Alteration of the critical arteriovenous oxygen saturation relationship by sustained afterload reduction after the Norwood procedure

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Objectives: Hemodynamic vulnerability after the Norwood procedure for hypoplastic left heart syndrome results from impaired myocardial function, and critical inefficiency of parallel circulation. Traditional management strategies have attempted to optimize circulatory efficiency by using arterial oxygen saturation (SaO_2) as an index of pulmonary/systemic flow balance, attempting to maintain SaO_2 within a theoretically optimal critical range of 75% to 80%. This optimal range of SaO_2 has not been verified clinically, and strategies targeting SaO_2 may be limited by the fact that SaO_2 is a poor predictor of systemic oxygen delivery. We have previously reported higher venous saturation (SvO_2), lower arteriovenous oxygen content difference, lower systemic vascular resistance, lower pulmonary/systemic flow ratio, and improved survival with the perioperative use of phenoxybenzamine and continuous monitoring of SvO_2 . In this investigation, we tested the hypothesis that intense afterload reduction with phenoxybenzamine would modify the SvO_2 - SaO_2 relationship by preventing deterioration of systemic oxygen delivery at high SaO_2 .

Methods: Seventy-one consecutive neonates undergoing the Norwood procedure with and without phenoxybenzamine were studied. Perioperative hemodynamic management targeted SvO_2 greater than 50%. Hemodynamic data were prospectively acquired for 48 hours postoperatively and analyzed to assess the effect of phenoxybenzamine on the relationship between SaO_2 and SvO_2 and other hemodynamic indices. Sixty-two patients received phenoxybenzamine 0.25 mg/kg on cardiopulmonary bypass; 9 who did not served as controls.

Results: In control patients, SvO_2 peaked at an SaO_2 of 77%, with reduced SvO_2 at $\text{SaO}_2 > 85\%$ and $\text{SaO}_2 < 70\%$ ($P < .01$), while arteriovenous oxygen content difference increased with SaO_2 greater than 80% ($P < .001$). In patients receiving phenoxybenzamine, the SvO_2 increased linearly with SaO_2 greater than 65% ($P < .001$), and arteriovenous oxygen content difference was constant at all SaO_2 ($P = \text{ns}$). The SvO_2 was higher, and the arteriovenous oxygen content difference lower, across the whole SaO_2 range with phenoxybenzamine ($P < .0001$).

Conclusions: A critical range of SaO_2 for optimizing systemic oxygen delivery was confirmed in control patients, and was effectively eliminated by phenoxybenzamine, specifically by eliminating the systemic hypoperfusion associated with high SaO_2 . This effect allows higher SaO_2 to be included in a rational hemodynamic strategy to improve systemic oxygen delivery in the early postoperative management of patients receiving intense afterload reduction with phenoxybenzamine. The predictability of SvO_2 from SaO_2 is low in both groups, emphasizing the importance of SvO_2 measurement in these patients.

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Cardiogenic shock remains a major cause of morbidity after the Norwood procedure. Following the Norwood procedure, the neonate has a unique convergence of physiologic vulnerabilities: myocardial dysfunction after ischemia, reperfusion, and cardiopulmonary bypass (CPB), potential limitations of a morphologically right ventricle, potential aorta-coronary flow limitation, and intrinsic inefficiency of parallel circulation.^{1,2} Management of the interactions of these multiple vulnerabilities in the postoperative period is complex and has been approached both theoretically via circulatory models and empirically by direct measurement of additional physiologic parameters such as systemic venous saturation (SvO₂)^{1,3,4} in an attempt to avoid or detect hemodynamic deterioration before cardiovascular collapse.

Several models with differing assumptions about complex univentricular circulation have been developed to guide management when clinical data are incomplete. Norwood and colleagues^{1,2,5} have argued that maintenance of arterial saturation (SaO₂) in the 75% to 80% range would optimize circulatory efficiency with a resulting SvO₂ of 50% to 60% and pulmonary/systemic flow ratio (Qp/Qs) near 1.0. This management strategy is based largely on circulatory modeling with a constant arteriovenous oxygen content difference, but highly variable Qp/Qs and therefore SaO₂.^{1,2,5,6} Alternatively, the SaO₂-SvO₂ relationship has been modeled at constant total cardiac output, with variable Qp/Qs and systemic flow, also resulting in a narrow optimum range of SaO₂ to maximize SvO₂ or systemic oxygen delivery.⁶ In either case, the circulatory models predict a critical range of SaO₂ for optimal circulatory efficiency, but the exact target SaO₂ remains dependent on other parameters such as oxygen consumption (VO₂), cardiac output, and hemoglobin, as well as knowledge of Qp/Qs to fully resolve the resulting SvO₂.⁶ Strategies to balance the circulation have typically relied on manipulation of medical gases to raise pulmonary vascular resistance (PVR) and restrict SaO₂ to the target range of 75% to 80%.^{1,2,5,7-10}

In a less restrictive model assuming complete systemic and pulmonary mixing, and permitting variability in both Qp/Qs and total cardiac output, we demonstrated a wide range of SvO₂ at any SaO₂, and the essential lack of predictability of SvO₂ from SaO₂.¹¹ This theoretical inadequacy of SaO₂ as a predictor of SvO₂, the intrinsic contradictions and complexities of management strategies which rely on SaO₂ limitation as a means of maximizing oxygen delivery, and less than optimal outcomes using approaches based on prediction of SvO₂ from SaO₂, motivated us to search for a better management method. Direct, continuous measurement of SvO₂ allowed the detection of critical reductions in systemic oxygen delivery and provided additional data to more closely estimate Qp/Qs and guide sub-

sequent intervention.^{3,12} We observed wide variability in SvO₂ despite maintenance of SaO₂ in the traditional target range,^{12,13} emphasizing the dynamic relationships between reduction in systemic oxygen delivery, reflex elevation in systemic vascular resistance (SVR), systemic-pulmonary flow tradeoff, and further reductions in systemic perfusion with systemic vasoconstriction, which, if unchecked, would lead to overt failure of systemic perfusion.

We hypothesized that the relevance of increases in SVR as a cause of instability after the Norwood procedure could be confirmed by examination of the relationship between SaO₂ and SvO₂ for evidence of deterioration of systemic oxygenation at higher SaO₂. In this investigation, we analyzed our prospectively collected physiologic database to attempt to confirm the existence of a critical SaO₂ range to maximize SvO₂, and to test the hypothesis that this relationship would be altered by intense afterload reduction with phenoxybenzamine.

Materials and Methods

Patient Population and Management Strategy

All patients undergoing the Norwood procedure for hypoplastic left heart syndrome from July 1996 to July 2000 were included in this study. After appropriate preoperative stabilization, all patients underwent surgical palliation consisting of anastomosis of the pulmonary artery to the ascending aorta combined with augmentation of the ascending aorta, transverse arch, and proximal descending aorta with pulmonary homograft, placement of a systemic-pulmonary artery shunt (3.0-4.5 mm), and creation of a nonrestrictive atrial septal defect.¹² This procedure was performed with synthetic opioid-based perioperative anesthesia,¹⁴ hypothermic CPB with pH-stat blood gas management to facilitate cooling to a temperature of 26°C, α -stat management before and after circulatory arrest at 16°C to 18°C, and modified ultrafiltration. On initiation of CPB, phenoxybenzamine 0.25 mg/kg was administered to 62 of 71 infants according to a prospective nonrandomized surgeon-directed protocol with Food and Drug Administration and institutional review board approval and parental informed consent. During rewarming, all patients received milrinone 50 $\mu\text{g} \cdot \text{kg}^{-1}$ followed by infusions of milrinone at 0.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and dopamine at 3 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Oximetric catheters (4F OxyCath, Abbott Laboratories, N Chicago, Ill) were surgically placed in the superior vena cava (SVC) to allow continuous monitoring of SvO₂. Before separation from CPB, infusions of nitroprusside or norepinephrine were titrated to achieve an approximate SVR index of 12 Wood units (mean arterial pressure of 40 mm Hg at CPB flow index of 3.2 L/m²/min), and epinephrine was added for additional inotropic support if necessary. Patients were transported to the pediatric intensive care unit (ICU) after hemostasis for postoperative management, which included routine delayed sternal closure.

Postoperative management targets included mean arterial blood pressure (MAP) greater than 45 mm Hg, SvO₂ greater than 50%, SaO₂ 70% to 85%, and clinical evidence of end-organ function (urine output of at least 1 mL $\cdot$ kg⁻¹ $\cdot$ h⁻¹, biochemical evidence of adequate gluconeogenesis, and behavioral responses after withdrawal of neuromuscular blockade). Systemic diastolic pressure

TABLE 1. Patient demographics

	Control (n = 9)	Phenoxybenzamine (n = 62)
Age (d)	7.2 ± 6.4	6.0 ± 3.3
Weight (kg)	3.7 ± 0.5	3.2 ± 0.6
Preoperative mechanical ventilation	6/9 (67%)	46/62 (75%)
Preoperative inotropic support	4/9 (44%)	29/62 (47%)
Aortic atresia	4/9 (44%)	35/62 (56%)
AAO diameter (mm)	3.33 ± 0.88	3.11 ± 1.31
CPB time (min)	157 ± 70	125 ± 52
DHCA time (min)	64 ± 13	62 ± 14
Shunt diameter (mm)	3.94 ± 0.47	3.67 ± 0.36
Normalized shunt size (mm ² /kg)	3.50 ± 0.83	3.43 ± 0.47
ECMO	1/9 (11%)	1/62 (2%)
Death		
Early	0/9 (0%)	3/62 (5%)
Late	3/9 (33%)	14/62 (22%)

Data are expressed as mean ± standard deviation or N and %. No significant differences between groups exist for demographic, preoperative, and operative factors. AAO, Ascending aortic diameter; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; ECMO, extracorporeal membrane oxygenation.

was not specifically targeted unless electrophysiologic evidence of ischemia was present with continuous ST analysis (Solar 3000, Marquette Electronics Inc, Milwaukee, Wis). All patients received continuous fentanyl infusions at 5 to 10 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, and neuromuscular blockade was maintained by vecuronium infusion until postoperative day 1. A normothermic environment was maintained with servo controlled warmers (Ohio Infant Warmer System, Ohmeda Inc, Columbia, Md). Ventilator settings were adjusted to maintain arterial normocapnia (Paco₂ 35 to 45 mm Hg) with inflating pressures of 24 to 28 cm H₂O, positive end-expiratory pressure of 4 to 5 cm H₂O, and an Fio₂ of 0.3 to 1.0 to assure fully saturated pulmonary capillary blood.¹⁵ Specifically, room air was not used as a ventilating gas, and Fio₂ was adjusted to maximize SvO₂. Low SvO₂ (40% or less) with Qp/Qs near 2.0 or greater was addressed by attempts to lower SVR with additional analgesia or sedation, nitroprusside, or, in patients who had received phenoxybenzamine on CPB, initiation of a phenoxybenzamine infusion (0.25 mg/kg per day or 10 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). A low SvO₂ with Qp/Qs near 1.0 was addressed by transfusion of red cells to achieve a hematocrit value in the 45% to 50% range, and additional inotropic support when necessary.

Monitoring and Data Collection

A prospective perioperative database for all patients undergoing the Norwood repair for hypoplastic left heart syndrome since July 1996 was maintained for demographic, surgical, and 48-hour postoperative hemodynamic and laboratory data. Physiologic parameters included invasive arterial (MAP) and atrial pressures (RAP), arterial saturation (N-200, Nellcor, Hayward, Calif), inspired oxygen and end-tidal carbon dioxide tension, and oximetric SvO₂ from the SVC as an approximation of mixed venous saturation.^{1,16}

Figure 1. The distribution of arterial and venous saturation values found over first 48 hours in all patients is shown. SaO₂ (mean 77.9, SD 5.5) was more tightly controlled than SvO₂ (mean 54.9, SD 10.7). Approximately 26% of the measured values for SvO₂ were less than the target of 50%, and 1.8% were less than the anaerobic threshold of 30% (shaded area).

These parameters were continuously displayed, digitally acquired, and averaged using either a dedicated personal computer-based monitoring cart (DAP-102; Microstar Labs, Bellevue, Wash; DasyLab, DasyTec GmbH, Concord, NH) or a multichannel clinical information system (Marquette Solar). Arterial and venous blood gases and co-oximetry (ABL, Radiometer, Copenhagen, Denmark) were obtained at clinically appropriate intervals. The physiologic parameters, laboratory data, ventilator parameters, and medication infusion rates were recorded hourly for the first 48 postoperative hours with a standardized, prospective data record.

From measurements of SaO₂, SvO₂, MAP, RAP, and hemoglobin concentration, hemodynamic and oxygen transport indices were derived according to standard formulas. These derived parameters included arteriovenous O₂ difference in saturation ($\Delta\text{Sa-vO}_2$) and content ($\Delta\text{Ca-vO}_2$), as well as oxygen extraction ratio (O_2ER , $[\Delta\text{Sa-vO}_2]/\text{SaO}_2$), and oxygen excess factor (Ω $\text{SaO}_2/[\Delta\text{Sa-vO}_2]$), both flow-independent indices of systemic oxygen status. Pulmonary/systemic flow ratio (Qp/Qs) was calculated from SaO₂ and SvO₂ using an assumed pulmonary capillary saturation of 97%.^{3,4,12,15} Additional parameters derived from an assumed oxygen consumption of 160 mL $\cdot$ min⁻¹ $\cdot$ m⁻²^{13,17-19} included pulmonary blood flow (Qp), systemic blood flow (Qs), systemic oxygen delivery (DO₂), systemic vascular resistance index (SVRI), and total pulmonary vascular resistance index (PVRI).

Statistical Analysis

Data were summarized as mean ± standard deviation (SD) when continuous, or number and percent when discrete. Oximetric data were excluded during extracorporeal membrane oxygenator (ECMO) support and when the SaO₂-SvO₂ difference was less than 8%.¹³ Exploratory analysis of the SvO₂-SaO₂ relationship was performed by locally weighted regression,²⁰ and fractional

Figure 2. The relationship between SvO₂ and SaO₂ over the first 48 hours is shown for patients managed with and without phenoxybenzamine. Hourly data and fitted fractional polynomial regression lines with 95% prediction intervals are shown for the control (*left panel*, n = 307) and phenoxybenzamine (*right panel*, n = 2513) groups; the SvO₂-SaO₂ relationship was distinctly different between groups, as shown by fitted fractional polynomial equations. The SvO₂ peaked at SaO₂ of 77% in control patients, but continuously increased as SaO₂ increased in phenoxybenzamine patients.

TABLE 2. Venous saturation at intervals of arterial saturation, and effect of phenoxybenzamine*

SaO ₂ range	Control	Phenoxybenzamine	Difference	P value
<65%	40.0 ± 9.2 (36.4–43.7)	40.9 ± 9.0 (38.7–43.2)	0.9 (–5.0–6.8)	ns
65–70%	41.5 ± 12.5 (38.5–44.3)	46.6 ± 8.7 (45.2–47.9)	5.1 (0.9–19.4)	<0.0001
71–75%	46.4 ± 12.3 (44.8–48.1)	51.5 ± 7.4 (50.8–52.3)	5.1 (2.7–7.5)	<0.0001
76–80%	50.6 ± 11.9 (48.9–52.5)	56.1 ± 7.7 (55.6–56.6)	5.5 (3.1–17.7)	<0.0001
81–85%	46.6 ± 9.3 (43.9–49.3)	59.5 ± 8.2 (58.9–60.1)	12.9 (9.6–16.2)	0.0194
>85%	40.2 ± 7.3 (35.2–45.2)	65.6 ± 9.1 (64.4–66.8)	25.4 (19.2–31.6)	0.0035

Data are mean, standard deviation, and 95% confidence intervals for SvO₂ at intervals of SaO₂. The SvO₂ peaked with SaO₂ in the 76% to 80% range in control patients, but continued to increase at higher SaO₂ in patients receiving phenoxybenzamine. Differences were tested by the Tukey WSD method after 2-way repeated-measures analysis of variance. There was a progressive increase in the difference between groups as SaO₂ increased (*P* < .0001 by test for trend).

polynomial regression models were fit for each group. The data were subsequently partitioned into 6 equal-width strata of SaO₂ values from 65% to 90% for quantitative analysis. A 2-way repeated-measures analysis of variance (ANOVA) model was used to test for differences in hemodynamic parameters across intervals of SaO₂, to test for the effect of phenoxybenzamine, and for the interaction of phenoxybenzamine on the SaO₂ effect. Potential confounding differences in other vasoactive drug doses, FiO₂, and shunt size, were addressed by entry of these parameters into the model as noninteracting covariates. Post-hoc tests of differences at high SaO₂ were performed with Tukey’s wholly significant difference (WSD) correction for multiple comparisons, with significance cutoff at *P* < .05 after correction. All analysis was performed with Stata statistical software (StataCorp, College Station, Tex).

Results

Data from 71 patients comprising 2820 patient-hours (mean 40, median 47, range 6 to 48 hours/patient) were analyzed. There were no significant demographic differences between patients managed with phenoxybenzamine (n = 62) or without (n = 9; Table 1). Two patients were placed on ECMO support within the first 48 hours for SvO₂ below 25%, metabolic acidosis, and impending cardiovascular collapse, one of whom survived; the overall hospital survival for patients in this study was 68 of 71 or 95.7%.

The distributions of SvO₂ and SaO₂ reveal a distinct tail at the lower range for SvO₂ (Figure 1). Variation in SvO₂

Figure 3. The means and 95% confidence intervals (CI) of SvO₂ and ΔCa-vO₂ at intervals of SaO₂ is shown for control and phenoxybenzamine groups. The SvO₂ was higher with phenoxybenzamine across the whole range ($P < .02$); the SaO₂ effect was highly significant ($P < .0001$). The ΔCa-vO₂ was lower with phenoxybenzamine across the whole range ($P < .001$); the SaO₂ effect was highly significant ($P < .0001$). With phenoxybenzamine, the ΔCa-vO₂ did not vary with SaO₂ ($P = \text{not significant}$). Significance was assessed by 2-way repeated measures analysis of variance with adjustment for differences in hemoglobin, FiO₂, Paco₂, shunt size, and doses of dopamine, milrinone, epinephrine, norepinephrine, and nitroprusside as covariates. Significant differences between groups by Tukey WSD post-tests at each SaO₂ interval are signified by *.

was much greater than in SaO₂ (SD 10.7 vs 5.5, $P < .0001$). Despite management directed at maintaining SvO₂ greater than 50%, actual SvO₂ was less than the target for 758/2820 hours or 26.8% of the time, and was less than the reported anaerobic threshold of 30%¹³ for 52 of 2820 hours or 1.8% of the time. For the 2768 hours without profound venous desaturation, the SaO₂ was out of the usual target range of 70% to 85% for 374 hours or 13.5% of the time. During the periods of hemodynamic deterioration and anaerobic risk, the SaO₂ was in the target range of 70% to 85% for 27 of 52 hours or 52% of the time. Thus, detection of hemodynamic

risk by high or low SaO₂ was poor, with a sensitivity of 48%, specificity of 84%, and positive predictive value of only 5%.

The fitted fractional polynomial regressions between SvO₂ and SaO₂ showed distinctly different patterns in the control and phenoxybenzamine groups:

$$\text{control: } SvO_2 = 49 - 0.064 \cdot (77 - SaO_2)^2$$

$$R^2 = 0.21, P < .0001$$

$$\text{phenoxybenzamine: } SvO_2 = 0.94 \cdot SaO_2 - 17$$

$$R^2 = 0.32, P < .0001$$

In control patients, the SvO₂-SaO₂ relationship showed reduction of SvO₂ at both high and low SaO₂, with a peak at SaO₂ of 77%, in an inverse-square pattern. In patients receiving phenoxybenzamine, the relationship between SvO₂ and SaO₂ was continuously and linearly positive over the range of SaO₂ from 60% to 90%. The mean predictive error was greater in control than phenoxybenzamine groups ($\pm 11.5\%$ vs $\pm 8.3\%$, $P < .001$). The actual data and fitted equations are shown in Figure 2.

The SaO₂-SvO₂ relationship was quantitatively assessed (Table 2). In control patients, this relationship was in fact convex, with maximal SvO₂ occurring at an SaO₂ of 75% to 80%, and with reduced SvO₂ at SaO₂ > 85% and SaO₂ < 70% ($P < .01$), while in patients receiving phenoxybenzamine, the SvO₂ increased linearly with SaO₂ > 65% ($P < .001$; Figure 3). In control patients, ΔCa-vO₂ increased with SaO₂ > 80% ($P < .001$), while in patients receiving phenoxybenzamine, ΔCa-vO₂ was constant at all SaO₂ ($P = \text{not significant}$; Figure 3). The SvO₂ was higher, and the ΔCa-vO₂ lower, across the whole SaO₂ range with phenoxybenzamine ($P < .0001$), and the difference in SvO₂ between groups increased progressively as SaO₂ increased ($P < .0001$ by test for trend).

Hemodynamic indices and treatments are summarized in Table 3. SVR was lower in the phenoxybenzamine group, despite higher nitroprusside doses in the control group and higher norepinephrine doses in the phenoxybenzamine group. Most hemodynamic parameters showed significant variation across intervals of SaO₂, and differences between treatment groups at high SaO₂ were significant for SvO₂ ($P < .0005$), MAP ($P < .0005$), Qp/Qs ($P < .0005$), SVRI ($P < .0005$), PVRI ($P < .0005$), and indices of oxygen delivery ($P < .005$). Patients receiving phenoxybenzamine had preservation of systemic oxygen delivery at high SaO₂ by stabilization of SVRI, resulting in more balanced Qp/Qs, and a stable reduction in MAP (Figure 4).

Discussion

The relationship between SaO₂ and SvO₂ is a complex function of total cardiac output, Qp/Qs, hematocrit, pulmo-

TABLE 3. Average 48 hour hemodynamic indices and support: Effects of arterial saturation and phenoxybenzamine

Parameter	Treatment group		ANOVA factors		Post-test
	Control (n = 9)	Phenoxybenzamine (n = 62)	Phenoxybenzamine	SaO ₂ interval	Difference at SaO ₂ > 80%
FiO ₂	0.41 ± 0.14 (0.33–0.50)	0.36 ± 0.12 (0.33–0.39)			*
Paco ₂ (mm Hg)	39.3 ± 7.7 (36–42)	41.9 ± 6.9 (41–43)			*
Hemoglobin (gm/dL)	16.0 ± 2.0 (15.2–16.9)	15.1 ± 1.5 (14.8–15.4)	*		‡
SaO ₂ (%)	75.3 ± 5.7 (72–79)	78.2 ± 5.4 (77–79)		‡	‡
Heart rate (min ⁻¹)	175 ± 16.6 (164–186)	169 ± 17.7 (165–173)			
Right atrial pressure, mean (mm Hg)	10.4 ± 1.9 (8.7–12.1)	10.2 ± 2.7 (9.6–10.7)			*
Systemic pressure, mean (mm Hg)	55.4 ± 6.9 (52–58)	51.3 ± 5.6 (50–52)	*		‡
SvO ₂ (%)	46.7 ± 11.9 (41–53)	56.2 ± 9.4 (54–58)	†	‡	‡
Qp/Qs	1.49 ± 1.0 (1.15–1.83)	1.30 ± 0.7 (1.18–1.41)		†	‡
ΔSa-vO ₂ (%)	28.6 ± 12.4 (24–33)	22.1 ± 7.9 (20–24)	*	†	‡
ΔCa-vO ₂ (mL/dL)	6.1 ± 2.7 (5.1–7.1)	4.5 ± 1.6 (4.1–4.8)	†	†	‡
DO ₂ (mL · min ⁻¹ · m ⁻²)	38.4 ± 18.1 (27–50)	49.2 ± 19.0 (45–53)			‡
O ₂ extraction ratio	0.38 ± 0.16 (0.32–0.44)	0.28 ± 0.10 (0.26–0.31)	*		‡
Qs (L · min ⁻¹ · m ⁻²)	3.19 ± 1.45 (2.26–4.12)	4.21 ± 1.66 (3.89–4.54)	*	*	†
Qp (L · min ⁻¹ · m ⁻²)	3.72 ± 1.09 (2.77–4.68)	4.72 ± 1.72 (4.40–5.06)		‡	*
SVRI (Wood units)	17.7 ± 9.7 (15.0–20.5)	11.3 ± 4.2 (10.3–12.2)	‡	*	‡
PVRI (Wood units)	12.8 ± 3.4 (11.1–14.5)	9.6 ± 2.9 (9.0–10.2)	†	‡	*
Dopamine (μg · kg ⁻¹ · min ⁻¹)	5.2 ± 3.0 (4.2–6.2)	3.2 ± 1.2 (2.9–3.6)	*		
Milrinone (μg · kg ⁻¹ · min ⁻¹)	0.57 ± 0.18 (0.44–0.69)	0.57 ± 0.22 (0.52–0.61)			*
Epinephrine (μg · kg ⁻¹ · min ⁻¹)	0.14 ± 0.13 (0.10–0.20)	0.07 ± 0.08 (0.05–0.09)	*		‡
Norepinephrine (μg · kg ⁻¹ · min ⁻¹)	0.0 ± 0.0 (0.0)	0.05 ± 0.09 (0.03–0.07)	*		*
Nitroprusside (μg · kg ⁻¹ · min ⁻¹)	0.95 ± 0.95 (0.43–1.46)	0.27 ± 0.73 (0.08–0.45)	*		*
PQB total dose (mg/kg)	0.0 ± 0.0 (0.0)	0.37 ± 0.12 (0.34–0.39)	‡		

Data are expressed as mean ± standard deviation and (95% confidence intervals). Results of a nested, repeated-measures analysis of variance model (significance of the main effects phenoxybenzamine and SaO₂ interval, and difference between treatment groups at SaO₂ ≥ 80% as post-test) for each parameter are presented as *P < .05; †P < .005; ‡P < .0005. FiO₂, Fraction concentration of inspired oxygen; Paco₂, arterial partial pressure of carbon dioxide; Qp/Qs, pulmonary/systemic flow ratio; ΔCa-vO₂, arteriovenous oxygen content difference; ΔSa-vO₂, arteriovenous oxygen saturation difference; DO₂, systemic oxygen delivery; Qs, systemic blood flow; Qp, pulmonary blood flow; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index.

nary venous saturation, and oxygen consumption. The data provide direct, clinical evidence to validate theoretical models of the critical Qp/Qs and cardiac output dependence of patients after the Norwood operation. The occurrence of systemic vasoconstriction in response to falling systemic perfusion, which will only worsen systemic perfusion in patients with ventricular dysfunction and aortopulmonary runoff, was evident at SaO₂ above 80% in patients managed without phenoxybenzamine-mediated afterload reduction. This situation has traditionally been managed by manipulation of medical gases to raise PVR and lower SVR, using SaO₂ as a rough index of Qp/Qs balance. In control patients, our data confirm the hypothetical deterioration of systemic oxygen delivery associated with high SaO₂, characterized by a dramatic increase in SVR, reduction in cardiac output, and increase in Qp/Qs. The reduction in cardiac output exceeded the increase in SaO₂ as predicted by modeling,²¹ since indices of systemic oxygen delivery fell. Thus, variable Qp/Qs in control patients resulted in a critical range of SaO₂ associated with maximum SvO₂.

In contrast, patients receiving afterload reduction with phenoxybenzamine did not demonstrate this hemodynamic

deterioration at high SaO₂, instead demonstrating a relatively constant arterial pressure, low SVR, and less variability in Qp/Qs. The hemodynamics in patients receiving phenoxybenzamine tended to behave as predicted by models with constant Qp/Qs and a variable total cardiac output, with both SaO₂ and SvO₂ increasing with cardiac output. The clinical effect was that SaO₂ as high as 90% was not associated with deterioration in SvO₂. Thus, high SaO₂ resulted, not from high Qp/Qs but from higher cardiac output, in the phenoxybenzamine group. The increasing difference between groups at increasing SaO₂ provides strong evidence for a fundamental alteration in the circulatory determinants of SaO₂ and SvO₂.

Errors in derived indices such as Qp/Qs and SVRI may result from the limitations imposed by assumptions of pulmonary vein saturation¹⁵ and oxygen consumption.^{17,18} We specifically did not wean FiO₂ to limit SaO₂ and would attempt to reduce work of breathing in unparalyzed patients with low SvO₂ by sedation and ventilator adjustment. No further benefit of pharmacologic paralysis on oxygen consumption has been demonstrated,¹⁹ and no systematic deviations in this clinical approach were evident between

Figure 4. The means and 95% confidence intervals of MAP, Qp/Qs, and SVRI at intervals of SaO_2 in control and phenoxybenzamine groups. The MAP, Qp/Qs, and SVRI were lower with phenoxybenzamine across the whole range ($P < .001$); the SaO_2 effect was highly significant ($P < .0001$). Significant differences between groups by Tukey WSD after 2-way repeated measures analysis of variance at each SaO_2 interval are indicated by *.

groups. Neither of these factors would change the primary finding of the alteration SaO_2 - SvO_2 relationship by phenoxybenzamine.

Although the analysis of clinical data in this study is unique, the early patients in this study have been the subjects of prior investigation.^{12,13} Differential expansion of

the size of the treatment group has occurred because we have since administered phenoxybenzamine for all Norwood procedures, except for 2 patients without parental consent for phenoxybenzamine; the resulting imbalance in group size would only reduce the power to detect a statistically significant pharmacologic effect. Because phenoxybenzamine was administered without randomization, the differences between treatment groups could result from existing differences in integrated cardiovascular reflex responses or in treatment variables between patients. However, the groups were highly similar in all factors except for the use of phenoxybenzamine, and the different patterns of response persisted after controlling for differences in other treatment variables.

With continuous recordings of oximetric SvO_2 in the acute postoperative period, we have demonstrated rapid deterioration in SvO_2 associated with systemic vasoconstriction in patients not receiving phenoxybenzamine.¹² Since norepinephrine is the postganglionic sympathetic neurotransmitter, α -adrenergic blockade would be expected to blunt the profound sympathetic vasomotor responses observed in high-risk neonates undergoing complex cardiovascular procedures.¹⁴ Although other drugs may be as effective as phenoxybenzamine in reducing SVR under resting conditions, we did not achieve similar results in the control group with routine use of milrinone and sodium nitroprusside.

The perioperative medical management of these patients requires synthesis of information from multiple sources to derive management decisions, which may involve compromise between competing goals. Our vasoactive drug strategy used milrinone for post- β receptor amplification of inotropy and vasodilation, and dopamine for dopaminergic effects only. A fixed dose of phenoxybenzamine was administered on CPB to all patients in the phenoxybenzamine group to block α -adrenergic vasoconstriction, and titration of short-acting drugs to modify SVR was necessary. We used epinephrine and norepinephrine liberally to modify SVR and to provide potent inotropy, and occasionally added low-dose nitroprusside for additional vasodilation. We added an infusion of phenoxybenzamine in 46 of 62 patients in the phenoxybenzamine group if the postoperative hemodynamic pattern showed a need for more consistent SVR reduction. Through multiple stepwise manipulations, the medication mixture could become complex in some patients, and this study did not specifically address strategies to simplify vasoactive drug use. However, our data suggest that α -adrenergic blockade is a more effective approach to modify the intense sympathetically mediated vasomotor responses in these infants, and the use of a very long-acting drug like phenoxybenzamine commits the patient to a treatment strategy based on sustained SVR reduction. Optimization of hemodynamics by control of SVR, as predicted in

a mathematical model of post-Norwood circulation,²² was confirmed by our data.

The data also provide direct evidence of the poor predictive value of SaO_2 for systemic oxygen delivery, as predicted from theoretical models,^{11,21-23} and emphasizing the importance of continuous SvO_2 monitoring¹¹⁻¹³ to indicate systemic oxygen status. A priori, we did not anticipate any predictable relationship between SaO_2 and SvO_2 ; instead, we relied on continuous SvO_2 measurement to guide management aimed at provision of adequate oxygen delivery. Even in the phenoxybenzamine group, only 32% of the SvO_2 variance could be explained by SaO_2 ; therefore, we do not advocate acute postoperative management of these patients without SvO_2 monitoring.

The findings of the current study support management strategies based on the measurement and maximization of SvO_2 , given the poor predictive value of SaO_2 for SvO_2 . The data provide support both for management strategies such as intentional hypercapnia²⁴ to raise PVR when SVR is relatively uncontrolled, and for pharmacologic control of SVR with phenoxybenzamine. With the latter strategy, higher SaO_2 is not deleterious, and is typically associated with improved systemic oxygen delivery.

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