Prolonged Central Venous Desaturation Measured by Continuous Oximetry Is Associated with Adverse Outcomes in Pediatric Cardiac Surgery

Ryan Crowley, M.D.,* Elizabeth Sanchez, B.S.,† Jonathan K. Ho, M.D.,* Kate J. Lee, B.S.,‡ Johanna Schwarzenberger, M.D.,§ Jure Marijic, M.D.,# Michael Sopher, M.D.,# Aman Mahajan, M.D., Ph.D.#

ABSTRACT

Background: The role of continuous central venous oxygen saturation ($ScvO_2$) oximetry during pediatric cardiac surgery for predicting adverse outcomes is not known. Using a recently available continuous $ScvO_2$ oximetry catheter, we examined the association between venous oxygen desaturations and patient outcomes. We hypothesized that central venous oxygen desaturations are associated with adverse clinical outcomes.

Methods: Fifty-four pediatric patients undergoing cardiac surgery were prospectively enrolled in an unblinded observational study. $ScvO_2$ was measured continuously in the operating room and for up to 24 h post-Intensive Care Unit admission. The relationships between $ScvO_2$ desaturations, clinical outcomes, and major adverse events were determined.

Results: More than 18 min of venous saturations less than 40% were associated with major adverse events with 100% sensitivity and 97.6% specificity. Significant correlations resulted between the $ScvO_2$ area under the curve less than 40% and creatinine clearance at 12 h in the Intensive Care Unit ($r = -0.58$), Intensive Care Unit length of stay ($r = 0.56$), max inotrope use ($r = 0.52$), inotrope use at 24 h ($r = 0.40$), inotrope index score ($r = 0.39$), hospital length of stay ($r = 0.36$), and length of intubation ($r = 0.32$).

Conclusions: We demonstrate that $ScvO_2$ desaturations by continuous oximetry are associated with major adverse events in pediatric patients undergoing cardiac surgery. The most significant associations with major adverse events are seen in patients with greater than 18 min of central venous saturations less than 40%. Our results support the further investigation of $ScvO_2$ as a potential target parameter in high-risk pediatric patients to minimize the risk of major adverse events.

What We Already Know about This Topic

- Intermittent monitoring of central venous oxygen saturation, as a surrogate for mixed venous oxygen saturation, has been used as an index of global tissue perfusion and may predict adverse events following cardiac surgery

What This Article Tells Us That Is New

- In this unblinded study, prolonged periods of venous desaturation on continuous oximetry were associated with increased adverse events in children with congenital heart disease who were undergoing cardiac surgery

PEDIATRIC patients undergoing cardiac surgery are at risk for adverse clinical outcomes in the perioperative period because of inadequate tissue perfusion. Although several clinical and laboratory markers associated with adverse clinical outcomes have been identified, the inability to readily and reliably assess global tissue perfusion and cardiac out-

◆ This article is accompanied by an Editorial View. Please see: Stuth EAE, Hoffman GM: A Sisyphean task: Identifying physiologic risk and improving outcomes in complex congenital heart surgery. ANESTHESIOLOGY 2011; 115:926–8.

* Assistant Clinical Professor, † Research Associate, ‡ Lab Assistant, § Associate Clinical Professor, # Clinical Professor, Department of Anesthesiology, David Geffen School of Medicine, University of California-Los Angeles, Los Angeles, California.

Received from the Department of Anesthesiology, David Geffen School of Medicine, University of California-Los Angeles, Los Angeles, California. Submitted for publication October 30, 2010. Accepted for publication June 29, 2011. Supported by intramural departmental funds; Project Grant (P01) HL078931 from the National Heart, Lung and Blood Institute and the National Institutes of Health (Bethesda, Maryland); and Research Project Grant (R01) HL084261 from the National Institutes of Health (Bethesda, Maryland). Edwards Lifesciences (Irvine, California) provided the software needed for recording of continuous central venous oxygen saturation data.

Address correspondence to Dr. Mahajan: Professor and Chief, Cardiothoracic Anesthesiology, David Geffen School of Medicine, University of California-Los Angeles, Ronald Reagan UCLA Medical Center, 757 Westwood Blvd., Suite 3325, Los Angeles, California 90095. amahajan@mednet.ucla.edu. Anesthesiology 2011; 115:1033–43

put remains a challenge in this patient group. Similar to results in adults, significant mixed venous (SvO_2) desaturations seen with surgically placed oximeters have shown to be predictive of worsening neurologic function and clinical outcomes in neonatal patients undergoing palliative repair for hypoplastic left heart syndrome.[1] Unfortunately, mixed venous oximetry using percutaneous catheters is not feasible or practical in most children.

Central venous saturation ($ScvO_2$), as a surrogate of SvO_2, can reliably be used as a marker of global tissue perfusion. Recent studies have suggested the predictive power of intermittently measured $ScvO_2$ for adverse events following cardiac surgery.[2,3] However, intermittent or "snapshot" measurements of $ScvO_2$ are not able to assess the duration or temporal pattern of venous desaturations, and may not allow early detection of occult venous desaturations in the absence of other hemodynamic disturbances. Therefore, the true impact of desaturations on clinical outcomes is not clearly evident. In addition, though previous studies have suggested hemodynamics variables such as blood pressure, heart rate, and venous pressures to be poor predicators of adverse outcomes,[1,4] these variables remain a mainstay of critical care management in pediatric patients. Therefore, further investigation of the relationships between continuous ScvO2 and the more commonly used clinical hemodynamic and biochemical markers are needed to clinically interpret the value of continuous $ScvO_2$ monitoring in pediatric patients.

Using a newly developed, percutaneously placed continuous $ScvO_2$ oximetry system for children,[5] we examined the association between postoperative venous desaturations and clinical outcomes in pediatric patients undergoing cardiac surgery. We hypothesized that prolonged low central venous saturations are associated with adverse clinical outcomes.

Materials and Methods

Upon receipt of approval and informed consent from The University of California, Los Angeles Institutional Review Board, Los Angeles, California, 54 high-risk pediatric patients scheduled to undergo cardiac surgery with complete repair (no residual shunting), with or without cardiopulmonary bypass, and requiring a central venous catheter were consented for prospective data acquisition. Patient exclusion criteria included contraindications for a central venous catheter placement in the right internal jugular vein and body weight less than 3 kg.

Clinical Protocol

Anesthetic induction consisted of inhaled sevoflurane and nitrous oxide, supplemented with intravenous fentanyl (3–5 μg/kg) and pancuronium (0.1 mg/kg). Isoflurane (1–1.5%) and fentanyl (10–15 μg/kg) were used to maintain anesthesia during the surgery. Following tracheal intubation, a central venous fiberoptic oximetry catheter (PediaSat™ oximetry catheter; Edwards Lifesciences, Irvine, CA) was calibrated *in vitro* and placed into the right internal jugular vein. Catheter size (4.5F/5 cm, 4.5F/8 cm, or 5.5F/8 cm) was determined according to patient size. Proper placement of the catheter tip at the lower portion of the superior vena cava and superior to the caval-atrial junction was verified by transesophageal echocardiography.

Following repair, patients received inotropic support as clinically indicated, including dopamine, dobutamine, epinephrine, and/or milrinone according to standard institutional protocols. Patients were transported to the Intensive Care Unit (ICU) and catheters were recalibrated on arrival *in vivo* with the most recent hemoglobin and venous blood gas co-oximetry values. Catheter tip location was reconfirmed with a chest radiograph and patients were monitored for clinical outcomes and major adverse events until the end of their hospital stay. All data were prospectively recorded.

Clinical Data Acquisition

In the Operating Room (OR), $ScvO_2$, heart rate, central venous pressure, mean arterial pressure, arterial saturation, cerebral regional tissue oxygen saturation (rSO_2) (INVOS® Cerebral Oximeter; Somanetics Corporation, Troy, MI), and core temperatures were recorded every minute. In the ICU, $ScvO_2$ and rSO_2 were recorded every minute, whereas heart rate, central venous pressure, mean arterial pressure, arterial saturation, and temperature gradients were recorded every 15 min. Data were recorded from the completion of surgical repair (if performed off cardiopulmonary bypass) or complete separation from cardiopulmonary bypass (if the procedure was performed on cardiopulmonary bypass) until 24 h after ICU admission. Data were collected until ICU discharge if patients were discharged before 24 h. In addition, $ScvO_2$ catheter measurements were compared to venous blood gas co-oximetry values of simultaneously drawn samples at predefined time points (OR baseline, prerepair, postrepair, chest closure, ICU admission, and 2, 4, 6, 8, 12, and 24 h postoperatively). Venous blood samples for co-oximetry measurement were drawn from the distal lumen of the catheter. Only those $ScvO_2$ catheter measurements with an adequate signal quality index from 1 to 3 were used. Serum lactate was measured at least every 6 h, or more frequently if indicated clinically. Serum creatinine measurements were drawn every 12 h. Complete rSO_2 data sets were acquired in a subset of 36 patients. For patients with bilateral cerebral rSO_2 sensors, the average was used for analysis. Postoperative clinical outcome data were prospectively recorded.

Clinical Outcomes

Major adverse events were defined as need for extracorporeal support, refractory cardiogenic shock or hypotension despite maximal medical therapy, sepsis, multi-organ dysfunction, and reoperation or reopening of chest in the first 24 h. We selected previously validated clinical outcome measures to assess the postoperative course of the study patients.[6–8] Total length of intubation, length of ICU stay, and length of hospital stay were measured in days for each patient. Creatinine

clearance was calculated by the Cockcroft-Gault formula at 12 h post-ICU admission.[9] The maximum number of inotropes used during the study period, the number of inotropes still in use at 24 h, and inotrope score at 24 h were recorded. The inotrope score was calculated as described by Wernovsky *et al.* with dosages in micrograms per kilogram per minute: dosages of dopamine + dobutamine + (epinephrine × 100) + (milrinone × 10) at 24 h post-ICU admission.[10]

$ScvO_2$ Desaturation Episodes. We investigated the frequency and temporal distribution of desaturation episodes detected by continuous $ScvO_2$. For a given threshold $ScvO_2$, we defined a desaturation episode as 5 or more consecutive min below the defined threshold, separated by 5 or more consecutive min above the threshold. These episodes were calculated for three separate time periods: from surgical repair/off cardiopulmonary bypass to OR discharge, first 12 h of ICU admission, and from 12 h following ICU admission until the end of data collection.

Statistical Analysis

$ScvO_2$ Area under the Curve. To relate intraoperative and postoperative $ScvO_2$ to clinical outcomes and hemodynamic or biochemical variables, we utilized the area under the curve (AUC) as a measure of degree of desaturation, where the area is calculated between a threshold $ScvO_2$ and the measured $ScvO_2$ values over time. The AUC is expressed as a product with the units of minute-percent and is determined as described below:

Y = measured $ScvO_2$ value, T = specified threshold value. We compute Z as the value of difference between the measured and specified threshold $ScVO_2$ according to the definition:

$$\text{if Y less than T, then } Z = T - Y$$

$$\text{if Y more than or} = T, \text{ then } Z = 0$$

The AUC for each patient is calculated by the following formula: $AUC = (\Sigma Z)^{*}t$, where t = total number of minutes from the end of surgical repair up to 24 h after ICU admission. The following threshold groups were selected for analysis: AUC 60–70%, AUC less than 60%, AUC less than 50%, and AUC less than 40%.

Time under Threshold and Receiver-operating Curve Analysis for Major Adverse Events. We computed the time a patient remained under each threshold or between thresholds and, for each, determined the optimal time that best discriminates between those with major adverse events and without them. The optimal time was chosen by carrying out a nonparametric receiver operating characteristic curve analysis and was chosen such that accuracy was maximized. The accuracy was defined as the average of the sensitivity and specificity (accuracy = 0.5 sensitivity + 0.5 specificity). For the optimal time we report the sensitivity, specificity, accuracy, and positive and negative predictive values, assuming that the major adverse event prevalence is the same as in our data.

Correlation of $ScVO_2$ with Other Clinical Outcomes. The associations of $ScvO_2$ AUC with clinical outcomes, standard hemodynamic measurements, and biochemical markers (lactate) were assessed using the Spearman rank test and by fitting restricted cubic splines. The nonparametric Spearman correlation and the corresponding splines using log scale AUC was used, because the relationship is not necessarily linear, even on the semilog scale. Using the spline fit, the average change in the outcome from the 25^{th} to 75^{th} percentile change in each log $ScvO_2$ AUC was computed. This is essentially a nonparametric, robust slope. A P value <0.05 was considered statistically significant. Agreement between the catheter measured saturation and co-oximetry measured saturation values was assessed using Bland-Altman plot analysis.

Continuous data are presented as mean ± SD, or median with range as appropriate. Statistical analysis was performed with SPSS 16.0 (SPSS Inc., Chicago, IL) and SAS 9.2 (SAS Inc., Cary, NC).

Results

Of the 54 patients enrolled, 3 patients were not included in the final analysis because of incomplete data sets caused by data storage errors. Another patient was excluded because of extracorporeal membrane oxygenation support being initiated in the operating room. Patient characteristics and surgical procedure for the 50 remaining patients are summarized in table 1. Given the diverse patient population, each patient's age, weight, preoperative diagnosis, and surgical procedure are provided in the appendix. No patient had a demonstrable intracardiac shunt on intra- and postoperative echocardiography regardless of undergoing single or bi-ventricular repair. Continuous $ScvO_2$ data were recorded from the end of surgical repair and up to the first 24 h postoperatively and lasted a median of 24 h (interquartile range 19.4–25.8 h). Only 2 patients were discharged from the ICU sooner than 24 h. There were no complications attributable to $ScvO_2$ monitoring or continuous data collection. Patient outcomes and clinical data are summarized in table 2.

Major adverse events were observed in 9 patients and are summarized in table 3. The sensitivity and specificity of $ScvO_2$ as a predictor for major adverse events were calculated using the time the $ScvO_2$ was less than 40%, less than 45%, less than 50%, less than 55%, less than 60%, and from 60 to 70%. The accuracy of each time was calculated as the average of sensitivity and specificity. For the time with the greatest accuracy, the positive and negative predictive values for major adverse events were determined for various venous saturation thresholds and are summarized in table 4. Using receiver operating characteristic curve analysis, it was determined that a time greater than 18 min of $ScvO_2$ less than 40% was the most predictive for major adverse events with 100% sensitivity, 97.6% specificity, 98.8% accuracy, 90% positive predicative value, and 100% negative predic-

Table 1. Patient Characteristics and Surgical Procedure

Demographics	
Age	32 months (7 d to 10 yr)
Neonate (0 to 1 month)	1 (2%)
Infant (1 month to 1 yr)	14 (28%)
Child (1 yr and older)	35 (70%)
Gender	—
Male	31 (62%)
Female	19 (38%)
Weight	12.9 kg (3.1–28 kg)
Length of surgery	323 min (105–707 min)
Cardiopulmonary bypass time (n = 47)	98 min (31–425 min)
Aortic cross clamp time (n = 36)	72 min (17–195 min)
Surgical procedure	—
Fontan	9 (18%)
Tetralogy of fallot repair	8 (16%)
Ventricular septal defect repair	7 (14%)
Atrioventricular canal repair, complete	3 (6%)
Right ventricular outflow tract procedure	3 (6%)
Arterial switch	2 (4%)
Conduit reoperation	2 (4%)
Pulmonary atresia, ventricular septal defect repair	2 (4%)
Pulmonary valve replacement	2 (4%)
Right ventricle to pulmonary artery conduit replacement	2 (4%)
Senning	2 (4%)
Aortic arch repair	1 (2%)
Aortic stenosis, subvalvar repair	1 (2%)
Ascending aorta to left pulmonary artery shunt	1 (2%)
Atrial septal defect repair	1 (2%)
Coarctation repair, end to end or extended	1 (2%)
Heart transplant	1 (2%)
Rastelli	1 (2%)
Total anomalous pulmonary venous return repair	1 (2%)

Data listed as median and range or n (%); n = 50.

tive value (fig. 1). Increasing time of $ScvO_2$, such as less than 45% and less than 50%, were only slightly less predictive. A time greater than 93 min of $ScvO_2$ less than 55 percent was still highly predictive of major adverse events with an accuracy of 80.5%, a positive predictive value of 50%, and a negative predictive value of 97.1%. A $ScvO_2$ of less than 60% was only predictive of major adverse effects with a duration exceeding 13 h. $ScvO_2$ of 60–70% was not predictive of major adverse effects at any length of time. Using $ScvO_2$ AUC instead of time produced similar results.

Table 2. Patient Outcomes and Clinical Data

Clinical Outcomes (n = 50)	
Length of intubation	1 day (0.5–15 days)
Length of stay in ICU	4 days (0.5–77 days)
Length of stay in hospital	7 days (2–79 days)
Inotrope score	5.9 (0–26)
Max ICU lactate (mM)	2.3 (0.9–6.7)
Creatinine clearance (mL/min)	—
12 h after surgery	63 (8–109)
$ScvO_2$ (n = 50)	(% min)
AUC 60–70%	599,857 (0–5,202,692)
AUC less than 60%	55,015 (0–30,346,211)
AUC less than 50%	490 (0–5,055,744)
AUC less than 40%	3 (0–866,889)

Data listed as median and range.

AUC = area under the curve; ICU = intensive care unit; $ScvO_2$ = central venous oxygen saturation.

Four $ScvO_2$ AUC groups were considered for analysis for correlation with clinical outcomes: AUC 60–70%, less than 60%, less than 50%, and less than 40%. These data are summarized in table 5. As AUC thresholds were decreased in 10% increments from AUC 60–70% to AUC less than 40%, an increasing number of associations with clinical outcomes were observed. At $ScvO_2$ AUC less than 40%, significant correlations were found between creatinine clearance at 12 h postoperatively ($r = -0.58$), length of ICU stay ($r = 0.56$), maximum number of inotropes used ($r = 0.52$), number of inotropes used at 24 h ($r = 0.40$), inotrope index score at 24 h post-ICU admission ($r = 0.39$), length of hospital stay ($r = 0.36$), and length of intubation ($r = 0.32$). Statistically significant, but slightly weaker, correlations resulted between $ScvO_2$ AUC less than 50% and creatinine clearance 12 h postoperatively ($r = -0.56$), length of ICU stay ($r = 0.44$), max inotrope use ($r = 0.39$), inotrope use at 24 h ($r = 0.33$), length of hospital stay ($r = 0.30$), and inotrope index score ($r = 0.30$). Significant correlations were observed only between AUC less than 60% and creatinine clearance 12 h postoperatively ($r = -0.52$), length of ICU stay ($r = 0.33$), and length of hospital stay ($r = 0.32$). $ScvO_2$ AUC 60–70% was not significantly correlated with any of the clinical outcomes.

In addition to the correlation of $ScvO_2$ AUC and clinical outcomes, the magnitude of effect of increasing AUC and the change in the outcome measure was determined between the 25th and 75th percentile in each $ScvO_2$ AUC range. For a $ScvO_2$ AUC less than 40%, length of intubation increased by 1.43 days, length of ICU stay increased by 4.32 days, length of hospital stay increased by 1.93 days, maximum inotrope use increased by 1.01, inotrope use at 24 h increased by 0.74, the inotrope index score increased by 6.05 mcg/kg/min, and creatinine clearance at 12 h decreased by 24.53 ml/min. For an ScvO2 AUC less than 50%, the length of ICU stay increased by 6.01 days, length of hospital stay increased by 6.9 days, the maximum inotrope use increased by 0.76, the maximum inotrope use at 24 h increased by 0.54, the inotrope

Table 3. Patients with Major Adverse Events

Cardiac Diagnosis	Surgery	Age	Weight (kg)	Clinical Event	Hospital Discharge Date
Atrioventricular canal, patent ductus arteriosus	Repair atrioventricular canal	1 month	3.1	1) Mediastinitis	—
—	—	—	—	2) Ventriculomegaly by magnetic resonance imaging	POD No. 79
—	—	—	—	3) E coli sepsis	—
Tetralogy of fallot	Tetralogy of fallot repair	2.8 months	6.7	1) Increased pulmonary vascular resistance, 50 mmHg pulmonary gradient	—
—	—	—	—	2) Poor cardiac output, dilated right ventricle, poor right ventricle contraction	POD No. 15
—	—	—	—	3) Atrioventricular dissociation	—
Coarctation of aorta	Hypoplastic aortic arch	2 months	4.3	1) Pulmonary edema	—
—	—	—	—	2) Upper respiratory infection	—
—	—	—	—	3) Enterobacter pneumonica	—
—	—	—	—	4) Renal hydronephrosis	POD No. 14
Pulmonary valve stenosis	Repair pulmonary atresia, replace conduit	10 months	10	1) Left pleural effusion	—
—	—	—	—	2) Bradycardia	POD No. 7
—	—	—	—	3) Heart failure	—
Pulmonary valve stenosis, pulmonary artery stenosis, left pulmonary artery stenosis	Pulmonary valve replacement	8 yr	23	1) Sinus rhythm with bundle branch block	—
	—	—	—	2) Right pleural effusion	—
		—	—	3) Severe hemorrhage, surgical re-exploration	POD No. 7
Tetralogy of fallot with pulmonary atresia	Tetralogy of fallot repair; ventricular septal defect closure	3 yr	14	1) Respiratory failure and pulmonary hemorrhage	—
—	—	—	—	2) Cardiac tamponade	POD No. 21
—	—	—	—	3) Extracorporeal membrane oxygenation, POD No. 3–7	—
—	—	—	—	4) Pericardial window	—
Double inlet left ventricle	Fontan procedure	6 yr	21	1) Complete heart block	—
—	—	—	—	2) High right chest tube output, re-exploration, POD No. 17	—
Dextro-transposition of the great arteries	Arterial switch	2 yr	9	1) High venous pressures	—
—	—	—	—	2) Depressed systemic right ventricle systolic function, POD No. 12	—
Dextro-transposition of the great arteries	Arterial switch	1 week	3.7	1) Left apical pneumothorax and small left pleural effusion	POD No. 25
—	—	—	—	2) Pulmonary edema and pulmonary vascular congestion	—
—	—	—	—	3) Troponins elevated	—
—	—	—	—	4) Atrial flutter, supraventricular tachycardia	—

For data listed, n = 9.
POD = postoperative day.

Table 4. Predictive Accuracy of $ScvO_2$ for Major Adverse Events

$ScvO_2$ Threshold	Time (min)	Specificity	Sensitivity	NPV	PPV	Accuracy (95% CI)
Time less than 40%	More than 18**	97.6%	100.0%	100.0%	90.0%	98.8% ± 1.2%
Time less than 45%	More than 19**	87.8%	100.0%	100.0%	64.3%	93.9% ± 2.6%
Time less than 50%	More than 34**	87.8%	100.0%	100.0%	64.3%	93.9% ± 2.6%
Time less than 55%	More than 93*	80.5%	88.9%	97.1%	50.0%	84.7% ± 6.1%
Time less than 60%	More than 822*	95.1%	66.7%	92.9%	75.0%	80.9% ± 8.0%

Threshold for each predictor and the corresponding specificity, sensitivity, and accuracy; n = 9.
* $P < 0.05$. ** $P < 0.001$.
CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value; $ScvO_2$ = central venous oxygen saturation.

index score increased by 3.79 mcg/kg/min, and the creatinine clearance at 12 h decreased by 26.93 ml/min. The ScvO2 AUC less than 60% demonstrated an increase in the length of ICU stay and hospital stay by 4.98 and 5.44 days, respectively, and a decrease in creatinine clearance at 12 h of 15.33 ml/min.

Desaturation episodes were calculated for $ScvO_2$ thresholds of less than 40%, less than 50%, less than 60%, and less than 70%, and are summarized in table 6. The highest number of observed desaturation episodes occurred within the first 12 h after surgical repair.

Regression analysis demonstrated no significant association between $ScvO_2$ measurements and hemodynamic variables such as blood pressure, heart rate, and central venous pressure ($P > 0.05$) in the ICU. Core temperature and temperature difference also did not correlate with $ScvO_2$. In addition, calculated AUC for greater than 25% change in mean arterial pressure or heart rate from clinically normal values for age[11] were not significantly associated with any clinical outcome.

Though serum lactate was found to not correlate with $ScvO_2$ AUC at any threshold, lactate levels proved to be an independent predictor of poor outcomes, demonstrating an association with creatinine clearance 12 h post-ICU admission (r = −0.4), length of ICU stay (r = 0.4), length of hospital stay (r = 0.4), inotrope use at 24 h (r = 0.4), inotrope index score (r = 0.4), and max inotrope use (r = 0.3).

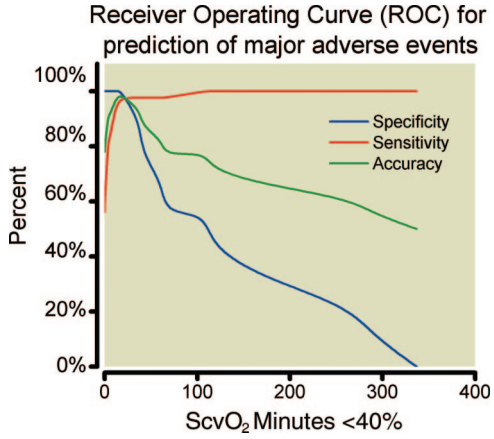

Fig. 1. Receiver operating characteristics curve for prediction of major adverse events by minutes of central venous oxygen saturation, $ScvO_2$, less than 40%. Accuracy, average of sensitivity, and average of specificity are shown. Optimal cutoff point is found at maximum accuracy. AUC = area under the curve; ROC = receiver operating characteristics curve.

In the subset of 36 patients in whom rSO_2 AUC was recorded in addition to $ScvO_2$ AUC, rSO_2 and $ScvO_2$ were found to be significantly correlated in the OR (r = 0.51) and ICU (r = 0.3). rSO_2 AUC less than 40% was significantly correlated with creatinine clearance (r = −0.48) and length of ICU stay (r = 0.40). Fewer significant associations were seen with rSO_2 AUC less than 50%, which correlated with only length of ICU stay (r = 0.39).

The accuracy and precision of the pediatric $ScvO_2$ oximetry system was monitored throughout the study. Bland-Altman plot analysis of 341 paired data sets of venous blood gases and $ScvO_2$ catheter simultaneous measurements showed difference of means (bias) and precision to be 0.41% ± 4.93%, respectively.

Discussion

Our investigation demonstrates that low perioperative $ScvO_2$ is associated with poor clinical outcomes in pediatric patients undergoing cardiac surgery. This is the first study to demonstrate that pediatric patients with a larger area under the curve of continuous $ScvO_2$ saturation below 40% had increased length of intubation, stay in the ICU, stay in the hospital and inotrope use, along with lower creatinine clearance in the perioperative period. An AUC less than 50% proved to be almost equally associated with poor clinical outcomes. An AUC less than 60% had weaker association with poor clinical outcomes, whereas AUC 60–70% had no significant associations.

Furthermore, $ScvO_2$ was also an excellent predictor of major adverse effects. Our results from receiver operating characteristic curve analysis demonstrate that periods as brief as 18 min below saturation of 40% are highly predictive of major adverse effects. We observed that venous saturations of less than 50% for greater than 34 min are also significantly predictive of major adverse effects. The data also show that more mild venous desaturations are well tolerated for significantly longer periods of time, without increasing the risk of major adverse effects. In addition, $ScvO_2$ values at various thresholds maintained a strong negative predictive value, demonstrating that avoidance of lower venous saturations is

Table 5. Clinical Outcomes and Magnitude of Change in Outcomes

$ScvO_2$	Length of Intubation (days)	Length of Stay in ICU (days)	Length of Stay in Hospital (days)	Max Inotrope Use (n)	Inotrope Use at 24 h (n)	Inotrope Index Score at 24 h (μg/kg/min)	Creatinine Clearance at 12 h (ml/min)
AUC less than 60%							
Correlation	0.05	0.33*	0.32*	0.24	0.13	0.17	−0.52**
Change	0.27	4.98	5.44	0.37	0.08	1.12	−15.33
AUC less than 50%							
Correlation	0.14	0.44**	0.30*	0.39**	0.33*	0.30*	−0.56**
Change	0.94	6.01	6.9	0.76	0.54	3.79	−26.93
AUC less than 40%							
Correlation	0.32*	0.56**	0.36**	0.52**	0.40**	0.39**	−0.58**
Change	1.43	4.32	1.93	1.01	0.74	6.05	−24.53

Change signifies average change in magnitude of outcome as the AUC inreases from 25th to 75th percentile; n = 50.
* $P < 0.05$. ** $P < 0.01$.
AUC = area under the curve; ICU = intensive care unit; $ScvO_2$ = central venous oxygen saturation.

a valid goal in pediatric patients undergoing cardiac surgery to decrease the risk of major adverse events.

Our findings indicate that the largest incidence of significant $ScvO_2$ desaturations predominantly occur within the first 12 h postoperatively. During these periods where $ScvO_2$ fluctuations are commonly anticipated, continuous $ScvO_2$ monitoring, rather than intermittent venous sampling, would be extremely valuable for detection of venous desaturations to prompt earlier interventions. Finally, $ScvO_2$ with fiberoptic oximetry was accurate with a low bias and good precision (0.41% ± 4.93%), supporting the potential use of continuous $ScvO_2$ as a reliable target parameter in high-risk pediatric patients.

The clinical value of $ScvO_2$ monitoring was originally proposed in patients with cardiac disease in 1970.[12] Adult clinical trials have suggested that low $ScvO_2$ saturations are associated with increased risk of mortality and independently associated with poor clinical outcomes. Suggested target $ScvO_2$ values from these studies ranged from 60 to 73%.[13–22] Surprisingly limited such data exists for pediatric congenital heart disease patients, and clinical practice is often dictated by experience from adult studies. Our results suggest that increasingly poor clinical outcomes are seen with $ScvO_2$ less than 60%, with significantly worse outcomes present with $ScvO_2$ less than 40%. However, poor correlations were found between continuous $ScvO_2$ and commonly measured hemodynamic variables, suggesting that $ScvO_2$ better reflects global cardiopulmonary changes and tissue perfusion. This observation is also supported by previous experimental findings demonstrating that decreases in $ScvO_2$ can reflect tissue hypoxia despite apparently normal hemodynamic parameters.[1,5]

While no study to date has investigated the relationship of lactate elevation resulting from anaerobic conditions and continuous $ScvO_2$, several pediatric studies have found that lactate was an independent predictor of poor clinical outcomes.[2,23–24] Our results agree with these findings in that higher lactate measurements were associated with longer stays in the ICU and hospital, higher inotrope use, and lower creatinine clearance postoperatively. It is not unexpected that of the other measured physiologic parameters, $ScvO_2$ would be most correlated with rSO_2, because the two parameters are affected by similar physiologic principles governing oxygen delivery. However, correlations in the ICU were much weaker when compared with those in the OR. In the 35

Table 6. Desaturation Episodes

	Hospital Department									
	Operating Room Post-repair			Intensive Care Unit						
				First 12 h			Second 12 h			
$ScvO_2$	No. of Patients	No. of Events	Average AUC (% per min)	No. of Patients	No. of Events	Average AUC (% per min)	No. of Patients	No. of Events	Average AUC (% per min)	Total Events
<70%	22	45	5,974	37	339	397,817	35	312	392,616	696
<60%	12	25	6,791	25	147	135,311	22	205	323,617	377
<50%	5	10	10,419	13	91	213,827	11	73	134,519	174
<40%	5	9	2,369	10	50	130,535	6	31	26,198	90

One episode is defined as more than 5 min, with at least 5 min between events.
AUC = area under the curve; $ScvO_2$ = central venous oxygen saturation.

patients with complete rSO_2 data sets, significant associations were also observed between rSO_2 AUC and clinical outcomes; these associations were not as significant as those seen with $ScvO_2$. This difference may be due to a more pronounced influence of pCO_2 on rSO_2 values, whereas $ScvO_2$ values are largely independent of ventilation. In part, the weaker association between rSO_2 and clinical outcomes may also be because of the assumptions incorporated into the algorithms used in the monitoring technology (site of measurement in forebrain), or because of the variability incurred as a result of altering sensor contact on the forehead when placed for extended periods. This also may be a statistical phenomenon because there were fewer patients with complete rSO_2 data sets.

Continuous fiberoptic venous oximetry in pediatric patients has recently been shown to be accurate and poses minimal additional risks compared with standard central venous catheter placement.[5,25] In the presence of tissue hypoxia, continuous monitoring of $ScvO_2$ may allow for detection of decreased tissue oxygen delivery earlier in comparison to traditional, and typically late, indicators of organ dysfunction, such as increased lactate, decreasing urine output, and increasing metabolic acidosis. Real-time information about tissue oxygenation in pediatric patients can have a profound impact in decreasing morbidity by detecting tissue hypoperfusion earlier than other hemodynamic and chemical parameters. In addition, the use of a real-time perioperative $ScvO_2$ monitor is particularly useful in pediatric patients to decrease the number of blood draws required for venous saturation monitoring. Since the monitoring of continuous $ScvO_2$ saturations is accurate, uses a parameter familiar to critical care physicians, and has no further risk to the patient than standard central venous catheter placement, it would seem a logical step to add this monitor to standard perioperative care in high-risk pediatric patients. Clinical utilization of continuous $ScvO_2$ monitoring should continue to take into account the complexity of the patient's surgical repair, other hemodynamic parameters, and biochemical monitors to make a comprehensive assessment.

Limitations

While the findings of our investigation are promising, we acknowledge several limitations. Our study was an observational, unblinded prospective trial, and although poor clinical outcomes and major adverse events strongly correlated with $ScvO_2$ less than 40% and 50%, a prospective trial to evaluate the utility of continuous $ScvO_2$ as a target parameter of goal-directed therapy to improve clinical outcomes is warranted. Technical limitations of the $ScvO_2$ catheter were minimal from our experience and included wall artifacts caused by impingement of the catheter tip on a vessel wall that led to an unreliable signal, as detected by a signal quality index value of 4. In all cases, repositioning of the catheter resulted in restoration of an appropriate signal. Although the study was not blinded, the practice in our ICU before the study and the study protocol required therapeutic interventions to be made primarily using confirmed venous desaturations from intermittent venous blood gas samples and/or other clinical indicators. There is some possibility that bias might have been introduced with the presence of the monitor and that the information could have been used to guide therapy. The availability of continuous venous oximetry may have influenced some of the clinical outcomes, such as escalation of inotropes, delayed extubation, or delayed discharge. However, the unblinded nature of the study should not have influenced the occurrence of major adverse events or parameters such as creatinine clearance. In addition, there was no treatment algorithm provided for the treatment of low continuous $ScvO_2$ and the physicians involved in the study were not obligated to use the continuous $ScvO_2$ values to guide therapy. The fact that the information was available to the treating physicians, but that significant adverse outcomes were still observed, may be demonstrative that even more aggressive intervention needs to be undertaken to resolve low venous saturations in a timely fashion.

In summary, our prospective observational study demonstrates a significant association between intraoperative and postoperative $ScvO_2$ desaturations and unfavorable clinical outcomes in pediatric patients. Further investigation should focus on quantifying $ScvO_2$ temporal responsiveness to changes in standard hemodynamic parameters and defining target $ScvO_2$ levels specific to patient groups as part of a blinded clinical trial.

The authors thank Jeffery Gornbein, Ph.D., Professor, Department of Biostatistics, University of California-Los Angeles, Los Angeles, California, for performing the statistical analysis used in the study and Jennifer Scovotti, M.A., and Cecilia Canales M.S. (Research Associates), Department of Anesthesiology, University of California-Los Angeles, for helping with the data collection.

References

1. Tweddell JS, Hoffman GM, Mussatto KA, Fedderly RT, Berger S, Jaquiss RD, Ghanayem NS, Frisbee SJ, Litwin SB: Improved survival of patients undergoing palliation of hypoplastic left heart syndrome: Lessons learned from 115 consecutive patients. Circulation 2002; 106:I82–9
2. Seear MD, Scarfe JC, LeBlanc JG: Predicting major adverse events after cardiac surgery in children. Pediatr Crit Care Med 2008; 9:606–11
3. McQuillen PS, Nishimoto MS, Bottrell CL, Fineman LD, Hamrick SE, Glidden DV, Azakie A, Adatia I, Miller SP: Regional and central venous oxygen saturation monitoring following pediatric cardiac surgery: Concordance and association with clinical variables. Pediatr Crit Care Med 2007; 8:154–60
4. Duke T, Butt W, South M, Karl TR: Early markers of major adverse events in children after cardiac operations. J Thorac Cardiovasc Surg 1997; 114:1042–52
5. Liakopoulos OJ, Ho JK, Yezbick A, Sanchez E, Naddell C, Buckberg GD, Crowley R, Mahajan A: An experimental and clinical evaluation of a novel central venous catheter with integrated oximetry for pediatric patients undergoing cardiac surgery. Anesth Analg 2007; 105:1598–604
6. Basaran M, Sever K, Kafali E, Ugurlucan M, Sayin OA, Tansel T, Alpagut U, Dayioglu E, Onursal E: Serum lactate level has prognostic significance after pediatric cardiac surgery. J Cardiothorac Vasc Anesth 2006; 20:43–7

7. Siegel LB, Dalton HJ, Hertzog JH, Hopkins RA, Hannan RL, Hauser GJ: Initial postoperative serum lactate levels predict survival in children after open heart surgery. Intensive Care Med 1996; 22:1418–23
8. Toraman F, Evrenkaya S, Yuce M, Aksoy N, Karabulut H, Bozkulak Y, Alhan C: Lactic acidosis after cardiac surgery is associated with adverse outcome. Heart Surg Forum 2004; 7:E155–9
9. Pong S, Seto W, Abdolell M, Trope A, Wong K, Herridge J, Harvey E, Kavanagh BP: 12-hour *versus* 24-hour creatinine clearance in critically ill pediatric patients. Pediatr Res 2005; 58:83–8
10. Wernovsky G, Wypij D, Jonas RA, Mayer JE, Jr., Hanley FL, Hickey PR, Walsh AZ, Chang AC, Castañeda AR, Newburger JW, Wessel DL: Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. Circulation 1995; 92:2226–35
11. Custer JW Rau RE, Lee CK (Eds.): The Harriet Lane Handbook, 18th edition. Philadelphia, Mosby/Elsevier, 2009
12. Muir AL, Kirby BJ, King AJ, Miller HC: Mixed venous oxygen saturation in relation to cardiac output in myocardial infarction. BMJ 1970; 4:276–8
13. Rady MY, Rivers EP, Nowak RM: Resuscitation of the critically ill in the ED: Responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate. Am J Emerg Med 1996; 14:218–25
14. Multicentre study on peri- and postoperative central venous oxygen saturation in high-risk surgical patients. Crit Care 2006; 10:R158
15. Bracht H, Hanggi M, Jeker B, Wegmuller N, Porta F, Tuller D, Takala J, Jakob SM: Incidence of low central venous oxygen saturation during unplanned admissions in a multidisciplinary intensive care unit: An observational study. Crit Care 2007; 11:R2
16. Wratney AT: Central venous saturation as a predictor of extubation failure. Crit Care Med;38: 708–9
17. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED: Changes in central venous saturation after major surgery, and association with outcome. Crit Care 2005; 9:R694–9
18. Rady MY, Rivers EP, Martin GB, Smithline H, Appelton T, Nowak RM: Continuous central venous oximetry and shock index in the emergency department: Use in the evaluation of clinical shock. Am J Emerg Med 1992; 10:538–41
19. Scalea TM, Hartnett RW, Duncan AO, Atweh NA, Phillips TF, Sclafani SJ, Fuortes M, Shaftan GW: Central venous oxygen saturation: A useful clinical tool in trauma patients. J Trauma 1990; 30:1539–43
20. Rivers EP, Martin GB, Smithline H, Rady MY, Schultz CH, Goetting MG, Appleton TJ, Nowak RM: The clinical implications of continuous central venous oxygen saturation during human CPR. Ann Emerg Med 1992; 21:1094–101
21. Rivers EP, Rady MY, Martin GB, Fenn NM, Smithline HA, Alexander ME, Nowak RM: Venous hyperoxia after cardiac arrest. Characterization of a defect in systemic oxygen utilization. Chest 1992; 102:1787–93
22. Di Filippo A, Gonnelli C, Perretta L, Zagli G, Spina R, Chiostri M, Gensini GF, Peris A: Low central venous saturation predicts poor outcome in patients with brain injury after major trauma: A prospective observational study. Scand J Trauma Resusc Emerg Med 2009; 17:23
23. Hamamoto M, Imanaka H, Kagisaki K, Yagihara T, Kitamura S, Nishimura M: Is an increase in lactate concentration associated with cardiac dysfunction after the Fontan procedure? Ann Thorac Cardiovasc Surg 2005; 11:301–6
24. Trittenwein G, Pansi H, Graf B, Golej J, Burda G, Hermon M, Marx M, Wollenek G, Trittenwein H, Pollak A: Proposed entry criteria for postoperative cardiac extracorporeal membrane oxygenation after pediatric open heart surgery. Artif Organs 1999; 23:1010–4
25. Mestrovic J, Ercegovic I, Polic SL, Omazic A, Capkun V: Use of central venous catheters in children. Signa Vitae 2006; 1:20–4

Appendix. Patient Characteristics

Patient	Age	Weight (kg)	Diagnosis	Procedure	Aristotle Basic Score
1	6 days	3.7	Dextro-transposition of the great arteries	Arterial switch	10.0
2	11 days	4.5	Dextro-transposition of the great arteries	Arterial switch; atrial septal defect closure	10.0
3	1 month	3.1	Aortic valve canal; patent ductus arteriosus	Aortic valve canal repair; patent ductus arteriosus band; patent ductus arteriosus ligation	9.0
4	2 months	4.3	Coarctation of aorta	Aortic arch augmentation	7.0
5	3 months	6.7	Tetralogy of fallot	Tetralogy of fallot repair; ventricular septal defect closure	8.0
6	4 months	4.5	Ventricular septal defect; atrial septal defect	Repair atrial septal defect and ventricular septal defect	6.0
7	4 months	6.0	Aortic valve canal	Aortic valve canal repair	9.0
8	5 months	5.7	Tetralogy of fallot	Tetralogy of fallot repair	8.0
9	5 months	3.9	Ventricular septal defect	Ventricular septal defect repair	6.0
10	6 months	5.6	Total anomalous pulmonary venous return	Total anomalous pulmonary venous return repair; atrial septal defect closure	9.0
11	7 months	8.5	Atrial septal defect; subpulmonic ventricular septal defect	Ventricular septal defect closure	6.0
12	9 months	7.5	Tetralogy of fallot; patent ductus arteriosus	Tetralogy of fallot repair; ventricular septal defect closure	8.0
13	10 months	10.0	Pulmonary valve atresia	Resection right ventricular outflow tract muscle; replace right ventricle to pulmonary artery conduit	8.0
14	10 months	5.9	Dextro-transposition of the great arteries	Senning procedure with patent ductus arteriosus ligation	8.5
15	1 year	10.0	Tetralogy of fallot	Tetralogy of fallot repair; ventricular septal defect closure	8.0
16	1 year	8.8	Aortic valve canal defect	Aortic valve canal repair	9.0
17	1 year	7.7	Tetralogy of fallot	Tetralogy of fallot repair; pulmonary artery banding; take down of central shunt	8.0
18	1 year	11.0	Tetralogy of fallot	Tetralogy of fallot repair	8.0
19	1 year	9.5	Ventricular septal defect	Ventricular septal defect repair; patent ductus arteriosus closure	6.0
20	2 years	10.0	Tetralogy of fallot, pulmonary atresia	Tetralogy of fallot repair; right ventricle to pulmonary artery conduit; repair pulmonary atresia	9.0
21	2 years	8.6	Pulmonary atresia, discontinuous pulmonary arteries	Redo aorta to left pulmonary artery shunt	6.8
22	2 years	14.3	Coarctation of aorta	Subvalvular aortic stenosis	6.3
23	2 years	11.4	Coarctation of aorta	Coarctation of aorta	8.0
24	2 years	12.9	Atrial septal defect	Partial anomalous pulmonary venous return repair; atrial septal defect closure; patent ductus arteriosus repair; ventricular septal defect closure	6.0
25	2 years	9.0	Atrial septal defect; transposition of the great arteries	Transposition of the great arteries repair; atrial baffle; senning procedure	8.5
26	3 years	14.0	Tetralogy of fallot	Tetralogy of fallot repair; ventricular septal defect closure; augmentation right ventricular outflow tract	9.0
27	3 years	12.8	Ischemic cardiomyopathy; redo orthotopic heart transplant	Orthotopic heart transplant	9.3

(*continued*)

Appendix. Continued

Patient	Age	Weight (kg)	Diagnosis	Procedure	Aristotle Basic Score
28	3 years	15.2	Ventricular septal defect; patent ductus arteriosus; aortic valve insufficiency	Ventricular septal defect, atrial septal defect repair; aortic valve repair/replacement; resection subaortic stenosis and right ventricular outflow tract	6.5
29	3 years	10.4	Dextro-transposition of the great arteries	Rastelli	10.0
30	3 years	13.2	Mitral atresia; pulmonary stenosis	Fontan	9.0
31	4 years	16.4	Ventricular septal defect	Ventricular septal defect repair	6.0
32	4 years	17.6	Ventricular septal defect	Ventricular septal defect closure; subaortic membrane resection; right ventricular outflow tract repair	6.5
33	4 years	14.0	Tetralogy of fallot	Atrial septal defect repair and ventricular septal defect repair; right ventricle to pulmonary artery conduit	8.0
34	4 years	18.0	Pulmonary valve atresia	Fontan	9.0
35	4 years	13.1	Pulmonary valve atresia; double outlet right ventricle	Fontan	9.0
36	5 years	21.0	Atrial septal defect	Atrial septal defect repair; partial anomalous pulmonary venous return; patch to superior vena cava	3.0
37	5 years	18.0	Ventricular septal defect	Ventricular septal defect and atrial septal defect closures	6.0
38	5 years	15.5	Hypoplastic left heart syndrome	Fontan	9.0
39	5 years	17.0	Left ventricular outflow tract obstruction; subaortic stenosis	Homograft pulmonary valve repair/replacement and left ventricle apical to aortic replacement	6.5
40	5 years	19.0	Pulmonary valve atresia; subpulmonic stenosis	Resection right ventricular outflow tract obstruction; infundibular stenosis	6.5
41	6 years	21.0	Double inlet left ventricle	Fontan	9.0
42	6 years	21.3	Double inlet left ventricle	Redo fontan completion	9.0
43	7 years	18.5	Tetralogy of fallot	Tetralogy of fallot repair; ventricular septal defect closure; resection right ventricular outflow tract	8.0
44	7 years	22.6	Tetralogy of fallot	Redo right ventricle to pulmonary artery conduit; aortic valve repair/replacement	7.5
45	7 years	22.0	Double outlet right ventricle; hypoplastic left heart syndrome	Fontan	9.0
46	7 years	20.7	Tricuspid atresia	Fontan	9.0
47	8 years	24.0	Pulmonary atresia; tetralogy of fallot	Redo right ventricle to pulmonary artery conduit; repair pulmonary atresia	9.0
48	8 years	23.6	Tricuspid atresia/stenosis status post pulmonary artery band	Fontan	9.0
49	9 years	23.0	Pulmonary insufficiency, status post tetralogy of fallot repair	Redo pulmonary valve repair/replacement	6.5
50	10 years	28.0	Conduit stenosis; truncus arteriosus	Repair pulmonary atresia; redo right ventricle to pulmonary artery conduit	8.0