Markers of peripheral perfusion during high-flow regional cerebral perfusion for aortic arch repair

Koichi Sugimoto, MD, PhD,^{a,b} Satoshi Kohira, PhD,^a Hidenori Hayashi, MD,^a Shinzo Torii, MD, PhD,^a Tadashi Kitamura, MD, PhD,^a Tetsuya Horai, MD, PhD,^a and Kagami Miyaji, MD, PhD^a

ABSTRACT

Objectives: High-flow regional cerebral perfusion (HFRCP) provides cerebral and somatic oxygen delivery through collateral vessels during aortic arch repair in small children; however, optimal flow conditions during HFRCP have not been established. We sought to identify markers of peripheral perfusion during HFRCP.

Methods: Between 2009 and 2016, in total 20 consecutive pediatric patients undergoing aortic arch repair with HFRCP were enrolled in this prospective, observational study. Median age was 20 days (range, 6-116 days); median body weight was 2.77 kg (range, 1.8-4.98 kg). Oxygen delivery ratio (DO_2R) was calculated as the oxygen delivery during HFRCP divided by the oxygen delivery before HFRCP. Regional oxygen saturations on the forehead and on the thigh (rSO_2T) were monitored during HFRCP, and postoperative creatinine kinase and lactate concentrations were measured as postoperative outcomes. Multivariate analyses were performed to clarify the effectiveness of DO_2R and rSO_2T as markers of peripheral perfusion during HFRCP.

Results: No deaths or neurologic impairments occurred. Multivariate analysis showed that the lowest rSO_2T ($P = .005$) and cardiopulmonary bypass time ($P = .012$) predicted postoperative creatinine kinase concentration. DO_2R was the only factor to predict postoperative lactate concentration ($P < .001$). Receiver operating characteristic analysis showed that DO_2R less than 0.66 predicted risk of high postoperative lactate concentration (>5.0 mmol/L), with area under the curve of 0.95.

Conclusions: For aortic arch repair in small children, rSO_2T and DO_2R during HFRCP are useful markers for predicting peripheral perfusion. Maintaining higher DO_2R during HFRCP minimizes postoperative increases in lactate and creatinine kinase concentrations. (J Thorac Cardiovasc Surg 2018;156:2251-7)

In this example, regional oxygen saturations were maintained during HFRCP.

Central Message

Flow during high-flow regional cerebral perfusion in aortic arch repair for small children can be optimized by closely monitoring the oxygen delivery ratio and regional oxygen saturation on the thigh.

Perspective

The optimal flow conditions of cardiopulmonary bypass during high-flow regional cerebral perfusion (HFRCP) in aortic arch repair for small children remain unclarified. We propose the oxygen delivery ratio (DO_2R) as a new reliable marker. DO_2R is calculated as oxygen delivery during HFRCP divided by that before HFRCP. DO_2R greater than 70% during HFRCP is associated with maintained peripheral perfusion.

See Editorial Commentary page 2258.

High-flow regional cerebral perfusion (HFRCP), defined as a flow greater than 70 mL/min/kg, is an effective and useful adjunct to the Norwood procedure and repairs of coarctation of the aorta or aortic arch interruption, enabling the delivery of maintained cerebral and somatic oxygen through collateral vessels during aortic arch repair in neonates and small infants.^{1,2} Our previous research demonstrated that regional cerebral perfusion flow is correlated with somatic

regional oxygen saturation (rSO_2), and inversely correlated with an increase in lactate concentration.² Optimal flow during HFRCP and sensitive markers of adequate somatic perfusion, however, have not been established. We therefore sought to identify markers of adequate peripheral perfusion during HFRCP by comparing rSO_2 on the trunk versus rSO_2 on the thigh and by evaluating the correlation between oxygen delivery (DO_2) and the level of lactate. A further aim of

From the ^aDepartment of Cardiovascular Surgery, School of Medicine, Kitasato University, Sagami-hara, Japan; and ^bMazankowski Alberta Heart Institute, Edmonton, Alberta, Canada.

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Address for reprints: Koichi Sugimoto, MD, PhD, Department of Cardiovascular Surgery, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagami-hara 252-0375, Japan (E-mail: ksugimoto@gmail.com).

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Abbreviations and Acronyms

HFRCP	= high-flow regional cerebral perfusion
rSo ₂	= regional oxygen saturation
Do ₂	= oxygen delivery
CO	= cardiac output
CPB	= cardiopulmonary bypass
So ₂	= hemoglobin oxygen saturation
Do ₂ R	= oxygen delivery ratio
CK	= creatinine kinase
CK-MB	= creatinine kinase myoglobin-binding isoenzyme
RBC	= red blood cell
ICU	= intensive care unit
IQR	= interquartile range

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this pilot study was to measure the chronologic changes in somatic and cerebral rSo₂ to evaluate the adequacy of somatic perfusion during HFRCP.

METHODS

Patients

From August 2013 to February 2016, a total of 20 consecutive neonates and infants (18 boys and 2 girls) with median age of 20 days (range, 6-116 days) and a median body weight of 2.77 kg (range, 1.8-4.98 kg) were enrolled in this prospective, observational study. The institutional review board approved the study and the collection of associated clinical physiologic data, and informed consent was obtained from the parents or guardians of all participating patients. All participants underwent arch reconstruction with HFRCP for either coarctation of the aorta ($n = 18$) or interruption of the aortic arch (type A, $n = 2$). Patients with univentricular circulation were excluded. Other associated diagnoses included ventricular septal defects ($n = 13$), atrial septal defects ($n = 18$), complete atrioventricular septal defect ($n = 1$), and supracardiac type total anomalous pulmonary venous drainage ($n = 1$). Three patients had Down syndrome (Table 1). All patients underwent aortic arch repair as their initial procedure, except for a patient who had undergone bilateral pulmonary artery banding before aortic arch repair.

Data Measurement

The rSo₂ values on both sides of the forehead, trunk, and thigh were monitored intraoperatively with near-infrared spectroscopy (INVOS 5100; Somanetics, Troy, Mich). The bilateral frontal cerebral rSo₂ values were measured and compared during the surgery.

Do₂ was calculated as follows: $Do_2 = CO \times [1.39 \times Hb \times So_2 + (0.003 \times Pao_2)]$, where CO (cardiac output, in L/min) is the total flow generated by cardiopulmonary bypass (CPB), Hb is the hemoglobin concentration, and So₂ is the hemoglobin oxygen saturation expressed as a fraction (%). The Do₂ ratio (Do₂R) was defined as the quotient of Do₂ during HFRCP divided by the Do₂ before HFRCP (Figure 1).

TABLE 1. Patient characteristics

Age (d)	
Median	20
Range	6-116
Body weight (kg)	
Median	2.77
Range	1.8-4.98
Sex (female/male)	2:18
Diagnosis	
Coarctation of aorta	18
Interruption of aortic arch (type A)	2
Associated diagnosis	
ASD	13
VSD	18
Complete AVSD	1
TAPVD supracardiac	1
Down syndrome	3

ASD, Atrial septal defect; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; TAPVD, total anomalous pulmonary venous drainage.

To investigate the optimal flow condition during HFRCP, we sought correlations between rSo₂, Do₂R, and other postoperative markers of peripheral perfusion, such as creatinine kinase (CK) and lactate dehydrogenase. The concentrations of alanine transaminase, aspartate transaminase, blood urea nitrogen, C-reactive protein, and lactate were also measured in the perioperative period. CK myoglobin-binding isoenzyme (CK-MB) was measured when considered necessary. Data sampling was conducted before the operation, during cooling, during HFRCP, during rewarming, at the time of cessation of CPB, at admission to the intensive care unit (ICU), and 12 hours after admission to the ICU.

Surgery and Cardiopulmonary Bypass System

The technique for performing CPB and management during this procedure have been reported previously (Video 1).¹⁻³ Before commencement of CPB, a 3.5-mm GORE-TEX tube (W. L. Gore & Associates, Flagstaff, Ariz) was anastomosed to the right innominate artery with a side-clamp and connected to the aortic cannula, after which the CPB was established between this aortic cannula and bicaval cannulations. The CPB system in all cases consisted of a distant roller pump, a remote-controlled unit (HAS-2; Senko Medical, Tokyo, Japan), a low-prime oxygenator, and a reservoir (priming volume 43 mL, Baby-FX; Terumo, Tokyo, Japan). The extracorporeal circuit tubing was selected in accordance with each patient's body weight. The priming volume of the tubing was 120 mL for patients weighing 6 kg or less. Blood gas balance was managed with the pH-stat strategy. Total circulatory arrest with deep hypothermia was not implemented; instead, systemic perfusion was maintained by using HFRCP under moderate hypothermia (28°C-30°C). Isosorbide dinitrate (2.0 µg/kg/min) and chlorpromazine (3.0 mg/kg) were administered during CPB to enhance collateral perfusion to the lower body. The conditions of flow during CPB are summarized in Table 2. After the neck vessels and descending aorta were clamped, aortic arch repair was performed with HFRCP. Pump flow was initially targeted at around 150 mL/kg/min and then lowered during HFRCP, with adjustments made in accordance with the rSo₂ and blood gas data. The Pao₂ during HFRCP was targeted at 250 mm Hg. The mean radial artery pressure was maintained at 35 to 45 mm Hg during the total bypass, and the maximal targeted radial artery pressure was then 45 mm Hg during HFRCP. The lower body temperature was controlled at around 28°C during HFRCP. Cardioplegic solution (10 mL/kg) was given every 20 minutes. After termination of CPB, modified ultrafiltration was performed with a polymethyl methacrylate hemofilter in all patients. After administration of the first cardioplegia, ductal tissue was excised, and an end-to-side anastomosis was performed for the arch repair. During CPB, the mixed venous

FIGURE 1. Example of oxygen delivery (DO_2) during cardiopulmonary bypass (CPB) and high-flow regional cerebral perfusion (HFRCP).

oxygen saturation and the rSO_2 s were maintained at greater than 70% and 50%, respectively. Heparinization was neutralized by protamine sulfate until the activated coagulation time had normalized.

RBC Transfusion

The minimum number of units of red blood cells (RBCs) to prevent hyperkalemia was transfused. RBCs were transfused during CPB to patients in whom the required mixed venous and regional tissue oxygen saturations could not be maintained by increasing the pump flow and fraction of inspired oxygen and increasing the hematocrit to 27% to 30%. The packs of RBCs were passed through a potassium adsorption filter (Kawasumi KPF-4; Kawasumi Laboratories, Tokyo, Japan) before administration to reduce the amount of potassium infused with the RBCs.

VIDEO 1. The concept and procedure of high-flow regional cerebral perfusion (HFRCP) are explained. The flow condition, chronologic changes of regional oxygen saturation (rSO_2) in different locations, lactate level, and oxygen delivery (DO_2) are demonstrated. CPB, Cardiopulmonary bypass; ePTFE, expanded polytetrafluoroethylene; rad a.BP, radial artery blood pressure. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)32492-9/fulltext](https://www.jtcvs.org/article/S0022-5223(18)32492-9/fulltext).

Statistical Analyses

Statistical analyses were performed with XLSTAT software (version 19.03; Addinsoft SARL, Paris, France). Continuous variables are presented as the median and interquartile range (IQR) for skewed distributions or as the mean $\pm$ SD for normally distributed variables. Patient follow-up was 100% for the corresponding patients. Multivariate linear regression modeling was used to determine which variables were associated with increases in lactate and CK concentrations. Patient characteristics and perioperative factors were included in the multivariate regression. The goodness of fit of the model was expressed by the determination coefficient (R). The optimal cutoff value of DO_2R with the highest combination of sensitivity and specificity for postoperative high level of lactate was determined with the receiver operating characteristic curve.

RESULTS

The sternum was closed at the end of surgery in all patients. Median duration of intubation was 7 days (IQR, 6-9 days), and median ICU stay was 13.5 days (range, 6-32 days). One patient required a tracheostomy and a gastrostomy tube because of recurrent nerve paralysis. No patient required peritoneal dialysis or dialysis filtration support. There were no operative or in-hospital deaths, and there were no deaths during a mean follow-up period of 3.2 ± 2.3 years. There was no neurologic impairment in any case. All patients were discharged from the hospital without major complications.

CPB Conditions and Intraoperative and Postoperative Measurements

The CPB time, crossclamping time, duration of clamping of the descending aorta, flow during CPB, flow during HFRCP, and pressure in the radial artery during HFRCP are summarized in Table 2.

TABLE 2. Perioperative variables

Variables	Median	IQR
CPB time (min)	133.5	114-180
Total bypass time (min)	86.4	65-99
Crossclamp time (min)	58.5	51-72
Descending aorta clamp time (min)	37.0	30-45
Lowest temperature (°C)	28.0	28-29.2
CPB flow		
Raw (mL/min)	395.5	325-437.5
Indexed (mL/min/kg)	136.0	127-145.1
Flow during RCP		
Raw (mL/min)	264.0	202.5-311
Indexed (mL/min/kg)	83.6	71.6-102.8
Flow ratio RCP/non-RCP	0.66	0.57-73
Systemic BP during RCP (mm Hg)	43.5	41.5-45.3
Circuit pressure during RCP (mm Hg)	97.0	85.8-135
Pressure difference between circuit and radial artery during RCP (mm Hg)	56.0	42.5-91.3
rSO ₂ (%)		
Forehead		
Before CPB	65.0%	59.5%-73.5%
CPB cooling	76.0%	69%-79.3%
RCP start	82.5%	77.8%-86.5%
RCP average	86.0%	79.5%-88.8%
RCP right-left difference	3.4%	-2.5% to 8.3%
CPB rewarming	67.0%	60%-71.5%
After CPB	63.0%	60%-68.5%
Trunk		
Before CPB	74.0%	66%-80%
CPB cooling	79.0%	74.5%-81.5%
RCP start	78.0%	72.5%-86%
RCP average	64.0%	50%-78%
CPB rewarming	86.0%	80.5%-90%
After CPB	92.0%	85.5%-95%
Thigh		
Before CPB	76.6%	74%-79%
CPB cooling	93.0%	88%-96%
RCP start	85.0%	69-91.5%
RCP average	94.0%	64.8-97.3%*
CPB rewarming	85.5%	83.8%-89.3%
After CPB	85.0%	77.8%-95%
Hemoglobin during RCP (g/L)	93.5	91-99.3
Do ₂ (mL/min)		
Before RCP	87.2	72.3-101.2
During RCP	57.9	42.8-72.6
Ratio (%)	69.8	60.1%-79.2
Vo ₂ (mL/min)		
Before RCP	11.7	10.6-14

(Continued)

TABLE 2. Continued

Variables	Median	IQR
During RCP	1.5	0.8-3.1
Intubation period (d)	7.0	6-9
PICU stay (d)	13.5	6-32†

IQR, Interquartile range; CPB, cardiopulmonary bypass; RCP, regional cerebral perfusion; BP, blood pressure; rSO₂, regional oxygen saturation; Do₂, oxygen delivery; Vo₂, oxygen consumption; PICU, pediatric intensive care unit. *P = .01 for comparison between trunk and thigh regional oxygen saturation during regional cerebral perfusion. †Total range rather than interquartile range reported.

During HFRCP, the rSO₂ on the forehead increased, whereas the rSO₂ on the thigh decreased and then recovered after declamping of the descending aorta (Figure 2, A and B). During HFRCP, the lowest rSO₂ measurements on the forehead, trunk, and thigh were 86.0% (IQR, 79.5%-88.8%), 64.0% (IQR, 50%-78%), and 94.0% (IQR, 64.8%-97.3%), respectively. The truncal rSO₂ was significantly lower than the thigh rSO₂ (*P* < .01). The right-sided frontal rSO₂ was greater than the left-sided frontal rSO₂ during HFRCP in 13 of 20 patients by 3.4% (IQR -2.5% to 8.3%). The perioperative measurements are shown in Table 3. On postoperative day 1, blood urea nitrogen and CK rose to 14.8 mg/dL and 0.63 mg/dL, respectively. Aspartate transaminase (103 U/L), lactate dehydrogenase (483.5 U/L), CK (999.5 U/L), and CK-MB (172 U/L) peaked at the time of admission to the ICU and then decreased. The highest postoperative lactate concentration was 4.9 mmol/L (IQR, 4.2-5.5 mmol/L).

Multivariate Analysis and Correlation Between Lactate Concentration and Do₂R

Multivariate analysis revealed that high postoperative CK concentrations were associated with prolonged CPB time (*P* = .012) and nadir rSO₂ on the thigh (*P* = .005), whereas only high postoperative lactate levels were associated with Do₂R (*P* < .001; Table 4). The highest postoperative lactate level was negatively correlated with Do₂R (*R* = 0.81; Figure 3, A and B). On receiver operating characteristic analysis, a Do₂R cutoff value of 0.66 had the largest summed sensitivity and specificity of 1.80, comprising a sensitivity of 0.80 (95% CI, 0.48-0.95) and a specificity of 1.00 (95% CI, 0.67-1.00), with an area under the curve of 0.95. This receiver operating characteristic analysis revealed that a Do₂R of 0.66 or less predicted the risk of high lactate concentration (>5.0 mmol/L).

DISCUSSION

Since the evolution of regional cerebral perfusion during aortic arch repair, various modifications have contributed to improved outcomes.⁴⁻⁶ The advantages of HFRCP are supported by previous research that confirmed low

FIGURE 2. Regional oxygen saturation (*rSO*₂) was measured on the forehead (A) and thigh (B) before, after, and during cardiopulmonary bypass (CPB). Values are expressed as the median and interquartile range. *HFRCP*, High-flow regional cerebral perfusion.

rates of adverse effects and seizures.⁷⁻⁹ After demonstrating the efficacy of HFRCP during aortic arch repair in previous reports,^{1,2} we sought to determine the optimal conditions for CPB flow by using criteria that are simple, feasible, and practical to use in the operating room. Although monitoring the radial artery pressure during aortic arch repair is one of the most important measurements, the radial artery pressure is an inadequately reliable marker during HFRCP.¹⁰ We therefore investigated *Do*₂ as an alternative, because *Do*₂ incorporates the factors of flow, hemoglobin, and dissolved oxygen content in the blood, and these values are measured and adjusted frequently during CPB. Before HFRCP, flow is gradually reduced to the anticipated level as the 2 neck vessels and descending aorta are clamped. In this study, the cutoff value for *Do*₂*R* was 0.66; we therefore believe that a safe *Do*₂*R* is 70% of the initial *Do*₂ after stabilization of the CPB. *Do*₂ can be altered

by controlling CPB flow and increasing or decreasing hemoglobin concentrations.

This study also revealed that *rSO*₂ on the thigh was the most sensitive marker of adequate peripheral perfusion. Measuring *rSO*₂ is a good tool with which to assess adequate tissue perfusion both during CPB and postoperatively.¹¹⁻¹³ Berens and colleagues¹⁴ reported that it is feasible to monitor the somatic *rSO*₂ during aortic arch repair and that somatic *rSO*₂ dropped to lower values in neonates and infants than in adults, suggesting that younger children have less collateral vessels formation. In this study, however, the truncal *rSO*₂ and the *rSO*₂ on the thigh during HFRCP were 64% and 94%, respectively, suggesting that collateral flow can be maintained during HFRCP.

The nadir *Do*₂ and hypotension are reportedly associated with acute kidney injury after cardiac operations in adults.¹⁵ Furthermore, *Do*₂ incorporates factors such as flow, perfusion pressure, and hemodilution anemia, which

TABLE 3. Measurement variables

Variable	Preoperative	CPB cooling	RCP	CPB warming	CPB off	PICU entrance	POH 12	POD 1
Lactate (mmol/L)	1.9 (1.3-2.2)	2.6 (2.4-3)	4.1 (3.8-4.9)	4.1 (3.7-5.4)	4.9 (4.2-5.5)	3.8 (3.0-5.3)	3.2 (2.2-4.9)	1.3 (1-2.8)
BUN (mg/dL)	8.5 (6.4-10.9)					8.7 (6.4-10.4)		14.9 (12.3-16.5)
Creatinine (mg/dL)	0.44 (0.35-0.48)					0.43 (0.34-0.52)		0.67 (0.48-0.80)
AST (U/L)	37.5 (28.3-48.3)					103.0 (88.8-138.3)		83.0 (58.8-110.3)
ALT (U/L)	16.0 (11.5-22)					11.5 (9-14.3)		15.5 (13.5-18.3)
LDH (U/L)	322.5 (306-409)					483.5 (403-535)	437.0 (365-541)	
CK (U/L)	128.5 (111-200)					999.5 (927-1157)	652.0 (471-927)	
CK-MB (U/L)*						172.0 (149-188)	55.0 (39-79)	
CRP (mg/L)						0.06 (0.03-0.11)	1.76 (1.36-3.22)	

Values are expressed as the median and interquartile range. *CPB*, Cardiopulmonary bypass; *RCP*, regional cerebral perfusion; *PICU*, pediatric intensive care unit; *POH*, postoperative hour; *POD*, postoperative day; *BUN*, blood urea nitrogen; *AST*, aspartate transaminase; *ALT*, alanine transaminase; *LDH*, lactate dehydrogenase; *CK*, creatinine kinase; *CK-MB*, creatinine kinase myoglobin-binding isoenzyme; *CRP*, C-reactive protein. *Creatinine kinase myoglobin-binding isoenzyme was measured in 9 of 20 patients.

TABLE 4. Multivariate analysis of increases in creatinine kinase and lactate concentrations

	Variable	Coefficient	95% CI	P value
CK (U/L)	CPB time (min)	4.23	1.06-7.45	.012
	Lowest rSO ₂ on thigh (%)	-23.26	-38.68 to 7.83	.005
Lactate (mmol/L)	DO ₂ ratio (%)	-0.11	-0.14 to -0.07	<.001

CI, Confidence interval; CK, creatinine kinase; CPB, cardiopulmonary bypass; rSO₂, regional oxygen saturation; DO₂, oxygen delivery.

are also reportedly risk factors for acute kidney injury.¹⁶⁻¹⁹ The nadir DO₂ during CPB is also reportedly associated with serum glial fibrillary acid protein, which is a biomarker for brain injury in pediatric patients undergoing heart surgery.²⁰ It thus makes sense to measure the DO₂ during CPB, especially in aortic arch repair. As mentioned earlier, our pump perfusion protocol for HFRCP comprises a body temperature of 28°C, a perfusion pressure in the right radial artery of 45 mm Hg, and a hematocrit of 27% to 30%. The results of this study indicate that these values are reasonable. Despite clamping of the descending aorta, none of our patients required postoperative dialysis, which confirms the adequacy of our current concept and strategy of HFRCP.

Regarding rSO₂ monitoring, we stress the importance of measuring rSO₂ on the thigh, because this was the most sensitive marker for peripheral perfusion during HFRCP and throughout CPB. We monitored rSO₂ throughout the operation through sensors attached to both sides of the forehead, the trunk (right back of the trunk), and both thighs (lateral aspects). Our target for rSO₂ on the trunk during HFRCP and CPB was more than 50%, as per a previous report.⁹ The rSO₂ on the thigh (94%) during HFRCP was higher than the truncal rSO₂ (64%), revealing that there were significant differences in the rSO₂ at various

monitoring sites during HFRCP. This is presumably because of the differential regulation and sensitivity of the regional tissue beds in the body. The brain and kidneys are the most important organs to be monitored, because the blood flow to the brain is highly autoregulated in normal circumstances and is a high extraction site, whereas the kidneys are a lower extraction site and are controlled by sympathetic innervation systems. In contrast, the thigh is composed of relatively homologous skeletal muscle tissue and has a lower oxygen demand during the anesthesia and neuromuscular blockade. These fundamental differences may contribute to the variation in rSO₂ at different monitoring sites. In addition, the advantages of multisite rSO₂ monitoring include the increased security and safety of the management of blood supply and distribution during aortic arch repair and the easy manipulation of the control of blood distribution between the upper and lower portions of the body. Furthermore, especially when using our method during HFRCP, we can speculate on the degree of collateral blood flow to the lower body and major organs. It is therefore also important to monitor rSO₂ on the trunk during HFRCP to maintain adequate DO₂. Balancing the flow between cerebral perfusion and peripheral perfusion is of paramount importance during HFRCP; however, we mostly rely on the cerebral rSO₂, because the

FIGURE 3. A, Correlations between the lactate concentration and oxygen delivery ratio (DO₂). B, Receiver operating characteristic (ROC) curve for the oxygen delivery ratio (DO₂). AUC, Area under the curve.

cerebral blood flow is crucial. We monitor the rSO₂ to facilitate appropriate adjustment of flow conditions by adjusting flow, vasodilator, and hematocrit levels. A Do₂R of 70% will be a new target value for patients undergoing HFRCP. We also monitor the radial artery pressure as a reference to enable maintenance above the lower limit of cerebral autoregulation, as previously described.²¹ We acknowledge, however, that flow conditions during HFRCP are variable; such variations can be related to anatomic features, such as coarctation of the aorta, interruption of the aortic arch, or other types of abnormal anatomy, or to preoperative factors such as whether the patient is stable or almost in shock. We plan to investigate these issues in further studies.

CONCLUSIONS

The rSO₂ on the thigh is a very sensitive marker of peripheral perfusion during HFRCP. This pilot study demonstrates that low Do₂R is associated with increased lactate concentrations, possibly indicating hypoperfusion. This method should be further studied in a larger group of patients with detailed early clinical outcomes reported.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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