Impact of Inspired Gas Mixtures on Preoperative Infants With Hypoplastic Left Heart Syndrome During Controlled Ventilation

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Background—Management strategies for preoperative infants with hypoplastic left heart syndrome (HLHS) include increased inspired nitrogen (hypoxia) and increased inspired carbon dioxide (hypercarbia). There are no studies directly comparing these 2 therapies in humans. This study compares the impact of hypoxia versus hypercarbia on oxygen delivery, under conditions of fixed minute ventilation.

Methods and Results—Ten anesthetized and paralyzed preoperative infants with HLHS were evaluated in a prospective, randomized, crossover trial comparing hypoxia (17% FIO₂) with hypercarbia (2.7% FICO₂). Each patient was treated in a random order (10 minutes per condition) with a recovery period (15 to 20 minutes) in room air. Arterial (SaO₂) and superior vena caval (SVO₂) co-oximetry and cerebral oxygen saturation (ScO₂) measurements were made at the end of each condition and recovery period. ScO₂ was measured by near infrared spectroscopy. Hypoxia significantly decreased both SaO₂ (−5.2±1.1%, P=0.0014) and SVO₂ (−5.6±1.7%, P=0.009) compared with baseline, but arteriovenous oxygen saturation (AVO₂) difference (SaO₂−SVO₂) and ScO₂ remained unchanged. Hypercarbia decreased SaO₂ (−2.6±0.6%, P=0.002) compared with baseline but increased both ScO₂ (9.6±1.8%, P=0.0001) and SVO₂ (6±2.2%, P=0.022) and narrowed the AVO₂ difference (−8.5±2.3%, P=0.005). Both hypoxia and hypercarbia decreased the balance between pulmonary and systemic blood flow (Qp:Qs) compared with baseline.

Conclusions—In preoperative infants with HLHS, under conditions of anesthesia and paralysis, although Qp:Qs falls in both conditions, oxygen delivery is unchanged during hypoxia and increased during hypercarbia. These data cannot differentiate cerebral from systemic oxygen delivery. (Circulation. 2001;104[suppl I]:I-159-I-164.)

Key Words: heart defects, congenital ■ hypoxia ■ cardiac output ■ blood flow ■ physiology

Survival of infants with hypoplastic left heart syndrome (HLHS) has improved dramatically. Hospital survival for the stage 1 reconstruction is currently as high as 84% to 94%.1–3 Preoperative stabilization and management are crucial to improved outcomes.4 One challenge is establishing and maintaining a balance between pulmonary and systemic blood flow (Qp:Qs).5 Excessive pulmonary blood flow (high Qp:Qs) can result in systemic hypoperfusion with associated hypertension, metabolic acidosis, coronary ischemia, and end organ dysfunction (liver failure, acute tubular necrosis, necrotizing enterocolitis,6 and cerebral ischemia). Diminished pulmonary blood flow (low Qp:Qs) may result in profound hypoxemia. The optimal management strategy to address excessive Qp:Qs, including hypoxia (14% to 20% FIO₂),7,8 hypercarbia (2% to 5% FICO₂),9,10 or hypoventilation,11 remains controversial.12 There are no reported studies comparing these management strategies in humans with single-ventricle physiology.

Our goal was to determine in a prospective, randomized, crossover study the impact of hypoxia (17% FIO₂) versus hypercarbia (2.7% FICO₂) on oxygen delivery in preoperative neonates with HLHS under conditions of anesthesia, paralysis, and fixed minute ventilation.

Methods

Patients

Between July 1, 1999, and April 1, 2000, 30 infants underwent stage 1 reconstruction for HLHS or variants of HLHS. Patients were excluded from the present study if they were hemodynamically unstable or if there was evidence of pulmonary pathology as determined by chest radiograph. The Institutional Review Board approved the inspired gas mixture study protocol, and parents of 19 patients gave informed consent. Eight patients who underwent the
inspired gas mixture study protocol did not have a catheter in the superior vena cava (SVC); therefore, oxygen delivery data could not be obtained. Results of the cerebral oxygen saturation (SpO2) measurements for these patients are reported elsewhere. One patient received >2.7% FiO2. Therefore, complete oxygen delivery data were obtained in 10 patients who completed the inspired gas mixture study protocol with a catheter in the SVC. Mechanical ventilation was necessary for the study protocol. Infants with a preoperative clinical indication for mechanical ventilation were studied in the cardiac intensive care unit (n=4). Infants breathing spontaneously were studied immediately before surgery after the induction of anesthesia and endotracheal intubation in the operating room (n=5). One infant required mechanical ventilation during cardiac catheterization and was studied in the catheterization laboratory.

Inspired Gas Mixtures
All patients were ventilated in a pressure-regulated volume control mode with a Servo 300 Ventilator (Siemens-Elema). Hypercarbic gas mixture was administered by using carbon dioxide metered into the ventilator outflow port. The flow was adjusted until the FiCO2 was 20 mm Hg (equivalent to a FiO2 of 2.7%) as directly measured by a capnometer in the inspiratory limb of the ventilator circuit. Hypoxic gas mixture was administered by using nitrogen metered into the ventilator O2 inflow port. The flow was adjusted until an FiO2 of 17% was directly measured in the ventilator circuit by using an oxygen analyzer. This configuration enabled maintenance of a constant minute ventilation throughout the study. Actual tidal volume was determined by subtracting the compressible volume lost in the ventilator circuit from the exhaled tidal volume measured on the ventilator. The ventilator measured minute ventilation.

Near-Infrared Spectroscopy
Near-infrared spectroscopy (NIRS) is an optical technology that has been shown in children to measure a mixed cerebral vascular oxygen saturation, SνO2 (including capillaries, venules, and arterioles), with the use of phase-shifted infrared light where oxygenated and deoxygenated hemoglobin have distinct absorption spectra. The near-infrared spectrophotometer used in the present study is a frequency-domain prototype cerebral oximeter (PMD 4002, NIM Inc). NIRS is noninvasive, with optical fibers contained in a foam rubber probe that is applied to the infant’s forehead below the hairline with hook-and-loop fastener (Velcro) straps. Light is generated by 3 class I laser diodes emitting at 754 nm, 785 nm, and 816 nm. Continuous SνO2 was computer-recorded and downloaded to a disk for storage. NIRS data were available for 8 of the 10 patients.

Vascular Access and Patient Monitoring
All patients had an indwelling umbilical or peripheral arterial catheter for continuous blood pressure monitoring and obtaining arterial blood gas and co-oximetry (SaO2) measurements. Infants with the intracardiac anatomy of mitral stenosis/aortic stenosis have the potential to generate antegrade flow in the ascending aorta with higher oxygen content than the pulmonary artery and ductal blood. Patients with aortic stenosis had arterial catheters in the umbilical artery (n=3) or posterior tibial artery (n=1) and, therefore, demonstrated no difference in baseline SaO2 compared with patients with aortic atresia. All patients had an indwelling SVC catheter for obtaining mixed venous co-oximetry measurements (SvO2). All patients had continuous end-tidal CO2, transcutaneous oxygen saturation, heart rate, and temperature monitoring.

Study Protocol
Patients were stabilized at a baseline of 21% FiO2, with a goal Paco2 of 40 mm Hg. Gas mixtures were administered in randomized order. Each condition (hypoxia or hypercarbia) was delivered for 10 minutes, followed by a baseline recovery of 15 to 20 minutes in 21% FiO2. The entire protocol took 65 minutes. Simultaneous measurements were made at the end of each condition and at the end of each baseline or recovery period, including heart rate, temperature, blood pressure, transcutaneous oxygen saturation, arterial blood gas and co-oximetry (SaO2), NIRS (SνO2), and SVC co-oximetry (SvO2).

Concurrent Therapies
No changes were made in prostaglandin E1 or inotropic infusions during the study period. No boluses of calcium, bicarbonate, or volume (crystalloid or blood products) were administered during the study period. All patients were anesthetized with a fentanyl bolus (median 20, range 10 to 20 μg/kg) and infusion (median 2.5, range 0 to 3 μg · kg−1 · h−1), and paralyzed with a pancuronium bolus (0.2 mg/kg for all patients).

Qp:Qs Calculations
The Qp:Qs ratio can be measured by applying the Fick principle to infants with HLHS: Qp:Qs = (SaO2 − SvO2)/(SpvO2 − SaO2), where SaO2, SpvO2, and SvO2 are the arterial, mixed systemic venous, and pulmonary venous oxygen saturations, respectively. SaO2 was directly measured. The SVC saturation was used to represent SvO2. The SpvO2 was calculated by using the alveolar gas equation: PICO2 = (PAM − Pwater) × Fio2/PCO2/RQ, where PICO2 is the alveolar partial pressure of oxygen (mm Hg), PAM is the atmospheric pressure (760 mm Hg at sea level), Pwater is the water vapor pressure (47 mm Hg at 37°C), Fio2 is the fraction of inspired oxygen, PCO2 is the arterial partial pressure of carbon dioxide, and RQ is the respiratory quotient (0.8). Fio2 and Pco2 were directly measured (see Table 3). Equations are as follows: for baseline, PICO2 = 713×0.17 − 360/8.17 = 76.2 mm Hg; and for hypercarbia, PICO2 = 713×0.21 − 540/0.8 = 82.2 mm Hg.

No patient had demonstrable pulmonary pathology by chest radiograph, and we assumed that the pulmonary vein oxygen saturation (SpvO2) was equal to the alveolar oxygen saturation (Sao2). The Hill equation describes the oxyhemoglobin dissociation curve: SpvO2 = Pao2/(Pao2 + P50), with use of a Hill coefficient (n) of 3, and if 80% hemoglobin F (P50 F = 18) and 20% hemoglobin A (P50 A = 27) are assumed, then SpvO2 = 0.8[Pao2/(Pao2 + 18)] + 0.2[Pao2/(Pao2 + 27)].

Therefore, SpvO2 = 0.990 in room air (Fio2 = 0.21), SpvO2 = 0.982 during hypoxia (Fio2 = 0.17), and SpvO2 = 0.985 during hypercarbia (Fico2 = 0.027). Because of the potential error with a very narrow SpvO2 − SaO2, a maximum Qp:Qs value of 5 was assigned if the calculated Qp:Qs was ≥5.

Oxygen Delivery Calculations
Oxygen delivery (Dvo2) is defined as the product of arterial oxygen content (CaO2) and cardiac output. Oxygen consumption (Vo2) is defined as the product of the oxygen extracted (CaO2−Cvo2), where Cvo2 is the mixed venous oxygen content, and the cardiac output. Oxygen content is defined as (Pao2×0.003)+(1.34×Hb×Sao2). Under conditions of normal or low Fio2, the quantity of dissolved oxygen (Pao2×0.003) is negligible, and oxygen delivery can be defined as follows: Dvo2 = VD×Vo2/(SaO2 − SvO2).

If it is assumed that (under the study conditions of anesthesia and paralysis) oxygen consumption remains unchanged, then oxygen delivery should be proportional to SaO2/(SaO2 − SvO2). For patients in which SaO2 remains constant, trends in oxygen delivery will reflect SvO2.

Statistical Analysis
Paired 2-tailed t test analysis was used to evaluate the significance of changes in measured variables between each condition and the

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patient Characteristics</th>
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<tbody>
<tr>
<td>Median</td>
<td>Range</td>
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<tr>
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</tr>
<tr>
<td>Weight, kg</td>
<td>3.5</td>
</tr>
<tr>
<td>Lowest presystolic pH</td>
<td>7.3</td>
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<tr>
<td>Highest presystolic PaO2</td>
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</table>
average of the precondition and postcondition baseline or recovery period. Data with nonnormal distribution was analyzed by the nonparametric Wilcoxon signed rank test. Statistical analyses were performed by using SigmaStat software (Jandel Scientific Software, SPSS Science).

Results
Between July 1, 1999, and April 1, 2000, 10 preoperative infants with HLHS or HLHS variants underwent the inspired gas mixture study protocol with a catheter in the SVC to enable oxygen delivery measurements. Table 1 describes the patient characteristics. The cardiac diagnosis was made in utero (n=4), in the newborn nursery (n=3), or as an outpatient readmission (n=3). Intracardiac anatomy included mitral stenosis/aortic stenosis (n=3), mitral stenosis/aortic stenosis with ventricular septal defect (n=1), mitral stenosis/aortic atresia (n=2), mitral stenosis/aortic atresia with left SVC (n=1), and mitral atresia/aortic atresia (n=3).

Two inspired gas conditions, hypoxia (17% FIO2) and hypercarbia (2.7% FICO2, equivalent to 20 mm Hg PICO2), were applied to each patient for 10 minutes each, in randomized order. Each condition was preceded and followed by a 15- to 20-minute baseline or recovery period in 21% FIO2. Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Hypoxia</th>
<th>P</th>
<th>Baseline</th>
<th>Hypercarbia</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation, %</td>
<td>93.2±1.5</td>
<td>89.8±2.8</td>
<td>0.004*</td>
<td>92±1.3</td>
<td>90.2±1.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>160±6</td>
<td>153±4</td>
<td>0.30</td>
<td>150±5</td>
<td>149±4</td>
<td>0.56</td>
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<tr>
<td>Systolic BP, mm Hg</td>
<td>61.7±3.6</td>
<td>61.2±3.4</td>
<td>0.79</td>
<td>60.6±2.6</td>
<td>68.5±4.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>35±2.1</td>
<td>33.7±1.9</td>
<td>0.57*</td>
<td>35±1.7</td>
<td>40±2.5</td>
<td>0.002</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. Values are mean±SEM. Oxygen saturation is transcutaneous measurement. Difference between condition and baseline was determined by paired t test.

*Data not normally distributed, with P value determined by Wilcoxon signed rank test.

Ventilation Parameters
All patients were ventilated with a Servo 300 ventilator in a pressure-regulated volume-control mode with the following set parameters: tidal volume of 8.9±0.7 cm3/kg, mandatory breath rate of 19±0.5 cycles per minute, and positive end-expiratory pressure of 0.5±0.5 cm H2O. Measured parameters included peak inspiratory pressure (21±0.9 cm H2O) and minute ventilation that did not significantly differ between condition and baseline (hypoxia 1.52±0.14 L/min, baseline 1.32±0.08 L/min; hypercarbia 1.37±0.08 L/min, baseline 1.32±0.08 L/min [P=0.06]).

Hemodynamic Data
Table 2 shows the transcutaneous oxygen saturation, heart rate, and systolic and diastolic arterial blood pressures. There was a significant decrease in transcutaneous oxygen saturation for both hypoxia and hypercarbia compared with baseline. There was a significant increase in both systolic and diastolic blood pressure with hypercarbia but not with hypoxia. There was no significant change in heart rate with either hypoxia or hypercarbia.

Arterial Blood Gas Data
Table 3 shows the arterial pH, oxygen tension (PO2), and carbon dioxide tension (PCO2) for hypoxia and hypercarbia compared with baseline. Hypoxia resulted in a significant decrease in PO2, a small but significant increase in pH, and an insignificant decrease in PCO2. Hypercarbia did not affect PO2 but significantly decreased pH and increased PCO2.

Co-Oximetry and NIRS Data
Table 4 shows the arterial (SaO2) and mixed venous (SvO2) co-oximetry and the arteriovenous saturation (AVO2) difference data. SaO2 co-oximetry was directly measured from an umbilical or peripheral artery catheter, SvO2 co-oximetry was directly measured from a superior vena cava catheter, and AVO2 difference is (SaO2−SvO2). Figure 1 shows the difference between hypoxia or hypercarbia and baseline for SaO2, SvO2, AVO2 difference, and ScO2, with significance deter-

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Hypoxia</th>
<th>P</th>
<th>Baseline</th>
<th>Hypercarbia</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.44±0.02</td>
<td>7.46±0.02</td>
<td>0.012</td>
<td>7.43±0.02</td>
<td>7.33±0.02</td>
<td>0.002*</td>
</tr>
<tr>
<td>PO2, mm Hg</td>
<td>50.3±1.9</td>
<td>42.2±1.8</td>
<td>&lt;0.0001</td>
<td>49.6±1.6</td>
<td>50.8±1.9</td>
<td>0.64</td>
</tr>
<tr>
<td>PCO2, mm Hg</td>
<td>37.5±1.8</td>
<td>35.7±2.0</td>
<td>0.055</td>
<td>39.4±1.6</td>
<td>53.7±1.6</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Difference between condition and baseline was determined by paired t test.

*Data not normally distributed, with P value determined by Wilcoxon signed rank test.
mined by paired t test. Hypoxia significantly decreased both SaO₂ (90.7 ± 1.9% vs. 85.6 ± 2.1%, P = 0.001) and SvO₂ (62.4 ± 3.3% vs. 56.7 ± 3.8%, P = 0.009), but AVO₂ difference (28.3 ± 3.2% vs. 28.8 ± 3.8%, P = 0.77) remained unchanged. Hypercarbia decreased arterial saturation SaO₂ (90.0 ± 1.2% vs. 87.4 ± 1.7%, P = 0.002) and SvO₂ (61.5 ± 3.5% vs. 67.5 ± 3.6%, P = 0.02) and narrowed the AVO₂ difference (28.5 ± 3.6% vs. 19.9 ± 3.8%, P = 0.005).

**Qp:Qs Calculations**

The Qp:Qs ratio was determined by (SaO₂ − SvO₂) / (SpvO₂ − SaO₂), where SaO₂ and SvO₂ were directly measured, and the pulmonary vein oxygen saturation (SpvO₂) was assumed as 99% for baseline, 98.2% for hypoxia, and 98.5% for hypercarbia (see Methods). Qp:Qs decreased for both hypoxia (2.55 ± 0.48 vs. 3.36 ± 0.46, P = 0.056) and hypercarbia (2.19 ± 0.55 vs. 3.11 ± 0.45, P = 0.026) compared with baseline (Figure 1).

**Oxygen Delivery Calculations**

Figure 1 shows that with hypoxia there was an insignificant decrease in DO₂ compared with baseline (3.62 ± 0.50 vs. 3.73 ± 0.49, P = 0.70); however, hypercarbia demonstrated a significant increase in DO₂ compared with baseline (6.14 ± 1.43 vs. 3.64 ± 0.45, P = 0.004).

**Discussion**

Perioperative care of neonates with HLHS is crucial to improving outcome. One management challenge is maintaining adequate DO₂ by methods designed to promote a balance between pulmonary and systemic blood flow (Qp:Qs). Pulmonary blood flow is dependent, in part, on the ratio of pulmonary vascular resistance (PVR) to systemic vascular resistance. In the postoperative period, the shunt mechanics and endothelial damage can increase resistance to pulmonary blood flow, preserving systemic blood flow. However, in the preoperative period, stabilization of an infant with pulmonary overcirculation and systemic hypoperfusion can be difficult.

Several animal studies have evaluated inspired gas mixtures after cardiopulmonary bypass. Immediately after surgical creation of a single-ventricle model in newborn piglets, increased FiCO₂ or decreased FiO₂ resulted in increased PVR and decreased Qp:Qs. Reddy et al report the only prebypass data by creating a single-ventricle model (proximal Damus-Kaye-Stansel anastomosis, placement of a 5-mm aortopulmonary shunt, and ligation of the distal main pulmonary artery) in near-term fetal lambs. The lambs demonstrated increased PVR (48%, P = 0.0003; 35%, P < 0.0001) and increased Qp:Qs (32%, I-162 Circulation September 18, 2001

![Figure 1. Difference in Qp:Qs between condition and baseline (mean ± SEM). Qp:Qs was calculated as (SaO₂ − SvO₂) / (SpvO₂ − SaO₂), where SaO₂ and SvO₂ were directly measured, and SpvO₂ was assumed as 99% at baseline, 98.2% for hypoxia, and 98.5% for hypercarbia. P values represent difference between condition and baseline as determined by paired t test.](image1)

![Figure 2. Difference in Qp:Qs between condition and baseline (mean ± SEM). Qp:Qs was calculated as (SaO₂ − SvO₂) / (SpvO₂ − SaO₂), where SaO₂ and SvO₂ were directly measured, and SpvO₂ was assumed as 99% at baseline, 98.2% for hypoxia, and 98.5% for hypercarbia. P values represent difference between condition and baseline as determined by paired t test.](image2)
We report the first human study to evaluate the effects of inspired gas mixtures on oxygen delivery. Our goal was to determine in a prospective, randomized, crossover study, the impact of hypoxia versus hypercarbia on oxygen delivery in preoperative infants with HLHS. In an effort to minimize patient variables, we evaluated only patients with stable hemodynamics and an absence of pulmonary pathology by chest radiograph. Additionally, all patients were under identical conditions of anesthesia, paralysis, and fixed minute ventilation. Patients (n=10) were exposed in a randomized order to 2 inspired gas conditions, hypoxia (17% FIO₂) and hypercarbia (2.7% FICO₂), for 10 minutes each. Each condition was preceded and followed by a 15- to 20-minute baseline or recovery period in 21% FIO₂. Throughout the study, patients were successfully maintained without a significant change in temperature, hemoglobin, or minute ventilation.

Barnea et al19 eloquently described a mathematical model of oxygen delivery (DO₂) in newborns with single-ventricle physiology.19 In the unique situation of a ductal-dependent (preoperative) or shunted (postoperative) patient with single-ventricle physiology, the DO₂ is dependent not only on the total cardiac output but also on the balance between pulmonary and systemic blood flow (Qp:Qs). Accurate measurements of cardiac output and Qp:Qs have been reported only from animal studies with flow probes on the pulmonary artery and aorta.16–18 In these studies, a close correlation has been shown between systemic mixed venous saturation (SvO₂) and both DO₂ and Qp:Qs, with a maximum Svo₂ at Qp:Qs of 1:1.18 In the absence of a pulmonary venous catheter, calculations of Qp:Qs require an estimation of Spvo₂. The errors introduced by estimations of Spvo₂ are minimized at higher values of Spvo₂.19 Calculations of Spvo₂ (see Methods) corrected for fetal hemoglobin but did not account for small but measurable changes in pH. Based on calculated estimations of Spvo₂ (baseline 99%, hypoxia 98.2%, and hypercarbia 98.5%), a small, but significant, decrease in Qp:Qs was found for both hypoxia and hypercarbia.

Total cardiac output can be augmented by elevated arterial PCO₂, with or without increases in heart rate.20 This effect is thought to be secondary to sympathetic stimulation and can be blunted by effective anesthesia. Although total cardiac output could not be measured in the present study, under conditions of hypercarbia, there was a significant increase in blood pressure without a change in heart rate compared with baseline. These changes were not observed with hypoxia.

Animal and clinical data suggest that Svo₂ increases particularly in conjunction with the AVO₂ difference,23 is a reliable estimate of systemic DO₂ in infants with HLHS. Others have argued that Sao₂−(Sao₂−SvO₂), where Sao₂ and Svo₂ were directly measured, P values were determined by paired t test comparing condition and baseline.

Figure 3. Difference in oxygen delivery between condition and baseline (mean±SEM). Oxygen delivery was calculated as SaO₂−(Sao₂−SvO₂), where Sao₂ and Svo₂ were directly measured. P values were determined by paired t test comparing condition and baseline.

P<0.001; −27%, P=0.001) after 5 minutes of profound alveolar hypoxia (10% FIO₂) or after 10 minutes of hypercarbia (35 mm Hg PICO₂), respectively.

The results of the present study apply for patients under anesthesia, paralysis, and controlled minute ventilation. This is clinically applicable to those infants with HLHS who have presented in shock or those with a functionally unrestricted atrial septum and hemodynamically compromising pulmo-
nary overcirculation. For these infants who most often require sedation, paralysis, and controlled minute ventilation, the present study suggests that hypercarbia is the preferred therapy. The present study also supports the use of hypercarbia during the induction and maintenance of general anesthesia before cardiopulmonary bypass irrespective of the surgical approach (stage 1 reconstruction or primary cardiac transplantation). However, the majority of preoperative infants with HLHS do not require controlled ventilation. Further studies are important to determine whether there is a role for manipulation of inspired gases in these patients, to assess what optimal inspired gas mixture may minimize the risks of pulmonary overcirculation (eg, necrotizing enterocolitis), and to maximize neurological outcome.

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References
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