Carbon dioxide—a complex gas in a complex circulation: Its effects on systemic hemodynamics and oxygen transport, cerebral, and splanchnic circulation in neonates after the Norwood procedure

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Objective: Carbon dioxide is suggested to increase oxygen delivery after the Norwood procedure. We sought to quantitatively define the effects of stepwise increases in arterial carbon dioxide tension on systemic oxygen transport and cerebral and splanchnic circulation after the Norwood procedure.

Methods: Seven sedated, paralyzed, and mechanically ventilated neonates were studied after the Norwood procedure. Arterial carbon dioxide tension increased from 40-50-60 mm Hg using inspired carbon dioxide. Each step was 30 minutes. Pulmonary and systemic blood flow, vascular resistance, and oxygen delivery were calculated with the measurement of oxygen consumption and blood gases and pressures from the aorta, superior vena cava, and pulmonary vein. Plasma epinephrine and norepinephrine were measured. Cerebral and splanchnic oxygen saturations were measured by near-infrared spectroscopy, and cerebral blood flow velocity was measured by transcranial Doppler.

Results: Stepwise increase in arterial carbon dioxide tension was associated with a decrease in systemic vascular resistance ($P < .001$) and an increase in systemic blood flow ($P < .01$) and oxygen delivery ($P < .0001$), but not with significant changes in total pulmonary vascular resistance and pulmonary blood flow. Cerebral oxygen saturation increased ($P < .0001$), and splanchnic oxygen saturation decreased ($P < .01$). Oxygen consumption decreased ($P < .01$), and epinephrine and norepinephrine increased ($P < .01$ and $.05$).

Conclusion: Moderate hypercapnia increases systemic blood flow because of its effect on systemic vascular resistance after the Norwood procedure. The increase in systemic blood flow is primarily a consequence of increased cerebral blood flow that compromises splanchnic circulation. The decrease in oxygen consumption improves oxygen transport, but the increase in catecholamines may be undesirable. Clinical use of carbon dioxide aiming to improve oxygen delivery should be with caution.

The important goal and challenge in the management of neonates after the Norwood procedure is to maintain adequate systemic blood flow (Q_s) and oxygen delivery (DO_2) to sustain tissue oxygenation. In these neonates, DO_2 is reduced because of impaired myocardial function, and systemic oxygen consumption (VO_2) is increased as a result of cardiopulmonary bypass (CPB) and secondary systemic inflammatory response.¹ The complex pathophysiology with univentricular and parallel circulation profoundly affects oxygen transport after the Norwood procedure and seriously limits the postoperative management. The lack of adequate animal models of single ventricle anatomy or physiology makes it difficult to study.²⁻⁴ Clinical studies have been limited because of the use of indirect indicators of arterial

and superior vena caval oxygen saturations as surrogates of DO_2 .^{5,6}

Carbon dioxide (CO_2) has been suggested to increase DO_2 in neonates both before and after the Norwood procedure.²⁻⁶ Consequently, it is a common practice to maintain a relatively high arterial CO_2 tension ($Paco_2$) mostly by hypoventilation. It is believed that the potent pulmonary vasoconstrictive effect of CO_2 decreases pulmonary blood flow (Q_p), and $Q_p:Q_s$ thereby increases Q_s . This may be incorrect. As we have recently reported, using directly measured systemic hemodynamics and oxygen transport, Q_p has little impact on DO_2 in the presence of mechanical limitation by the Blalock-Taussig shunt and relative fixed total pulmonary vascular resistance (tPVR) (inclusive of the resistance of the Blalock-Taussig shunt and pulmonary vascular bed), and DO_2 is mostly determined by SVR.¹ Given the potent vasodilating effect of CO_2 on systemic circulation,⁷ particularly the cerebral vascular bed,^{8,9} it was hypothesized that the increase in Q_s and DO_2 by CO_2 may be the result of its effect on systemic circulation rather than the pulmonary vasculature, and that the increase in Q_s may be the result of an increase in cerebral blood flow instead of splanchnic perfusion.

Near-infrared spectroscopy (NIRS) measures the equilibrium of oxyhemoglobin and deoxyhemoglobin in a mixture

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Abbreviations and Acronyms

CO ₂	= carbon dioxide
CPB	= cardiopulmonary bypass
DO ₂	= systemic oxygen delivery
NIRS	= near-infrared spectroscopy
Paco ₂	= arterial carbon dioxide tension
Pao ₂	= arterial oxygen tension
PVR	= pulmonary vascular resistance
Qp	= pulmonary blood flow
Qs	= systemic blood flow
ScO ₂	= cerebral oxygen saturation
SsO ₂	= splanchnic oxygen saturation
SVR	= systemic vascular resistance
tPVR	= total pulmonary vascular resistance
VO ₂	= systemic oxygen consumption

of veins, arteries, and capillaries in the underlying tissue and provides a noninvasive, continuous method to monitor regional tissue oxygenation.¹⁰ NIRS has been extensively evaluated in the cerebral¹⁰ and splanchnic¹¹ circulations of newborn infants and was adapted to continuously monitor cerebral oxygen saturation (ScO₂) and splanchnic oxygen saturation (SsO₂) in the present study.

This study aimed to quantitatively define the effects of a stepwise increase in Paco₂ on the systemic hemodynamics, oxygen transport, and redistribution of systemic DO₂ between cerebral and splanchnic circulations in neonates during the early postoperative period after the Norwood procedure.

MATERIALS AND METHODS**Patients**

This study was approved by the Research Ethics Board at the Hospital for Sick Children, Toronto, Canada. Written informed consent was obtained from the parents of 7 neonates (4 boys and 3 girls, age range 4–7 days) undergoing the classic Norwood procedure with Blalock-Taussig shunt between September of 2004 and October of 2006. The clinical characteristics of the patients are shown in Table 1. Neonates undergoing the Norwood procedure with right ventricular to pulmonary arterial shunt or the Hybrid procedure with bilateral pulmonary artery bands and arterial duct stent during this period were excluded from the present study in the concern of their different characteristics in systemic hemodynamics and oxygen transport¹² and potential different responses to CO₂.

Intraoperative Procedures

All patients were intubated with cuffed endotracheal tubes (Microcuff-Heidelberg-Pediatric, Microcuff GmbH, Weinheim, Germany). A central venous line was inserted preoperatively through the internal jugular vein or the subclavian vein to the superior vena cava just above the atrium junction. A standard Norwood procedure with the 3.5-mm right modified Blalock-Taussig shunt was performed in all patients. Circulatory arrest was performed in 6 patients for 1 to 46 minutes and selected cerebral perfusion in 6 patients for 30 to 70 minutes at 30 to 35 mL/min/kg (Table 1). Phenoxybenzamine (0.25 mg/kg) was given in the heart-lung machine circuit after initiation of CPB. Before termination of CPB, milrinone

(100 µg/kg) was given and dopamine (5 µg/kg/min) was initiated. A pulmonary venous line was inserted into the orifice of the right upper pulmonary vein.

Postoperative Management

The central temperature (esophageal) was maintained between 36°C and 37°C. Postoperative monitoring included arterial, superior vena caval, and pulmonary venous pressures, and heart rate. Sedation consisted of continuous intravenous infusion of morphine and intermittent injections of a muscle relaxant (pancuronium). Patients received time-cycled pressure control/pressure support ventilation. Hemoglobin was maintained between 14 and 16 mg/dL. Inotropic and vasoactive agents (dopamine, milrinone, and phenoxybenzamine) and volume infusions (5% albumin or blood) were administered according to our standard protocol.¹³

Methods of Measurements

Systemic oxygen consumption. VO₂ was measured continuously using an AMIS2000 respiratory mass spectrometer (Innovision A/S, Odense, Denmark). This is a sensitive and accurate method for continuous gas analysis that allows simultaneous measurements of multiple gas fractions.¹ Inspired and end-tidal partial pressures of CO₂ were continuously monitored using inlet sampling from the connection of the ventilator circuit to the endotracheal tube. This was used to estimate the rate of CO₂ delivery into the inspired gas mixture.¹⁴ The setup of the CO₂ delivery and respiratory mass spectrometer with the ventilator circuit is described elsewhere.¹⁵

Calculations of hemodynamics and oxygen transport.

Blood samples were taken from the arterial, superior vena caval, and pulmonary venous lines for the measurements of blood gases. Qp, Qs, SVR, tPVR, DO₂, and oxygen extraction ratio (ERO₂) were calculated using standard equations (Table 2).

Regional oxygenation. Measurements of cerebral and splanchnic oxygenation were made using NIRS to measure ScO₂ and SsO₂. The 2 NIRS probes (Somanetics INVOS 5100A, Troy, Mich) were placed in the midline on the forehead of the patient (ScO₂) and slightly to the right of midline on the thoracic-lumbar flank (SsO₂),¹⁶ and recordings were made at 1-minute intervals.

Cerebral blood flow velocity. The flow velocity was measured with transcranial Doppler with a 2 MHz pulse-wave ultrasound transducer, which was fixed above the zygomatic arch (Medasonics Inc, Fremont, Calif) and interrogated the portion of middle cerebral artery near its junction with the anterior cerebral artery.⁹

Plasma norepinephrine and epinephrine. An arterial blood sample of 2 mL was withdrawn into an EDTA tube. The simultaneous determination of plasma norepinephrine and epinephrine was measured by high-performance liquid chromatography coupled with electrochemical detection.¹⁷

Study Protocol

The study protocol was instituted during the period of 48 to 72 hours after the Norwood procedure when a relatively cardiorespiratory steady state was achieved. Inspiratory O₂ fraction was 0.21 to 0.25. The protocol consisted of 4 stages. At baseline, Paco₂ was adjusted to 40 mm Hg by modifying minute ventilation. Subsequently, CO₂ was delivered to the inspired gas mixture to reach Paco₂ tensions of 50 and 60 mm Hg sequentially. Finally, additional CO₂ was withdrawn and the measurements were repeated at a Paco₂ of approximately 40 mm Hg. Each stage was for 30 minutes. At the end of each stage, blood gases (including arterial lactate), systemic hemodynamics and oxygen transport, ScO₂ and SsO₂, and cerebral arterial blood flow velocity were recorded, and arterial blood samples were taken for the measurements of plasma epinephrine and norepinephrine. Before the study, echocardiography was performed to ensure that the aortic arch and Blalock-Taussig shunt were unobstructed.

TABLE 1. Clinical data for the 7 patients

Patient	Age (d)	Weight (kg)	BSA (m ²)	CPB (min)	ACC (min)	Circulatory arrest (min)	Cerebral perfusion (min)	Diagnosis
1	7	4	0.25	167	64	17	44	HLHS, AS, MS
2	6	2.9	0.2	142	62	1	62	HLHS, AS, MS
3	5	4.5	0.28	103	75	45	30	TA, TGA, IAA
4	7	3.6	0.24	156	86	0	0	TGA, hypoplastic aortic arch, criss-cross heart, VSDs
5	5	2.5	0.18	170	126	46	60	HLHS, AA, MS
6	4	4.2	0.27	124	99	44	49	HLHS, MA, AA, TAPVC
7	7	3.2	0.21	164	66	9	54	TA, TGA, Hypo AA

AA, Aortic atresia; AS, aortic stenosis; ACC, aortic crossclamp; BSA, body surface area; CPB, cardiopulmonary bypass; HLHS, hypoplastic left heart syndrome; Hypo AA, hypoplastic aortic arch; IAA, interrupted aortic arch; LV, left ventricle; MA, mitral atresia; MS, mitral stenosis; TA, tricuspid atresia; TAPVC, total abnormal pulmonary venous connection; TGA, transposition of great arteries; VSD, multiple ventricular septal defect.

Statistics

The results are given as mean ± standard deviation. The data, collected at 4 levels of Paco₂ (40, 50, and 60 mm Hg, and then 40 mm Hg), were analyzed by repeated-measures analysis of variance for quadratic effect. A quadratic effect was indicated by a statistically significant parameter estimate for the time sequence effect. The actual estimate for the inverted parabolas was negative, indicating a return toward baseline for the outcome. Pairwise comparison was performed between the data at different levels of CO₂. The overall *P* value and adjusted *P* value for multiple comparisons were calculated using the Tukey-Kramer adjustment. We used the statistical software SAS version 8.2 (Cary, NC).

RESULTS

Patients

All 7 patients received an infusion of milrinone (0.66–0.99 µg/kg/min), and 3 of them received phenoxybenzamine (0.5–2.0 mg/kg/d) during the study period. Dopamine had been terminated within the first 36 hours in all patients. None of the patients received epinephrine or norepinephrine during the postoperative period. Patients were extubated 4 to 25 days (median 9 days) after the operation.

Changes During the Study Protocol

The stepwise increase in Paco₂ from 40 ± 4 to 53 ± 5 to 61 ± 6 mm Hg led to a decrease in arterial pH from 7.39 ±

0.05 to 7.28 ± 0.07 to 7.23 ± 0.08 (*P* < .0001) (Table 3; Figure 1). This was not associated with any significant change in tPVR, Qp, SaO₂, or pulmonary venous O₂ saturation. The stepwise increase in Paco₂ was associated with a significant decrease in SVR (*P* < .001) and Qp:Qs (*P* < .05), and a significant increase in arterial oxygen tension (Pao₂) (*P* < .0001), Qs (*P* < .01), and DO₂ (*P* < .0001). A significant decrease in central body temperature (*P* < .05), VO₂ (*P* < .01), ERO₂ (*P* < .01), and lactate (*P* < .001) were observed. Norepinephrine (*P* < .05) and epinephrine (*P* < .01) significantly increased. Cerebral arterial blood flow peak velocity and ScO₂, as well as superior vena caval O₂ saturation, significantly increased (*P* < .0001 for all), whereas SsO₂ significantly decreased (*P* < .01). These changes were significantly greater when Paco₂ increased from 40 to 50 mm Hg compared with Paco₂ from 50 to 60 mm Hg, including Pao₂ (*P* < .0001), VO₂ (*P* < .05), lactate (*P* < .05), cerebral arterial blood flow peak velocity (*P* < .01), ScO₂ (*P* < .0001), superior venous O₂ saturation (*P* < .0001), and norepinephrine (*P* < .05). DO₂ increased significantly at both stages of Paco₂ (*P* < .05). The changes in the remaining variables (temperature, SVR, Qs, Qp:Qs, CO, ERO₂) did not achieve statistical significance between either of the 2 sequential stages, despite the significant changes over the 3 levels of Paco₂. There was a small although insignificant increase in heart rate and arterial blood pressure over the stepwise increase in Paco₂. As Paco₂ decreased from 60 ± 6 mm Hg to 44 ± 5 mm Hg with discontinuation of added CO₂, these variables returned toward baseline.

The levels of norepinephrine and epinephrine at baseline Paco₂ (40 mm Hg) varied widely between patients (3.4–25.0 nmol/L for norepinephrine and 0.1–14.0 nmol/L for epinephrine). The levels of norepinephrine and epinephrine at each level of Paco₂ were not correlated with VO₂ or any of hemodynamics and oxygen transport variables (*r*² < 0.20, *P* > .05 for all).

DISCUSSION

This is the first quantitative assessment of the effects of moderate hypercapnia with respiratory acidosis on systemic

TABLE 2. Equations using oxygen consumption to calculate hemodynamics and oxygen transport parameters

Parameters	Equations
Qp (L/min/m ²)	VO ₂ /(CpvO ₂ -CaO ₂)
Qs (L/min/m ²)	VO ₂ /(CaO ₂ -CvO ₂)
SVR (Wood unit × m ²)	(MAP-MVP)/Qs
tPVR (Wood unit × m ²)	(MAP-MPVP)/Qp
DO ₂ (mL/min/m ²)	Qs × CaO ₂
ERO ₂	VO ₂ /DO ₂

CaO₂, Arterial oxygen content; CpvO₂, arterial pulmonary venous content; CvO₂, arterial superior vena caval oxygen content; DO₂, oxygen delivery; ERO₂, oxygen extraction ratio; MAP, mean arterial pressure; MVP, mean venous pressure MPVP, mean pulmonary venous pressure, respectively; Qp, pulmonary blood flow; Qs, systemic blood flow; SAP, systolic arterial pressure; SVR, systemic vascular resistance; tPVR, total pulmonary vascular resistance (including the resistance from the BT shunt and pulmonary vascular bed); VO₂, systemic oxygen consumption.

TABLE 3. Arterial blood gas, systemic, cerebral and splanchnic oxygen transport, and circulating norepinephrine and epinephrine during the staged increases of carbon dioxide in 7 neonates after the Norwood procedure

	Baseline	Added CO ₂ I	Added CO ₂ II	CO ₂ discontinued
Paco ₂ (mm Hg) ^a	40 ± 4 ^g	53 ± 5 ^g	61 ± 6 ^c	43 ± 5
pH ^a	7.39 ± 0.05 ^g	7.28 ± 0.07 ^g	7.23 ± 0.08 ^c	7.36 ± 0.06
Temperature (°C) ^d	36.4 ± 0.2	36.2 ± 0.1	36.0 ± 0.3	36.2 ± 0.2
Heart rate (beats/min)	151 ± 17	156 ± 16	162 ± 10	156 ± 13
Mean arterial pressure (mm Hg)	48 ± 7	48 ± 6	50 ± 7	45 ± 7
Pao ₂ (mm Hg) ^a	41.2 ± 7.1 ^g	47.5 ± 7.6	49.4 ± 7.1 ^f	41.2 ± 8.1
Sao ₂ (%)	78 ± 7	80 ± 6	78 ± 5	76 ± 7
SsvcO ₂ (%) ^a	58 ± 14 ^c	67 ± 11	67 ± 9 ^f	57 ± 13
SpvO ₂ (%)	96 ± 3	95 ± 4	94 ± 4	95 ± 2
tPVR (Wood unit × m ²)	18 ± 11	15 ± 7	16 ± 8	16 ± 6
SVR (Wood unit × m ²) ^b	17 ± 8	12 ± 3	10 ± 6	16 ± 6
Qp (L/min/m ²)	2.7 ± 1.0	2.7 ± 1.0	2.8 ± 1.3	2.6 ± 1.0
Qs (L/min/m ²) ^c	2.6 ± 1.3	3.5 ± 1.3	4.1 ± 1.5 ^h	2.6 ± 0.9
Qp:Qs ^d	1.1 ± 0.3	0.8 ± 0.2	0.7 ± 0.3	1.1 ± 0.3
DO ₂ (mL/min/m ²) ^a	386 ± 214 ^h	503 ± 196 ^h	609 ± 232 ^g	369 ± 153
VO ₂ (mL/min/m ²) ^c	86 ± 18 ^h	79 ± 19	78 ± 20	86 ± 22
ERO ₂ ^c	0.27 ± 0.14	0.17 ± 0.06	0.14 ± 0.07 ^g	0.26 ± 0.11
Lactate (mmol/L) ^b	1.4 ± 0.4 ^h	1.1 ± 0.2	1.0 ± 0.2 ^g	1.2 ± 0.3
Cerebral arterial blood flow peak velocity (cm/sec) ^a	56 ± 2 ^g	80 ± 11	83 ± 14 ^h	67 ± 8
ScO ₂ (%) ^a	56 ± 12 ^c	68 ± 13	68 ± 14 ^f	54 ± 12
SsO ₂ (%) ^c	68 ± 10	63 ± 7	60 ± 7	64 ± 12
Norepinephrine (nmol/L) ^d	10.2 ± 9.2 ^h	15.1 ± 7.8	18.4 ± 6.9	12.6 ± 8.1
Epinephrine (nmol/L) ^c	3.9 ± 5.7	5.1 ± 7.1	5.8 ± 6.9	4.6 ± 6.7

CO₂, Carbon dioxide; DO₂, oxygen delivery; ERO₂, oxygen extraction ratio; Qp, pulmonary blood flow; Qs, systemic blood flow; SVR, systemic vascular resistance; tPVR, total pulmonary vascular resistance; Paco₂, arterial carbon dioxide tension; ScO₂, cerebral oxygen saturation; SsO₂, splanchnic oxygen saturation; Pao₂, arterial oxygen tension; Sao₂, oxygen saturation; SsvcO₂, superior vena cava oxygen saturation; SpvO₂, superior pulmonary venous oxygen saturation. Data are mean ± standard deviation *P* values (analysis of variance) for any difference during the increases in Paco₂: ^a*P* < .0001; ^b*P* < .001; ^c*P* < .01; ^d*P* < .05. *P* values (analysis of variance) for the comparisons between 2 sequential stages: ^e*P* < .0001; ^f*P* < .001; ^g*P* < .01; ^h*P* < .05.

hemodynamics, oxygen transport, cerebral, and splanchnic circulation in neonates early after the Norwood procedure. The present data demonstrate that a stepwise increase in Paco₂ is not associated with significant changes in tPVR and Qp, whereas a significant decrease in SVR resulted in a significant increase in Qs and DO₂. The increase in Qs occurred mainly as a consequence of increased cerebral blood flow, as indicated by increased ScO₂ and cerebral arterial blood flow velocity, compromising splanchnic oxygenation, as indicated by a decreased SsO₂. The decrease in VO₂ further improved the balance of systemic oxygen transport as demonstrated by the significant decrease in ERO₂ and arterial lactate. In paradox to the decrease in VO₂, plasma norepinephrine and epinephrine increased. This is associated with a small increase in heart rate and arterial blood pressure.

Carbon Dioxide Effects: Pulmonary Versus Systemic Circulation

CO₂ increases pulmonary vascular resistance (PVR) in biventricular circulation, and this has been generally used to explain the mechanisms for the increase in Qs and DO₂ in the univentricular and parallel circulation as by decreasing Qp and Qp:Qs.²⁻⁵ On the basis of this speculation, hypoxia and hypercapnia as potent pulmonary vasoconstrictors were advocated. Although hypoxia fails to improve DO₂

and may even be deleterious,^{3,5} induced hypercapnia mostly by hypoventilation remains a common practice aiming to improve DO₂.^{5,6} Although the present data support previous findings, they reveal that the increase in Qs and DO₂ during hypercapnia is due to the direct effect on the systemic circulation rather than the pulmonary circulation. This is supported by little changes in tPVR and Qp. In other words, in the presence of mechanical limitation by the Blalock-Taussig shunt, the change in PVR per se plays a limited role to determine tPVR and Qp. We have recently demonstrated that tPVR has little impact on DO₂, and that SVR is the most important determinant of Qs and DO₂ in neonates after the Norwood procedure.¹ It should be remembered that CO₂ is also a potent systemic vasodilator via its action on smooth muscle cells and endothelium of peripheral and cerebral arteries.^{7,8} The decrease in SVR and the consequent increase in Qs and DO₂ during hypercapnia are clearly demonstrated in the present data. Systemic afterload reduction with agents such as alpha-blockade phenoxybenzamine nitric oxide donor sodium nitroprusside or a phosphodiesterase III inhibitor milrinone has been increasingly used as a primary management strategy in these patients both before and after the Norwood procedure, with improved postoperative outcomes.^{13,18-20} Therefore, in the concept of optimization of DO₂ in the Norwood or single-ventricle physiology,

FIGURE 1. Changes (mean $\pm$ standard deviation) in systemic hemodynamics and oxygen transport, including systemic vascular resistance, *tPVR*, *Qp*, *Qs*, *VO₂*, *DO₂*, *ERO₂*, lactate, *ScO₂*, *SsO₂*, and plasma epinephrine and norepinephrine concentration during the stepwise increases in *Paco₂* from 40 to 50 to 60 mm Hg and after the termination of the additional inspired CO₂ at *Paco₂* 40 mm Hg. *SVR*, Systemic vascular resistance; *tPVR*, total pulmonary vascular resistance; *ERO₂*, oxygen extraction ratio; *DO₂*, oxygen delivery; *VO₂*, oxygen consumption; *Paco₂*, arterial carbon dioxide tension; *ScO₂*, cerebral oxygen saturation; *SsO₂*, splanchnic oxygen saturation; *Qp*, pulmonary blood flow; *Qs*, systemic blood flow.

emphasis should shift from *PVR* and *Qp*, even beyond *Qp:Qs*, directly to *SVR* and *Qs*.

In addition, hypercapnia produced a significant increase in *Pao₂*, with no significant change in *SoO₂* in the present study. This apparent contradiction is likely explained by the fact that increased *Paco₂* and acidosis cause a rightward shift in the oxyhemoglobin dissociation curve (Bohr effect), and for any given systemic saturation, *Pao₂* is higher. The increase in *Pao₂* may also contribute, to some extent, to the increase in *DO₂*. Indeed, judicious use of higher inspired oxygen fraction has been suggested to improve *DO₂* in patients undergoing the Norwood procedure.^{21,22} Bradley and colleagues²¹ recently showed an improved *DO₂* (using indirect indicator of oxygen excess factor) by high inspired oxygen fraction, even with its potent pulmonary vasodilating effect. This further emphasizes the limited contribution of *PVR* to *DO₂* in the Norwood circulation.

Carbon Dioxide Effects: Upper Body Versus Lower Body Blood Flow

All the previous clinical studies have used superior vena caval oxygen saturation as a surrogate of *DO₂*. This could not be completely avoided in the present study; the superior

vena caval blood gas was also used as an estimate of the mixed venous oxygen content to calculate *SVR* and *Qs*. The derived *SVR*, *Qs*, and *DO₂* in the present study primarily reflect the cerebral vascular bed and may be different from the lower body.²³ This difference is most likely to be greater in the induced increases in *Paco₂*, because CO₂ is a potent cerebral vasodilator in normal subjects,⁸ as well as in patients after CPB.^{9,24} As a result, the present data, as those in previous clinical studies, may have overestimated the overall changes in *SVR*, *Qs*, and *DO₂* in response to CO₂. In animal studies, this limitation was overcome with direct measurement of aortic flow (*Qs*) using an ultrasonic flow probe placed at the ascending aorta.²⁻⁴ The percentage of increase in *Qs* was considerably less when compared with that in our patients (15% vs 57%) for the similar range of *Paco₂* changes.² Therefore, caution is needed when interpreting the increase in *Qs* and *DO₂* by CO₂ in clinical practice as the overall *DO₂* to the whole body. As further shown in the present data, the increase in *Qs* at *Paco₂* from 40 to 60 mm Hg was associated with an increase in *ScO₂* and a decrease in *SsO₂*, although to a lesser degree (12% $\pm$ 4% vs -8% $\pm$ 7%). It seems that the increase in *Qs* is primarily the consequence of a significant increase in cerebral blood flow at

a certain cost of splanchnic perfusion. This is not entirely surprising, considering that the systemic vasodilating effect of CO₂ occurs predominately in the brain and to some extent in the heart and nonrespiratory skeletal muscles, whereas little occurs in splanchnic organs.^{25,26} Although ischemic brain injury is a major noncardiac morbidity in patients after the Norwood operation,^{27,28} the increase in cerebral blood flow may be beneficial for brain function; the tradeoff of flow distribution with splanchnic perfusion may be undesirable in these patients. It has been shown that splanchnic organs may be at a higher risk of ischemia because of the lower critical oxygen extraction compared with the other organs;²⁹ inadequate splanchnic organ perfusion may be associated with adverse post-CPB outcomes.³⁰ It has been reported that gastrointestinal complications are common and related to mortality in patients after the Norwood procedure.³¹ Therefore, it may be unwise to concentrate on maximizing DO₂, ignoring regional and tissue perfusion. Further studies are warranted with direct measurements of both superior and inferior vena caval oxygen saturations in addition to NIRS monitoring to provide a clearer picture of CO₂ effects on systemic and cerebral and splanchnic DO₂.

Carbon Dioxide Effects: Decreased Systemic Oxygen Consumption Versus Increased Circulating Catecholamines

A significant decrease in VO₂ was observed during hypercapnia in neonates after the Norwood procedure. This was accompanied with a significant decrease in central body temperature. This is the second time that this phenomenon has been observed in an intact organism, including animals and humans. The first report was in infants after bidirectional cavopulmonary anastomosis.¹⁴ Hypercapnic acidosis exerts dual and opposite effects on metabolism and cardiovascular function.¹⁴ Acidosis (respiratory or metabolic) directly depresses and alkalosis stimulates cellular metabolism in isolated cells and organ.³² In intact organisms, acidosis stimulates a significant release of epinephrine and norepinephrine from sympathetic nerve endings and adrenal glands,^{33,34} thus indirectly stimulating metabolism and cardiovascular function. The opposing effects may be essential to maintain metabolic and circulatory homeostasis. It has been shown that myocardia,³⁵ cerebral,⁸ and systemic VO₂^{36,37} remain unchanged or slightly increased in subjects with normal biventricular circulation. The mechanisms for the unique decrease in VO₂ were speculated in our previous report,¹⁴ as either reduced metabolic response to or decreased release of catecholamines in the unique circulations. In the present study, plasma epinephrine and norepinephrine were measured. The data showed that the baseline levels of epinephrine and norepinephrine at Paco₂ of 40 mm Hg were markedly higher in our patients compared with healthy humans³³ and infants pre-CPB.³⁸ Although it has been well documented that hypothermic CPB for complete correction

of congenital heart defects may induce significant increases in circulating epinephrine and norepinephrine, the levels largely return to preoperative baseline at 24 hours.³⁸ It is likely that the present group of neonates remained hemodynamically and metabolically stressed longer. It is somewhat surprising the altitude of increases in epinephrine and norepinephrine in our patients is comparable to that in healthy persons over the similar range of Paco₂ increase.³³ If the release of catecholamines is not the case, the decreased response might be attributable to the decreased VO₂ in our patients during hypercapnic acidosis. CPB may decrease the metabolic response to catecholamines.³⁹ The mechanism for the paradoxical changes in VO₂ and circulating catecholamines remains unclear, and the clinical implication of the increased circulating catecholamines on cardiovascular function is uncertain. A small increase in heart rate and systemic arterial blood pressure was observed that is consistent with previous findings.^{33,36} Any increase in cardiovascular work load might be undesirable in these post-Norwood neonates with marginal reserve of cardiovascular function. In addition, α -adrenergic receptor stimulation in the splanchnic vascular bed by epinephrine and norepinephrine may reduce the regional blood flow.⁴⁰ This might be partly attributable to the decrease in SsO₂.

Study Limitations

The order of exposure to the different CO₂ tensions was not randomized. However, it is unlikely that the findings were due merely to the sequence of changes because the final CO₂ level of 40 mm Hg demonstrated a reversal of changes noted with each previous sequential increase in CO₂ tension.

The changes were monitored for 30 minutes at each level of Paco₂, and therefore we could not address the effects of prolonged or severe hypercapnia. The use of superior vena caval blood as an estimation of the mixed venous gas for the calculations of SVR, Qs, and DO₂ may be a limitation and was discussed above.

NIRS was used to estimate cerebral and splanchnic oxygenation in our study. As mentioned above, NIRS measures oxygen saturation in the mixture of arteries, capillaries, and veins in a small part of underlining tissue and thus may not precisely reflect the overall balance of cerebral or splanchnic oxygen transport or precisely measure the regional blood flow or DO₂. Nonetheless, in the patients who were sedated and paralyzed, VO₂ was minimized. The change in regional oxygen saturation as measured by NIRS may largely reflect the changes in regional blood flow and DO₂ (ie, in the brain and splanchnic organs) in our current study.

CONCLUSIONS

CO₂ exerts complex effects on systemic and regional oxygen transport in neonates after the Norwood procedure.

Moderate hypercapnia with acidosis increases Q_s and DO_2 via the direct systemic vasodilatation effect, rather than the effect on pulmonary vasoconstriction as previously proposed. The increase in Q_s and DO_2 is primarily the consequence of increase cerebral blood flow, with an undesirable tradeoff of splanchnic oxygenation. In addition, CO_2 decreases VO_2 , contributing to the balance of systemic oxygen transport. The implication of the increase in circulating catecholamines remains uncertain. Clinical use of CO_2 aiming to improve DO_2 in patients with univentricular and parallel circulation should be with caution. Our data ask further understanding of oxygen transport, not only at the systemic level but also at the regional and tissue level, when designing any intervention aiming to improve oxygen status in critically ill patients after CPB.

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