J Extra Corpor Technol. 2017;49:168–173
The Journal of ExtraCorporeal Technology

The Effect of Autologus Blood Priming on Cerebral Oximetry in Congenital Cardiac Surgery Patients

Ashley Hodge, MBA, CCP, FPP;* Apryl Cohen, BS, CCP;† Peter Winch, MD;‡ Dmitry Tumin, PhD;‡ Jeffrey Burnside, BS, CCP, FPP;* Todd Ratliff, BS, CCP;* Mark Galantowicz, MD;* Aymen Naguib, MD‡

**The Heart Center at Nationwide Children's Hospital, Columbus, Ohio; †Department of Cardiovascular Perfusion, College of Health Professions, SUNY Upstate Medical University, Syracuse, New York; and ‡Anesthesia and Pain Management, Nationwide Children's Hospital, Columbus, Ohio*

Abstract: Hemodilution is one of the sequelae of cardiopulmonary bypass (CPB). Autologous blood priming (retrograde autologous priming [RAP]/venous antegrade priming [VAP]) and acute normovolemic hemodilution (ANH) may be effective techniques to minimize hemodilution. The primary objective of this study is to investigate the impact of RAP/VAP combined with ANH on changes in cerebral saturations. A retrospective analysis of 52 patients undergoing congenital cardiac surgery requiring CPB between July 2014 and March 2015 was performed. Bivariate analysis correlated RAP/VAP and ANH volumes. S_rO_2 change scores were regressed on all covariates using multivariable least-squares models. The average percent of circulating blood volume (CBV) removed during RAP/VAP was 21 ± 10% in the cyanotic group and 15 ± 5% in the acyanotic group (p =.006). There was a decrease in S_rO_2 from 70 ± 11% at baseline to 55 ± 13% at CPB initiation, although this decrease did not differ by cyanosis (p = .668) or use of ANH (p = .566). Bivariate correlation and multivariable regression analysis of the S_rO_2 change score further demonstrated no statistically significant correlation between percent of CBV removed during RAP/VAP or ANH and the magnitude of the decline in S_rO_2. RAP and VAP help minimize hemodilution at the onset of CPB. This study further supports the use of these techniques in a pediatric population by demonstrating declines in S_rO_2 during RAP/VAP were consistent among cyanotic and acyanotic, including those who underwent ANH. **Keywords:** autologous prime, retrograde autologous priming, venous antegrade priming, cerebral oximetry, pediatric, cardiac surgery, congenital, cyanotic. *J Extra Corpor Technol. 2017;49:168–173*

The brain is highly metabolically active, and accounts for 20% of the body's resting oxygen consumption despite weighing only 2% of the total body mass (1). As a result of this metabolic demand, the brain requires consistent perfusion and is very susceptible to ischemic injury. At the same time, the cranial vault is defined by a fixed space, and an excess of perfusion or flow into this space can also be problematic. Headaches, seizures, encephalopathy, and strokes are in part caused by a breakdown of the blood–brain barrier, and an excess of cerebral perfusion and the transudation of fluid into the interstitial space (2). Cerebral autoregulation is essential to maintain perfusion over a wide range of physiologic conditions.

Received for publication January 11, 2017; accepted March 22, 2017.
Address correspondence to: Ashley Hodge, MBA, CCP, FPP, The Heart Center, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205-2664. E-mail: ashley.hodge@nationwidechildrenshospital.org
The senior author has stated that the authors have reported no material, financial, or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

Our earliest understanding of cerebral autoregulation is founded on studies in physiology done in the 1950s and published by Lassen (3). This work suggests that cerebral blood flow is maintained as constant over a wide range of mean arterial pressures (MAPs) (60–150 mmHg). This conclusion was based on blood pressure measurements done in adults with hypertensive and hypotensive disorders. More recent work has looked at the dynamics of blood flow at rest and acknowledged that observed over seconds, blood flow moves in a complex pulsatile waveform and changes in body position, exercise, straining, or volume status all profoundly alter the dynamics of cerebral perfusion (4,5).

If we accept that cerebral perfusion is dynamic and that the autoregulation of cerebral blood flow remains poorly understood, it becomes difficult to determine the optimal volume status, mean arterial blood pressure, or cerebral perfusion pressure for children and neonates on cardiac bypass. This is partly a function of the fact that the majority of studies on cerebral autoregulation involved adult patients and is further complicated by the fact that all patients

Article available at https://ject.edpsciences.org or https://doi.org/10.1051/ject/201749168

undergoing bypass surgery are also receiving anesthetics that further alter the cerebral auto regulatory curve (6,7).

In the interest of understanding our clinical experience and elucidating any identifiable relationship between changes in volume status and cerebral perfusion, we reviewed the change in cerebral oxygenation as reflected by near infrared spectroscopy (NIRS) readings for patients that underwent both acute normovolemic hemodilution (ANH), combined with retrograde autologous priming (RAP), and venous antegrade priming (VAP). The use of RAP/VAP reduces the amount of hemodilution on bypass and the subsequent need for transfusions in adult patients undergoing bypass (8). It has also been demonstrated to improve cerebral oxygenation while adult patients are on bypass (9). Whether or not the combination of ANH and RAP/VAP helps reduce the incidence of blood product transfusions for pediatric patients is a topic in need of further exploration (10).

Patients that undergo ANH according to our protocol at Nationwide Children's Hospital, prior to the onset of cardiac surgery, are hypovolemic as compared to their initial presenting volume status. Our process involves removing 10–20% of the circulating blood volume (CBV), and replacing it with crystalloid only if evidence of end-organ ischemia develops (11–13). Our previous work supports good correlation between changes in cerebral saturations and jugular venous oxygen content (14). The purpose of this analysis was to review whether patients who underwent ANH and RAP/VAP according to our protocol had any appreciable change in cerebral saturation. We examined variables including age, weight, gender, hemoglobin/hematocrit, and changes in systolic blood pressure, and then statistically stratified our analysis by comparing both cyanotic and acyanotic patients.

METHODS

After obtaining institutional review board (no: 15–00248) approval, a retrospective analysis of 59 patients who underwent congenital cardiac surgery requiring CPB between July 2014 and March 2015 was performed. The retrospective review excluded cases in which RAP/VAP was not used, and only included cases in which the starting priming volume in the circuits was consistent. Patient characteristics evaluated for analysis included height, weight, age, gender, amount of blood removed during ANH and RAP/VAP, change in hematocrit, change in systolic blood pressure, and cyanosis.

At the start of each case, standard American Society of Anesthesiologists monitors were placed along with a FORESIGHT® cerebral oximeter (CAS Medical Systems Inc, Brandford, CT). The cerebral oximeter was placed on the right forehead and a baseline cerebral saturation was recorded. After induction of general anesthesia and placement of a radial arterial line, blood samples were drawn and a starting hematocrit using the i-STAT® (Abbott Laboratories, Abbott Park, IL) blood gas-monitoring device was calculated.

Our protocol for ANH is to withdraw 10–20% of the total CBV prior to surgical incision in patients above 5 kg or 10–20 mL/kg in patients weighing less than 5 kg. The total amount withdrawn is based on the baseline hematocrit and the estimated target hematocrit on CPB (12,13). A transfusion bag or syringe (depending on the intended volume removed) was attached to the patient's arterial line stopcock. Each syringe or bag of ANH contained 8 mL of Anticoagulant Citrate Dextrose (Gambro BCT Inc., Lakewood, CO) per 52 mL of whole blood. During the process of ANH, we support the hemodynamics as indicated by utilizing small boluses of vasopressors like phenylephrine. This is guided by changes in cerebral saturation, electrocardiogram (EKG), and MAP (11). In the event that a patient became hemodynamically unstable, ANH was discontinued.

Following ANH we follow a protocol that minimizes the intraoperative administration of crystalloids. This is accomplished by maintaining all infusions using pumps set at a minimal delivery rate, and administering fluids only with evidence of diminished end-organ perfusion as reflected by changes in NIRS from baseline recordings, mean arterial blood pressure changes or EKG changes. The goal of this technique is to minimize unnecessary hemodilution and to decrease edema following CPB.

Following placement of the arterial and venous cannulas, RAP and VAP are performed. According to our protocol, arterial blood is passively removed from the arterial line of the CPB circuit into a transfusion bag off the manifold of the oxygenator. Once the entire arterial limb of the CPB circuit is primed with autologous blood, VAP is commenced. The venous blood is then used in an antegrade manner to prime the venous line of the CPB circuit into the venous reservoir of the CPB circuit. During the process of RAP and VAP, the anesthesiologist supports the circulation with small boluses of vasopressors typically including phenylephrine and epinephrine. These doses are guided by changes in the cerebral saturation, arterial blood pressure, and EKG.

The total volume of crystalloid removed from the CPB circuit during RAP/VAP was determined by measuring the amount of crystalloid that was displaced into the transfusion bag during this process. Real-time patient parameters including cerebral oximetry, EKG, and blood pressure monitoring were recorded using the Maquet-Jocap XL Perfusion Electronic Charting system (Maquet Getinge Group, Rastatt, Germany).

Continuous data were presented as means with standard deviations, whereas categorical data were presented as

counts with percentages. Descriptive analysis was performed while stratifying the cohort by cyanosis and total ANH blood removed. Change in saturations was assessed using paired *t* tests, and change scores of S_rO_2 (from baseline to CPB initiation) were calculated for further analyses. Bivariate analysis correlated RAP/VAP and ANH volumes, expressed as percent of CBV, with change in S_rO_2 from the baseline to bypass initiation. Multivariable least-squares models were used to regress S_rO_2 change scores (bypass initiation value less baseline value, with negative scores indicating decline in S_rO_2) on RAP/VAP volume, ANH volume, demographic characteristics, cyanosis, baseline hematocrit, change in hematocrit from pre-CPB to post-CPB initiation, and change in systolic blood pressure from pre-RAP/VAP to CPB initiation. Further multivariable analyses stratified the analytic sample by cyanosis to determine if covariates in the analysis were differently associated with S_rO_2 change in cyanotic as compared to acyanotic patients. All analyses were performed in Stata/IC 13.1 (StataCorp LP, College Station, TX), and a $p < .05$ was considered statistically significant.

RESULTS

Fifty-three patients met inclusion criteria for the study. Patient characteristics were compared by cyanotic defect and use of ANH as shown in Table 1. Cyanotic patients tended to be younger and weigh less than acyanotic patients, with no differences in gender composition between the two groups. The proportion of RAP/VAP volume compared to the CBV was greater among cyanotic patients. There was no variability within each group when comparing those patients who underwent ANH vs. those who did not. Baseline S_rO_2 was 70 ± 11% in the overall cohort, but was particularly low (59 ± 13%) among cyanotic patients with no ANH performed. In all subgroups, hematocrit significantly decreased from the baseline to the earliest observation after CPB initiation, although repeated-measures analysis of variance identified no statistically significant variation in this decrease by cyanosis or use of ANH.

Certain subgroups exhibited statistically significant declines in S_rO_2 from the baseline to the initiation of CPB, with this overall decline averaging 15 ± 14%. The change score of S_rO_2 from baseline to CPB initiation was used in further analyses, and did not significantly differ by cyanosis ($p = .668$) or use of ANH ($p = .566$). Figure 1 demonstrates a lack of correlation ($r = -.02$, $p = .881$) between change in S_rO_2 and %CBV removed during RAP/VAP, whereas Figure 2 demonstrates a lack of correlation between S_rO_2 change and %CBV removed during ANH ($r = -.13$, $p = .433$).

Multivariable analysis was performed on 52 cases with complete data on covariates, excluding 1 case with missing data on baseline hematocrit. For inclusion in multivariable models, ANH volume was coded as 0% CBV in cases

Table 1. Patient characteristics compared by cyanotic defect and use of ANH.

	Cyanotic Patients			Acyanotic Patients			*p* (cyanotic vs. acyanotic)	*p* (cyanotic vs. acyanotic)
	ANH + RAP/VAP	No ANH + RAP/VAP	P(ANH vs. No ANH)	ANH + RAP/VAP	No ANH + RAP/VAP	P(ANH vs. No ANH)	ANH + RAP/VAP	No ANH + RAP/VAP
Number of patients	17	9	N/A	20	7	N/A	N/A	N/A
Age (months)	41 ± 49	13 ± 17	.106	115 ± 103	78 ± 106	.432	.011	.087
Weight (kg)	14 ± 14	7 ± 4	.120	36 ± 30	22 ± 22	.270	.008	.049
Gender	11F/6M	5F/4M	.648	8F/12M	5F/2M	.152	.134	.515
ANH volume (mL/kg) + (% CBV)	11 ± 4 (14 ± 5%)	0	N/A	9 ± 3 (13 ± 5%)	0	N/A	.173	N/A
RAP/VAP volume (mL/kg) + (% CBV)	15 ± 7 (19 ± 10%)	20 ± 7 (26 ± 8%)	.091	11 ± 3 (16 ± 5%)	10 ± 3 (14 ± 3%)	.755	.039	.003
Starting HCT (%)	43 ± 9	42 ± 12	.849	36 ± 4	38 ± 4	.424	.007	.376
HCT pre RAP/VAP (%)	38 ± 8*	40 ± 12	.634	33 ± 4*	35 ± 4*	.354	.023	.301
HCT at start of CPB (%)	31 ± 8*†	32 ± 16*†	.722	29 ± 4*†	27 ± 4*†	.340	.387	.388
Baseline cerebral saturation (%)	69 ± 10	59 ± 13	.029	74 ± 9	74 ± 11	.990	.113	.026
Cerebral saturation after ANH or pre-RAP/VAP (%)	59 ± 15‡	53 ± 13	.301	69 ± 8	63 ± 11‡	.142	.019	.129
Cerebral saturation after RAP/VAP (%)	51 ± 15‡§	46 ± 13‡§	.422	63 ± 9‡§	51 ± 11‡§	.013	.008	.413
Systolic blood pressure at start of RAP/VAP (mmHg)	69 ± 22	61 ± 19	.366	74 ± 22	64 ± 15	.288	.504	.722
Systolic blood pressure after RAP/VAP (mmHg)	62 ± 23	51 ± 20	.258	74 ± 22	45 ± 13¶	.004	.101	.531

Symbols denote statistically significant difference ($p < .05$) from: *starting HCT, †HCT pre RAP/VAP, ‡baseline cerebral saturation, §cerebral saturation pre RAP/VAP, and ¶systolic blood pressure at start of RAP/VAP.

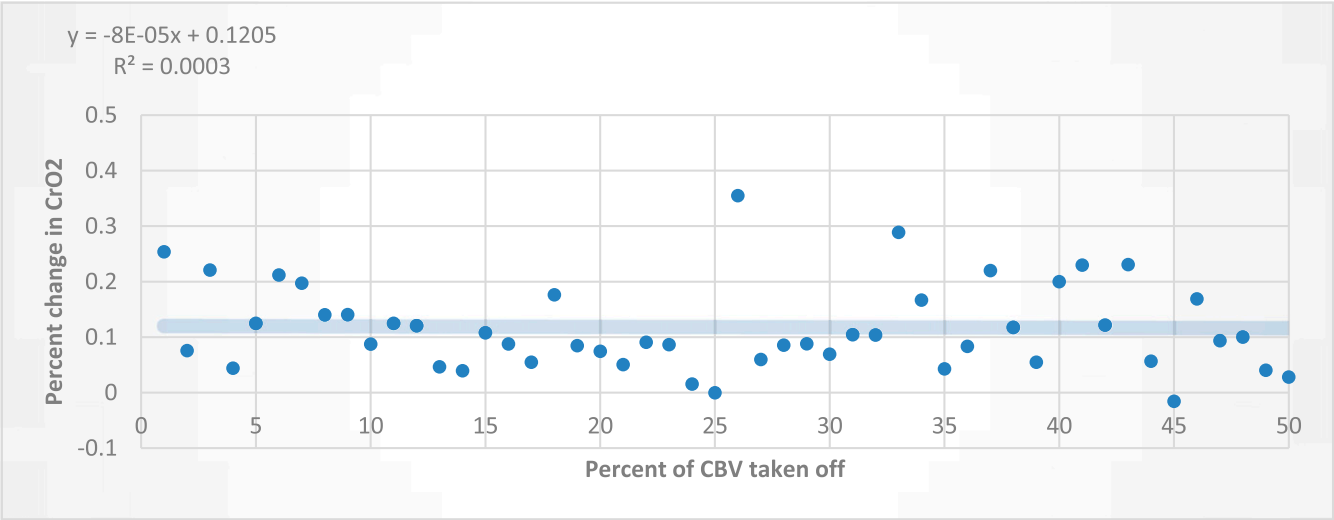

Figure 1. Average baseline CrO_2 compared to average CrO_2 at the initiation of bypass. Change in cerebral oxygen saturation from baseline to CPB initiation vs. percent of circulating blood volume removed during RAP/VAP.

where ANH was not used. Table 2 presents the multivariable least-squares model of change in S_rO_2 from baseline to CPB initiation in the overall cohort. Neither %CBV removed during RAP/VAP (b = .09; 95% confidence interval [CI] = −.47, .66; p = .744) nor %CBV removed during ANH (b = −.09; 95% CI = −.65, .47; p = .743) were significantly correlated with change in S_rO_2. Furthermore, no statistically significant difference in S_rO_2 decline was found between cyanotic (b = 3.61; 95% CI = −5.96, 13.17; p = .451) and acyanotic patients after adjusting for potential confounders. Table 3 presents the multivariable model fitted separately for cyanotic and acyanotic patients, confirming that change in S_rO_2 was not associated with %CBV removed either during RAP/VAP or during ANH in both groups. There were no statistically significant differences in model coefficients between the cyanotic and acyanotic subgroups, as determined by a model fitted to the entire sample with each variable interacted with cyanosis (data not shown).

DISCUSSION

Our approach to cardiac bypass and associated techniques including the use of ANH, RAP/VAP have been

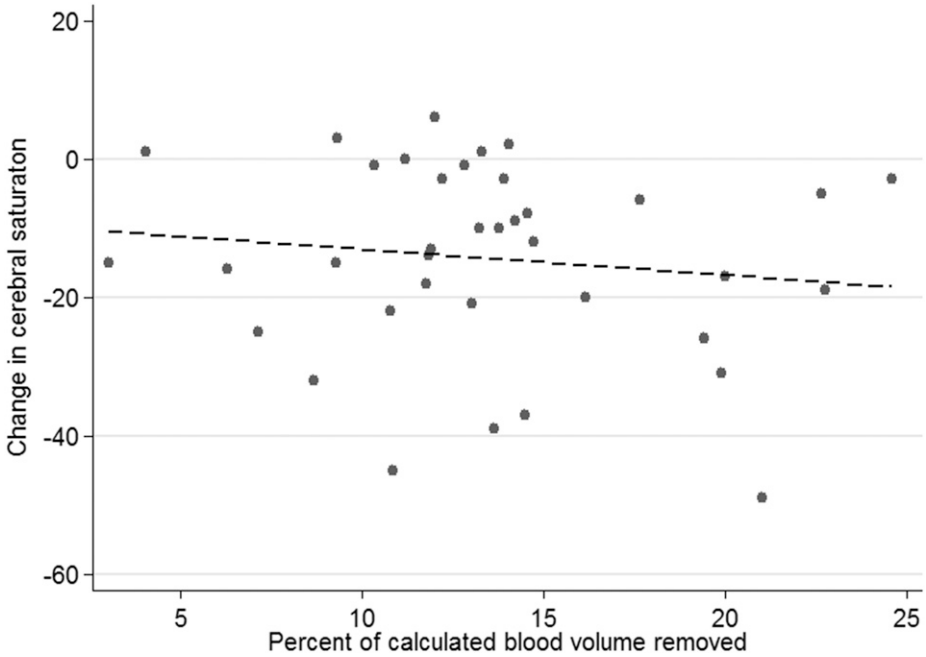

Figure 2. Change in cerebral oxygen saturation from baseline to CPB initiation vs. percent of circulating blood volume removed during ANH.

developed to reduce the need for blood product transfusions and were first pioneered to serve our large population of Jehovah's Witness patients. These previously described techniques are more challenging in smaller patients, secondary to relatively large prime volumes of the CPB circuit in comparison to the patients' CBV. Our methods differ from other published reports in that we minimize crystalloid fluid replacement during ANH and use end-organ perfusion parameters to guide fluid replacement. This can be uniquely challenging in neonates and particularly so with patients who have single ventricle physiologies and other cyanotic lesions.

The effects of RAP/VAP on cerebral perfusion are yet to be quantified. It is widely believed that hypovolemia has consequences for cerebral perfusion, but to what extent is this clinically relevant for patients that are undergoing general anesthesia and have an attenuated metabolic demand? This review attempts to provide insight into this topic by utilizing NIRS data for patients undergoing RAP/VAP, and looking for evidence of statistically significant declines in S_rO_2. The review considers both cyanotic and acyanotic patients some of whom have already undergone ANH without fluid replacement and are thus already hypovolemic. Indeed, the lack of associations between cerebral saturation decline and covariates included in the analysis underscores the need to prospectively identify risk factors for excessive decline in cerebral saturation leading up to initiation of CPB. In addition, it is of paramount importance to quantify the limit of such decline and its possible impact on the clinical and ultimately the long-term neurodevelopmental outcome for these patients.

This study is limited by the retrospective nature of data collection and a small cohort size that potentially restricts the feasibility of complex analyses. Furthermore, cerebral oximetry has been shown to reflect systemic venous oxygenation, but it does not provide an absolute value of oxygenation (15). Therefore, the present study has focused on within-subject change in cerebral oxygenation as the primary outcome. In the future, the availability of additional measures and larger cohorts may provide ancillary data related to tissue oxygenation, and may potentially enable identifying factors that predispose patients to a particularly large decline in oxygenation while undergoing ANH and RAP/VAP.

The utilization of ANH and RAP/VAP are techniques that assist in accomplishing the goal of bloodless pediatric heart surgery. This review highlights a lack of statistically significant change in S_rO_2 as a result of the utilization of these techniques in both cyanotic and acyanotic patients. The brain has a remarkable ability to auto-regulate over a wide variety of perfusion pressures and under the condition of hypovolemic physiologic states. This review provides further evidence that the hypovolemia induced by ANH and RAP/VAP causes no statistically significant decline in S_rO_2 and further supports the utility of these techniques.

Table 2. Multivariable least-squares regression of change in SrO2 from baseline to initiation of bypass (n = 52).

Variables	b*	95% CI	p
%CBV removed during RAP/VAP	.09	(−.47, .66)	.744
%CBV removed during ANH	−.09	(−.65, .47)	.743
Age (months)	.04	(−.09, .16)	.587
Female	−1.31	(−9.36, 6.73)	.743
Weight (kg)	−.03	(−.52, .46)	.890
Baseline hematocrit	−.30	(−.84, .23)	.261
Change in hematocrit†	.89	(−.18, 1.96)	.101
Change in systolic pressure‡	−.02	(−.21, .17)	.804
Cyanosis	3.61	(−5.96, 13.17)	.451
Constant	−1.17	(−26.21, 23.88)	.926
R^2	.17		

*Unstandardized coefficient for change in cerebral oxygen saturation between baseline and initiation of cardiopulmonary bypass.
†Change from pre-RAP/VAP value to post-CPB initiation.
‡Change from pre-RAP/VAP value to post-RAP/VAP value.

Table 3. Multivariable least-squares regression of change in SrO2 from baseline to initiation of bypass, by cyanosis (n = 52).

	Cyanotic (n = 25)			Acyanotic (n = 27)		
Variables	b*	95% CI	p	b*	95% CI	p
%CBV removed during RAP/VAP	.14	(−.54, .81)	.675	−.35	(−1.81, 1.10)	.619
%CBV removed during ANH	−.13	(−1.02, .77)	.768	.20	(−.64, 1.03)	.624
Age (months)	.39	(−.32, 1.11)	.262	.06	(−.06, .19)	.320
Female	.49	(−12.55, 13.53)	.937	.44	(−10.20, 11.07)	.932
Weight (kg)	−2.40	(−5.19, .39)	.087	−.14	(−.71, .42)	.597
Baseline hematocrit	−.42	(−1.10, .27)	.213	.06	(−1.46, 1.57)	.940
Change in hematocrit†	1.35	(−.37, 3.07)	.116	2.03	(−.25, 4.31)	.078
Change in systolic pressure‡	.31	(−.21, .83)	.229	.03	(−.19, .26)	.756
Constant	29.00	(−12.98, 70.98)	.162	−4.17	(−55.52, 47.18)	.866
R^2	.38			.50		

*Unstandardized coefficient for change in cerebral oxygen saturation between baseline and initiation of cardiopulmonary bypass.
†Change from pre-RAP/VAP value to post-CPB initiation.
‡Change from pre-RAP/VAP value to post-RAP/VAP value.

REFERENCES

1. Sokoloff L. *Mechanisms of regulation of cerebral blood flow*. Maturation Phenomenon in Cerebral Ischemia Iii. 1999;291–307.
2. van Mook WN, Rennenberg RJ, Schurink GW, et al. Cerebral hyperperfusion syndrome. Lancet Neurol. 2005;4:877–88.
3. Lassen NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev. 1959;39:183–238.
4. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet. 2010;375:938–48.
5. Aaslid R, Lash SR, Bardy GH, Gild WH, Newell DW. Dynamic pressure–flow velocity relationships in the human cerebral circulation. Stroke. 2003;34:1645–9.
6. Reinsfelt B, Westerlind A, Houltz E, Ederberg S, Elam M, Ricksten SE. The effects of isoflurane-induced electroencephalographic burst suppression on cerebral blood flow velocity and cerebral oxygen extraction during cardiopulmonary bypass. Anesth Analg. 2003;97: 1246–50.
7. Reinsfelt B, Westerlind A, Ricksten SE. The effects of sevoflurane on cerebral blood flow autoregulation and flow-metabolism coupling during cardiopulmonary bypass. Acta Anaesthesiol Scand. 2011;55: 118–23.
8. Trapp C, Schiller W, Mellert F, et al. Retrograde autologous priming as a safe and easy method to reduce hemodilution and transfusion requirements during cardiac surgery. Thorac Cardiovasc Surg. 2015; 63:628–34.
9. Hwang J, Huh J, Kim J, et al. The effect of retrograde autologous priming of the cardiopulmonary bypass circuit on cerebral oxygenation. J Cardiothorac Vasc Anesth. 2011;25:995–9.
10. Sebastian R, Ratliff T, Winch PD, et al. Revisiting acute normovolemic hemodilution and blood transfusion during pediatric cardiac surgery: a prospective observational study. Paediatr Anaesth. 2017;27: 85–90.
11. Naguib AN, Winch PD, Tobias JD, et al. A single-center strategy to minimize blood transfusion in neonates and children undergoing cardiac surgery. Paediatr Anaesth. 2015;25:477–86.
12. Dewhirst E, Naguib A, Winch P, et al. Accuracy of noninvasive and continuous hemoglobin measurement by pulse co-oximetry during preoperative phlebotomy. J Intensive Care Med. 2014;29:238–42.
13. Dewhirst E, Winch P, Naguib A, Galantowicz M, Tobias JD. Cerebral oximetry monitoring during preoperative phlebotomy to limit allogeneic blood use in patients undergoing cardiac surgery. Pediatr Cardiol. 2013;34:75–80.
14. Naguib AN, Winch PD, Sebastian R, et al. The correlation of two cerebral saturation monitors with jugular bulb oxygen saturation in children undergoing cardiopulmonary bypass for congenital heart surgery. J Intensive Care Med. 2016;4:1–6.
15. Ginther R, Sebastian VA, Huang R, et al. Cerebral near-infrared spectroscopy during cardiopulmonary bypass predicts superior vena cava oxygen saturation. J Thorac Cardiovasc Surg. 2011;142:359–65.