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Noninvasive dual-channel broadband diffuse optical spectroscopy of massive hemorrhage and resuscitative endovascular balloon occlusion of the aorta (REBOA) in swine

Jesse H. Lam¹, Thomas D. O'Sullivan, PhD², Tim S. Park, MD³, Jae H. Choi, PhD³, Robert V. Warren, MS.¹, Wen-Pin Chen, MS.⁴, Christine E. McLaren, PhD⁴, Leopoldo C. Cancio, MD³, Andriy I. Batchinsky, MD³, and Bruce J. Tromberg, PhD¹

¹Laser Microbeam and Medical Program, Beckman Laser Institute and Medical Clinic, University of California, Irvine, 1002 Health Sciences Road, Irvine, CA 92617

²Department of Electrical Engineering, University of Notre Dame, 275 Fitzpatrick Hall Notre Dame, IN 46556

³US Army Institute of Surgical Research, 3698 Chambers Pass STE BJBSA FT Sam Houston, TX 78234

⁴Biostatistics Shared Resource, Chao Family Comprehensive Cancer Center, School of Medicine, University of California, Irvine, 101 The City Drive Bldg. 23 Route 81 Orange, CA 92868

Abstract

Objective—To quantitatively measure tissue composition and hemodynamics during resuscitative endovascular balloon occlusion of the aorta (REBOA) in two tissue compartments using non-invasive two-channel broadband diffuse optical spectroscopy (DOS).

Methods—Tissue concentrations of oxy- and deoxyhemoglobin (HbO₂ and HbR), water, and lipid were measured in a porcine model (n=10) of massive hemorrhage (65% total blood volume over 1-hour) and 30-minute REBOA superior and inferior to the aortic balloon.

Results—After hemorrhage, hemoglobin oxygen saturation (StO₂ = HbO₂ / (HbO₂ + HbR)) at both sites decreased significantly (–29.9% and –42.3%, respectively). The DOS measurements correlated with mean arterial pressure (MAP) (R²=0.79, R²=0.88), stroke volume (SV) (R²=0.68, R²=0.88), and heart rate (HR) (R²=0.72, R²=0.88). During REBOA, inferior StO₂ continued to decline while superior StO₂ peaked 12 minutes after REBOA before decreasing again. Inferior DOS parameters did not associate with MAP, SV, or HR during REBOA

Conclusions—Dual-channel regional tissue DOS measurements can be used to non-invasively track the formation of hemodynamically-distinct tissue compartments during hemorrhage and

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The Conflict of Interest Office of the University of California, Irvine, has reviewed both patent and corporate disclosures and did not find any concerns. No potential conflicts of interest were disclosed by the other authors.

REBOA. Conventional systemic measures MAP, HR, and SV are uncorrelated with tissue status in inferior (downstream) sites. Multi-compartment DOS may provide a more complete picture of the efficacy of REBOA and similar resuscitation procedures.

Keywords

hemodynamics; oxygenation; hemorrhage; DOS; REBOA

Introduction/Background

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is an emergency resuscitation medical procedure applied in the treatment of severe, non-compressible hemorrhage.^{1,2} While initially explored in the 1950's during the Korean War, the procedure has recently regained international interest in both the military and civilian sectors.³⁻⁷ The REBOA is a minimally invasive alternative to thoracotomy with aortic clamping, an invasive surgical procedure requiring direct access to the aorta.^{2,8} The primary rationale behind REBOA is to induce aortic occlusion using an endovascular balloon in order to stop or slow the rate of uncontrollable hemorrhage.² In general, a REBOA device is guided up the femoral artery of a patient and then inflated in the aorta. The induced occlusion restores potentially life-saving perfusion to the heart and brain, slows the rate of hemorrhage, and ultimately provides medical practitioners more time to stabilize the patient.⁹

While REBOA is an emerging non-transfusion-based resuscitation technique, assessment of the "two-compartment" REBOA hemodynamics and its effect on tissue oxygenation ($StO_2 = HbO_2 / [HbO_2 + HbR]$) and metabolism has yet to be quantified. More specifically, the inflation of an aortic balloon essentially separates the body into two blood volume compartments: 1) upstream from the aortic occlusion, in which blood pressure is restored to critical organs necessary to prolong life; and 2) downstream from the aortic occlusion. Clinical measures obtained invasively, such as mean arterial pressure (MAP) and stroke volume (SV) do not provide complete information about StO_2 and metabolism in these two compartments, and they may be inconvenient to use in emergency settings. In contrast, noninvasive broadband diffuse optical spectroscopy (DOS) quickly and easily extracts hemodynamic information based on subsurface tissue chromophore concentrations at multiple sensor locations. Thus, multichannel DOS provides a non-invasive, continuous and quantitative solution to understand hemodynamics and monitor the effectiveness of REBOA.

The DOS technology employed in this study utilizes a combination of four intensity-modulated lasers and continuous wave (CW) broadband light to quantitatively measure tissue near-infrared absorption and reduced scattering spectra spanning from 650–1000nm.^{10,11} Tissue concentrations of oxyhemoglobin (HbO_2), deoxyhemoglobin (HbR), water (H_2O) and lipid (FAT) are derived¹⁰ from broadband absorption spectra. Unlike conventional near-infrared spectroscopy (NIRS), broadband DOS directly measures tissue optical scattering, as well as water and lipid concentrations to provide accurate quantification of tissue chromophores. Previous preclinical studies have shown that broadband DOS is sensitive to hemoglobin and StO_2 levels during hemorrhagic shock and transfusion-based resuscitations.^{12,13}

In this study, we apply a two-channel broadband DOS instrument to assess tissue hemodynamics in a swine model of severe hemorrhage and REBOA resuscitation. Typical systemic parameters, namely, MAP, SV, and HR are contrasted with regional DOS parameters.

Methods

This analysis involved a subset (N=17) of male Sinclair miniature swine (Sinclair Bio Resources, MO, USA), weighing 37 ± 7 kg, that were involved in a larger (N=35) study of massive hemorrhage and resuscitation.³ Seven subjects were excluded due to low signal-to-noise ratio (SNR) (N=3), absent data at critical time points such as baseline (N=2), and unusually low baseline HbO₂ values below 1 μ M (N=2), resulting in 10 analyzable subjects. Low SNR and total hemoglobin values were likely due to variations in probe placement on Sinclair swine, which have thick a vascular subcutaneous tissue. The study was approved by the U.S. Army Institute of Surgical Research Animal Care and Use Committee (protocol number A-14-002). It was conducted in compliance with the Animal Welfare Act and the implementing Animal Welfare Regulations, and in accordance with the principles of the *Guide for the Care and Use of Laboratory Animals*. It was performed at a facility accredited by AAALAC International.

Surgical procedures are described in greater detail in Park et al.³ Briefly, the swine were anesthetized, and then monitored using an anesthesia machine (Dräger Fabius GS, Dräger Medical Inc., PA, USA). The animal was then placed in a custom sling, allowing it to rest in an anatomic quadruped position. Controlled hemorrhage was achieved using a programmable peristaltic pump (Masterflex, Cole-Parmer, IL, USA). Blood was recovered from the animal into blood collection bags. The blood-collection bags rested on a digital scale in order to provide a metric on the amount of fluid removed. The hemorrhage consisted of 65% total-blood-volume (TBV) hemorrhage over 60 minutes, where TBV was estimated as 65 ml/kg. The hemorrhage rate was approximately exponential, with the target values listed in Table 1.

After the hemorrhage period, the peristaltic pump was stopped. Immediately following, the REBOA device was introduced via the common femoral artery and placed between the subclavian and the celiac arteries (aortic zone 1).⁹ The endovascular device utilized was an investigational catheter (ER-REBOA, Pryor Medical, Inc., TX, USA) designed specifically for REBOA applications. After device placement, the balloon was inflated for 30 minutes using 8 ml of saline solution. Successful occlusion was confirmed by arterial blood pressure dropping to near 0 downstream from the occlusion. Balloon placement was also verified after the experiment by computed tomography and necropsy. A high-pressure monitoring line (Smith Medical ASD INC., OH, USA) was used with an Infinity HemoMed Pod (Dräger Medical Inc., Schleswig-Holstein, Germany) for arterial-blood-pressure measurements. An EKG device (Osyka Medical Inc., CA, USA) was used to record heart rate. Sensor data was averaged over 6 minutes.

Optical measurements were collected with a broadband, dual-channel DOS research device (Beckman Laser Institute, University of California, Irvine, CA, USA). A custom plasticfiber-

coupled probe with a source-detector separation distance of 20 mm was secured to the neck (DOS channel 1) and ham (DOS channel 2) of the subjects using sutures, as shown in Figure 1. Measurements were taken approximately every 15 seconds, and 6-minute block averages are presented in this report.

The technology behind the DOS instrument has been extensively detailed in previous studies.^{10,11,14} Briefly, the device contains a frequency-domain photon migration (FDPM) component consisting of four discrete wavelength sources (660, 690, 785, and 830 nm laser diodes, 20mW average optical power) and an avalanche photodiode module (C5658 module with S6045-03 photodetector, Hamamatsu, Japan). The broadband steady-state component consists of a tungsten-halogen broadband source (Ocean Optics HL-2000, FL, USA) and spectrometer (AvaSpec-ULS2048X64-USB2, Apeldoorn, Netherlands). Fiber bundles deliver and collect the light to/from the tissue. After calibration by use of a reference optical phantom, the FDPM amplitude and phase are fit using the P_1 diffusion approximation to the radiative transport equation in order to recover the absorption (μ_a) and reduced scattering (μ_s') coefficients for each laser diode wavelength.^{15,16} The broadband state-state reflectance spectrum is calibrated with a reflectance standard (Labsphere Inc., NH, USA). The μ_s' is recovered across the near-infrared wavelength range by fitting μ_s' values from the FDPM component of the DOS device to a power law, $\mu_s'(\lambda) = A\lambda^{-B}$, in which A is the scatter amplitude, λ is the wavelength, and B is the scattering slope.^{10,17,18}

Total data-acquisition time including both the frequency-domain and steady-state component is typically under 5 seconds. Chromophore concentrations are calculated by performing a least-squares minimization including HbO₂, HbR, H₂O, and FAT to the broadband near-infrared absorption spectrum. In addition, a spectrally flat baseline offset was included in the fit, which has been shown to improve the chromophore fits for broadband DOS devices.¹⁹ Additional indices are derived from these parameters, including total hemoglobin (THC = HbO₂+ HbR) and StO₂.

Because of the correlation in the percentage change from baseline across measurement times, generalized estimating equations (GEE) analyses were performed for DOS parameters, with a normal link function and an exchangeable working matrix. From GEE models, the estimated mean and standard error of the percentage change from baseline was obtained and used to construct scatter plots.

Linear regression analysis was performed in which the data for the 10 subjects were averaged for each time point. The mean and standard error for baseline DOS parameters were calculated for each channel. The coefficient of determination (R^2) and p-value was estimated using the MATLAB “corr” function as a measure of the linear relationship between DOS and systemic parameters.

Results

Baseline DOS parameters for each channel before hemorrhage are shown in Table 2. Recovered “A” and “B” parameters from the scattering power law in equation (1) are also provided. We note the relatively low StO₂ at these tissue sites in the Sinclair model, likely

due to the relatively low perfusion and total hemoglobin content in their thick fatty subcutaneous tissue ($\text{HbO}_2 = 7$ and $8 \mu\text{M}$, $\text{FAT}\% = 33$ and 45 ; neck and ham, respectively).

Time-varying DOS parameters and standard cardiac measures (MAP, HR, and SV) from the GEE model during hemorrhage and REBOA are shown in Figure 2. Because of subject-to-subject variation in baseline DOS values, the data are presented as percent change from baseline values. The total experiment duration was 90 minutes, described by three major events: baseline at 0 minutes, hemorrhage until 60-minute mark, and REBOA between the 60- and 90- minute marks. For all subjects, channel 1 measured upstream from the occlusion (neck), while channel 2 measured downstream (ham).

Hemodynamic trends are shown in Figure 2a. The mean difference between the two DOS channels was calculated using a GEE model. Red asterisks are used to denote when the difference between channels was statistically significant (i.e., the 95% confidence interval of the mean differences did not cross the zero value). In both measurement sites HbO_2 and StO_2 , which are reflective of tissue microvascular perfusion and metabolism, respectively, decreased during hemorrhage while HbR increased. This is consistent with increased oxygen extraction accompanying diminished perfusion during hemorrhage. The HbR increased rapidly in the ham region, and then leveled off to match the change in the neck region by the end of the hemorrhage period. During REBOA HbO_2 increased in the neck, while it continued to decrease in the ham. The HbR increased significantly in the ham during REBOA from minutes 72 until 84. By the end of the REBOA, HbO_2 , HbR , and StO_2 in both channels converged and no longer remained significantly different.

In Figure 2b, bulk tissue H_2O , FAT , and THC trends are displayed. For the majority of the experiment, H_2O , FAT and THC remained within a few percent from baseline. No significant difference was observed between channels for most time points. However, broadband DOS characterization of H_2O and FAT composition played an important role in the ability of DOS to accurately assess hemodynamics due to the relatively high fat and low hemoglobin levels in the skin of the Sinclair swine model.

Typical cardiac parameters are shown Figure 2c. During hemorrhage, MAP and SV deteriorated while HR increased. During REBOA, MAP and SV exhibited a sudden increase after inflation of the aortic balloon. However, as the aortic balloon remained inflated, MAP and SV began to decrease below baseline values, but stayed above end-hemorrhage levels. Heart rate responded in similar, but opposite trends, showing a decline soon after REBOA inflation, but increased as REBOA was maintained.

Linear regression analysis was performed comparing HbO_2 to MAP and SV as shown in Figure 3a and 3b for the neck and ham region, respectively. Data for the 10 subjects was averaged at each time point for each channel. Coefficients of determination (R^2) and p-values characterizing the linear relationship between DOS and cardiac parameters were calculated. During the hemorrhage, HbO_2 was strongly associated with MAP in neck ($R^2=0.76$, $P=0.001$) as well as ham regions ($R^2=0.89$, $P<0.001$). During REBOA, neck HbO_2 remained correlated with MAP ($R^2=0.83$, $P=0.03$), while ham HbO_2 was no longer associated ($R^2=0.06$, $P=0.70$). Similar associations observed between HbO_2 and SV. The

HbO₂ and SV were correlated in both measurement sites during hemorrhage (neck R²=0.65, P=0.01;ham R²=0.90, P<0.001), but only in neck during REBOA (neck: R²=0.92, P=0.01;ham:R²=0.03, P=0.77).

Table 3 further details the coefficients of determination relating DOS and cardiac parameters. During hemorrhage, all DOS parameters are associated (P<0.05) with cardiac parameters in both channels. During REBOA, HbO₂ and StO₂ remained associated with all systemic parameters in channel 1. For channel 2, no associations with cardiac parameters were observed.

Discussion

There has been much interest in assessing the potential of REBOA to replace thoracotomy with aortic clamping as a minimally invasive approach to treat non-compressible hemorrhage.¹⁻⁷ In previous work we were able to assess the efficacy of transfusion-based resuscitation using a single channel DOS that monitored systemic hemoglobin levels with a non-invasive probe.^{12,20} However, REBOA necessitates occlusion of the aorta, and thus, the subsequent creation of two distinct blood volume compartments: an upstream compartment, and a downstream compartment. Accordingly, in this study we employ a dual-channel DOS instrument in order to follow regional tissue hemodynamics from two different blood volume compartments in a model of massive hemorrhage and REBOA.

Baseline concentrations of HbO₂, HbR, StO₂, THC, and H₂O were similar at each measurement site, while FAT levels were slightly elevated in the ham region. However, because of the thick sub-cutaneous fat layer of the swine model, we observed relatively high overall FAT% and low THC at baseline. This is consistent with a previous study²¹ which reported a similar adipose composition measured in humans as well as our own observations (data not shown) of resected skin showing up to 2 cm-thick adipose in the ham region. Under these conditions, the ability of broad band DOS utilizing hundreds of optical wavelengths to quantitatively measure all major tissue components can improve sensitivity to hemodynamics during hemorrhage and REBOA.

During the hemorrhage period, the resulting HbO₂, HbR and StO₂ trends were as expected for a blood loss model: HbO₂, and StO₂ decreased over time, while HbR remained elevated from baseline. This is indicative of hemorrhage-induced reductions in microvascular perfusion accompanied by an increase in tissue oxygen extraction. No significant difference was observed between neck and ham in the rate of HbO₂ and StO₂ decrease during hemorrhage. The values for HbR in the neck were significantly different from the ham for a period of 18 minutes as seen in Figure 2a. However, by the end of the hemorrhage period, HbR trends in both channels were no longer statistically different. This temporary divergence in HbR may have been the result of initially different metabolic rates of the two underlying tissue sites. Overall, DOS and conventionally-measured systemic parameters (MAP, HR, and SV) were significantly correlated in both channels between during the hemorrhage period, as shown in Table 3. These results indicate that both DOS channels were capable of tracking hemorrhage with similar performance to invasively obtained systemic parameters.

During REBOA, significant differences between DOS channels were observed for HbO₂ and StO₂ between 66 to 84 minutes as seen in Figure 2a; differences were also observed between 72 to 84 minutes for HbR. This observation is explained by the fact that the neck channel interrogated an area in which blood pressure was restored as a result of REBOA inflation, while the ham channel probed a region in which no intervention was provided. In other words, two blood volume compartments with unique hemodynamics were formed as a direct consequence of the aortic occlusion. Two measurement sites, and thus, two-channel systems are recommended for investigating REBOA models.

During severe hemorrhage, loss of blood volume leads to a reduction of systemic blood pressure. Under these conditions, HR increases in an attempt to compensate for reduced SV to meet tissue metabolic demands. Throughout the hemorrhage period, DOS parameters in both channels were significantly correlated with systemic parameters as presented in Table 3. However, upon REBOA inflation, the DOS channel measuring downstream (ham) from the occlusion loses all association with systemic parameters. This clear discrepancy between systemic and tissue-level assessments suggests that conventional metrics such as MAP, HR and SV cannot be used to characterize the impact of REBOA on downstream tissue viability. In contrast, as shown in Figure 2a, despite isolation from blood flow, DOS recovers hemodynamics as well as tissue status in this region. Thus, during hemorrhage, two-channel DOS tracks conventional systemic parameters and during REBOA, DOS can provide additional information this is not available systemically. One potential application of these findings is studying standard REBOA procedures, such as the length and degree of occlusion. Maximizing survival rates while minimizing harmful physiological consequences of ischemia is desirable, but remains challenging.^{4,22}

Several limitations can be identified in this study. While DOS is capable of recovering tissue hemoglobin and oxygenation status, the highly scattering nature of light propagation in skin and the 2 cm source-detector separation of our DOS probe limits the mean interrogation depth to ~6–9 mm for typical 2cm thick tissues.²³ While this is sufficient for recovering subsurface microvascular hemodynamics, deeper organ status cannot be evaluated non-invasively. We also utilized Sinclair swine subjects with variably-thick, low-blood-volume, fatty, skin. In addition, fiber coupling inefficiencies with light sources as well as detector components resulted in lower-than-expected DOS signal-to-noise ratios (SNR). Finally, the effect of anesthesia on hemodynamic responses is difficult to quantify.

The results of this study demonstrate the feasibility of a non-invasive, two-channel DOS device to assess hemodynamics in different tissue regions during hemorrhage and REBOA-induced resuscitation. Highly correlated relationships between DOS and systemic parameters were seen during hemorrhage and maintained during REBOA upstream of the aortic occlusion. Downstream of the occlusion, systemic MAP, HR, and SV are uncorrelated with tissue status while DOS maintains sensitivity to regional changes in tissue perfusion and metabolism. We conclude that dual-channel DOS measurements of regional tissue perfusion and metabolism can be used successfully to non-invasively track the formation of hemodynamically-distinct tissue compartments during hemorrhage and REBOA resuscitation. Because conventional systemic measures (MAP, HR, SV) correlate with DOS upstream of REBOA but do not provide information on downstream tissue status, multi-

compartment non-invasive DOS monitoring may provide a more complete picture of the efficacy of REBOA and similar resuscitation procedures.

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None

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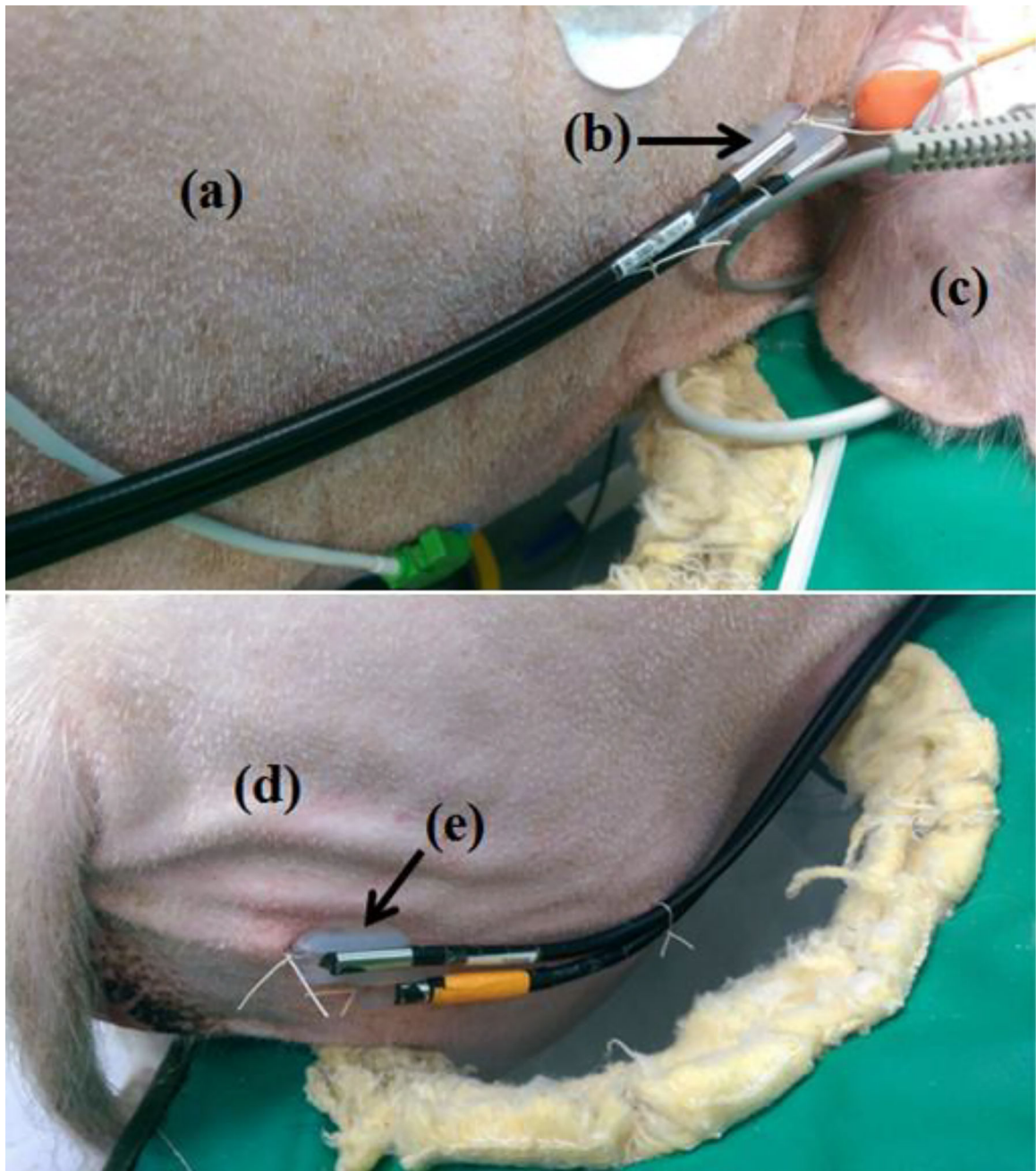


Figure 1.
Location of the measurement sites shown (a) neck (b) DOS channel 1 probe (c) ear (d) ham
(e) DOS channel 2 probe.

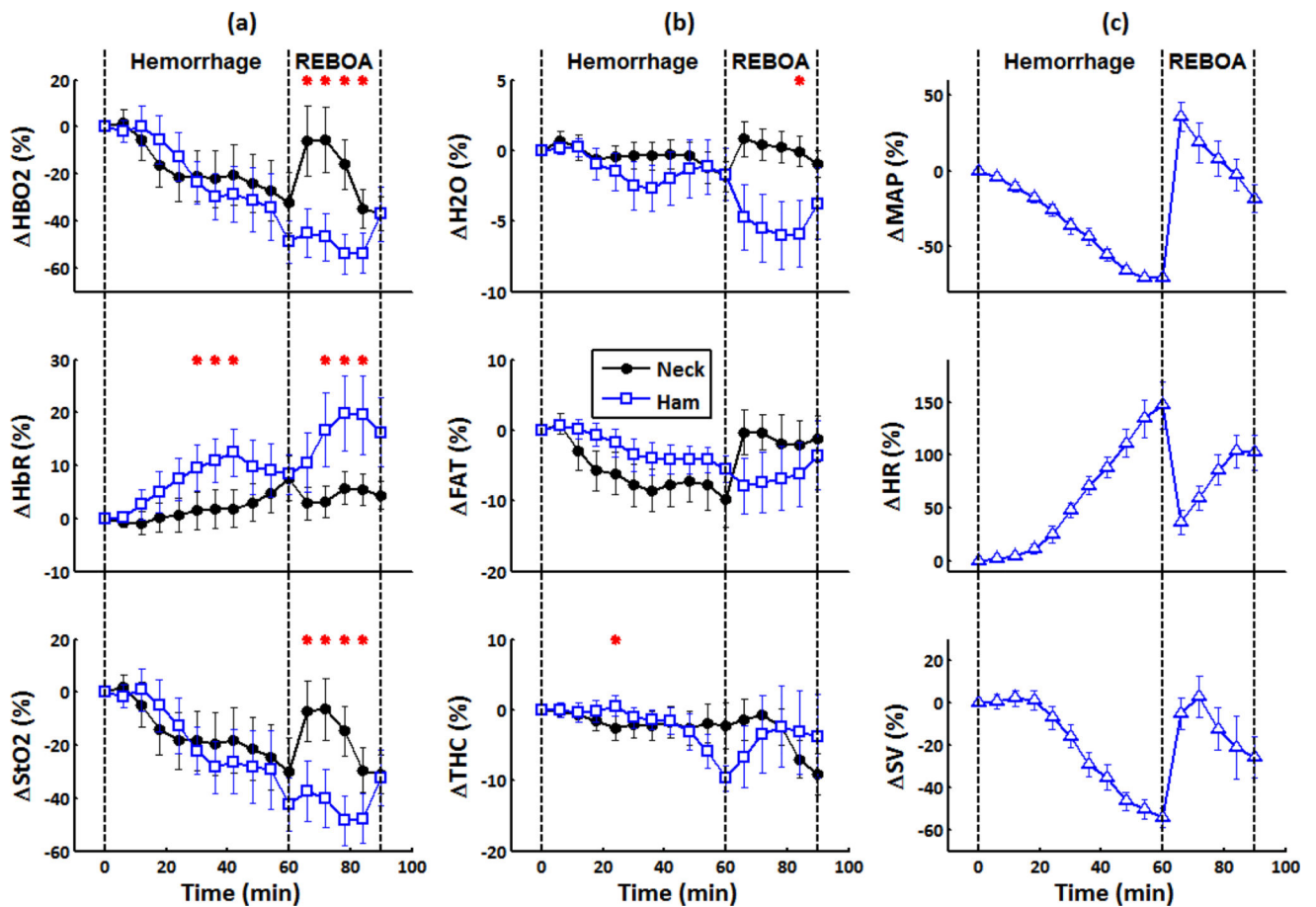


Figure 2.

Diffuse optical spectroscopy (DOS) and cardiac parameters from a generalized estimating equations model over time. Hemorrhage occurred from 0–60 minutes followed by REBOA at 60–90 mins. For all animals, channel 1 measured upstream from the aortic occlusion site (neck), while channel 2 measured downstream (ham). Each time point is an average of 6 minutes of data and is presented as the percent change from its baseline value. Significant difference between channels is denoted by a red asterisk (*). (a) Hemodynamic trends HbO_2 , HbR , and StO_2 from the dual-channel DOS device (b) H_2O , FAT and THC tissue parameters from the dual-channel DOS device (c) MAP , HR , and SV systemic parameters from various clinical instruments. (Note: HbO_2 = Oxyhemoglobin; HbR = Deoxyhemoglobin; StO_2 = Hemoglobin oxygenation saturation; THC = Total hemoglobin; H_2O = Water; FAT = Lipid; MAP = Mean arterial pressure; HR = Heart rate; SV = Stroke volume)

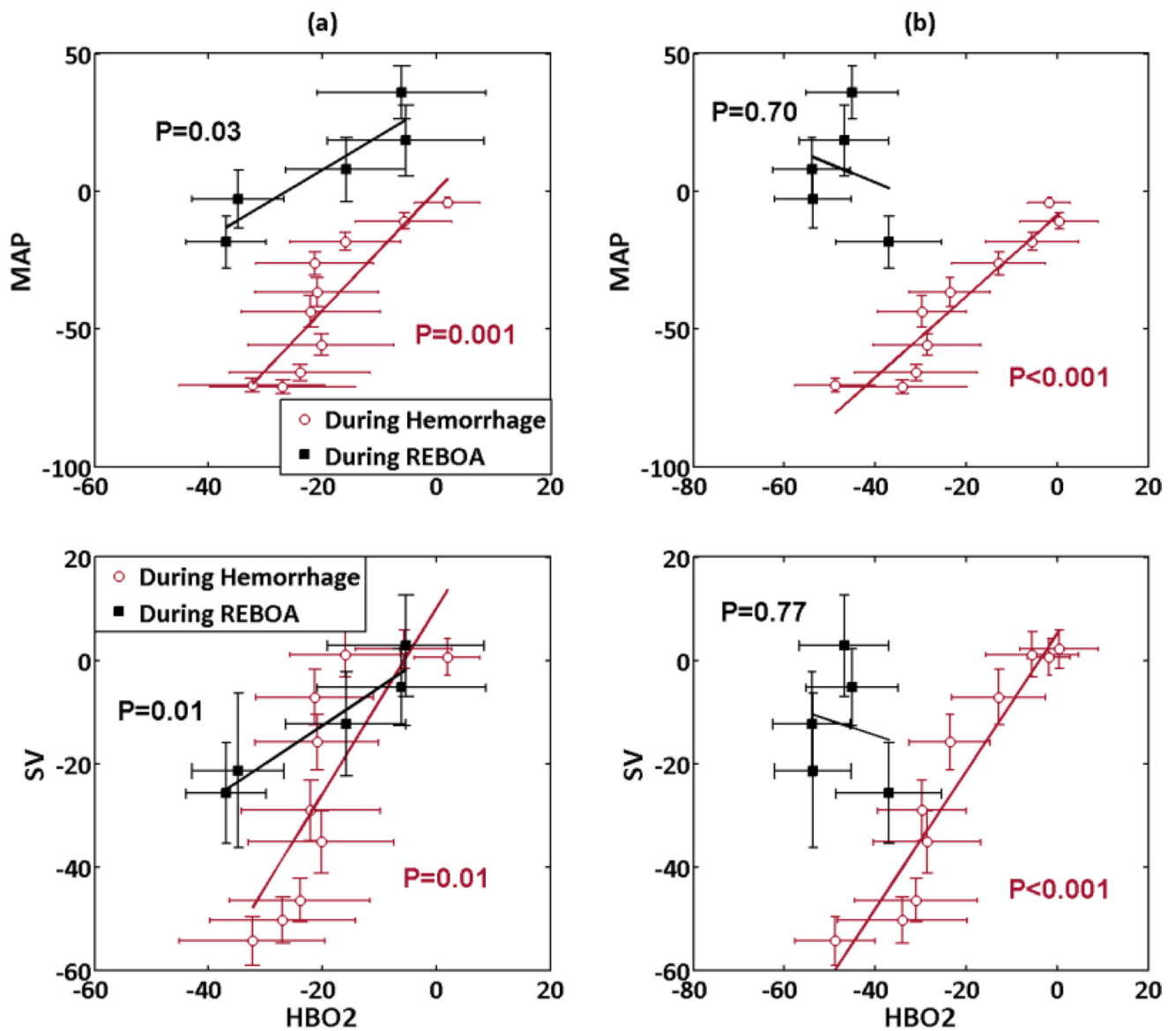


Figure 3.

Linear regression analysis of HbO₂ with systemic parameters SV and MAP. (a) Neck HbO₂ is significantly associated with MAP and SV during the hemorrhage and maintains significance during REBOA (b) Ham HbO₂ is highly correlated with MAP and SV during hemorrhage, but loses significant association during REBOA. (Note: HbO₂ = Oxyhemoglobin; MAP = Mean arterial pressure; SV = Stroke volume)

Table 1

Targeted blood loss volumes for the controlled hemorrhage period. Blood was drawn from each animal using a peristaltic pump. By 60 minutes, approximately 65% of total blood volume was removed from each subject.

Time (min)	TBV Hemorrhaged (%)
7.5	13
19	26
31	39
44	52
60	65

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Table 2

Tabulated absolute quantities from neck (channel 1) and ham (channel 2) of the diffuse optical spectroscopy instrument at baseline are shown. Recovered “A” and “B” parameters from the scattering power law in equation (1) are also provided. The baseline for each subject was defined as a 6 minute average prior to the start of hemorrhage.

Parameter	Neck	Ham
HbO₂ (μM)	6.7±1.8	7.8±2.4
HbR (μM)	10.1±0.9	11.2±0.8
StO₂ (%)	36.3±5.8	35.7±7.0
THC (μM)	16.6±1.6	18.7±2.3
H₂O (%)	50.0±1.2	51.3±3.7
FAT (%)	32.7±2.7	45.2±2.8
Scattering Parameter A	2.1±0.1	2.1±0.3
Scattering Parameter B	-1.6±0.1	-1.6±0.2

Errors are reported as standard error.

(Note: HbO₂ = Oxyhemoglobin; HbR = Deoxyhemoglobin; StO₂ = Hemoglobin oxygenation saturation; THC = Total hemoglobin; H₂O = Water; FAT = Lipid)

Diffuse optical spectroscopy (DOS) Channel 1 (top) and Channel 2 (bottom) coefficients of determination for all 10 subjects. During REBOA, DOS parameters in Channel 1 associate with systemic parameters while Channel 2 is not.

Table 3

Channel 1 Coefficients of Determination (R ²)						
	Hemorrhage			REBOA		
	MAP	HR	SV	MAP	HR	SV
HbO₂	0.76*	0.69*	0.65*	0.83*	0.82*	0.92*
HbR	0.79*	0.88*	0.82*	0.40	0.69	0.43
StO₂	0.79*	0.72*	0.68*	0.82*	0.82*	0.92*

Channel 2 Coefficients of Determination (R ²)						
	Hemorrhage			REBOA		
	MAP	HR	SV	MAP	HR	SV
HbO₂	0.89*	0.91*	0.90*	0.06	0.01	0.03
HbR	0.61*	0.46*	0.49*	0.38	0.62	0.14
StO₂	0.88*	0.88*	0.88*	0.01	0.06	0.00

The asterisk (*) is used to denote if the relationship is statistically significant ($P < 0.05$). Cases with high coefficients of determination ($R^2 > 0.90$) are displayed as bolded text. (Note: HbO₂ = Oxyhemoglobin; HbR = Deoxyhemoglobin; StO₂ = Hemoglobin oxygenation saturation; MAP = Mean arterial pressure; HR = Heart rate; SV = Stroke volume).