plasmalyte boluses over 9 minutes each followed by a 6-minute pause. The animal then underwent a 25% mixed auto/homologous blood transfusion followed by four more 500 mL plasmalyte boluses over 9 minutes. Finally, the animals underwent a 25% mixed auto/homologous blood transfusion followed by an additional four rounds of 500-mL plasmalyte boluses over 9 minutes. Left thoracic limb NIRS, descending thoracic aortic flow (dAF), arterial blood pressure (MAP), central venous pressure (CVP), and mixed central venous oxygen saturation (SvO_2) were measured continuously for comparison.

RESULTS: The area under the receiver operating curve for an increase in dAF of 10% in response to a 500 mL bolus based on a percent increase in the proximal NIRS was 0.82 with 95% CI, 0.72–0.91; SvO_2, 0.86 with 95% CI, 0.78–0.95; MAP, 0.75 with 95% CI, 0.65–0.85 and CVP, 0.64 with 95% CI, 0.53–0.76.

INTERPRETATION AND CONCLUSIONS: A dynamic relative increase in NIRS in response to a crystalloid challenge has moderate discriminatory power for cardiac output augmentation during shock in a swine model of ischemia-reperfusion injury. NIRS performed as well as invasive measurements (SvO_2 and MAP) and better than CVP.

Near-infrared spectroscopy (NIRS) is a noninvasive tool that uses 600–1,000 nanometer light waves to penetrate superficial tissues and the differential refraction of the oxygenated and deoxygenated hemoglobin to calculate a percentage of oxygenated blood (1). The premise of NIRS is intriguing as a tool to measure the microcirculation, as this is the level at which oxygen is used and is hypothesized to be dysfunctional during states of shock. Therefore, the quantification of the microcirculation as provided by NIRS might provide a tool for the critical care physician to guide resuscitation in shock.

Research surrounding NIRS has been substantial, gaining interest initially as a noninvasive technique for monitoring cerebral perfusion during cardiac

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surgery (2). The technology has been validated by numerous studies in cardiac surgery patients to predict outcomes and direct therapy (3). In addition, NIRS has been explored in the setting of intraoperative decision-making for selective shunting during carotid endarterectomy, but Kondov et al (4) concluded a lack of evidence to support or refute the use of NIRS for determination of shunting. NIRS has also been examined in states of traumatic shock for the measurement of shock severity with reported relevant discriminatory power for prognostication of mortality (5, 6). Additionally, NIRS was used as a resuscitation end point for management of hemorrhagic shock in a translational model of closed-loop resuscitation with intriguing results (7). Finally, NIRS for sepsis diagnosis have mixed results, possibly due to the disconnect between macrovascular oxygen delivery and microvascular oxygen consumption (8). But an interesting study by Thooft et al (9) demonstrated that at various supratherapeutic blood pressure targets in patients with septic shock that dynamic NIRS was able to identify patients with persistent microcirculatory dysfunction.

Historically, NIRS has failed to become clinically relevant outside of cardiac surgery because the intersubject absolute values variability has made interpretation difficult (10). Many studies have focused on the use of NIRS for prognostication and less so on the use to create a simple bedside tool for incorporation into a treatment model (8).

Determination of fluid responsiveness as defined by augmentation of cardiac output is a cornerstone of the resuscitation of shock. NIRS has been explored for determination of fluid responsiveness and has been examined in conjunction with a vascular occlusion test in cardiac surgery patients and infants to predict an increase in blood pressure (11, 12). These examples demonstrate a bedside use of NIRS to aid with clinical decision-making in a common clinical scenario. However, a blood pressure change in healthy infants, while interesting, is not the gold standard of fluid responsiveness, and vascular occlusion tests are not a simple procedure that can be performed by a nurse at the bedside.

We hypothesize that relative changes (percent change from baseline) in the oxygen saturation of peripheral tissue (change in tissue oxygen balance) assessed using NIRS will correlate with cardiac output augmentation in response to a crystalloid challenge during a controlled resuscitation in a swine model of controlled hemorrhage with ischemia-reperfusion injury leading to shock.

MATERIALS AND METHODS

Overview

The Institutional Animal Care and Use Committee at Wake Forest Baptist Medical Center approved this study (Fluid Responsiveness, institutional animal care and use committee A20-017, March 26, 2020). All animal care and use were in strict compliance with the Guide for the Care and Use of Laboratory Animals in a facility accredited by Association for Assessment and Accreditation of Laboratory Animal Care. The Animal Research: Reporting of In Vivo Experiments guidelines were used to prepare this article (13).

A priori exclusion criteria were a white blood cell count greater than 25×10^9 cells/L or cardiovascular collapse before the end of study as defined by a proximal mean arterial blood pressure (pMAP) less than 20 mm Hg for 5 minutes. Animals were also excluded if norepinephrine rate was greater than 0.06 μg/kg/min prior to the initiation of experiment or deviation from experimental protocol.

Blood Donor Animal

Healthy adult, Yorkshire-cross swine (Oak Hill Genetics, Ewing, IL) were fasted for 12 hours, and then premedicated with 5–7-mg/kg intramuscular tiletamine/zolazepam. General anesthesia was induced and maintained with 2% isoflurane, and animals were mechanically ventilated to maintain end-tidal CO_2 at 35–45 mm Hg. To offset the vasodilatory effects of isoflurane, an IV infusion of norepinephrine (0.02 μg/kg/min) was initiated to achieve a target mean arterial pressure greater than 60 mm Hg after which it was not titrated further. An IV infusion of Plasma-Lyte A at 10 mL/kg/hr was started during preparation. An underbody warmer was used to maintain core body temperature between 37°C and 39°C.

Experimental Animal Preparation

The bilateral external jugular veins were surgically exposed and cannulated with a 9-Fr sheath on the right for right heart catheterization and 9-Fr sheath on the left for continuous medication infusions. The right brachial artery was surgically exposed for placement of

a 5-Fr micropuncture sheath for frequent arterial sampling. The left axillary artery was surgically exposed for placement of a 7-Fr sheath for proximal arterial blood pressure measurement. The right femoral artery was surgically exposed and cannulated with a 7-Fr sheath for distal arterial blood pressure measurement. The left femoral artery and vein were surgically exposed for placement of a 9-Fr sheath for supraceliac aortic balloon placement and a 9-Fr dual lumen resuscitation line for hemorrhage, transfusion, and crystalloid boluses.

Then, the animal underwent a laparotomy with splenectomy to minimize autotransfusion. The left diaphragm was divided with circumferential exposure of the supraceliac aorta for placement of an ultrasonic flow probe (Transonic, Ithaca, NY) and the intraaortic balloon confirmed to be just distal to the aortic flow probe by palpation. At this point, the animal was administered heparin, 50-U/kg bolus followed by infusion at 10 U/kg/hr during the use of the intra-aortic balloon to prevent catheter-associated thrombotic complications. Finally, the abdomen was closed over a plastic sheet to decrease insensible losses, and maintenance IV fluid rates were decreased to 5 mL/kg/hr.

Hemodynamic Monitors

NIRS probes (Foresight Elite Tissue Oximetry, Edwards Lifesciences, Irvine, CA) were placed on the skin overlying distal left thoracic limb muscle compartment prior to start of experimentation and confirmed to be reading a signal prior to initiation of experimentation. NIRS data were recorded at a frequency of 0.5 Hz (CAS Medical System, Branford, CT).

An 8-Fr 110-cm Swan-Ganz CCOmbo catheter (Edwards Lifesciences, Irvine, CA) was advanced via the right 9-Fr external jugular sheath and was confirmed to be positioned appropriately based on distal pressure interpretation. Continuous cardiac output (CCO), continuous mixed central venous oxygen saturation (Svo_2), and signal quality index (SQI) were recorded at a frequency of 0.5 Hz (Vigilance II, Edwards Lifesciences, Irvine, CA). An SQI of 1 or 2 was required for inclusion into analysis.

Physiologic Data Collection

Physiologic measurements of pMAP, distal blood pressure, descending thoracic aortic flow (dAF), central venous pressure (CVP), and electrocardiography (ECG) were collected in real time with a multichannel data acquisition system at 1,000 Hz (Powerlab, AD Instruments, Colorado Springs, CO).

Experimental Protocol

Experimental animals first underwent 20% estimated total blood volume controlled hemorrhage over 30 minutes. Shed blood was stored in Citrate-Phosphate-Dextrose storage bags at 38°C in a water bath. Over the next 10 minutes, the animals were allowed to remain at hypovolemia without intervention to allow for equilibration at a state of compensated hemorrhagic shock. At T40, the balloon-tipped catheter in the supraceliac aorta was inflated for 20 minutes to support proximal blood pressure and create a variable ischemia-reperfusion injury (randomized to partial aortic occlusion at 400 mL/min and complete aortic occlusion). At the end of aortic occlusion, the aortic balloon was deflated continuously over 5 minutes and then removed.

At this point (defined as state I), an IV infusion sequence was begun as follows: 100 mL of Plasma-Lyte infused over 1 minute, repeated every 2 minutes for a total of 500 mL over 9 minutes, followed by a 6-minute lockout period. This bolus sequence was repeated four times for a total of 2 L of infused crystalloid. At the end of this sequence, the animal underwent mixed auto/homologous whole blood transfusion of 25% of estimated blood volume over 30 minutes (25% was used to offset the citrate volume in the bags) to bring the animals to State II. The crystalloid infusion sequence was then repeated. Finally, the animal was again transfused 25% of the estimated total blood volume of mixed auto/homologous whole blood over 30 minutes to state III. The animal then underwent the crystalloid bolus sequence a third time. Once complete, the animals were euthanized (**Fig. 1**). This sequence of controlled resuscitation was designed to explore the hemodynamic response to crystalloid infusions throughout a range of intravascular volume (hypovolemia to hypervolemia).

For each 500-mL plasmalyte bolus, a dAF average of the 10 seconds prior to a bolus and 10 seconds after a bolus was used to calculate a percent change (delta %). This was used to create a binary label of boluses that were considered a response to a fluid challenge (≥10% increase in dAF) and boluses that were considered nonresponsive (<10% increase in dAF). The definition of fluid responsiveness has been reported in the

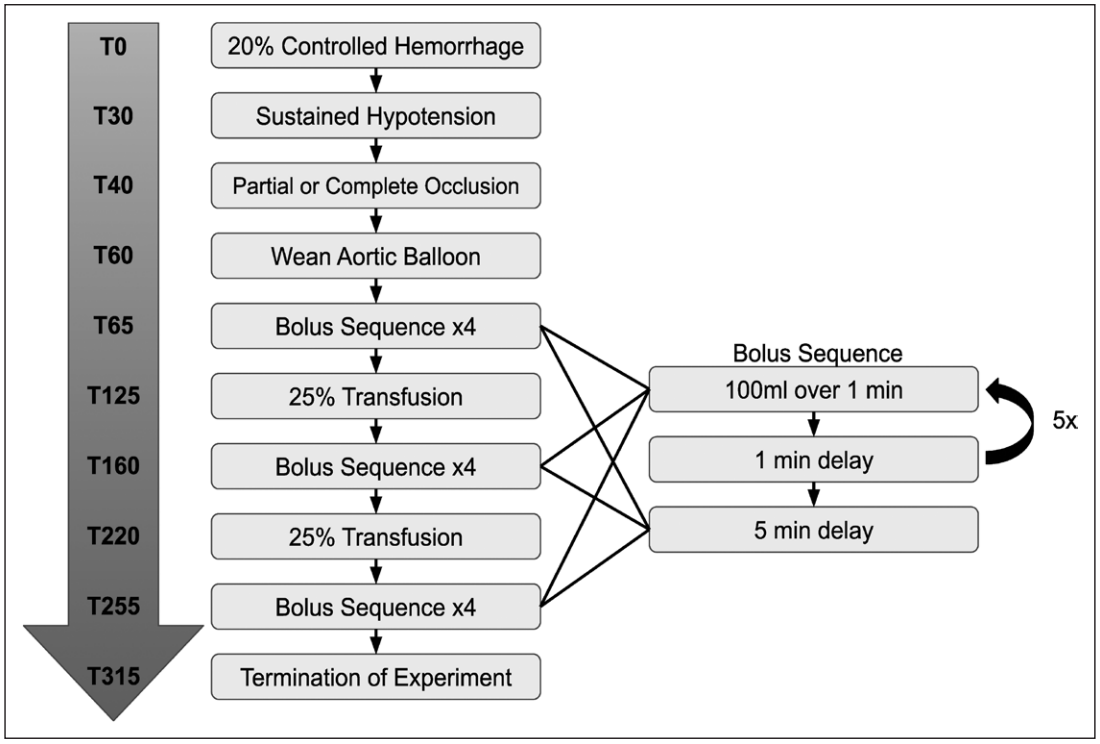

Figure 1. Experimental flow, all times are in minutes. All crystalloid infusions are plasmalyte. Transfusion is mixed autologous and donor whole blood.

literature from 10% to 15%; examination of our data demonstrated a more even distribution between fluid-responsive boluses and nonfluid-responsive boluses when using a cutoff value of 10% (compared with 15%) in dAF (14).

The primary outcome was to determine if a relative increase in NIRS, in response to a fluid challenge, is associated with a 10% increase in cardiac output as measured by dAF compared with traditional markers of cardiac output augmentation (pMAP, CVP, Svo_2, and CCO).

Data Analysis

This analysis was performed with R statistical software (R Foundation for Statistical Computing, Vienna, Austria). The experimentation and data analysis were not blinded. Continuous data were presented as medians with interquartile range (IQR), and continuous variables were compared with Kruskal-Wallis analysis of variance with Dunn test for pairwise comparison. A repeated measures variance component model was used to estimate a common intraclass correlation between NIRS and hemodynamic variables (15). Receiver operating curves (ROC) are presented as an area under the curve (AUC) with 95% CI calculated using the DeLong statistical method. The best performance thresholds were defined as the minimum Euclidean distance from 100% sensitivity and 100% specificity and ties broken with random selection. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are presented as a percent with a 95% CI using a bootstrap statistical method (2,000 replicates). The area under the ROCs was compared using the DeLong method for full ROCs or Bootstrap method (2,000 replicates) for partial ROCs. The statistical package used for these calculations of ROC was pROC (16).

RESULTS

Overall

Fourteen animals were available for the analysis. Two animals had poorly positioned Swan-Ganz catheters based on missing continuous cardiac output and poor SQI (3, 4) for the duration of the experiment and, thus, were excluded from analysis. Three animals were excluded due to hemodynamic collapse before the end of study (**Supplemental 1**, http://links.lww.com/CCX/B45).

The median peak lactate was 8.55 mmol/L (IQR, 5.87–9.83 mmol/L), and median final lactate was 4.11 mmol/L (IQR, 3.67–8.82 mmol/L). The median baseline hemoglobin was 10.5 g/dL (IQR, 9.9–11.2 g/dL). The median minimum hemoglobin was 7.8 g/dL (IQR, 7.5–8.2 g/dL), and the median maximum hemoglobin was 12.2 g/dL (IQR, 11.9–13.3 g/dL) (**Supplemental 2**, http://links.lww.com/CCX/B45).

The median heart rate in beats per minute as measured by ECG at the start of state I was 178 beats/min (IQR, 163–181 beats/min), at the start of state II was 122 beats/min (IQR, 116–130 beats/min), and at the start of state III was 113 beats/min (IQR, 110–117 beats/min). The median pMAP at the start of state I was 56.8 mm Hg (IQR, 49.2–70.6 mm Hg), at the start of state II was 63.1 mm Hg (IQR, 57.8–67.8 mm Hg), and at the start of state III was 82.6 mm Hg (IQR, 73.8–87.8 mm Hg) (**Supplemental 3**, http://links.lww.com/CCX/B45).

Boluses

There were 108 boluses in nine animals potentially available for analysis based on the experimental design. Due to technical issues with bolus timing and administration during state III, 10 of 108 boluses (9.2%) were excluded from the analysis. However, because these errors occurred during the final phase, prior boluses in the same animals were included for analysis. Therefore, there were 98 boluses with adequate NIRS signals, pMAP, and CVP for analysis. When examining the Svo_2, 84 of 98 boluses (77.8%) were adequate for analysis, based on exclusion of poor SQI in boluses otherwise included for analysis. CCO data had 33 boluses adequate for inclusion and were not analyzed (**Supplemental 4**, http://links.lww.com/CCX/B45).

The median increase in proximal NIRS for a bolus during state I is 3.2%, state II is 3.0%, and state III is 1.1% (I vs II: $p = 0.12$, I vs III: $p = 0.02$, II vs III: $p = 0.11$). The median increase in dAF for a bolus during state I is 20.6%, state II is 7.2%, and state III is 1.2% (I vs II: $p \leq 0.01$, I vs III: $p \leq 0.01$, II vs III: $p = 0.01$). The median increase in Svo_2 for a bolus during state I is 6.1%, state II is 1.2%, and state III is 0.0% (I vs II: $p \leq 0.01$, I vs III: $p \leq 0.01$, II vs III: $p = 0.01$). The median increase in pMAP for a bolus during state I is 10.1%, state II is 4.9%, and state III is 0.9% (I vs II: $p = 0.01$, I vs III: $p \leq 0.01$, II vs III: $p = 0.01$). The change in CVP had no statistical differences between volume states in response to a bolus ($p = 0.49$) (**Table 1**).

TABLE 1.

For Each 500-mL Crystalloid Bolus Over 9 Minutes the Average of 10 Seconds Before the Bolus and 10 Seconds After Each Bolus Is Used to Calculate a Percentage Change for Each Hemodynamic Variable

Change From Start of Bolus to End of Bolus	State I	State II	State III	*P* Value I: State I II: State II III: State III
Proximal near infrared spectroscopy	3.2% (0.4–9.8%)	3.0% (0.0–5.1%)	1.1% (0.1–2.1%)	I vs II: 0.124 I vs III: 0.017 II vs III: 0.107
Distal aortic flow	20.6% (14.8–31.4%)	7.2% (2.3–13.3%)	1.2% (–3.2 to 5.2%)	I vs II: <0.001 I vs III: <0.001 II vs III: 0.012
Mixed central venous oxygen saturation	6.1% (2.8–10.9%)	1.2% (0.2–2.5%)	0.0% (–1.2 to 0.2%)	I vs II: <0.001 I vs III: <0.001 II vs III: 0.010
Proximal mean arterial blood pressure	10.1% (4.9–15.4%)	4.9% (0.8–8.9%)	0.9% (–3.0 to 3.0%)	I vs II: 0.014 I vs III: <0.001 II vs III: 0.013
Central venous pressure	15.0% (9.1–22.6%)	16.0% (12.3–21.1%)	14.4% (10.5–18.5%)	0.490

Data are represented as medians with interquartile range in parentheses.

Correlation With Cardiac Augmentation

An ROC using a percent change in hemodynamic parameter as a threshold for an associated 10% increase in dAF demonstrated an area under the curve for proximal NIRS: 0.82 with 95% CI, 0.72–0.91; SvO2, 0.86 with 95% CI of 0.78–0.95; pMAP, 0.75 with 95% CI of 0.65–0.85 and CVP, 0.64 with 95% CI of 0.53–0.76 (**Fig. 2**). There was a statistical difference between NIRS versus CVP AUC ($p = 0.03$, Bootstrap method) and SvO2 versus CVP AUC ($p \leq 0.01$, Bootstrap method). There was no statistical difference in NIRS AUC versus SvO2 or pMAP AUC ($p = 0.47$ and $p = 0.28$, respectively, both using DeLong method). There was also no statistical difference between SvO2 versus pMAP AUC ($p = 0.10$, DeLong method) or pMAP versus CVP AUC ($p = 0.18$, Bootstrap method).

Examination of the performance of the thresholds for each hemodynamic parameter at the minimum Euclidean distance from maximal sensitivity/specificity for each ROC demonstrated that a proximal NIRS increase of 2.7% yielded a sensitivity of 75.0% (95% CI, 61.4–86.4%) and specificity 83.3% (95% CI, 66.7–94.4%) with a PPV of 78.1% (95% CI, 65.3–92.1%) and an NPV of 80.0% (95% CI, 72.2–88.5%). An increase in Svo_2 of 1.7% yielded a sensitivity of 88.9% (95% CI, 77.8–97.2%) and a specificity of 83.3% (95% CI, 72.9–91.7%) with a PPV of 79.5% (95% CI, 69.6–89.5%) and an NPV of 90.2% (95% CI, 82.0–97.6%). An increase in pMAP of 5.7% yielded a sensitivity of 75% (95% CI, 61.4–86.4%) and a specificity of 74.1% (95% CI, 59.3–85.2%) with a PPV of 70.2% (95% CI, 60.4–81.0%) and an NPV of 78.2% (95% CI, 69.8–87.5%). A CVP increase of 14.4% yielded a sensitivity of 63.6% (95% CI, 47.7–81.8%) and specificity of 68.5% (95% CI, 50.0–83.3%) with a PPV of 62.5% (95% CI, 52.3–75.7%) and an NPV of 70.0% (95% CI, 62.2–80.5%).

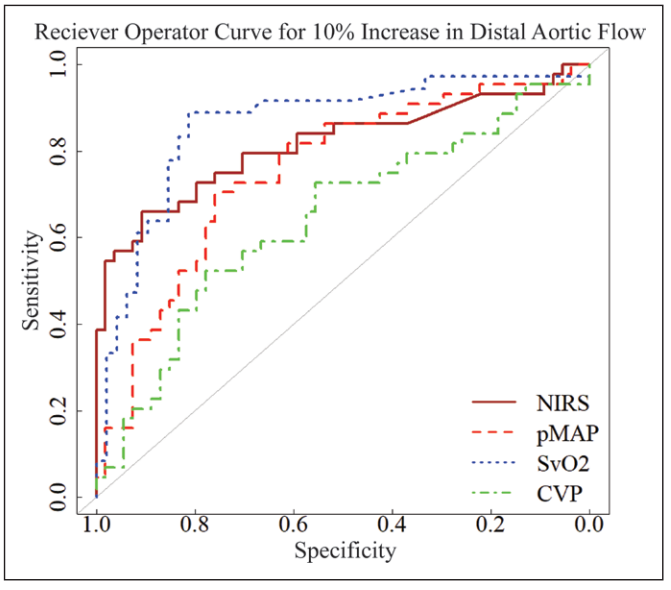

Figure 2. A comparison of receiver operating curve for determination of a 10% increase in distal aortic flow in response to a 500 mL bolus over 9 min. CVP = central venous pressure, NIRS = near-infrared spectroscopy, pMAP = proximal mean arterial pressure, Svo_2 = mixed central venous oxygen saturation.

Correlation of NIRS and Hemodynamic Parameters

The proximal NIRS values were also assessed against hemodynamic parameters to understand if a relationship existed between these values (**Fig. 3**). When compared with dAF, NIRS yielded a repeated measures correlation coefficient of 0.65; 95% CI, 0.65–0.66. When compared with Svo_2, NIRS yielded a repeated measures correlation coefficient of 0.74; 95% CI, 0.73–0.74. When compared with pMAP, NIRS yielded a repeated measures correlation coefficient of 0.66; 95% CI, 0.65–0.67. When compared with CVP, NIRS

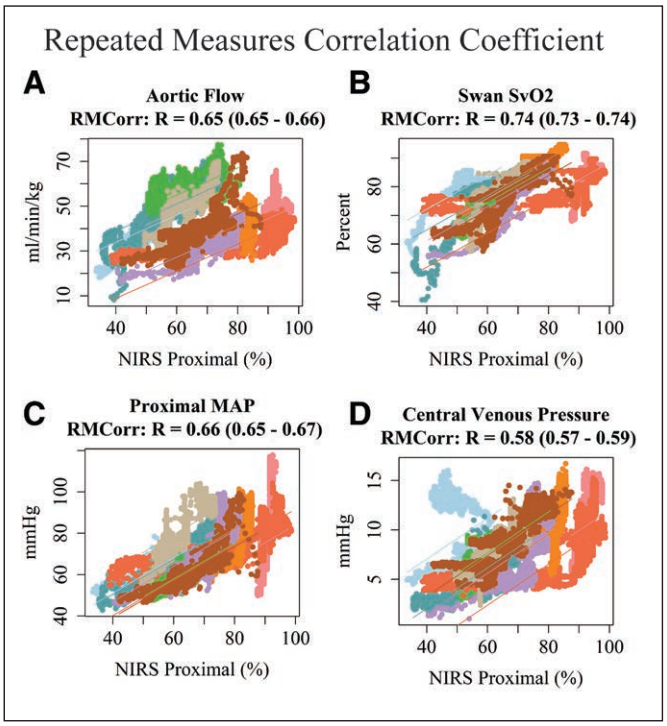

Figure 3. Repeated measures correlation coefficients for proximal near-infrared spectroscopy (NIRS) versus hemodynamic data. Repeated measures correlation coefficient with coefficient and 95% CI in parentheses. MAP = mean arterial pressure, RMCorr = repeated measures correlation coefficient, Svo_2 = mixed central venous oxygen saturation.

yielded a repeated measures correlation coefficient of 0.58; 95% CI, 0.57–0.59.

DISCUSSION

The primary finding in this study is that an increase in upper extremity peripheral tissue NIRS appears to be associated with an increase in cardiac output in response to a fluid challenge in a swine model of ischemia-reperfusion injury with shock. The use of NIRS for correlation with cardiac output augmentation is comparable to using an increase in invasive pMAP or increase in continuous Svo_2 obtained by right heart catheterization. NIRS and Svo_2 performed better than CVP for determination of cardiac output augmentation in response to crystalloid bolus.

Plasma volume expansion is a key component of critical care during resuscitation of shock. However, in recent years, it has become apparent that excess fluid resuscitation is associated with worse outcomes (17, 18), and several groups have proposed a more goal-directed (19–21) if not overly restrictive (22, 23) resuscitation strategy to improve outcomes. In order to achieve this, it is essential to determine fluid-responsiveness status. Our results show that NIRS may have value as a noninvasive guide for assessing responsiveness to fluid resuscitation. This is especially relevant in settings (austere/military and prolonged transport) where central access and/or other more invasive modalities for assessing cardiac output in the setting of shock may not have been established or may present increased risk. For example, monitoring continuous Svo_2 requires obtaining central venous access, right heart catheterization with an oximetric pulmonary artery catheter, and calibrated specialized monitors. Peripheral arterial catheterization can be time-consuming and challenging or unreliable in vasoconstricted shock states. In contrast, NIRS requires only an adhesive probe on the skin, which makes it an attractive option for monitoring resuscitation in remote, austere, or mobile environments when a patient might not have access to invasive hemodynamic monitoring capabilities. In addition, the relative change of NIRS is an easily calculable measurement that a bedside nurse could perform and does not require the intricate procedure of performing a vascular occlusion test or historical/normal baseline values for a given patient.

Prior reports have validated NIRS to reflect peripheral perfusion during acute compartment syndrome (24), extracorporeal membrane oxygenation (25, 26), free flap reconstruction (27), and regional anesthesia (28). Although research into use of NIRS has examined end points of resuscitation and prognostication tools, which is important for the translation from bench to bedside, there has been less work in the area of fluid responsiveness. Butler et al (11) studied peripheral NIRS as an indicator of fluid responsiveness in patients after heart surgery. When used in conjunction with a vascular occlusion test, they found that forearm NIRS correctly discriminated fluid responsiveness in 82% of cases, and continuous tissue oxygen saturation showed a small but statistically significant change after volume expansion. Hilly et al (12) studied cerebral NIRS in infants anesthetized for noncardiac surgery and found that a change in NIRS from baseline in anesthetized healthy infants was able to predict a 15% increase in mean arterial blood pressure response to a fluid bolus. Fellahi et al (29) studied the response of NIRS and Svo_2 to a fluid bolus in adults after cardiac surgery and found a small but statistically significant increase in peripheral NIRS after fluid bolus. Interestingly, in that study, NIRS did not correlate with Svo_2 (29). Our study is in agreement with Fellahi et al (29) with a change in NIRS correlating with cardiac output augmentation (they used a 15% increase in cardiac output as measured by thermodilution to dichromate fluid boluses). Of note, their patients were not in shock with a mean lactate ~1 mmol/L.

There are several limitations to this study. First, this is a proof-of-concept animal study under highly controlled experimental and resuscitation conditions that may not translate directly to care in humans. It was not designed to discern clinical outcomes in the experimental animals, only the hemodynamic response. Second, this animal model has been designed to produce a specific physiologic insult and result in shock, but may be physiologically different from other shock states. The use of NIRS in this manner would still need validation in other shock states. Third, this was not a goal-directed therapy study, and therefore, these parameters developed based on hemodynamics need to be tested in a prospective manner to guide resuscitation to understand if they can have an effect on outcomes for resuscitation of patients in shock. Fourth, the plan was to correlate these data with the data from

the continuous cardiac thermistor. However, during the experiment, room temperature crystalloid boluses were being infused so frequently that the highly sensitive temperature sensor was disrupted and had large gaps in the data. This was disappointing and, therefore, analysis relied upon the dAF probe for cardiac output assessments.

CONCLUSIONS

NIRS may provide a noninvasive tool for assessing cardiac output augmentation in response to the administration of IV fluids during resuscitation of shock after ischemia-reperfusion injury in swine. NIRS performed as well as mean arterial blood pressure and Svo_2 and better than CVP. Further study is required to understand the applicability of this technique for treatment of shock in humans.

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