Retinal venous oxygen saturation and cardiac output during controlled hemorrhage and resuscitation

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Denninghoff, Kurt R., Matthew H. Smith, Art Lompa, and Lloyd W. Hillman. Retinal venous oxygen saturation and cardiac output during controlled hemorrhage and resuscitation. J Appl Physiol 94: 891–896, 2003; 10.1152/japplphysiol.01197.2001.—The objective was to test calibration of an eye oximeter (EOX) in a vitiligo swine eye and correlate retinal venous oxygen saturation (SrvO₂), mixed venous oxygen saturation (SvO₂), and cardiac output (CO) during changes in blood volume. Ten anesthetized adult Sinclair swine with retinal vitiligo were placed on steplwise decreasing amounts of oxygen. At each oxygen level, femoral artery oxygen saturation (SraO₂) and retinal artery oxygen saturation (SraO₂) were obtained. After equilibration on 100% O₂, subjects were bled at 1.4 ml·kg⁻¹·min⁻¹ for 20 min. Subsequently, anticoagulated shed blood was reinfused at the same rate. During graded hypoxia, SraO₂ correlated with SrvO₂ (r = 0.92). SrvO₂ correlated with SvO₂ (r = 0.89) during exsanguination and reinfusion. SvO₂ and SrvO₂ correlated with CO during blood removal and resuscitation (r = 0.92). Use of vitiligo retinas improved the calibration of EOX measurements. In this robust hemorrhage model, SrvO₂ correlates with CO and SvO₂ across the range of exsanguination and resuscitation.

Several key parameters are indicators of blood loss; these include central venous oxygen saturation, cardiac output, serum lactate, and gastric pH (2, 32, 40, 53). Perhaps the most important of these in the situation of acute blood loss is cardiac output (8, 19, 32, 38). However, cardiac output alone can be deceptive as is demonstrated by increased cardiac output during septic and spinal shock (32). Indeed, when autoregulation fails, cardiac output may increase as the patient’s condition worsens. However, in the situation of acute blood loss, as normally seen in trauma, autoregulation is maintained and cardiac output is a principal indicator of decreasing blood volume associated with blood loss (32).

The clinician faced with a patient in shock or impending shock attempts to improve oxygen delivery, especially to the central organs, by improving cardiac output or blood oxygen-carrying capacity (40, 54). Several outcome studies have shown that central venous oxygen saturation is a reliable index of oxygen delivery, facilitating these clinical decisions (1, 36, 39, 41, 50). Because obtaining mixed venous oxygen saturation (SvO₂) requires invasive monitoring and has associated complications (7, 39, 40), a noninvasive, rapidly applicable technique that provides a comparably reliable index of oxygen delivery from early blood loss to profound shock would be a valuable adjunct to patient management (1, 39, 41, 54).

The large vessels of the retina are a potential source of noninvasive perfusion data and are relatively easily observed (10, 11, 25). Previous attempts at retinal vessel oximetry were able to detect changes in oxygen saturation as small as ±4% (6, 10, 12, 26). These devices were not used to monitor retinal saturation changes during shock states and were not reduced to clinical use. Studies of the retinal circulation have shown a strong correlation between retinal perfusion and regional cerebral blood flow (21, 30). The blood flow to the central circulation including the retina (30) is relatively preserved during shock states (40, 41), and we have demonstrated that retinal venous oxygen saturation (SrvO₂) is sensitive to early blood loss in anesthetized swine (14, 15).

Over the last seven years, we have developed an experimental, noninvasive eye oximeter (EOX). The device is used to noninvasively measure the optical density of the large retinal vessels, arteries, and veins (44) and uses a spectroscopic model to calculate their oxygen saturation.

In a pilot test of the device in which swine were bled at 0.4 ml·kg⁻¹·min⁻¹ to a total of 16 ml/kg, there was a strong correlation between blood loss and SrvO₂ (r = −0.93) (14). In another study, SrvO₂ correlated with the rate of blood loss during three intermediate rates of early blood loss and subsequent reinfusion and was...
more sensitive to blood loss than vital sign measurements in the same animals (15).

Published studies using an EOX to measure \( \text{Sr} \text{V}_\text{O}_2 \) during exsanguination used a mild amount of blood removal (20% of total blood volume) and did not demonstrate calibration of measurements (14, 15, 44, 45). We believe that calibration of data is desirable because it may allow for a single measurement to be used when making decisions about resuscitation or triage. Trending data can be used to monitor patients, but this requires repeated measures over time in the initial period of resuscitation when decisions must be made rapidly if a patient is to survive (2, 54). After an extensive review of the literature, we are unable to find any reports comparing \( \text{Sr} \text{V}_\text{O}_2 \) to cardiac output, \( \text{Sv}_\text{O}_2 \) or blood volume across the range of profound blood removal and subsequent reinfusion. It is unknown what changes will occur in \( \text{Sr} \text{V}_\text{O}_2 \) measurements during more life threatening blood removal and during resuscitation from blood removal.

Studies using a model eye and the human eye have demonstrated that the highly absorbing fundus and pigment variation in the retina make calibration of oximetry measurements difficult (3, 17, 46). We have performed experiments using a model eye with a highly reflective background that allowed for calibration in this model (13). We have also performed experiments in a model eye and in the human eye that utilized a detection pathway filter to correct for fundus pigmentation (17, 46). However, in this study, we used a device without a detection pathway filter to study swine from Sinclair Research that spontaneously develop melanoma and then reject the tumor during adolescence. These swine sometimes develop vitiligo of the retina, making them an ideal test subject because increasing fundus reflectivity increases the effective light pathlength and simplifies our data reduction (33). We hypothesized that utilizing an animal model that had retinal vitiligo would increase retinal reflectivity similar to our model eye (i.e., have a highly reflective background) and consequently improve the calibration of our data. We also hypothesized that \( \text{Sr} \text{V}_\text{O}_2 \) changes would correlate with cardiac output and \( \text{Sv}_\text{O}_2 \) during profound exsanguination (40% of total blood volume) and subsequent resuscitation.

MATERIALS AND METHODS

The EOX scans low-power lasers across the retinal vasculature. The light scattered and reflected back out of the eye is collected and analyzed, and the optical density of the blood within the vessels is determined from the collected signals. These optical density measurements are made at multiple wavelengths, and a spectroscopic model is used to calculate the oxygen saturation of the blood within the vessels (6, 10, 26, 44, 52).

Through an eyepiece, the EOX provides an image of the subject’s ocular fundus to the operator. The operator then targets a retinal artery or vein and initiates the measurement procedure. A full data set is acquired within 0.1 s. Typically, 8–16 data sets are averaged to comprise a single saturation determination (44). A detailed description of the device used for these experiments is provided elsewhere (45).

This study adhered to National Institutes of Health guidelines for the use of laboratory animals and was approved by the Institutional Animal Care and Use Committee.

Ten mature Sinclair swine (2–6 yr old) with retinal vitiligo, weighing 55–95 kg, were fasted overnight but allowed water ad libitum. On the morning of the experiment, the animals were given intramuscular preanesthetic ketamine 50 mg/kg and xylazine 2 mg/kg. The swine were placed in the supine position, intubated endotracheally, and placed on a ventilator. The swine were placed on 2–4% isoflurane during the surgical procedures, and the depth of anesthesia was monitored by using web space stimulation. An esophageal temperature probe was used to monitor core body temperature, and continuous electrocardiographic monitoring was utilized. The eyes were treated with two drops of 1% cyclopentolate hydrochloride. At the beginning of the surgical preparation, the animal was given a bolus of 1,000 ml of normal saline. A solution of 5% dextrose in half normal saline with 10 milliequivalents of KCl per liter was infused at 80–110 ml/h. A celiotomy was performed by using an inframamillary approach, the bladder was exposed, and a Foley catheter was placed in the bladder via cystotomy. The abdominal wall was closed around the bladder catheter. A femoral cut down was performed, a 7.0-Fr catheter was placed in the femoral artery, and an 8.0-Fr introducer was placed in the femoral vein. The femoral artery catheter was connected to a Hewlett-Packard 78203 physiological pressure monitoring system, and a 7.5-Fr Abbott continuous mixed \( \text{Sv}_\text{O}_2 \) monitoring catheter was placed in the central circulation via the introducer in the femoral vein. The distal port of the central venous catheter was connected to a Hewlett-Packard 78203 physiological pressure monitoring system. Placement of the central venous catheter was verified by waveform. The catheter oximeter calibration was verified by using mixed venous blood obtained from the distal port. All blood gas analysis was performed by use of an IL 482 CO\textsubscript{2} oximeter system. The eyelids were sutured open, and sutures were placed in the conjunctiva to hold the eye in place. A catheter, attached to a 60-ml syringe filled with buffered 0.9% saline (pH = 7.0), was sutured to the periorcular skin and used to bathe the eye every 30–45 s to maintain corneal hydration throughout the experimental protocol. When the surgical preparation was completed, the isoflurane was decreased to 1.0–1.5% as needed to maintain anesthesia. The respiratory rate was adjusted such that arterial CO\textsubscript{2} tension was between 36 and 44 Torr and the blood pH was between 7.35 and 7.45. The end-tidal CO\textsubscript{2} was measured continuously by using a Datex 254 airway gas monitor. The central venous catheter placed in the pulmonary artery was used to record continuous mixed \( \text{Sv}_\text{O}_2 \), and the thermodilution technique was used to measure cardiac output at 2-min intervals during exsanguination and reinfusion. The EOX was aimed at a large artery near the optic disk, and the swine were placed on stepwise decreasing amounts of oxygen. At each level of oxygen, femoral artery oxygen saturation and retinal artery oxygen saturation were obtained. After the arterial study was complete, the animals were placed on 100% oxygen and allowed to equilibrate for 20 min. The EOX was then aimed at a large vein near the optic disk, and the \( \text{Sr} \text{V}_\text{O}_2 \) was measured every minute for 5 min to obtain baseline data. After the baseline data were acquired, each animal was exsanguinated by a 28 ml/kg/min until a total of 28 ml/kg had been removed. Shed blood was anticoagulated by using anti-coagulant citrate phosphate dextrose (ACD) solution. When the exsanguination was complete, the animal was resuscitated by reinfusing the anticoagulated shed blood at 1.4 ml·kg\textsuperscript{-1}·min\textsuperscript{-1}.
After the exsanguination and reinfusion, the retina was examined for laser damage by using direct ophthalmoscopy. At the conclusion of the experimental protocol, the anesthetized swine were euthanized by using supersaturated potassium chloride.

RESULTS

Retinal artery oxygen saturation (SraO₂) correlated with femoral artery oxygen saturation during graded hypoxia ($r = 0.92$). SrvO₂ correlated with SvO₂ ($r = 0.89$), blood volume ($r = 0.9$), and cardiac output ($r = 0.92$) during the baseline blood loss and resuscitation periods of the experiment. Figure 1 shows how SraO₂ correlated with femoral artery oxygen saturation during graded hypoxia. The linear best fit for the conglomerate data from all the swine tested for arterial calibration is shown as the heavy line on the figure ($r = 0.92$, slope = 0.93, intercept = 0.03). The data set from each individual swine is shown by using a different symbol, and the linear best fit for each animal is shown as a fine line. The average residual retinal artery saturation for this calibration plot was 1.5 ± 8.9%.

Figure 2 shows the tight correlation of SrvO₂ and normalized cardiac output (the cardiac output at the beginning of the baseline period divided into each subsequent measurement in that swine) measured during blood removal and resuscitation. For comparison purposes, Fig. 3 shows SvO₂ and normalized cardiac output. Figure 4 shows the correlation plot of SrvO₂ with normalized cardiac output during exsanguination and reinfusion; the data shown are extracted from Fig. 2 and are the average cardiac output and SrvO₂ measured concurrently with the cardiac output during exsanguination and resuscitation. Figure 5 shows the correlation between average SrvO₂ and SvO₂ during exsanguination ($r = 0.97$) and resuscitation ($r = 0.82$). All error bars shown and reported ranges are the standard deviation from the mean.

DISCUSSION

We performed model eye experiments by using a highly reflective background that demonstrated improved calibration in our instrument. On the basis of these results, we expected improved calibration in this in vivo retinal vitiligo model. The need for calibration to a range of 3 to 4% is evident from our exsanguination and reinfusion experiments in which a change of 10% oxygen saturation correlated with a 5% change in blood volume (15). The hypothesis that retinal vitiligo would improve calibration of our measurements is supported by our data. In previous studies using Yorkshire swine with normal retinal pigmentation, we had significant variations in slopes and intercepts of our calibration plots (14), and the overall correlation coefficient when all data from all swine were plotted...
together was significantly inferior to our results here (with the Yorkshire swine $r = 0.646$, slope = 0.57, intercept = 0.235). However, the average residuals from our calibration experiment had an error of $\pm 8.9\%$ saturation; thus we were still unable to achieve our goal of 3 or 4% error in calibration. As noted in the introduction, our laboratory utilized detection pathway filters and scanning systems (46) to address this concern (17).

There have been several devices advocated as noninvasive systems for the direction of trauma resuscitation. Previously, noninvasive blood oxygenation measurements have been attempted (29, 35). Various limitations exist with these approaches. Near infrared spectroscopy is potentially erroneous because differences in skull and scalp thickness alter pathlength (29). Pulse oximetry is sometimes inaccurate as a result of optical shunting (presence of light that alters the true reading) (28, 48) and is sometimes associated with thermal injury (34, 43, 47). The device measures peripheral arterial oxygenation only (42) and is of limited efficacy in patients with anemia or hypoxia (27, 42). More recently, gastric tonometry, retinal oximetry, and sublingual capnometry have been tested in animal and human models (17, 35a, 45, 53).

In this swine model, we have demonstrated a strong correlation between cardiac output and Srvo₂ across the spectrum of survivable blood loss and resuscitation (40% of total blood volume). This is important because vital signs may be maintained until large amounts of blood have been lost. To be used for clinical care, a monitoring tool must be superior to present technology and must change predictably across the breadth of the clinical spectrum to allow the clinician to make accurate decisions about care. Also, calibration is important because a single measurement, in conjunction with vital signs and clinical assessment, may be all that is available for critical decision making during time-sensitive trauma resuscitation (2).

The change in Srvo₂ and central venous oxygen saturation seen during resuscitation demonstrates the monitoring capacity of these tools (see Figs. 2 and 3). Both indicated a rapid response to initial reinfusion and a marked flattening of this response after $\sim 5-6\%$ of total blood volume had been infused. The nonlinear response to the reinfusion of autologous blood seen in this model has been described in a study using autologous blood transfusions in swine (20) and is similar to changes that we have seen during resuscitation from mild blood loss (14, 15). During resuscitation, Srvo₂ increased more dramatically than SvO₂ and behaved more like cardiac output than SvO₂. In Fig. 5, where Srvo₂ and SvO₂ are correlated, the bimodal grouping of data is evident as Srvo₂ and SvO₂ remain correlated but the slope changes during resuscitation. This is probably a result of total body autoregulation shunting flow to the central organs and may represent an advantage in monitoring Srvo₂ because the resuscitation of trauma victims before definitive repair using traditional end points can lead to overresuscitation and increased mortality in swine and humans (4, 9).

In conclusion, we have demonstrated improved calibration of a spectroscopic EOX achieved by use of an in vivo model of increased retinal reflectivity by using swine with retinal vitiligo. We have also demonstrated the use of an experimental EOX during profound blood loss and resuscitation in a specialized anesthetized swine model. Changes in Srvo₂ correlated with blood volume, SvO₂, and cardiac output during profound blood removal and subsequent resuscitation. The response to changes in blood volume was nearly linear during exsanguination. There was a nonlinear response to the reinfusion of autologous blood seen in this model. This nonlinear response has been described elsewhere and is probably a physiological response to autologous blood transfusions and physiological hysteresis in swine (20). Use of a calibrated EOX to noninvasively monitor trauma patients for unrecognized

![Fig. 4. Correlation plot of Srvo₂ and normalized cardiac output during the baseline, exsanguination, and resuscitation periods of the experiments.](image-url)

![Fig. 5. Correlation between Srvo₂ and SvO₂ throughout the study period.](image-url)
blood loss and during resuscitation from exsanguination hemorrhage warrants further study.

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