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

Mark A. Fogel, MD; Suzanne Durning, RRT; Gil Wernovsky, MD; Avrum N. Pollock, MD; J. William Gaynor, MD; Susan Nicolson MD;

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. \( \textit{Circulation. 2004;110[suppl II]:II-147–II-152.} \)

Key Words: cerebrovascular circulation ■ blood flow ■ heart defects ■ congenital ■ magnetic resonance imaging

In the staged surgical reconstruction of single ventricles leading to the total cavopulmonary connection (modified Fontan operation), the intermediate stage designed to improve survival is a “partial” Fontan circulation created as a hemiFontan2,3 or bidirectional Glenn procedure (superior cavopulmonary connection [SCPC]). This operation routes superior vena cava flow directly into the pulmonary arteries, excluding flow into the right atrium, whereas the inferior vena cava and coronary blood flow enter the single ventricle directly.

A unique consequence of the SCPC2,3 circulation is that the cerebral and pulmonary circulations are connected exclusively \textit{in series} with each other with only a small contribution of blood from the upper extremities; aortic blood flows into the brain and then directly into the lungs via the superior vena cava. In this physiology, the cerebral and pulmonary autoregulatory mechanisms are in direct competition with each other and the net result on organ perfusion will be different than in normal individuals.

In terms of humoral autoregulation, it has been known for years that the brain vasculature dilates in response to hypercarbia4,5 and the lung vasculature vasoconstricts.5–8 The opposite holds true for hyperoxia; that is, there is a vasoconstrictory effect in the lungs and a vasoconstrictory effect in the brain.4 It is unclear which effect predominates when these 2 opposite control mechanisms come into direct competition.

The SCPC physiology, where the autoregulatory responses of the brain and the lungs are in direct competition with each other, provides a unique opportunity to study this question. Besides answering this basic physiological question, the cerebral blood flow (CBF) and its autoregulation may have important clinical implications in postoperative management and neurological outcome after SCPC because there is a suggestion that total CBF is linked to intelligence in children10–12 and adults.13–15
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 numerous techniques in the past as a measure of CBF.¹⁶,¹⁷

**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, coarctation of the aorta, a left superior vena cava, or obvious neurological deficits. No significant bronchial collaterals were present on preoperative catheterization. No patients had patent systemic venous 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 (Siemens Medical Systems). The scanning protocol is listed here.

**Magnetic Resonance Imaging**

Our study used a Siemens 1.5-Tesla Vision MRI system (Siemens Medical Systems). The scanning protocol is listed here.

After localizers in multiple planes, T₁-weighted, spin-echo axial images were acquired spanning the entire thorax and neck. These images evaluated cardiovascular anatomy and were used for localizing for through plane velocity mapping. The effective repetition time was the R-R interval (range, 450 to 650 ms), the echo time was 15 ms, number of excitations was 2, the image matrix size was 128×256 pixels, interpolated to 256×256, the field of view ranged from 180 to 250 mm, and slice thickness were 3 to 5 mm.

"Multiplanar reconstruction," a software package resident on the Siemens MRI system, used the transverse images to calculate the exact slice position and double-oblique angles to obtain a "candy cane" view of the aorta and long-axis images of the jugular veins and superior vena cava. An imaging plane perpendicular to flow was then determined for: (1) ascending aorta, distal to the aortic to pulmonary anastomosis (if present) but proximal to the innominate artery; (2) jugular vein above the superior vena cava; and (3) for 3 patients, the superior vena cava proximal to the pulmonary artery anastomosis and distal to the innominate and subclavian veins.

**Through-Plane Phase-Encoded Velocity Mapping in the Aorta, Jugular Veins, and Superior Vena Cava**

The velocity encoding sensitivity used was 150 cm/seconds for the aorta and 75 cm/seconds for the veins. The repetition time was 25 ms, which yielded ~18 to 26 images. The echo time was 7.3 ms, the number of excitations was 2, and image matrix was 256×256 pixels. The field of view ranged from 180 to 250 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 ± 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 $20.9 \pm 0.5$ months before MRI and had undergone SCPC surgery at $5.4 \pm 2.8$ months of age. All patients tolerated the procedure without incident.

During hypercarbia, P$_{CO_2}$ 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 m$^2$).

Figure 2D shows the percentage increase during inspired CO$_2$ 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 CO$_2$. In room air, only the right jugular vein is visualized and the left jugular vein is collapsed. During conditions of increased CO$_2$, 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 $1.4\pm0.1$ L/min per meter$^2$, whereas jugular flow measured $1.2\pm0.04$ L/min per meter$^2$. During hypercarbia, SVC flow measured $2.9\pm0.34$ L/min per meter$^2$, whereas jugular flow measured $2.8\pm0.37$ L/min per meter$^2$. This suggested that the contribution to PBF from the subclavian and innominate veins were negligible relative to CBF.

**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 neurodevelopment deficits and other forms of congenital heart disease than the general population.18,19 Linked with intelligence and neurodevelopment is CBF and its autoregulation.10–15 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.11

The CBF humoral autoregulation is dependent on mostly CO2 and O2. Normally, in adults, CBF is 15% to 20% of resting cardiac output.6 It is known that CO2 plays an important role in determining CBF; an increase in Pco2 in arterial blood greatly increases CBF.4,5,7,20 In patients immediately after SCPC surgery, hyperventilation causes a decrease21 and hyperventilation causes an increase in CBF velocity.9 Oxygen, however, does the reverse. If CO2 cannot deliver the needed O2, vasodilation occurs, returning cerebral blood levels of O2 to near-normal whereas hyperoxia will decrease CBF.4

The control of PBF is different and opposite CBF. When alveolar oxygen concentration is high, PBF increases; when it becomes low, adjacent vessels slowly constrict and vascular resistance can triple.22 Similarly, an increase in CO2 will increase pulmonary artery pressure and increase pulmonary vascular resistance.6

The SCPC2,3 is the only circulatory arrangement in humans in which the cerebral and pulmonary circulations are exclusively and directly in series with each other and can be used a model to determine the hierarchy of these control mechanisms, which can have far reaching clinical implications. Aortic blood flows into the brain and then directly into the lungs via the superior vena cava. In this physiology, the autoregulatory control mechanisms for CBF and PBF directly compete with each other and it is unclear which predominates.

This study shows that when cerebral and pulmonary autoregulatory feedback loops come in direct competition, CO2 cerebral control mechanism overrides the pulmonary one. The response to O2 was balanced because no change to CBF or PBF occurred. In our study, hypercarbia markedly increased CBF and PBF, determined by Pco2. As a consequence, PO2 and O2 saturation increased. This augmentation of CBF/PBF was dependent on the increase in cardiac output, preserving blood flow to the rest of the body caused by the increased cardiac index, heart rate, and probable mobilization of sympathetic drive.

Cerebral oxygen transport also increased markedly under hypercarbic conditions because of a combination of augmented CBF and increased PO2, whereas the modest increase under
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'O2 during hypercarbia, O2 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'O2, 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% O2. 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'O2 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.23,24 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

---

**Figure 4.** Oxygenation parameters. Significant increases in P'O2 (A) and O2 saturation (B) were observed under hyperoxia as well as hypercarbia. Oxygen delivery to the brain (C) was significantly increased under hypercarbic conditions.

**Figure 5.** Relationship between total jugular flow and P'CO2. This plot of total jugular flow on the X-axis and P'CO2 on the Y-axis demonstrates a significant relationship, signifying the reliance of CBF/PBF on P'CO2. The area in white is the region of the graph in room air, and the area enclosed by the dashed rectangle is the region of the graph during hypercarbic conditions.
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 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 represents 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**

Brain Versus Lung: Hierarchy of Feedback Loops in Single-Ventricle Patients With Superior Cavopulmonary Connection
Mark A. Fogel, Suzanne Durning, Gil Wernovsky, Avrum N. Pollock, J. William Gaynor and Susan Nicolson

_Circulation_. 2004;110:II-147-II-152
doi: 10.1161/01.CIR.0000138346.34596.99

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/110/11_suppl_1/II-147

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/