0031-3998/63536/0-0521
PEDIATRIC RESEARCH
Vol. 58, No. 3, 2005
Printed in U.S.A.

Monitoring of Cerebral Oxygenation during Hypoxic Gas Management in Congenital Heart Disease with Increased Pulmonary Blood Flow

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ABSTRACT

ABSTRACT In the preoperative management of congenital heart disease (CHD) with increased pulmonary blood flow, hypoxic gas management to control pulmonary blood flow is useful. However, the cerebral oxygenation state has rarely been studied, and there is concern about neurologic development. In eight infants with CHD accompanied by increased pulmonary blood flow, hypoxia was induced after a 1-h baseline period in room air (FiO_2, 0.21). The infants were simultaneously monitored in both the front-temporal region and the right-brachial region for 90 min using near-infrared spectroscopy (NIRS). The minimum SaO_2 (pulse oximetry) after hypoxic gas administration was 80.8 ± 2.9% when the minimum FiO_2 was 16.2 ± 1.1%. With a decrease in SaO_2, oxy-Hb (O_2Hb) decreased and total Hb [cHb: O_2Hb + deoxy-Hb (HHb)] increased in both regions in the majority of infants. HHb increased in both regions with a decrease in SaO_2. The maximum change in the tissue oxygenation index (TOI: $O_2Hb/cHb \times 100$) was −8.3 ± 2.6% in the front-temporal region and −3.6 ± 2.3% in the right-brachial region. Cerebral oxygenation decreased despite an increase in cerebral blood flow during hypoxic gas management. The change in TOI was ≤10% when the SaO_2 was ≥80%. Safer control of SaO_2 should be maintained over 80% for hypoxia management in CHD based on the results of the present study. (***Pediatr Res* 58: 521–524, 2005**)

Abbreviations

cHb, total hemoglobin
CHD, congenital heart disease
HHb, deoxy-hemoglobin
HLHS, hypoplastic left heart syndrome
NIRS, near-infrared spectroscopy
O_2Hb, oxy-hemoglobin
Qp/Qs, the ratio of pulmonary to systemic blood flow
ScO_2, cerebral oxygen saturation
TOI, tissue oxygenation index

Congenital heart disease (CHD) with increased pulmonary blood flow is the most common cause of congestive heart failure in the neonate and young infant, and proper management is a determinant of surgical outcome. Balancing blood flow between the pulmonary and systemic circulations is important for preoperative management (1,2). In particular, during the neonatal period, rapid reduction of pulmonary vascular resistance causes pulmonary congestion by increasing pulmonary blood flow and systemic hypotension by decreasing systemic blood flow. To maintain the balance between the pulmonary and systemic circulations, hypoventilation (3,4), hypercarbia (5,6), or hypoxia (7,8) is approved as an effective method of preoperative management. Hypoxic gas treatment has been reported to be useful because systemic management is safe and easy, and arrest of spontaneous respiration is not required. However, there is concern about the possible development of neurologic complications due to cerebral hypoxia. A few studies have evaluated the cerebral oxygenation state during hypoxic gas management in infants, and the safety range of low oxygen treatment has not yet been established. Tabbutt *et al.* (9) recently compared brain and systemic circulations between hypoxia and hypercarbia management in 10 infants with hypoplastic left heart syndrome (HLHS) immediately before surgery. The ratio of pulmonary to systemic blood flow (Qp/Qs) was decreased in both hypoxia and hypercarbia but there was no change and an increase in cerebral oxygen delivery in hypoxia and hypercarbia, respectively. They also monitored their patients by near-infrared spectroscopy (NIRS) and reported that ScO_2 did not change in hypoxia but increased in hypercarbia during a 10-min period of observation. However, for clinical use, longer observation under hypoxic treatment gives more information regarding safety.

Received June 16, 2004; accepted January 4, 2005.
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DOI: 10.1203/01.pdr.0000176913.41568.9d

We evaluated serial changes in the oxygenation state simultaneously in the head and body by NIRS during preoperative hypoxia in infants with congenital heart disease and increased pulmonary blood flow. Our ultimate goal was to establish the optimal level of FiO_2 to prevent brain damage.

METHODS

Patients. The subjects were eight infants with CHD accompanied by increased pulmonary blood flow, who were admitted to the Heart Institute of Japan, Tokyo Women's Medical University from April 2002 to March 2003. Infants with anomalies in organs other than the heart were excluded. Informed consent for hypoxic gas administration was obtained from the parents of all infants. The study was approved by the Research Ethics Committee of the Tokyo Women's Medical University.

Treatment and procedure. Six infants underwent controlled ventilation using a respirator in a pressure-regulated volume control mode (BP 2001, Bear Medical Systems, Palm Springs, CA), and two infants were managed using a head box (OX-900, Atom Medical, Tokyo, Japan). In management using a respirator, nitrogen gas was delivered to the inhalation side of the circuit and mixed with air, and the FiO_2 was calculated from the ratio of nitrogen gas to air. In management using a head box, nitrogen gas was mixed with air and delivered from the upper part of head box, and the oxygen concentration was monitored at level of the mouth in each infant.

NIRS. The NIRS apparatus (NIRO-300, Hamamatsu Photonics KK, Shizuoka, Japan) uses a semiconductor laser as a light source, and near-infrared light with four different wavelengths (775, 810, 850, 910 nm) is irradiated *via* light fibers from one side of the skin. Changes in transmitted light are detected on the other side, and the oxygenated and deoxygenated Hb concentrations are monitored based on known absorption spectra of Hb. Two sets of light fiber optodes of the NIRS apparatus were secured to the front-temporal and right-brachial (biceps brachii muscle) regions and were inserted into a black optode receptacle to provide an interoptode distance of 40 mm. Oxy-Hb (O_2Hb), deoxy-Hb (HHb), total Hb (cHb: O_2Hb + HHb), and tissue oxygenation index (TOI: O_2Hb/cHb $\times$ 100) were continuously monitored. The results were recorded and stored as graphs and numerical values in a personal computer. TOI was calculated as the median value of 150 measurements (5 min) during the examination period.

Study design. In all the infants under hypoxic gas management, after a 1-h baseline period in room air (FiO_2: 0.21), a nitrogen gas mixture was administered, and measurements were performed for 90 min. SaO_2 was measured continuously in the right upper arm using a pulse oximeter (Nellcor Pulse Oximeter N-200, Tyco Healthcare Japan, Tokyo, Japan). Oxygen content was adjusted by gradually increasing the flow of nitrogen gas to achieve a target SaO_2 of 80%. The heart rate was monitored in all infants, and the systolic and diastolic pressures were monitored invasively from the radial artery in the six infants under respirator management (BSM-2303, Nihon Kohden Corporation, Tokyo, Japan).

The post-NIRS data (O_2Hb, HHb, cHb, and TOI) were compared with the pre-NIRS data (baseline period). Each infant served as their own control. All variables were expressed as mean ± SD. Differences between the heart rate and systolic and diastolic aortic blood pressures before and after hypoxic gas administration were analyzed by the paired *t* test, and $p < 0.05$ was considered significant.

RESULTS

Table 1 shows subject clinical profiles of eight infants with CHD accompanied by increased pulmonary blood flow. Their mean gestational age was 36 ± 3 wk and birth weight was 2537 ± 576 g. Seven infants were neonates within 13 d of birth, and one was a 2-mo-old with a very low birth weight.

There were three infants with two functional ventricles including coarctation of the aorta with ventricular septal defect, truncus arteriosus communis (TAC), and interruption of the aortic arch (type A). A single functional ventricle was observed in the other five infants; three had HLHS and the other two had tricuspid atresia (type Ic). Of the eight infants, six underwent respiratory management by intermittent mandatory ventilation with a ventilator rate of 12.8 ± 2.9, peak inspiratory pressure of 18.4 ± 0.8 mm Hg, and positive end-expiratory pressure of 3.0 ± 0.0 mm Hg; the other two were managed using a head box. All infants, except for the one with TAC, were treated by prostaglandin E1 infusion, and seven infant was treated with midazolam for sedation. The mean duration of hypoxic gas management was 33.4 ± 62.6 d, and the age at the time of the study was 15.9 ± 16.8 d.

Table 2 shows the oximetric and hemodynamic data. The SaO_2 before the initiation of hypoxia was 97.0 ± 2.1%, and the minimum SaO_2 after initiation of hypoxia was 80.8 ± 2.9%, and the change in SaO_2 (post- SaO_2 – pre- SaO_2) was –16.3 ± 3.2% (range, –22 to –10%), when the minimum FiO_2 was 16.2 ± 1.1% (range, 14.6–18.6%). The mean arterial pH on the day of study was 7.44 ± 0.03, and $PaCO_2$ was 43.2 ± 4.9 mm Hg. No significant changes were observed in heart rate or systolic and diastolic pressures before or after administration of the hypoxic gas mixture.

Table 3 shows the NIRS data. With a decrease in SaO_2 after the initiation of hypoxia, O_2Hb decreased in the front-temporal region in all infants, and decreased in the right-brachial region in seven of eight infants. With the decrease in SaO_2 during hypoxia, HHb increased in the front-temporal region in all infants, and increased in the right-brachial region increased in seven of eight infants. With an increase in SaO_2 after discontinuation of the hypoxic gas, O_2Hb increased and HHB decreased in these regions in all infants. Similarly, with a decrease in SaO_2, cHb increased in the front-temporal region in

Table 1. *Subject demographics*

Pt. No.	GA (week)	BW (g)	Gender	Diagnosis	Ventilation	PGE1	Sedation	Duration of hypoxia (days)	Age at study (day)
1	39	2942	F	CoA with VSD	IMV	+	+	17	8
2	36	2676	F	TAC(I)	IMV	–	–	5	12
3	34	2429	M	IAA(A)	IMV	+	+	18	6
4	37	2500	F	HLHS	IMV	+	+	7	7
5	40	3308	M	HLHS	Head BOX	+	+	12	13
6	32	1820	F	HLHS	Head BOX	+	+	10	10
7	39	3100	M	TA(IIc)	IMV	+	+	10	11
8	32	1520	M	TA(IIc)	IMV	+	+	188	60
Mean ± SD	36 ± 3	2537 ± 576						33.4 ± 62.6	15.9 ± 16.8

GA, gestational age; BW, birth weight; CoA with VSD, coarctation of the aorta with ventricular septal defect; TAC, truncus arteriosus communis; IAA, interruption of aortic arch; HLHS, hypoplastic left heart syndrome; TA, tricuspid atresia; IMV, intermittent mandatory ventilation; PGE 1, prostagrandin E1infusion.

Table 2. *Oximetry and hemodynamic data*

Pt. No.	Pre SaO_2 (%)	Post $SaO_2$2 (%)	ΔSaO_2 (%)	Minimum FiO_2 (%)	pH	$PaCO_2$ (mmHg)	Pre HR (bpm)	Post HR (bpm)	Pre sBP (mmHg)	Post sBP (mmHg)	Pre dBP (mmHg)	Post dBP (mmHg)
1	98	76	-22	14.6	7.45	43	145	140	58	61	33	35
2	98	83	-15	15.6	7.46	41	131	125	60	56	28	28
3	99	83	-16	15.6	7.47	35	136	134	64	64	35	32
4	93	78	-15	16.8	7.46	47	142	135	61	61	44	44
5	96	78	-18	16.8			152	154				
6	95	85	-10	15.6			145	141				
7	97	81	-16	18.6	7.4	44	138	132	79	83	57	55
8	100	82	-18	16.2	7.41	49	121	122	68	69	39	39
Mean ± SD	97.0 ± 2.1	80.8±2.9	-16.3 ± 3.2	16.2 ± 1.1	7.44 ± 0.03	43.2 ± 4.9	138.8 ± 9.0	135.4 ± 9.4	65 ± 6.5	66.7 ± 8.7	39.3 ± 9.3	38.8 ± 8.8

SaO_2, systemic or right hand saturation of oxygen; HR, heart rate; sBP, systolic arterial blood pressure; dBP, diastolic arterial blood pressure.

Table 3. *NIRS data*

	Front-temporal			Brachial			Pre TOI (%)		ΔTOI (%)	
Pt. No.	O_2Hb	HHb	cHb	O_2Hb	HHb	cHb	Front-temporal	Brachial	Front-temporal	Brachial
1	↓	↑	↑	↓	↑	↑	66	55	-13	-3
2	↓	↑	↑	↓	↑	↑	65	60	-7	-4
3	↓	↑	↑	↓	↑	→	63	49	-3	-3
4	↓	↑	↑	↓	↑	↑	55	60	-8	-5
5	↓	↑	→	→	→	→	52	53	-8	-8
6	↓	↑	↑	↓	↑	↑	63	57	-9	-1
7	↓	↑	↑	↓	↑	→	42	59	-8	-1
8	↓	↑	↑	↓	↑	↑	55	66	-10	-6
Mean ± SD							57.6 ± 7.7	57.4 ± 4.8	-8.3 ± 2.6	-3.6 ± 2.3

↑, the values during hypoxia increased compared to baseline; ↓, the values during hypoxia decreased compared to baseline; →, no change between hypoxia and baseline.

seven of eight infants and increased in the right-brachial region increased in five of eight infants. The changes in cHb were reversed when the SaO_2 increased. During the baseline period, TOI in the front-temporal region was 57.6 ± 7.7% (range, 42–66%) and was 57.4 ± 4.8% (range, 49–66%) in the right-brachial region. The maximum change in TOI (post TOI-pre TOI) during hypoxic gas administration was –8.3 ± 2.6% (range, –3 to –13%) in the front-temporal region and –3.6 ± 2.3% (range, –1 to –8%) in the right-brachial region. When the hypoxic gas was discontinued, SaO_2 increased and TOI recovered to its baseline value in all infants. The change in TOI was ≤ 10% when SaO_2 was ≥80%. Patient 1 showed a maximum TOI change of –13% with a SaO_2 of 76%, but a maximum TOI change of ≤–9% with a SaO_2 of ≥80%.

DISCUSSION

In CHD with increased pulmonary blood flow, a physiologic decrease of pulmonary arterial resistance after birth readily increases Qp/Qs. Acute reduction of pulmonary arterial resistance causes severe pulmonary congestion; the resulting decrease in systemic blood flow induces hypotension, end organ dysfunction, coronary ischemia, metabolic acidosis, and hypoxic-ischemic brain injury. Therefore, the maintenance of high pulmonary vascular resistance and low Qp/Qs is necessary in the preoperative management of CHD with increased pulmonary blood flow. The methods of maintaining high pulmonary vascular resistance include hypoventilation (3,4), hypercarbia (5,6), and hypoxia (7,8). The advantages of hypoxia over hypercarbia or hypoventilation are that general anesthesia, including a muscle relaxant, is not necessary even in the presence of a respirator, and enteral nutrition, including maternal antibodies, can be given. Therefore, hypoxia is preferred for patients who need a longer period of control of pulmonary-systemic flow balance, including the recovery period from so-called ductal shock or intracranial bleeding or premature infants. However, it has been reported that preoperative cardiorespiratory instability and cerebral vasoregulatory disturbances cause brain injury in infants with CHD, which raises concerns about preoperative hypoxic-ischemic injury due to decreased oxygen delivery to the brain during hypoxia (10).

NIRS is a noninvasive real-time monitoring technique that provides information on the oxygenation state of the brain by determining the concentrations of intracranial O_2Hb and HHb. Since Jobsis *et al.* (11) applied NIRS to study the human brain in 1977, clinical studies have been performed mainly in the neonatal field (12). Meek *et al.* (13) reported that cerebral blood flow increased over 72 h after birth, irrespective of blood pressure or $PaCO_2$ in neonates with low birth weight. Yoxall *et al.* (14) calculated cerebral oxygen consumption (CVO_2) from cerebral blood flow and cerebral venous O_2Hb saturation and showed an increase in CVO_2 with gestational age. In addition, they suggested that the measurement of cerebral oxygen consumption gives more information than the measurement of cerebral blood flow for the prevention of cerebral hypoxia and ischemia (15) We monitored cerebral tissue oxygenation by NIRS and SaO_2 by pulse oximetry during preoperative hypoxia in eight infants with CHD. The FiO_2 was determined based on the report of Barnea *et al.* (2), and

management was performed using a target SaO_2 of 80% measured in the right brachial region with a pulse oximeter. In our study, O_2Hb, HHb, and cHb reflected changes in tissue oxygenation in the front-temporal region and right-brachial region in infants with two functional ventricles as well as a single functional ventricle. A decrease in O_2Hb and an increase in HHb indicate hypoxic states of the brain and an increase in cHb may indicate an increase in cerebral blood flow. Clinically, an increase in blood flow did not compensate the oxygenation during hypoxic gas management. An increase in cHb was more frequently observed in the front temporal region than in the brachial region. However, based on this finding alone, it is difficult to conclude that there was a selective increase in cerebral blood flow. CBF was increased by a flow shift from the lung to systemic circulation.

O_2Hb and HHb are relative parameters for the evaluation of changes in the Hb concentration. However, TOI is a new absolute parameter for the evaluation of the oxygenation state. Due to differences among the types of devices for measuring NIRS in the brain, the results of this measurement are expressed as TOI, cerebral oxygen saturation (ScO_2), cerebral venous oxygen saturation (SvO_2), or regional cerebral oxygen saturation (rSO_2). Although the rate of change differs, these are basically similar parameters (16). Naulaers *et al.* (17) evaluated TOI on the first 3 d after birth in premature infants (median postmenstrual age, 28 wk) and observed an increase in this value over time: 57% on d 1, 66.1% on d 2, and 76.1% on d 3. Fortune *et al.* (18) measured TOI in the front-temporal region in various neonatal diseases and reported considerable differences (38–99%) depending upon the type of disease. Kurth *et al.* (19) compared ScO_2 among various congenital heart diseases and observed no differences between healthy subjects and patients with ventricular septal defect, aortic coarctation, or a single ventricle after the Fontan operation but a significant decrease (10–30%) in patients with patent ductus arteriosus, tetralogy of Fallot, HLHS, pulmonary atresia, or single ventricle after aortopulmonary shunt or bidirectional Glenn operation. Another study in adults who underwent carotid endarterectomy showed that the change in TOI during clamping of the internal carotid artery was $-9.4 \pm 7.1\%$ without any brain damage (20). However, Tabbutt *et al.* (9) evaluated preoperative hypoxia management, and reported no decrease in ScO_2 during hypoxia. A reduction in ScO_2 may have been missed in that study because the measurement time with NIRS was only about 10 min. In our study, TOI was measured for 90 min, and a decrease in this index was observed during hypoxia in both infants with two functional ventricles as well as a single functional ventricle. The decrease in TOI in the front-temporal region was about half the decrease in brachial SaO_2 in the present study.

Barnea *et al.* (2) reported that oxygen delivery to body tissue is optimal at a Qp/Qs of 1 under hemodynamic conditions resembling a single functional ventricle, and recommended a target SaO_2 of 75–80%. Day *et al.* (8) reported that maintaining SaO_2 at about 75% during hypoxia is useful for systemic circulations as preoperative management of a single functional ventricle and ductal-dependent systemic perfusion. However, there have been no studies on the adequate range of the oxygen concentration in hypoxia in terms of the prevention of central nervous complications. A decreased oxygen concentration due to hypoxia causes hypoxic-ischemic injury to the brain, *i.e.* long-term low TOI may promote neurodevelopmental disability in the neonate. An animal study only showed a relationship between ScO_2 and hypoxia-ischemia in piglets, in terms of EEG, brain ATP, and lactate concentrations, and indicated that hypoxic-ischemic thresholds for functional impairment occur at an ScO_2 change of –24% to –35% from a baseline ScO_2 level of 68% (21). In our study, the percent decrease in TOI did not exceed 10% when the SaO_2 was $\geq$80%. Based on the results of the present study, it is reasonable to suppose that brachial SaO_2 over 80% may be an important index of hypoxic management. Further studies with larger sample sizes are necessary to make more definitive conclusions and should also address the relationship between brain damage and TOI.

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