The influence of pH strategy on cerebral and collateral circulation during hypothermic cardiopulmonary bypass in cyanotic patients with heart disease: Results of a randomized trial and real-time monitoring

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Objective: The optimal pH strategy during hypothermic cardiopulmonary bypass remains controversial. Systemic pulmonary collateral circulation may develop in patients with cyanotic anomalies. The purpose of this study was to evaluate the effect of pH strategies on cerebral oxygenation and systemic pulmonary collateral circulation during hypothermic cardiopulmonary bypass in cyanotic patients with heart disease.

Methods: Forty cyanotic patients (age > 1 year) with heart disease were prospectively randomized into 2 groups. Group 1 (n = 19, 14.3 ± 1.5 kg) underwent hypothermic cardiopulmonary bypass with alpha-stat strategy and group 2 (n = 21, 12.5 ± 0.9 kg) with pH-stat. Cardiopulmonary bypass was established with pump-assisted drainage. Cerebral oxygenation was assessed by near-infrared spectroscopy and the systemic pulmonary collateral circulation was calculated by pump flows [% systemic pulmonary collateral circulation = perfusion flow - drainage flow]/perfusion flow × 100]. Lactate was measured as an index of systemic anaerobic metabolism.

Results: There were no significant differences in preoperative hematocrit, oxygen saturation, Qp/Qs, cardiopulmonary bypass duration, minimum temperatures, perfusion flow and pressure, urine output, and depth of anesthesia between the groups. Oxyhemoglobin signal and tissue oxygenation index of near-infrared spectroscopy monitoring were significantly lower in group 1 compared with group 2 ($P = .008$ and $P < .0001$, respectively), suggesting inadequate cerebral oxygenation with alpha-stat. Deoxygenated hemoglobin signal was significantly higher in group 1 relative to group 2 ($P < .0001$). The % systemic pulmonary collateral circulation was significantly lower in group 2 compared with group 1, suggesting a reduced pulmonary collateral circulation with pH-stat ($P < .0001$, average; group 1, 20.1% ± 1.2%; group 2; 7.7% ± 0.7%). Serum lactate was significantly lower in group 2 ($P < .0001$).

Conclusions: The pH-stat strategy results in an improved environment, including sufficient cerebral oxygenation, decreased systemic pulmonary collateral circulation, and lower lactate level during hypothermic cardiopulmonary bypass in cyanotic patients with heart disease. Future studies should investigate the long-term neurological outcome.

The preference for the use of alpha-stat or pH-stat strategy as a choice for pH control during hypothermic cardiopulmonary bypass (CPB) has been a matter of controversy for a number of years. There are many reports that support the advantage of pH-stat strategy relative to alpha-stat strategy.¹⁻³ In addition, use of pH-stat strategy has been common in pediatric cardiac surgery.⁴ However, some cardiac centers are still using alpha-stat strategy, mainly for adult patients with heart disease. The most important effect of gas management should be on cerebral oxygenation during CPB. On the other hand, systemic pulmonary collateral circulation (SPCC) may develop in patients with cyanotic anomalies. Age and degree of cyanosis would be associated with the development of SPCC.⁵ In these circumstances, real-time monitoring of both cerebral oxygenation and extent of SPCC should be important for safe management of pediatric CPB. Near-infrared spectroscopy (NIRS) is a new device for monitoring tissue oxygenation and has been used in cardiac surgery.^{6,7} The purpose of this study was to evaluate the effect of pH strategies on cerebral oxygenation and SPCC during hypothermic CPB in cyanotic patients with heart disease by using a real-time monitoring system.

Material and Methods

Patients

Between April 2001 and July 2002, a total of 82 cyanotic patients (age > 1 year) with heart disease underwent definitive surgery at our institution. Among these, 40 patients were prospectively randomized into 2 groups after institutional review board approval and informed parental consent had been obtained. Group 1 (n = 19, mean body weight 14.3 ± 1.5 kg) underwent hypothermic CPB with alpha-stat strategy and group 2 (n = 21, mean body weight 12.5 ± 0.9 kg) with pH-stat strategy. Patients with chromosomal anomalies or preexisting mental retardation were excluded from the current study. CPB was established with pump-assisted bicaval drainage by using direct roller pump suction in all patients. The preoperative diagnoses, the number of patients, and the surgical procedures used are shown in Table 1.

Methods

CPB technique. The circuit consisted of a roller-pump, membrane oxygenator (D902 Lilliput 2, Dideco, Mirandola, Italy) and sterile tubing with 40- μ m arterial filter (Tow Nok, Technowood, Tokyo, Japan). Anticoagulation was initiated by systemic injection

TABLE 1. Preoperative diagnoses and surgical procedures

	Group 1 (alpha-stat)	Group 2 (pH-stat)
Diagnosis		
TA	2	1
SV	3	6
VSD + PA	5	4
Heterotaxia	3	4
Others	6	6
Surgical procedure		
Fontan	9	11
Rastelli	7	6
Others	3	4

TA, Tricuspid atresia; SV, single ventricle; VSD + PA, ventricular septal defect with pulmonary atresia; Fontan, Fontan-type operation; Rastelli, Rastelli-type operation.

of heparin of 200 U/kg body weight and priming of 2 U/mL total priming volume into the pump. Activated coagulation time was controlled over 400 minutes during CPB. Methylprednisolone (30 mg/kg) and ulinastatin (5000 U/kg) were given intravenously just before CPB. Full bypass flow was set at 100 to 120 mL/kg/min. Perfusion pressure was controlled within appropriate range (40-80 mm Hg) under this bypass flow. Either pH-stat or alpha-stat strategy was selected according to the study protocol. Mixed gas tank of 95% O₂ and 5% CO₂ was used for the pH-stat strategy. CPB was started and patients were cooled to an esophageal and rectal temperatures of 27°C to 28°C. Before aorta was declamped, methylprednisolone (30 mg/kg), ulinastatin (5000 U/kg), sodium bicarbonate (20 mL), and mannitol (20 mL) were administered by injection into the pump.

Blood gas and solute measurement. Arterial blood gas values and electrolyte, glucose, and lactate concentrations were measured before, during, and after CPB. Also, mixed venous samples were measured during CPB.

Neuromonitoring. Cerebral oxygenation was assessed by NIRS. After induction of anesthesia a pair of fiberoptic optodes was attached to the patient's head with a probe holder. The optode spacing was 4.0 or 5.0 cm in a coronal plane. The 2 optodes were comprised of a transmitter and a receiver of near-infrared laser light and were connected to an NIRS device (NIRO300; Hamamatsu Photonics K.K., Hamamatsu, Japan). This device calculated the relative concentration changes in oxyhemoglobin (HbO₂), deoxyhemoglobin (HHb), total hemoglobin (HbT), and oxidized cytochrome a,a3 (CytO₂) as well as tissue oxygenation index (TOI), which is the ratio of HbO₂ to HbT. Data was recorded every 10 seconds after the induction of anesthesia through 1 hour after discontinuation of CPB.

TABLE 2. Comparison of perioperative conditions of the 2 groups

	Group 1 (alpha-stat)	Group 2 (pH-stat)	P value
Body weight (kg)	14.3 ± 1.5	12.5 ± 0.9	.29
Preop Hct (%)	52.3 ± 1.1	54.9 ± 1.6	.20
TP (mg/dL)	7.2 ± 0.1	7.2 ± 0.1	.76
Pao ₂ (mm Hg)	51.1 ± 1.0	48.6 ± 1.8	.22
SaO ₂ (%)	82.5 ± 0.9	81.3 ± 1.6	.51
Qp/Qs	1.5 ± 0.1	1.3 ± 0.1	.11
Mean PAP (mm Hg)	16.9 ± 1.1	15.6 ± 1.1	.39
PA index (mm ² /m ²)	365.8 ± 32.4	360.2 ± 22.0	.89
CPB time (minutes)	151.3 ± 9.2	165.9 ± 8.9	.26
Aortic clamp time (minutes)	86.7 ± 8.0	96.6 ± 8.6	.43
Fentanyl dose (μg/kg/h)	6.9 ± 0.5	7.4 ± 0.6	.53
Bicarbonate dose (mL/kg/h)	2.9 ± 0.2	3.1 ± 0.4	.54
Urine output (mL/kg/h)	8.0 ± 1.7	6.2 ± 1.1	.38

Hct, Hematocrit; TP, total protein; PAP, pulmonary artery pressure; CPB, cardiopulmonary bypass.

Data are expressed as mean ± standard error of the mean.

Evaluation of collateral circulation. The SPCC was calculated according to the following equation using the pump flow rates and was recorded every 5 minutes: %SPCC = (perfusion flow – drainage flow)/perfusion flow × 100. Drainage flow is from all systemic venous return and does not contain the return from the left atrial vent and all suckers.

Statistical analysis. All results were expressed as mean ± standard error of the mean. Student *t* test was used to compare absolute quantitative values between the groups. Repeated measures of analysis of variance (ANOVA) were used for sequential, time-based measurements. One-way ANOVA was used to compare parameters between the groups. Data were further compared by Student *t* test if ANOVA was significant. All data were analyzed by a statistical analysis software package (Stat View 5.0, Abacus Concepts, Berkeley, Calif).

Results

There were no hospital deaths in either group. Acute epidural bleeding occurred as a complication in 1 patient in group 1 although he recovered after undergoing acute drainage. One patient with polysplenia in group 2 died of congestive heart failure 11 months later. No patient showed neurological dysfunctions in the follow-up period.

Perioperative conditions are shown in Table 2. There were no significant difference in age, body weight, preoperative hematocrit, total protein, oxygen saturation, Qp/Qs, pulmonary artery pressure, pulmonary artery index (PA index), CPB duration, aortic crossclamp time, depth of anesthesia, and urinary output between the 2 groups. Patients in group 1 had undergone palliative surgery in 1.4 ± 0.2 times and patients in group 2 in 1.1 ± 0.2 times, prior to definitive surgery, respectively ($P = .29$). There was also no significant difference in perfusion flow and pressure, esophageal and rectal temperature, and central venous pres-

sure during CPB. Both pH and Paco₂ were well controlled according to each pH strategy.

NIRS monitoring indicated the significantly lower HbO₂ signal ($P = .008$) and TOI ($P < .0001$) in group 1. Conversely, HHb signal was significantly higher in group 1 relative to group 2 ($P < .0001$). However, there was no significant difference in HbT signal ($P = .95$) and CytO₂ signal ($P = .69$) between the groups (Figure 1, A-E).

The average of %SPCC during cardiac arrest was $20.1\% \pm 1.2\%$ in group 1 and $7.7\% \pm 0.7\%$ in group 2, and this was significantly different ($P < .0001$). Maximum %SPCC of 57.6% was recognized in 1 patient in group 1 during cardiac arrest (Figure 2). Serum lactate was significantly lower in group 2 compared with group 1 ($P < .0001$). However, there was no significant difference in SvO₂ between the 2 groups ($P = .26$; Figure 3).

Discussion

This study demonstrates the advantage of pH-stat strategy during hypothermic CPB for cyanotic patients with heart disease through real-time monitoring. Adequate cerebral oxygenation as well as a decrease in collateral circulation could be obtained with the pH-stat strategy as opposed to the alpha-stat strategy. It was also demonstrated that NIRS could detect dramatic change in cerebral oxygenation during pediatric CPB.

Neurological and neuropsychological impairments are common after cardiac surgery and remain a major cause of postoperative morbidity and mortality. Temporary deficits are reported to occur in up to 30% of adult patients.⁸ Neurological deficits following pediatric CPB are estimated at 2% to 25%.⁹ They are mainly attributed to embolic events and cerebral ischemia.^{10,11} Athelosclerotic embolism is extremely rare in children and air embolism can now be avoided by meticulous air evacuation with the help of transesophageal echocardiography.¹² However, cerebral ischemia is relatively difficult to detect by the standard monitoring system such as perfusion pressure. The main causes of cerebral ischemia during pediatric CPB are cerebral hypoperfusion, intracerebral congestion due to inadequate superior vena caval (SVC) drainage, and uncoupling of the cerebral blood flow and metabolism due to high brain temperature exceeding 38°C.¹³ Among these factors, intracerebral congestion can be avoided by monitoring of the SVC pressure, and careful management of the rewarming of blood during CPB can prevent high brain temperature. Cerebral hypoperfusion is associated with cerebral capillary spasm due to blood alkalosis under alpha-stat strategy¹⁴ and results in a decrease of cerebral oxygen delivery to brain tissue. Also, cerebral oxygen delivery decreases according to hemodilution although increased cerebral blood flow can compensate for the deficit in oxygen delivery.¹⁵ Therefore, hematocrit and pH strategy should be particularly important

Figure 1. Changes in near-infrared spectroscopy data. **A**, Oxyhemoglobin (*HbO2*) signal: ANOVA, $P = .008$, $\#P < .05$, $*P < .01$. **B**, Deoxyhemoglobin (*HHb*) signal: ANOVA, $P < .0001$, $\#P < .05$, $*P < .01$. **C**, Total hemoglobin (*HbT*) signal: ANOVA, $P = .95$.

in the management of cerebral oxygen delivery during CPB. At this point, in cyanotic patients with heart disease, pre-operative hematocrit is usually high so that during CPB hematocrit is kept at over 25% even when straight hemodilution is performed with a low-prime CPB circuit. Also, during CPB hematocrit is often over 30% as CPB priming with whole blood is performed at many cardiac centers.¹⁶ Therefore, pH strategy should be taken into account for

ΔCytO_2 ($\mu\text{M} \times \text{DPF}$)

D

Perfusion Phase

TOI (%)

E

Perfusion Phase

Figure 1. Cont'd. D, Oxidized cytochrome a,a3 (CytO₂) signal: ANOVA, $P = .69$. E, Tissue oxygenation index (TOI): ANOVA, $P < .0001$, $\#P < .05$, $*P < .01$. BL, baseline; S-my, sternotomy; CPB(0), cardiopulmonary bypass (0 minutes); ACC, aortic crossclamp; REP, reperfusion; END, at the end of CPB.

cyanotic patients with heart disease who have a well-developed collateral circulation.

Clinical and experimental studies in children and young animals have shown beneficial neurological and neuropsychological effects of pH-stat strategy in comparison to alpha-stat strategy.^{17,18} These findings contrast with findings in adults in whom alpha-stat strategy resulted in improved neurological outcome.¹⁹ Cerebral blood flow varies linearly with Paco_2 .^{20,21} Therefore, increasing Paco_2 with pH-stat management may lead to an increased embolic load in the adult patient's atheromatous vasculature, although in a child the same process may protect the brain by increasing oxygen delivery. In addition, there have been few studies that elucidate the difference in cerebral oxygenation between

alpha-stat and pH-stat strategies by using a real-time monitoring system. This might be the main reason why in many cardiac centers deployment of optimal pH strategy is still controversial and alpha-stat strategy is being used even for the pediatric patients. Also, alpha-stat strategy is easy to perform because a mixed gas tank is not necessary. The result of the current study strongly supports the use of pH-stat strategy by demonstrating adequate cerebral oxygenation as well as decreased pulmonary collateral circulation.

In a recent clinical follow-up study, the use of pH-stat strategy during infant cardiac operations with deep hypothermic CPB was not found to be related to either improved or impaired early neurodevelopmental outcomes.²² Another

Figure 2. Change in %SPCC. The SPCC was calculated according to the following equation using the pump flow rates, and recorded every 5 minutes. ANOVA, $P < .0001$, $*P < .01$. $\%SPCC = (\text{perfusion flow} - \text{drainage flow})/\text{perfusion flow} \times 100$.

Figure 3. Change in (A) SvO₂ and (B) lactate. A, ANOVA, $P = .26$; B, ANOVA, $P < .0001$, $\#P < .05$, $*P < .01$.

recent laboratory study demonstrated that the use of pH-stat strategy in combination with high hematocrit could improve the neurological outcome after deep hypothermic circulatory arrest (DHCA).³ Also, Pearl and colleagues²³ reported

in their clinical retrospective study that pH-stat strategy in combination with hyperoxia resulted in the lowest level of acid production and therefore is the optimal strategy during CPB with DHCA. These studies were performed with circulatory arrest and it might be considered that differences in pH strategies are not related to the neurological outcome when circulatory arrest is not used. However, the patients studied were neonates and young infants who have little or no SPCC. The results of the current study showed that well-developed collateral circulation causes cerebral hypoperfusion under alpha-stat strategy, and therefore pH-stat strategy is a preferable procedure even without circulatory arrest. In addition, it should be considered that the use of pH-stat strategy is likely to provide improved cardiac function.²⁴ Even if circulatory arrest is not employed, we recommend using the pH-stat strategy for gas management during CPB due to its advantageous effects on cardiac function as well as prevention of neurological impairment. These effects are also supported by significantly lower lactate level during CPB in group 2 in the current study and demonstrated by others.²³

An NIRS device can measure the change in oxyhemoglobin signal, deoxyhemoglobin signal, total hemoglobin signal, and oxidized cytochrome signal, as well as TOI, which represents tissue oxygenation. Previous monitoring methods such as jugular venous saturation and electroencephalogram are not reliable under deep hypothermia. In addition, because there is presently no clinically applicable method for direct monitoring of cerebral oxygen delivery, the degree of hematocrit, perfusion flow, pH, and temperature remain surprisingly arbitrary. Although there was no difference in perfusion pressure and mixed venous saturation between alpha-stat and pH-stat strategies, in the current study, NIRS monitoring detected a lower cerebral oxygenation under alpha-stat strategy. NIRS technology has been proven to be useful in many different clinical settings, especially neonatology, neurosurgery, and cardiac surgery.^{6,7} Pediatric cardiac surgery seems to be particularly suited to application of this method because the changes in brain oxygenation are global.¹¹ In contrast to most other methods of brain monitoring, NIRS provides information on cerebral oxygenation even with minimal brain metabolism, cerebral blood flow, or brain function. Therefore, we believe that in future, NIRS monitoring should be used routinely during cardiac surgery.

In the current study, there was no patient who showed neurological dysfunctions in the mid-term postoperative period. However, the long-term neurological outcome is still unknown. Also, there has been no evidence that maintaining cerebral oxygenation above a certain level will prevent the long-term neurodevelopmental abnormalities. On the other hand, it is important to consider the results of animal experiment where many animals with ischemic his-

tologic changes revealed normal behavioral appearances.²⁵ Therefore, further studies are needed to investigate the long-term neurological outcome after pediatric cardiac surgery. In addition, cardiac surgeons should note that CPB parameters may have subtle but important effects on postoperative neurological outcome.

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Discussion

Dr Randall B. Griep (New York, NY). The degree of hypothermia here that we're talking about is not nearly as profound as many people use in this particular field, and so the degree of difference between alpha-stat and pH-stat is not quite as great.

I think the question is still open, though, as to if one is going to use a long period of hypothermic circulatory arrest whether preparation for that using pH-stat or alpha-stat is better. And it's certainly true that pH-stat gives you a higher cerebral blood flow because of the cerebral vasodilatation. It also gives you a lower intracellular pH. And if you're preparing for a long period of hypothermic circulatory arrest, it's unclear whether those 2 effects balance

each other out. And I think it's been Richard Jonas' group that has suggested that perhaps it's best to cool with pH-stat and then convert to alpha-stat to try and raise the intracellular pH prior to arrest.

What you have pointed out, I think, is in the patients with aortopulmonary collaterals that significantly steal from the bypass flow can occur even at these relatively high temperatures, 28°C to 30°C, and that by keeping the pH more acidotic that one reduces that and one also increases the cerebral flow. Now, I was interested to see that you said that the mixed venous saturations didn't vary. But I wonder whether you can say anything about the jugular venous return? In other words, that what you were demonstrating in part was that with your alpha-stat you really didn't have adequate cerebral oxygen delivery.

Dr Sakamoto (Tokyo, Japan). Thank you very much for your kind comment, Dr Griep. Actually, we measured the venous saturation by drawing venous blood through the side port of drainage line, so we did measure just the mixed venous saturation. If we checked the jugular venous blood, I think, it might be that jugular venous saturation in alpha-stat group is lower than that in pH-stat group. But we do not have any evidence about it in the current study, so it's still unknown. However, I would say here that there could be a lower level of jugular venous saturation in alpha-stat group compared with pH-stat group during cardiopulmonary bypass, particularly the rewarming phase. I think that near-infrared spectroscopy data supported this speculation.

Dr Andrew S. Wechsler (Philadelphia, Pa). No changes were made, if you saw a change in the near-infrared spectrometry during the operation, the anesthesiologist or the perfusionist made no change, that was a fixed protocol for perfusion?

Dr Sakamoto. Thank you very much, Dr Wechsler. Actually, anesthesia and other protocols were the same in both groups. No changes were made even when we saw a change in near-infrared spectroscopy during the operation in all patients. Therefore, we believe that there was no bias regarding perfusion protocol in the current study.