Medicine®

CLINICAL TRIAL/EXPERIMENTAL STUDY

OPEN

Effects of Hypothermic Cardiopulmonary Bypass on Internal Jugular Bulb Venous Oxygen Saturation, Cerebral Oxygen Saturation, and Bispectral Index in Pediatric Patients Undergoing Cardiac Surgery: A Prospective Study

Zhiyong Hu, MD, Lili Xu, MD, Zhirui Zhu, MD, Robert Seal, MD, and Patrick M. McQuillan, MD

Abstract: The objective of this study was to evaluate the effect of hypothermic cardiopulmonary bypass (CPB) on cerebral oxygen saturation (rSO2), internal jugular bulb venous oxygen saturation (SjvO2), mixed venous oxygen saturation (SvO2), and bispectral index (BIS) used to monitor cerebral oxygen balance in pediatric patients.

Sixty American Society of Anesthesiologists Class II-III patients aged 1 to 4 years old with congenital heart disease scheduled for elective cardiac surgery were included in this study. Temperature, BIS, rSO_2, mean arterial pressure, central venous pressure, cerebral perfusion pressure (CPP), and hematocrit were recorded. Internal jugular bulb venous oxygen saturation and SvO_2 were obtained from blood gas analysis at the time points: after induction of anesthesia (T0), beginning of CPB (T1), ascending aortic occlusion (T2), 20 minutes after initiating CPB (T3), coronary reperfusion (T4), separation from CPB (T5), and at the end of operation (T6). The effect of hypothermia or changes in CPP on rSO_2, $SjvO_2$, SvO_2, and BIS were analyzed.

Compared with postinduction baseline values, rSO_2 significantly decreased at all-time points: onset of extracorporeal circulation, ascending aortic occlusion, 20 minutes after CPB initiation, coronary reperfusion, and separation from CPB ($P < 0.05$). Compared with measurements made following induction of anesthesia, $SjvO_2$ significantly increased with initiation of CPB, ascending aortic occlusion, 20 minutes after initiating CPB, coronary reperfusion, and separation from CPB ($P < 0.05$). Compared with induction of anesthesia, BIS significantly decreased with the onset of CPB, aortic cross clamping, 20 minutes after initiating CPB, and coronary reperfusion ($P < 0.05$). Bispectral index increased following separation from CPB. There was no significant change in SvO_2 during cardiopulmonary bypass ($P > 0.05$). Correlation analysis demonstrated that rSO_2 was positively related to CPP ($r = 0.687$, $P = 0.000$), with a low linear correlation to temperature ($r = 0.453$, $P = 0.000$). Internal jugular bulb venous oxygen saturation was negatively related to temperature ($r = -0.689$, $P = 0.000$). Bispectral index was positively related to both temperature ($r = 0.824$, $P = 0.000$) and CPP ($r = 0.782$, $P = 0.000$). Cerebral oxygen saturation had a positive linear correlation with CPP and a low linear correlation to temperature. Internal jugular bulb venous oxygen saturation had a negative linear correlation to temperature.

Pre-and and early postbypass periods are vulnerable times for adequate cerebral oxygenation. Anesthetic management must aim to optimize the supply and demand relationship.

(*Medicine* 95(2):e2483)

Abbreviations: ASA = American Society of Anesthesiologists, BIS = bispectral index, CaO_2 = arterial O_2 content, CEO_2 = cerebral oxygen extraction rate, $CjvO_2$ = internal jugular venous O_2 content, CPB = cardiopulmonary bypass, CPP = cerebral perfusion pressure, CVP = central venous pressure, Da-jvLac = lactate content differences, Da-jvO_2 = arteriovenous O_2 content difference, EEG = electroencephalography, Hb = hemoglobin, Hct = hematocrit, Lac = arterial lactate concentrations, Lacjv = jugular venous lactate concentrations, MAP = mean arterial pressure, NIRS = Near-infrared spectroscopy, $PaCO_2$ = arterial blood carbon dioxide partial pressure, PaO_2 = arterial blood oxygen partial pressure, $PjvCO_2$ = internal jugular vein carbon dioxide partial pressure, $PjvO_2$ = internal jugular venous blood oxygen partial pressure, $PvCO_2$ = mixed venous carbon dioxide partial pressure, rSO_2 = cerebral oxygen saturation, SaO_2 = arterial oxyhemoglobin saturation, $SjvO_2$ = internal jugular bulb venous oxygen saturation, SvO_2 = mixed venous oxygen saturation, SvO_2 = mixed venous oxygen saturation, TCD = Transcranial Doppler.

INTRODUCTION

Perioperative and postoperative injury of the central nervous system is one of the most severe complications in children for cardiac surgery with cardiopulmonary bypass (CPB).[1] Moreover, children less than 4 years of age are more likely

Editor: Kazuo Hanaoka.
Received: October 17, 2015; revised and accepted: December 11, 2015.
From the Department of Anesthesiology, School of Medicine, The Children's Hospital, Zhejiang University (ZH, ZZ); Department of Anesthesiology, The Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China (LX); Department of Anesthesia and Pain Medicine, Stollery Children's Hospital, University of Alberta, Edmonton, Canada (RS); and Department of Anesthesiology, Penn State Hershey Medical Center, Penn State College of Medicine, Hershey, PA (PMM).
Correspondence: Zhiyong Hu, MD, Department of Anesthesiology, School of Medicine, The Children's Hospital, Zhejiang University, Hangzhou, China (e-mail: huzhiyong777@126.com).
The trial was registered at the Chinese Clinical Trial Registry (ChiCTR) (www.chictr.org), registration number ChiCTR-ONRC-14005050.
Author's Contributions: Zhiyong Hu: study design, patient recruitment, data collection, data analysis, and article preparation.
Lili Xu: study design, patient recruitment, data collection, data analysis, and article preparation (xulili1202@hotmail.com).
Zhirui Zhu: patient recruitment and data collection (zzr9750@163.com).
Robert Seal: manuscript preparation and revision (rseal@ualberta.ca).
Patrick M. McQuillan: article preparation and revision (pmcquillan@hmc.psu.edu).
This work was supported by the National Natural Science Foundation of China (81471240)(81400929), the Science and Technology Agency, Zhejiang, China (2014C33170), the Medical Technology Project, Zhejiang, China (2016KYA152)(2013ZDA011), and the clinical scientific research fund of the Chinese Medical Association (13081370522).
The authors have no conflicts of interest to declare

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002483

to have cerebral ischemia caused by hypotension during cardiac surgery.[1] Cardoso et al[2] has shown that although the detailed mechanism of brain damage was unclear, cerebral oxygen supply and demand imbalances caused by cerebral hypoperfusion or cerebral embolism formation were the main causes of brain damage. Nonphysiologic conditions during cardiopulmonary bypass, including hypothermia, hypotension, hemodilution, and nonpulsatile blood flow interfere with the normal cerebral oxygen supply and demand balance and make it difficult to monitor changes by conventional methods.

At present, cerebral oxygen saturation (rSO_2), mixed venous oxygen saturation (SvO2) and bispectral index (BIS) have been used to monitor cerebral oxygen supply and demand balance in pediatric patients undergoing cardiac surgery. Cerebral oxygen saturation,[3] however, reflects mainly local cerebral (the frontal lobes) venous blood oxygen saturation and may miss cerebral ischemia outside of the detected area. BIS[4] reflects mainly local cerebral cortical electrical activity and has been shown to represent the hypnotic component of the anesthetic state. Internal jugular bulb venous oxygen saturation[5] reflects global systemic oxygen supply and demand, not specifically cerebral supply and demand.

Internal jugular bulb venous oxygen saturation[6] can accurately reflect the relationship between cerebral blood flow and cerebral oxygen consumption. It has been reported[7,8] that a significant positive linear correlation exists between rSO_2 and $SjvO_2$ in children undergoing cardiac catheterization. Therefore, whether rSO_2, SvO_2, or BIS can offer a noninvasive, real time, reliable, and practicable means of monitoring cerebral hemoglobin oxygenation changes in children with noncyanotic congenital heart disease during cardiopulmonary bypass is still uncertain. This study aims to evaluate the value of monitoring rSO_2 $SjvO_2$, SvO_2, and BIS as an assessment of cerebral oxygen supply and demand balance during children's heart surgery. Such measures may contribute to the prevention and early detection of central nervous system complications and aid in providing brain protection during hypothermic cardiopulmonary bypass.

METHODS

This was a prospective trial performed in Department of Anesthesiology, The Children's Hospital, School of Medicine, Zhejiang University. Ethical approval for this study (Ethical Committee No. 2014112) was provided by the Ethical Committee of the Children's Hospital, School of Medicine, Zhejiang University, Hangzhou, China (Chairman, Zhengyan Zhao). Informed consent was obtained from the parents of the patients. Sixty ASA II-III patients included in this study were comprises 31 boys and 29 girls with an age range of 1 to 4 years (mean age 2.6 ± 1.2 years) and a weight range of 7 to 17 kg (mean weight 12.5 ± 4.4 kg) with congenital heart disease scheduled for elective cardiac surgery (Table 1). All patients were diagnosed with either an atrial or ventricular septal defect by preoperative echocardiogram. Patients with asthma, neurologic disease, or abnormal renal or hepatic function were excluded from the study. Patients received no anesthetic premedication. After arriving the operating room and application of routine noninvasive monitors, an inhalation induction with 8% sevoflurane and oxygen by mask was performed. Following placement of an intravenous line, Ringer solution was infused. All patients received midazolam (0.2 mg/kg), etomidate (0.3 mg/kg), rocuronium (0.6 mg/kg), sufentanil (0.5 μg/kg), atropine (0.01 mg/kg), and dexamethasone (0.3 mg/kg) before tracheal intubation.

TABLE 1. Demographic Data (Mean ± Standard Deviation)

Sex (male/female)	31/29
Age, y	2.6 ± 1.2
Weight (kg)	12.5 ± 4.4
American Society of Anesthesiologists (II/III)	38/22
Duration of surgery (minutes)	93 ± 11
Hematocrit (%) (cardiopulmonary bypass)	24.7 ± 2.8

Mean ± SD was given in age, weight, and duration of surgery.

After intubation and institution of intermittent positive pressure ventilation, radial arterial and internal jugular venous catheters were inserted. One internal jugular catheter was directed toward the superior vena cava and the other toward the jugular bulb (with the tip of the catheter at the level of external auditory canal confirmed by echocardiogram). Intraoperative monitoring consisted of 5-lead electrocardiography (with ST-segment analysis), invasive arterial blood pressure, central venous pressure (CVP), pulse oximetry, capnography, nasopharyngeal and rectal temperature, and urine output. After the forehead skin was cleaned with 70% ethyl alcohol, BIS electrodes (VISTA, Aspect Medical Systems, Inc., Norwood, USA) and a near infrared cerebral oxygen probe (Fore-sight, MC-2030cv cerebral oximeter, CAS Medical Systems, Inc., Branford, USA) were positioned according to the manufacturer's recommendations. All patients received the same anesthetic maintained with inhalation of sevoflurane (1%–2% end-tidal concentration) with oxygen with the addition of sufentanil (0.5 μg/kg) and rocuronium (0.6 mg/kg) before initiating CPB. Cardiopulmonary bypass was performed using standard techniques according to the age, weight, and hematocrit (Hct) of the patients. The membrane oxygenator was primed with both crystalloid and colloid. Mannitol, albumin, or blood products were added to the circuit as needed. Cardiac cannulation was performed after intravenous injection of heparin (400–450 U/kg). Confirmation of a kaolin-activated clotting time (ACT-plus; Medtronic Inc, Minneapolis, MN) value exceeding 450 seconds was obtained before initiating CPB. Perfusion flow was maintained at 100 mL/kg/min and Hct was maintained above 20% whereas perfusion temperature was reduced to 29.5 °C. Protamine was used to neutralize heparin according to a 1.5:1 ratio. Ultrafiltration was used in all patients after bypass. Temperature, BIS, rSO2, MAP, CVP, cerebral perfusion pressure (CPP) (determined as $CPP = MAP - CVP$)[9] and Hct were recorded. Blood samples were collected from the jugular venous bulb catheter, the confluence drainage tube from the superior and inferior vena cava catheters, and radial arterial catheter for blood gas analysis by ABL 700 blood-gas analyzer (Radiometer Co, Denmark) and determination of $SjvO_2$, internal jugular vein carbon dioxide partial pressure, SvO_2, mixed venous carbon dioxide partial pressure, arterial oxyhemoglobin saturation), arterial blood oxygen partial pressure(PaO_2), arterial blood carbon dioxide partial pressure, internal jugular venous blood oxygen partial pressure, hemoglobin, arterial lactate concentrations , and jugular venous lactate concentrations after induction of anesthesia (T0), beginning of cardiopulmonary bypass (CPB) (T1), ascending aortic occlusion (T2), 20 minutes after instituting CPB (T3), coronary reperfusion (T4), separation from CPB (T5), and at the end of operation (T6). Arterial O_2 content, internal jugular venous O_2 content, arteriovenous O_2 content difference, cerebral oxygen extraction rate, and lactate content differences were

calculated by the Fick formula (Appendix 1). The effect of hypothermia or changes in CPP on rSO_2, $SjvO_2$, SvO_2, and BIS were analyzed.

Statistical Analysis

SPSS 17.0 (SPSS, Inc., Chicago, IL) was used for statistical analysis. A minimum required sample size per group of 30 was determined to be needed to detect an anticipated effect size of 0.75, and a desired statistical power level of 0.8 at a probability level of 0.05. Numerical data including rSO_2, $SjvO_2$, SvO_2, BIS, MAP, CVP, CPP, Hct, and temperature, were analyzed by repeated measures analysis of variance. The effect of hypothermia or changes in CPP on rSO_2, $SjvO_2$, SvO_2, and BIS were performed by a multiple linear regression analysis. Statistical significance was accepted as $P < 0.05$.

RESULTS

Compared with the initial measurements following the induction of anesthesia, rSO_2 significantly decreased at all-time points following the onset of CPB ($P < 0.05$) (Table 2, Fig. 1). As compared with initial postinduction measurements, BIS significantly decreased at all measurement points whilst on CPB ($P < 0.05$), and then increased following separation from CPB (Table 2). As compared with following induction of anesthesia, $SjvO_2$ significantly increased with initiation of CPB and remained elevated at subsequent points while on CPB ($P < 0.05$) (Table 3). There was no significant change in SvO_2 during cardiopulmonary bypass ($P > 0.05$) (Table 3). Correlation analysis revealed that rSO_2 had weak linear correlation with temperature ($r = 0.453$, $P = 0.000$) and Hct ($r = 0.523$, $P = 0.000$) but had a positive correlation to CPP ($r = 0.687$, $P = 0.000$) (Table 4, Fig. 2). Internal jugular bulb venous oxygen saturation was inversely related to temperature ($r = -0.689$, $P = 0.000$), whereas BIS was positively related to temperature ($r = 0.824$, $P = 0.000$) and CPP ($r = 0.782$, $P = 0.000$) (Table 4).

DISCUSSION

In this study, we found that rSO_2 had positive correlation to CPP. Cerebral oxygen saturation also had a weak linear correlation with temperature. Bispectral index had a positive linear correlation with both temperature and CPP whereas $SjvO_2$ had a negative linear correlation with temperature. Cerebral oxygen saturation reflects whether or not the brain is getting enough blood flow and oxygen.

Cerebral oxygen saturation monitoring[3] uses a noninvasive optical probe placed on the forehead skin to penetrate body tissues to the depth of the cerebral cortex with near infrared (65–1100 mm) light so as to obtain the cerebral blood oxygen saturation of a zone of cerebral circulation comprised of small arteries, capillaries and venules. Venules account for 80% of the normal baseline value of $72 \pm 6\%$. Unlike peripheral pulse oximetry, rSO_2 also can be used during extracorporeal circulation and hypothermic circulatory arrest as no pulsatility is required for signal acquisition.[10]

The pre-bypass and early postbypass phases are vulnerable times for the provision of adequate cerebral oxygenation because of blood-pressure instability at a time when the brain is not yet protected by hypothermia. Our study showed that rSO_2 gradually decreased following the onset of CPB and dipped at the time of aortic cross clamping. This is attributed to the decreased MAP and CPP. After this point, rSO_2 gradually increased during CPB. Additional contributing factors at this point in time include hemodilution, PaO_2, reduced oxygen release and the hypothermia-induced reduction in cerebral oxygen metabolism.[11]

Our study demonstrated that coronary reperfusion and rewarming were associated with a gradual decrease in rSO_2 to its nadir. During rewarming, cerebral metabolism and oxygen consumption increases in excess of the increase in cerebral blood flow. With Transcranial Doppler, others have shown that after rewarming, cerebral blood flow velocity increased 65% whilst rSO_2 fell 25%.[12] At the commencement of rewarming, cerebral oxygen supply may be compromised by a reduced cerebral instantaneous perfusion flow and a low CPP at a time when temperature and cerebral metabolism is increasing. It has been recommended that an rSO_2 less than 35% should be avoided during CPB to prevent depletion of brain tissue oxygen stores and potential brain damage.[13] Therefore, vigilance is required during rewarming in order that it should not be too rapid. As well, 1 must ensure adequate cerebral perfusion by supporting the systemic arterial pressure (and hence the CPP) through the use of vasoconstrictors (such as phenylephrine). Cereberal oxygen delivery during this phase can be further aided by improving the Hct by transfusion, diuresis, and ultrafiltration.[14] The blood gas analysis results of jugular venous bulb, superior and inferior vena cava, and radial arterial

TABLE 2. Changes in Temperature, Mean Arterial Pressure, Central Venous Pressure, Cerebral Perfusion Pressure, Bispectral Index, Cerebral Oxygen Saturation, and Hematocrit (Mean ± Standard Deviation)

Time	Temperature (°C)	MAP (mm Hg)	CVP (mm Hg)	CPP (mm Hg)	BIS	rSO_2 (%) Average	Hct (%)
T0	36.3 ± 0.4	56.7 ± 2.8	7.8 ± 1.4	48.9 ± 2.9	60.7 ± 4.4	72.3 ± 8.0	33.5 ± 2.7
T1	35.2 ± 1.1	42.6 ± 5.3	7.3 ± 1.4	35.3 ± 5.8	52.3 ± 6.5*	59.8 ± 7.5*	24.3 ± 2.3
T2	32.6 ± 1.7	31.9 ± 4.2	7.1 ± 1.8	24.8 ± 4.2	42.2 ± 5.0*	49.3 ± 5.0*	24.0 ± 2.1
T3	30.9 ± 1.7	40.3 ± 5.0	8.2 ± 1.8	32.0 ± 5.0	40.1 ± 4.8*	63.6 ± 7.3*	24.5 ± 2.2
T4	29.5 ± 1.8	31.6 ± 3.6	8.4 ± 1.7	23.0 ± 3.2	37.7 ± 4.1*	47.4 ± 5.5*	24.5 ± 1.8
T5	36.0 ± 0.8	51.9 ± 7.9	8.7 ± 1.6	44.0 ± 7.8	58.8 ± 7.5	58.1 ± 7.1*	27.4 ± 2.6
T6	36.6 ± 0.4	62.0 ± 5.7	9.1 ± 1.6	52.9 ± 5.9	63.8 ± 4.7*	69.0 ± 7.4*	31.7 ± 2.6

CPP = MAP − CVP.
BIS = bispectral index, CPP = cerebral perfusion pressure, CVP = central venous pressure, Hct = hematocrit, rSO_2 = cerebral oxygen saturation.
* $P < 0.05$ from T0.

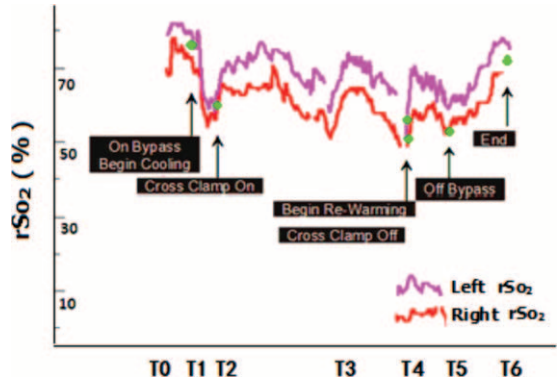

FIGURE 1. Changes in cerebral oxygen saturation during cardiopulmonary bypass. As compared with after induction of anesthesia, cerebral oxygen saturation significantly decreased at the point of beginning cardiopulmonary bypass, aortic occlusion, 20 minutes after extracorporeal circulation, coronary reperfusion, and extracorporeal circulation withdrawal ($P < 0.05$).

(including the changes in arterial O_2 content, arteriovenous O_2 content difference, cerebral oxygen extraction rate, and lactate content differences) demonstrate that cerebral oxygen extraction and cerebral oxygen consumption are significantly reduced as temperature decreases. During rewarming, they increase in excess of the increase in cerebral blood flow, reflecting a change in cerebral cellular oxygen supply and demand during CPB. These changes are consistent with the results for rSO_2 (Table 5).

Brain tissue is very sensitive to ischemia and hypoxia. Changes in cerebral blood flow (CBF) are known to be proportional to changes in CPP. In our study, rSO_2 had a positive linear correlation with CPP, determined as CPP = MAP − CVP.[9] These findings are consistent with the results of Menke et al[9] who went on to state that near-infrared spectroscopy (NIRS) may therefore become a monitoring device for the neuroprotective optimization of parameters influencing cerebral perfusion. Their study, however, showed that rSO_2 correlated inversely with body temperature, which may be because of the differences in the population of patients and types of surgery. In addition, the changes in rSO_2, BIS, CPP, and MAP during cardiopulmonary bypass showed that rSO_2 changed with the change of MAP and CPP indicating the 3 values are clearly closely related (Fig. 2).

TABLE 3. Changes in Internal Jugular Bulb Venous Oxygen Saturation, Internal Jugular Vein Carbon Dioxide Partial Pressure, Mixed Venous Oxygen Saturation, and Mixed Venous Carbon Dioxide Partial Pressure (Mean ± Standard Deviation)

Time	$SjvO_2$ (%)	$PjvCO_2$ (mm Hg)	SvO_2 (%)	$PvCO_2$ (mm Hg)
T0	56.6 ± 6.1	43.6 ± 4.4	ND	ND
T1	68.5 ± 7.7*	44.5 ± 4.9	78.8 ± 4.3	46.2 ± 3.5
T2	74.2 ± 6.5*	46.6 ± 4.9	81.1 ± 4.7	44.8 ± 5.3
T3	77.5 ± 6.1*	45.4 ± 4.0	82.8 ± 5.7	45.2 ± 5.3
T4	79.3 ± 4.7*	47.1 ± 4.2	82.1 ± 4.4	46.7 ± 4.6
T5	62.0 ± 7.1*	46.7 ± 4.9	80.5 ± 4.4	46.1 ± 5.4

$PjvCO_2$ = internal jugular vein carbon dioxide partial pressure, $PvCO_2$ = mixed venous carbon dioxide partial pressure, $SjvO_2$ = internal jugular bulb venous oxygen saturation, SvO_2 = mixed mixed venous oxygen saturation.
* $P < 0.05$ from T0.

Blood flows from cerebral venous sinuses into the internal jugular venous bulb. The bulb is the dilated orifice of the origin of the internal jugular vein. As samples at this level are not contaminated by blood from the external jugular vein, $SjvO_2$ can accurately reflect the relationship between cerebral oxygen supply and oxygen consumption.[15] The normal baseline value of $SjvO_2$ is 54% to 75%.[16] Cerebral oxygen supply more than meets cerebral oxygen consumption if its value is more than 75%. Values less than 50% mean that cerebral oxygen supply is less than the cerebral oxygen consumption. If CBF cannot meet the needs of cerebral oxygen metabolism, hypoperfusion related hypoxia may ensue. When $SjvO_2$ is less than 40%, cerebral anoxia may occur.[16] Alten et al[17] reported that a $SjvO_2$ less than 55% was associated with a 2-fold increase in poor neurologic prognosis. Internal jugular bulb venous oxygen saturation is also influenced by changes in CPB, temperature, whole body pH, blood pressure, oxygenator type, and patient age.

Our study demonstrates that $SjvO_2$ gradually increases as body temperature decreases and reaches the highest point 20 minutes after the onset of CPB. During coronary reperfusion and rewarming, $SjvO_2$ gradually decreases. These changes are consistent with the expected changes in cerebral metabolic rate and hence oxygen demand that occur with temperature changes. Similar changes have been described during adult CPB.[18] In addition, our study found a negative correlation between $SjvO_2$ and temperature, supporting the important influence of temperature on cerebral oxygen supply and demand balance during CPB in pediatric congenital heart surgery. Mixed venous oxygen saturation reflects the systemic oxygen supply and demand balance as influenced by hemodynamic changes. Stein et al[19] evaluated the relationship between anesthetic depth measuring BIS and SvO_2 in patients undergoing cardiac surgery with cardiopulmonary bypass. They found there was no overall association between BIS and SvO_2 suggesting that low SvO_2 values on bypass are unlikely to be because of light or inadequate anesthesia. The relationship between temperature, BIS and SvO_2 deserves further study. Mixed venous oxygen saturation is always higher than $SjvO_2$ and is positively correlated with $SjvO_2$ and temperature.[20] We speculate that cerebral oxygen consumption and hence $SjvO_2$ is more sensitive to changes in organ temperature than whole body oxygen consumption as reflected by SvO_2.

Bispectral index is an index value computed from electroencephalography subparameters, including frequency, amplitude, phase, bispectral, spectral, quazi suppression, and time domain (burst suppression ratio) parameters giving rise to a value between 99 (awake) and 0 (no electrical brain activity).[21] Bispectral index can directly reflect electric activity of the cerebral cortex and is negatively correlated with degree of sedation. It can also reflect the degree of inhibition of brain metabolism by anesthetic agents where a BIS = 0 indicates the cessation of cerebral cortical neuronal activity. The depth of either anesthesia or sedation correlates with changes in BIS. Hypotension, hemodilution, nonpulsatile blood flow, changes in cerebral blood flow, temperature and blood gas during CPB, however, can also have a confounding influence.[22] Our results demonstrate that the BIS significantly decreased at all points while on CPB and increased after separation from CPB. A component of this change of BIS is attributed to the linear correlation that we found with hypothermia. There are several reasons for these findings: Firstly, cerebral blood flow is related to both systemic blood pressure and systemic blood flow. When

TABLE 4. Relation of Cerebral Oxygen Saturation, Internal Jugular Bulb Venous Oxygen Saturation, Mixed Venous Oxygen Saturation, or Bispectral Index to Temperature, Cerebral Perfusion Pressure or Hematocrit

	rSO_2		$SjvO_2$		SvO_2		BIS	
	Regression Coefficients	*P* Value	Regression Coefficients	*P* Value	Regression Coefficients	*P* Value	Regression Coefficients	*P* Value
Temperature	0.453	0.000	−0.689	0.000	−0.192	0.005	0.824	0.000
CPP	0.687	0.000	−0.635	0.000	ND	ND	0.782	0.000
Hct	0.523	0.000	−0.571	0.000	−0.007	0.330	ND	ND

BIS = bispectral index, CPP = cerebral perfusion pressure, Hct = hematocrit, rSO2 = cerebral oxygen saturation, SjvO2 = internal jugular bulb venous oxygen saturation, SvO2 = mixed venous oxygen saturation.

FIGURE 2. Changes in cerebral oxygen saturation, bispectral index, cerebral perfusion pressure, and mean arterial pressure during cardiopulmonary bypass. Cerebral oxygen saturation changed with the change of mean arterial pressure and cerebral perfusion pressure indicating the 3 values are clearly closely related.

the perfusion flow rate is constant, decreases in peripheral vascular resistance and MAP because of hemodilution during CPB may lower CPP. Artificial oxygenation may lead to a high PaO_2 and low $PaCO_2$, which can also lead to decreased cerebral blood flow resulting in an inhibition of brain electrical activity. Secondly, hypothermia reduces brain cellular electrical activity in combination with overall body metabolism. The threshold of reaction to external stimuli increases under hypothermia whereas the transfer of neural electrical activity slows. Therefore, hypothermia has additive influence on the depth of anesthesia. When the temperature falls to 32 °C, the electroencephalogram begins to be suppressed and at 30 °C, consciousness is lost with an accompanying BIS value of 48 in 95% of patients .[23]

Our study also demonstrates that BIS is significantly reduced as temperature decreases. This suggests that the depth of anesthesia increases as the temperature decreases. During rewarming, the electrical activity of brain cells increases as demonstrated by an increasing BIS. This represents a decreasing depth of anesthesia. We speculate that BIS reflects the influence of temperature on depth of anesthesia as related to the adequacy of cerebral oxygen supply-demand balance.

There are some limitations to our study. Firstly, CPP was determined as CPP = MAP − CVP. A measurement based on cerebrospinal fluid pressure might more accurately reflect CPP but was realized to be excessively invasive for children undergoing total body heparinization for elective cardiac surgery. Secondly, although many cerebral oxygenation variables and values were measured in our study, cerebral blood flow itself was not measured. This can be performed with Transcranial Doppler but because of logistical and equipment limitations, it was not included. Thirdly, our study was limited by a relatively small number of patients (60). We plan to validate our results with a larger study. Near-infrared spectroscopy has inherent limitations. It measures blood oxygenation changes only within the illuminated area, which includes both intracranial and extracranial tissues and thus may be influenced by changes in scalp blood flow. In addition, NIRS do not measure cerebral blood oxygenation changes in the whole brain including deep brain structures.

In conclusion, rSO_2 had a positive correlation with CPP and a weak linear correlation with temperature. BIS had a positive linear correlation with temperature and CPP. $SjvO_2$

TABLE 5. Changes in Arterial O2 Content, Arteriovenous O2 Content Difference, Cerebral Oxygen Extraction Rate, and Lactate Content Differences (Mean ± Standard Deviation)

Time	CaO_2 (mL/L)	Da-jvO_2 (mL/L)	CEO_2 (%)	Da-jvLac (mmol/L)
T0	147.4 ± 5.5	51.3 ± 2.6	33.4 ± 3.9	0.19 ± 0.03
T1	106.2 ± 5.7*	37.0 ± 3.4*	28.6 ± 3.0*	0.18 ± 0.02*
T2	103.7 ± 7.6*	26.8 ± 3.4*	22.9 ± 3.0*	0.14 ± 0.02*
T3	104.6 ± 5.9*	19.5 ± 3.7*	18.3 ± 3.7*	0.14 ± 0.01*
T4	106.3 ± 6.8*	49.0 ± 3.2*	45.7 ± 3.2*	0.17 ± 0.02*
T5	108.8 ± 5.6*	45.0 ± 3.4*	44.5 ± 2.4*	0.16 ± 0.02*

CaO_2 = arterial O2 content, CEO_2 = cerebral oxygen extraction rate, Da-jvLac = arteriovenous O2 content difference.
* $P < 0.05$ from T0.

had a negative linear correlation with temperature. Cerebral oxygen saturation reflects whether or not the brain is getting enough blood flow and oxygen.

REFERENCES

1. Hayashida M, Kin N, Tomioka T, et al. Cerebral ischaemia during cardiac surgery in children detected by combined monitoring of BIS and near-infrared spectroscopy. *Br J Anaesth.* 2004;92:662–669.
2. Cardoso I, Acevedo K, Hernández M, et al. Refractory status epilepticus in children: characterisation of epilepsies, continuous electroencephalographic monitoring and response to treatment. *Rev Neurol.* 2013;56:401–408.
3. Sanchez-de-Toledo J, Chrysostomou C, Munoz R, et al. Cerebral regional oxygen saturation and serum neuromarkers for the prediction of adverse neurologic outcome in pediatric cardiac surgery. *Neurocrit Care.* 2014;21:133–139.
4. Romanov A, Moon RS, Wang M, et al. Paradoxical increase in the bispectral index during deep anesthesia in New Zealand white rabbits. *J Am Assoc Lab Anim Sci.* 2014;53:74–80.
5. Pan C, Zhang H, Liu J. Values of mixed venous oxygen saturation and difference of mixed venous-arterial partial pressure of carbon dioxide in monitoring of oxygen metabolism and treatment after open-heart operation. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue.* 2014;26:701–705.
6. Ikeda K, MacLeod DB, Grocott HP, et al. The accuracy of a near-infrared spectroscopy cerebral oximetry device and its potential value for estimating jugular venous oxygen saturation. *Anesth Analg.* 2014;119:1381–1392.
7. Abdul-Khaliq H, Troitzsch D, Berger F, et al. Regional transcranial oximetry with near infrared spectroscopy (NIRS) in comparison with measuring oxygen saturation in the jugular bulb in infants and children for monitoring cerebral oxygenation. *Biomed Tech (Berl).* 2000;45:328–332.
8. Douds M, Straub E, Kent A, et al. A systematic review of cerebral oxygenation-monitoring devices in cardiac surgery. *Perfusion.* 2014;29:545–552.
9. Menke J, Möller G. Cerebral near-infrared spectroscopy correlates to vital parameters during cardiopulmonary bypass surgery in children. *Pediatr Cardiol.* 2014;35:155–163.
10. Kim JW, Shin WJ, Park I, et al. Splanchnic oxygen saturation immediately after weaning from cardiopulmonary bypass can predict early postoperative outcomes in children undergoing congenital heart surgery. *Pediatr Cardiol.* 2014;35:587–595.
11. Schwartz AE. Cerebral blood flow is determined by arterial pressure and not bypass flow rate. *Br J Anaesth.* 2014;112:1123.
12. Kotlinska-Hasiec E, Czajkowski M, Rzecki Z, et al. Disturbance in venous outflow from the cerebral circulation intensifies the release of blood-brain barrier injury biomarkers in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth.* 2014;28:328–335.
13. Nybo L, Wanscher M, Secher NH. Influence of intranasal and carotid cooling on cerebral temperature balance and oxygenation. *Front Physiol.* 2014;5:79.
14. Ashmore J, Pickett J, Alder J, et al. Whole body oxygen delivery and consumption during cardiopulmonary bypass surgery. *Adv Exp Med Biol.* 2012;737:229–234.
15. Kumagai M, Ogawa S, Doe A, et al. Cerebral oxygenation measured by near-infrared spectroscopy and jugular vein oxygen saturation during robotic-assisted laparoscopic radical prostatectomy under total intravenous anaesthesia. *Int J Med Robot.* 2014Oct 21.
16. Kadoya T, Kurosaka S, Shiraishi M, et al. Monitoring of jugular venous oxygen saturation during superficial temporal artery-middle cerebral artery anastomosis under intraaortic balloon pumping: a case report. *Masui.* 2014;63:890–893.
17. Alten J, Mariscalco MM. Critical appraisal of Perez et al: jugular venous oxygen saturation or arteriovenous difference of lactate content and outcome in children with severe traumatic brain injury. *Pediatr Crit Care Med.* 2005;6:480–482.
18. Ali MS, Sayed SA, Mohamoud MS, et al. Effect of slow versus rapid rewarming on jugular bulb oxygen saturation in adult patients undergoing open heart surgery. *Saudi J Anaesth.* 2014;8:178–182.
19. Stein EJ, Glick DB, Minhaj MM, et al. Relationship between anesthetic depth and venous oxygen saturation during cardiopulmonary bypass. *Anesthesiology.* 2010;113:35–40.
20. Romagnoli S, Ricci Z, Balsorano P, et al. Comparison between mixed and central venous oxygen saturation in patients with severe acute heart failure after cardiac surgery: a prospective observational study. *Int J Cardiol.* 2014;175:566–567.
21. Baars JH, Rintisch U, Rehberg B, et al. Prediction of motor responses to surgical stimuli during bilateral orchiectomy of pigs using nociceptive flexion reflexes and the bispectral index derived from the electroencephalogram. *Vet J.* 2013;195:377–381.
22. Chandran Mahaldar DA, Gadhinglajkar S, Sreedhar R. Sevoflurane requirement to maintain bispectral index-guided steady-state level of anesthesia during the rewarming phase of cardiopulmonary bypass with moderate hypothermia. *J Cardiothorac Vasc Anesth.* 2013;27:59–62.
23. Nigro Neto C, Landoni G, Cassarà L, et al. Use of volatile anesthetics during cardiopulmonary bypass: a systematic review of adverse events. *J Cardiothorac Vasc Anesth.* 2014;28:84–89.

APPENDIX 1

Fick formula:

$$CaO2 = PaO2 \times 0.0031 + SaO2 \times Hb \times 1.36$$

$$CjvO2 = PjvO2 \times 0.0031 + SjvO2 \times Hb \times 1.36$$

$$Da\text{-}jvO2 = (PaO2 - PjvO2) \times 0.0031 + (SaO2 - SjvO2) \times Hb \times 1.36$$

$$CEO2 = (SaO2 - SjvO2)/SaO2 \times 100\%$$

$$Da\text{-}jvLac = Laca - Lacjv$$