Brain Versus Lung: Hierarchy of Feedback Loops in Single-Ventricle Patients With Superior Cavopulmonary Connection

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Background—CO₂ vasodilates and O₂ vasoconstricts the cerebral vascular bed; the opposite is true in the lungs. When the brain and lungs are connected exclusively in series, which feedback loop predominates is unknown. The circulation of the superior cavopulmonary connection (SCPC) provides a unique physiology to answer this question.

Methods and Results—To determine cerebral and pulmonary blood flow and to establish the hierarchy of cerebral and pulmonary feedback mechanisms, 12 intubated, ventilated, single-ventricle patients in SCPC physiology (age 2.2±0.5 years) underwent magnetic resonance imaging velocity mapping of their jugular veins and aorta in room air, hypercarbia, and 100% O₂. Flows in these vessels and arterial blood gases were measured. With 22±6 torr CO₂ (Pco₂ increased from 40 to 63 mm Hg, P<0.01), flow to the brain and lungs increased (1.5 to 2.7 L/min per m², P=0.0003), PO₂ improved (48 to 60 mm Hg, P=0.0004), and cardiac index increased (4.3 to 5.4 L/min per m², P=0.0003). The increased cardiac index accounted for the increased cerebral and pulmonary blood flow (R=0.73, P=0.02) and cerebral O₂ transport increased by 80% (P=0.0005) while preserving body O₂ delivery. Hyperoxia did not change cerebral and pulmonary blood flow; PO₂ increased 94% (P=0.01).

Conclusion—The cerebral CO₂ feedback loop predominates over the pulmonary one when they directly compete with each other. CO₂ has a major impact on flow distribution whereas O₂ has little impact. Increased CO₂ improves cerebral oxygenation in SCPC patients. This may provide a clue in determining neurological sequelae in SC physiology and may influence timing of Fontan completion. (Circulation. 2004;110[suppl II]:II-147–II-152.)

Key Words: cerebrovascular circulation ■ blood flow ■ heart defects ■ congenital ■ magnetic resonance imaging
PCO₂ and heart rate significantly increased and pH significantly decreased relative to room air (P < 0.01), whereas during hyperoxia, no significant change was noted. HR indicates heart rate measured in beats per minute (BPM); Pco₂ measured in mm Hg (millimeters of mercury).

The purpose of this study was to determine the hierarchy of cerebral and pulmonary humoral autoregulatory control mechanisms using the SCPC physiology as a model. We used magnetic resonance imaging (MRI) through-plane, phase-encoded velocity mapping to measure CBF, pulmonary blood flow (PBF), as well as cardiac index under conditions or room air, hypercarbia, and hyperoxia immediately before Fontan completion. Flow across the ascending aorta was used to measure cardiac index, and flow in the jugular veins was used to assess CBF/PBF; jugular flow has been validated by oxygen extraction, no significant change was noted. HR indicates heart rate measured in beats per minute (BPM); Pco₂ measured in mm Hg (millimeters of mercury).

**Materials and Methods**

**Patients**

Between October 2002 and June 2003, we prospectively studied 12 children, ages 2.2 ± 0.5 years of age (mean ± standard deviation) who underwent cardiac MRI within 2 hours of Fontan completion. These patients were prepared for surgery and studied under general anesthesia, intubated, and mechanically ventilated with arterial and venous access. Exclusion criteria included pulmonary artery stenosis, neurological deficits. No significant bronchial collaterals were present on preoperative catheterization. No patients had patent systemic to pulmonary artery shunts. After premedication with pentobarbital (4 mg/kg), anesthesia was induced and maintained with fentanyl (20 μg/kg) and pancuronium. The protocol was approved by the Institutional Review Board and informed consent was obtained from the parents.

**Study Protocol**

After preoperative preparation for Fontan completion in the operating room, patients were transported to and set up in the MRI scanner. On each image, the slice thickness was 5 to 6 mm, depending on the patient’s size, and a rectangular field of view was used when appropriate. The slice thickness was 5 to 6 mm, depending on the patient’s size. This was repeated in all 3 sets of conditions.

**Image and Data Analysis**

Images were analyzed using the ARGUS software package (Siemens Medical Solutions), resident on the scanner. On each image, the ascending aorta and jugular and subclavian veins were identified in cross-section and a mouse was used to trace around the vessel. Flow at each phase of the cardiac cycle (each image) was calculated by: (1) measuring the signal intensity in each pixel of the quadrant and deriving a velocity; (2) multiplying the velocity by the pixel size; and (3) summing the flows in each pixel over the entire cross-section of the vessel. Integration of the flow over the entire cardiac cycle yielded the stroke volume and multiplication by the heart rate during image acquisition yielded flow in liter/minute per meter².

**Statistics**

Because comparing hypercarbia to room air and comparing hyperoxia to room air were in fact 2 separate experiments, the 2-way Student t-test was used instead of analysis of variance. Normality was confirmed by the χ² goodness-of-fit test. Pearson correlation was used to assess association between 2 separate variables. Statistical analysis was performed using Sigma Stat (Jandel Corporation, San Rafael, Calif). All values are mean ± SD. Significance was defined as a P < 0.05.

**Results**

**Patients**

Anatomic diagnoses included hypoplastic left heart syndrome (N = 7), complex double outlet right ventricle (N = 2), tricuspid atresia (N = 2), and pulmonary atresia with intact ventricular septum (N = 1). Patients with hypoplastic left heart syndrome underwent stage I reconstruction at 4.0 ± 2.5 days of age. Physical characteristics for the study group included a height of 85 ± 4.5 cm, weight of 11.8 ± 1.4 kg, body surface area of 0.51 ± 0.04 m², and hemoglobin of 15.2 ± 0.6 mg/dL.
On average, these patients had been exposed to SCPC physiology for 20.9±0.5 months before MRI and had undergone SCPC surgery at 5.4±2.8 months of age. All patients tolerated the procedure without incident.

During hypercarbia, Pco₂ and heart rate significantly increased and pH significantly decreased relative to room air (P<0.01), whereas during hyperoxia, no significant change was noted (Figure 1). All studies were adequate for interpretation.

**Flow Parameters**

Figures 2A through C, respectively, demonstrate what occurred to total cardiac index and jugular flow expressed 2 ways—as absolute flow indexed to body surface area and as a percent of the total cardiac index. During hypercarbia, total cardiac index increased significantly from room air by 28% (P=0.0003), whereas during hyperoxia, the 6% increase was not statistically significant. Jugular flow, expressed both ways, significantly increased from room air values during hypercarbic conditions as well—an 80% increase when expressed as absolute flow indexed to body surface area (P=0.0003) and a 45% increase when measured as a percentage of the cardiac index (P=0.002). During hyperoxia, no significant change was observed in CBF/PBF. Flow to the body (ie, total cardiac index minus CBF/PBF) was not significantly different in all 3 sets of inspired gases (2.7 to 2.9 L/min per m²).

Figure 2D shows the percentage increase during inspired CO₂ of CBF/PBF versus the percentage increase in total cardiac index over the room air values. A significant correlation existed between these 2 variables (r=0.73, P=0.02), indicating the dependence of the increase in CBF/PBF during hypercarbia on the increase in total cardiac index.

Figure 3 shows 2 anatomic images extracted from the velocity mapping data, 1 during room air and 1 during hypercarbia, which demonstrate an exuberant response to increased CO₂. In room air, only the right jugular vein is visualized and the left jugular vein is collapsed. During conditions of increased CO₂, the left jugular vein has expanded and can easily be visualized from the increased CBF.

**SVC and Jugular Flow**

In room air, SVC flow measured 1.4±0.1 L/min per meter², whereas jugular flow measured 1.2±0.04 L/min per meter². During hypercarbia, SVC flow measured 2.9±0.34 L/min per meter², whereas jugular flow measured 2.8±0.37 L/min per meter². This suggested that the contribution to PBF from the subclavian and innominate veins were negligible relative to CBF.

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**Figure 2.** Flow parameters in all 3 sets of inspired gases. Total cardiac index (A), total jugular flow indexed to body surface area (B), and the percent of the cardiac index (CI) to the brain/lungs (C) all demonstrated a significant (*) increase under hypercarbic conditions. A plot of the percent (%) increase above room air in CI and total jugular flow during hypercarbia (D) demonstrate a significant correlation between these 2 variables, indicating CBF/PBF dependence on increased CI during hypercarbia.
Oxygenation

Figure 4A and 4B demonstrate what occurred to PO2 and O2 saturation, respectively. During hypercarbic and hyperoxic conditions, PO2 increased 27% (P=0.0004) and 94% (P=0.01), respectively. O2 saturation increased 11% during hyperoxia (P=0.00006) but only 3% during hypercarbia (P=0.19). Using the hemoglobin, PO2, and O2 saturation data, Figure 4C demonstrates O2 delivery to the brain, which increased by 80% (P=0.0005) during hypercarbia but only 14% during hyperoxia (P=0.06). Body O2 delivery (minus the brain/lungs) was unchanged during all 3 sets of conditions (53±17, 54±21, and 59±23 mL O2/min per meter2 in room air, hypercarbia, and hyperoxia, respectively).

Relationship Between Arterial Blood Gases, CBF/PBF, and Patient Characteristics

A significant correlation existed between PCO2 and total jugular flow (r=0.63, P=0.002) as demonstrated in Figure 5, signifying the reliance of CBF/PBF on PCO2.

A physical limit was observed to the amount of increase in CBF/PBF in hypercarbia. Room air total jugular flow, total jugular flow as a percent of the total cardiac index, and PCO2 displayed significant inverse relationships with the increase in total jugular flow in hypercarbia (r=−0.69, −0.69, and −0.74, respectively, all with a P<0.02). In addition, room air PO2 demonstrated a significant inverse relationship with the increase in PO2 during hypercarbia. The higher the initial CBF/PBF and PO2, the less increase was observed when administration of CO2 occurred.

No relationships were observed in the amount of time under SCPC physiology, age at cardiac MRI, or months before SCPC operation with any of the measured flow or arterial blood gas parameters.

Discussion

Patients with single-ventricle physiology have, in general, greater neurodevelopmental deficits and other forms of congenital heart disease than the general population. Linked with intelligence and neurodevelopment is CBF and its autoregulation. In general, decreased CBF is associated with decreased intellectual abilities and abnormal neurodevelopment. Defective cerebral autoregulation is suspected in pathologic states (eg, hypoxic–ischemic encephalopathy) in which a negative correlation between CBF and intelligence was found.

The CBF humoral autoregulation is dependent on mostly CO2 and O2. Normally, in adults, CBF is 15% to 20% of resting cardiac output. It is known that CO2 plays an important role in determining CBF; an increase in Pco2 in arterial blood greatly increases CBF, whereas the modest increase under hyperoxic conditions, PO2 increased 27% (P=0.0004) and 94% (P=0.01), respectively. O2 saturation increased 11% during hyperoxia (P=0.00006) but only 3% during hypercarbia (P=0.19). Using the hemoglobin, PO2, and O2 saturation data, Figure 4C demonstrates O2 delivery to the brain, which increased by 80% (P=0.0005) during hypercarbia but only 14% during hyperoxia (P=0.06). Body O2 delivery (minus the brain/lungs) was unchanged during all 3 sets of conditions (53±17, 54±21, and 59±23 mL O2/min per meter2 in room air, hypercarbia, and hyperoxia, respectively).

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Hyperoxia was not statistically significant. Similar to the blood flow to the body under hypercarbia, oxygen transport to the body under hypercarbic conditions was preserved. Although there was an increase of 27% in \( P_{O_2} \) during hypercarbia, \( O_2 \) saturation only increased by 3%. This can be explained by the decreased pH observed in association with exogenous CO₂ administration and the Bohr effect, which shifts the oxyhemoglobin dissociation curve to the right. For any given level of \( P_{O_2} \), there will be a decrease in the amount of hemoglobin saturation, hence the small increase noted in this study.

The inverse relationship observed between room air measures of CBF/PBF and the increase CBF/PBF in hypercarbic conditions implied a physical limit to the amount the body could augment this flow. Higher flows at baseline could not be augmented as much as lower flows because of the physiological ceiling imposed by the cerebral and pulmonary vasculature.

We also measured flow in the superior vena cava and jugular veins in both hypercarbia and room air, which ranged from 0.1 to 0.2 L/min per meter², respectively, to confirm that the contribution to PBF from the upper extremity veins were negligible relative to CBF. CBF essentially equals PBF.

This study differs considerably from the recent report by Bradley et al⁹ who studied younger SCPC patients immediately after cardiopulmonary bypass while on inotropic support, afterload reduction, and on 100% \( O_2 \). Importantly, their study attempted to correct for the decrease in pH by administering sodium bicarbonate (pH decreased from 7.39 to 7.36, \( P < 0.05 \)); our study did not. Finally, their study produced hypercarbia by hypoventilation and not exogenous CO₂, which decreased mean airway pressure, which could have had variable effects on pulmonary vascular resistance and CBF.

This study has a number of implications. Postoperatively in the intensive care unit, it adds to the work of Bradley et al suggesting that both hypoventilation and/or the addition of exogenous CO₂ would increase \( P_{O_2} \) and oxygen delivery, especially to the brain. If prolonged administration of exogenous CO₂ is undertaken, it would be prudent to correct the acidosis. Only a well-controlled study in the postoperative patient comparing administration of exogenous CO₂ with hypoventilation and to standard care combined with outcome data can truly answer the question of the usefulness of this approach.

Besides its obvious importance, hypoxia has been implicated in patient mortality after SCPC surgery. Bradley et al²³ noted that lower systemic oxygenation at the time of preoperative cardiac catheterization as well as elevated pulmonary vascular resistance were significantly associated with death. Reddy et al²⁴ reported only 2 early postoperative deaths (out of 42 patients), both associated with poor oxygen saturation; 1 of 3 late postoperative deaths (out of 37 patients) was also associated with poor oxygen saturation.

CBF and its autoregulation may be different at various stages of single ventricle reconstruction or from that of...
normal children. Similar to patients with normal hearts, it may be linked to intelligence and neurodevelopment in single ventricle patients as well. Because these patients are compromised to a certain degree in this respect, it would be important to determine if CBF and its autoregulation in the SCPC physiology is a help or a hindrance to cerebral development. This would have implications for timing of Fontan completion. If, for example, CBF and its autoregulation in the SCPC are found to be a risk factor for adversely affecting neurodevelopment, consideration might be given to complete the Fontan procedure sooner, whereas the reverse would hold true if it aided neurodevelopment.

Limitations
This study did not separate out the effects of pH and hypercarbia on CBF/PBF. Acidosis causes cerebral vasodilation and increases CBF. Administration of CO2 is linked with decreased pH, and this effect is difficult to separate. Even the study by Bradley et al, which administered sodium bicarbonate, showed a small but significant decrease in pH with hypoventilation. Time considerations did not allow this project to tease out this difference, and was not the goal, either.

The amount of exogenous CO2 and exposure time was not varied, and a dose–response curve was not generated. In addition, this study did not combine exogenous CO2 and O2 to determine its combined effect on CBF/PBF and oxygen transport.

This study did not collect simultaneous pressure measurements during the various inspired gases or calculate vascular resistances in conjunction with the flow data. The invasive nature of these data in conjunction with our MRI system at the present time made this prohibitive.

We used a matrix size of 256×256 for each patient, regardless of the field of view, which yields different pixel sizes for each patient. Although the pixel size variations are small because our patients were very close in size, they do not represent a different resolution for flow accuracy in various patients. In addition, our fixed temporal resolution of 25 ms regardless of the heart rate also represent a different temporal resolution for flow accuracy in each patient. These are minor considerations and do not affect the results or conclusions.

Conclusion
In the hierarchy of cerebral and pulmonary control systems, the cerebral feedback loop using CO2 overrides the pulmonary one and determines CBF/PBF. The O2 feedback loops appear to be balanced between brain and lungs.

In single-ventricle patients under the SCPC physiology, hypercarbia markedly increases CBF/PBF and cerebral oxygen transport while preserving blood flow and oxygen transport to the body. PO2 markedly increases. Pco2 determines CBF/PBF. During hyperoxia, no change in CBF/PBF was noted, although a slight increase in cerebral O2 transport was noted that almost reached statistical significance.

References
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