Analytical Identification of Ideal Pulmonary-Systemic Flow Balance in Patients With Bidirectional Cavopulmonary Shunt and Univentricular Circulation

Oxygen Delivery or Tissue Oxygenation?

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Background—In the present study, we extended previous mathematical modeling work on patients with bidirectional cavopulmonary ("bidirectional Glenn") anastomosis to assess the potential utility of several descriptors of oxygen status. We set out to determine which of these descriptors best represents the overall tissue oxygenation. We also introduce a new descriptor, SO2min, defined as the lower of the superior and inferior vena cava oxygen saturations.

Methods and Results—The application of differential calculus to a model of oxygen physiology of patients with bidirectional Glenn allowed simultaneous assessment of all possible distributions of blood flow and metabolic rate between upper and lower body, across all cardiac outputs, total metabolic rates, and oxygen-carrying capacities. When total cardiac output is fixed, although it may intuitively seem best to distribute flow to maximize oxygen delivery (total, upper body, or lower body), we found that for each variable, there are situations in which its maximization seriously deprives flow to the upper or lower circulation. In contrast, maximizing SO2min always gives physiologically sensible results. If the majority of metabolism is in the upper body (typical of infancy), then oxygenation is optimized when flow distribution matches metabolic distribution. In contrast, if the majority of metabolism is in the lower body (typical of older children and during exercise), oxygenation is optimal when flows are equal.

Conclusions—In patients with bidirectional cavopulmonary anastomosis, because there is a tradeoff between flow distribution and saturation, it is unwise to concentrate on maximizing oxygen delivery. Maximizing systemic venous saturations (especially SO2min) is conceptually different and physiologically preferable for tissue oxygenation.

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Key Words: heart defects, congenital ■ pediatrics ■ cavopulmonary anastomosis ■ oxygen delivery ■ oxygen ■ mathematics

Patients with univentricular circulation present with abnormal cardiovascular physiology and, without surgery, have a poor prognosis.1 Surgical repair is generally performed in stages.2,3 The bidirectional cavopulmonary anastomosis is used as part of this staged approach to reduce the volume load of the single ventricle (SVC) blood flow into series with the lungs (Figure 1).4 This allows gradual ventricular remodeling in preparation for Fontan completion.5 Although mortality is lower for cavopulmonary shunt procedures than the initial palliative operation,6-8 postoperative management is still complex and difficult.9 To increase pulmonary blood flow and thus

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oxygenation postoperatively, filling pressures can be changed and oxygen or nitric oxide (a pulmonary vasodilator) and/or carbon dioxide (a cerebral vasodilator)10,11 can be administered. Inotropic and vasoactive agents12 can be infused to affect the relative flows through the different vascular beds.13 In addition, beyond the perioperative period, the underlying pathophysiology remains important in limiting exercise capacity of these patients, in whom pulmonary blood is provided only via the SVC. Moreover, the quantitative aspects of
The work of Santamore et al.\(^{17}\) used iterative simulations of a range of scenarios. We sought a way to enhance the accessibility of the model to enable broader conclusions to be reached with greater confidence and transparency. Differential calculus is a technique widely used for locating maxima in complex systems of equations. We have introduced this method in the situation of the univentricular circulation before the bidirectional Glenn procedure.\(^ {16}\) By combining the powerful representational capacity of the model described by Santamore and colleagues\(^ {17}\) with the simplicity of calculus analysis, we sought to illuminate the complex relationships between flow balance, metabolic balance, and oxygenation of tissues that arise in the circulation after the bidirectional cavopulmonary anastomosis procedure.

### Methods

A standard model of the univentricular circulation after the bidirectional cavopulmonary anastomosis was used, as shown in Figure 1 and explained in the legend. We adopt the simplified view of treating the Glenn circulation as the only source of blood to the lungs. (For those patients who have a significant second source of pulmonary blood flow, such as an aortopulmonary shunt or occasionally persistent right ventricle–to–pulmonary artery communication, this model is not applicable.) We also adopt a nomenclature of “upper body,” defined as all territories supplied by systemic vasculature that drains into the SVC, and “lower body,” defined as the territories that drain into the IVC or right atrium. Thus, for example, the myocardium itself is considered part of the lower body (because the coronary sinus drains into the right atrium), even though anatomically, the heart is situated above the diaphragm.

CO is considered to have 2 components, Qsvc and Qivc, with coronary sinus flow considered to be part of IVC flow. CaO\(_2\) represents the oxygen-carrying capacity of blood. A steady state is assumed. One simple observation derives all the physiological equations required for this analysis: In general, when blood flowing at Q L/min gains oxygen at a rate of V L/min while passing through an organ (eg, the lungs), its oxygen concentration must rise by V/Q. Its saturation, being the ratio between oxygen content and carrying capacity [CapO\(_2\)], must therefore rise by (V/Q)/CapO\(_2\). This (Fick) principle applies to all 3 locations where oxygen is transferred. Across the lung bed,

\[
(2) \quad Ssvco_2 = Spvo_2 - \frac{V O_2}{Qsvc \cdot CapO_2}
\]

Across the upper part of the systemic circulation,

\[
(3) \quad SaO_2 = Ssvco_2 + \frac{k V O_2}{Qsvc \cdot CapO_2} = Spvo_2 + \frac{(k-1)V O_2}{Qsvc \cdot CapO_2}
\]

Across the lower part of the systemic circulation,

\[
(4) \quad Sivco_2 = SaO_2 - (1 - k) \frac{V O_2}{Qivc \cdot CapO_2}
\]

### Mathematical Analysis

The ultimate aim is to maximize tissue oxygen tension. An increase in CO, a decrease in total-body metabolism, or an increase in oxygen-carrying capacity would clearly increase oxygen tension. However, the effect on oxygenation of changes in metabolic balance between upper and lower parts of the body and changes in blood flow to these 2 parts is less obvious.

Differential calculus provides simple and well-validated methods for analyzing the behavior of such complex systems of equations without a computer. We applied differential calculus to the formulas

\[
(1) \quad CaO_2 \cdot CO = Cpvo_2 \cdot CO - \left(1 + \frac{Qsvc}{Qvc} \cdot \frac{Qsvc}{Qivc} \right) \cdot (1-k) \cdot V O_2
\]

where CaO\(_2\) is arterial oxygen content; Cpvo\(_2\) is pulmonary vein oxygen content; Qivc and Qsvc indicate blood flow to the inferior vena cava (IVC) and SVC, respectively; V O\(_2\) is total-body oxygen consumption; and k is the proportion of V O\(_2\) consumed in the upper body.
above to study the effect of changes in the proportion of metabolism occurring in the upper body (k) and changes in the proportion of blood flow to the upper body (Q˙svc/CO) on total oxygen delivery to the systemic circulation and on saturation in the systemic arteries, SVC, and IVC.

We examined the effect on the conventional parameters of oxygen status: total oxygen delivery, upper-body oxygen delivery, lower-body oxygen delivery, and the oxygen saturations SaO2, SsvcO2, and SivcO2. Of these, the last 2 may best represent tissue oxygen status, because they refer to blood that has been in equilibrium with tissues. However, choosing between them is not straightforward. SsvcO2 is the lower of the 2 in some circumstances and SivcO2 in others. We therefore considered a novel parameter, SO2min, which we defined as the lower of these 2 values.

Graphical Display
As an alternative method of displaying the results to the symbolic mathematics, a computer was used to generate graphs showing the effect of changes in metabolic and flow balance on oxygen status. Computer calculations are not as general as the analytical approach, because specific values must be chosen. We used 0.2 L · kg⁻¹ · min⁻¹ for CO and 0.009 L · kg⁻¹ · min⁻¹ for oxygen consumption, which are suitable approximations for the postsurgical situation in neonates. Oxygen-carrying capacity of blood was taken as 1.38 L of O₂ per liter of blood, based on conventional values of 1.38 L of O₂ per gram of hemoglobin and a hemoglobin concentration of 150 g/L. Pulmonary venous saturation was taken as 98%. These specific values were used only to obtain specific oxygen saturations for the purposes of graph plotting. The conclusions derived from the calculus analysis apply, in contrast, to all possible values of these 4 variables.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results
Effect of Changes in Metabolic and Flow Balance on Arterial Parameters
The 4 conventional arterial parameters of oxygenation are SaO2, total oxygen delivery (CO×CapO2, SaO2), and its 2 components, upper-body oxygen delivery and lower-body oxygen delivery. Because total oxygen delivery is SaO2 multiplied by a constant factor (CO×CapO2), studying the effect on SaO2 is sufficient to determine the effect of flow distribution and metabolic balance on total oxygen delivery.

Inspection of Equation 3 reveals that SaO2 is a linear function of (k–1)/Qsvc. Because k is always =1, a rise in k or a rise in Qsvc always causes a rise in SaO2. For any given distribution of metabolism (k), SaO2 is therefore maximal when Qsvc is maximal (Figure 2a). Therefore, complete diversion of all the blood through the upper part of the body, with none to the lower part, achieves the greatest SaO2 (and thus the greatest total oxygen delivery).

Upper-body oxygen delivery (Qsvc×CapO2×SaO2) equals, by application of Equation 3, Qsvc×CapO2×SpvO2×(1–k)VO2. This expression increases linearly with Qsvc and with k, and so again for any k, it is maximal when Qsvc is maximal (Figure 2b), ie, when all the flow goes to the upper body and none to the lower.

Lower-body oxygen delivery (Qivc×CapO2×SaO2) equals, by application of Equation 3, (CO–Qsvc)×CapO2×SpvO2×(1–k)VO2×(CO/Qsvc–1). Applying calculus, the derivative of this expression with respect to Qsvc is (1–k)VO2×CO/Qsvc×CapO2×SpvO2. For maximal lower-body oxygen delivery, CO/Qsvc must be as small as possible (and thus k must be as large as possible), and SpvO2 must be as high as possible (and thus k must be as small as possible).
oxygen delivery, this derivative must be zero, ie, the proportion of blood flowing to the upper body is:

\[
\frac{Q_{svc}}{CO} = \frac{(1 - k) \cdot V_O_2}{CO \times Cap_o_2 \times Spv_o_2}
\]

The dependence of lower-body oxygen delivery on the distribution of flow and metabolism is shown in Figure 2c. The highest achievable lower-body oxygen delivery (for a given k) is marked with a dot. These dots form a parabola, which corresponds to Equation 5. As k increases, the Qs/CO fraction required falls, until it reaches zero when k = 1.

**Effect of Changes in Metabolic and Flow Balance on Venous Parameters**

There are 2 conventional venous oxygenation parameters: SsvcO2 and SivcO2. SsvcO2 represents blood that has recently been in equilibrium with the tissues of the upper part of the body; its value therefore gives useful information about tissue oxygenation in that region. Equation 2 shows that SsvcO2 is independent of k and increases with increasing Qsvc. It is therefore maximal when all the blood flows through the upper body (Figure 3a), regardless of any other physiological variables.

SivcO2 represents blood that has recently been in equilibrium with the tissues of the lower body; its value therefore conveys information about lower-body tissue oxygenation. From Equation 4, we can see that SivcO2 is a nonlinear function of k and blood flow distribution, the maximum point of which may not be obvious by inspection. By calculus, its first derivative with respect to Qsvc is

\[
(1 - k) \frac{V_O_2}{Cap_o_2} \left( \frac{1}{Q_{svc}} - \frac{1}{Q_{ivc}} \right)
\]

For SivcO2 to be maximal, this derivative must be zero; this occurs when Qsvc = Qivc, ie, half the flow passes to each part of the circulation. Again, this is true for any value of k and of the other parameters (Figure 3b).

Because SsvcO2 and SivcO2 peak at different flow balances, the question might arise: Which of them is more important? We contend that both are important and that in any scenario, the lower of the 2 values represents the greater degree of tissue hypoxia.

We therefore defined a parameter, SO2min, which takes the value of SsvcO2 when SsvcO2 < SivcO2 and of SivcO2 when SivcO2 ≤ SsvcO2. From Equations 2 and 4, it can be seen that the former situation occurs when

\[
\frac{V_O_2}{Cap_o_2} \frac{1}{Q_{svc}} \geq (1 - k) \frac{V_O_2}{Cap_o_2} \frac{1}{Q_{ivc}}
\]

or

\[
\frac{Q_{ivc}}{CO} \geq (1 - k)
\]

which means Qsvc/CO ≤ k. In other words, where the fraction of blood perfusing the upper body is less than the fraction of

![Figure 3](http://circ.ahajournals.org/)

*Figure 3. Effect of changes in metabolic and flow balance on venous oxygenation parameters: a, SVC saturation; b, IVC saturation; and c, SO2min, which is defined as the lower of these 2.*
metabolism occurring in the upper body, \( S_{\text{O}_2}\text{min} \) is \( S_{\text{SvCO}_2} \); otherwise, it is \( S_{\text{ivo}CO}_2 \).

Thus, the situations are markedly different depending on whether \( k \) is above or below 0.5. For \( k \leq 0.5 \), \( S_{\text{O}_2}\text{min} \) is maximized when flow is equally distributed to the upper and lower parts of the body, whereas for \( k \geq 0.5 \), \( S_{\text{O}_2}\text{min} \) is maximized by distributing flow in proportion to metabolism (Figure 3c).

**Discussion**

This study examined the effect of bidirectional cavopulmonary anastomosis on oxygenation in patients with univentricular heart using a quantitative model of the circulation and oxygen saturation. It developed the known relationships between physiological variables into equations suitable for analytical solution by differential calculus, which allowed consideration of all conditions of \( CO \), metabolic rate, oxygen-consuming capacity, and pulmonary venous saturation simultaneously.

**Difficulties With Arterial Parameters of Oxygenation**

Arterial parameters are an initially attractive choice in attempting to quantify oxygenation. The most obvious of these is arterial oxygen saturation, but this gives at best an incomplete picture. In particular, it peaks when all the blood is diverted to the upper body, and the lower body is starved of oxygen, which is not a clinically desirable outcome. Total oxygen delivery to systemic tissues has also been considered as a variable to be maximized, yet for any given \( CO \), it is simply proportional to arterial saturation, and so this choice would also favor a complete diversion of blood to the upper body, regardless of the status of the lower body. Choosing 1 of the 2 parts of the systemic circulation individually offers no advantage: Maximizing upper-body oxygen delivery would require diverting all the blood to the upper body; maximizing lower-body oxygen delivery, although plausible at low values of \( k \), would require diverting almost all the blood to the lower body at higher values of \( k \), which represent relatively less metabolism in the lower body (Figures 2b and 2c). Thus, the 2 partial-body oxygen-delivery parameters favor widely differing flow balances. We conclude that because they favor discordant and clinically unsuitable flow distributions, no oxygen-delivery parameter is suitable for maximization in seeking to optimize tissue oxygenation in a circulation with a cavopulmonary anastomosis.

The concept of oxygen delivery was originally advanced in high-risk adult surgical patients without congenital heart disease as a means of combining into a single parameter \( CO \), oxygen-carrying capacity, and oxygen saturation (simply by multiplying them together). Because increasing any one of them increases their product and would intuitively be expected to be beneficial, oxygen delivery is attractive as a summary of overall oxygenation.\(^{30}\)

In congenital heart disease with a single functioning ventricle, however, there can be an unavoidable sharp tradeoff between blood flow and arterial oxygen saturation. This means that it becomes important how the summary parameter values the relative merits of flow and saturation. Oxygen delivery considers them to be inter-changeable; in such circumstances, therefore, oxygen delivery can be a seriously misleading measure of oxygenation.\(^{16}\)

**Does Matching Oxygen Delivery to Oxygen Consumption Optimize Oxygenation?**

Although maximization of oxygen delivery may be unwise, a possible alternative would be to distribute flow in proportion to the balance of oxygen uptake. Previous theoretical work\(^{17}\) has proposed this to be optimal (in the situation in which \( k=0.6 \)). The present study supports this choice but observes that it is valid only as long as \( k \) remains in excess of 0.5.

For values of \( k \) below 0.5, the present study indicates that such a choice would cause unnecessarily poor oxygenation in both upper- and lower-body circulations. Figure 4 shows the difference between a strategy of matching oxygen delivery to consumption\(^{17}\) (which equalizes SVC and IVC saturation, shown as circles and crosses superimposed) and a modified strategy of holding the flow balance constant at 50:50 when \( k \) falls below 0.5 (resulting in different oxygen saturations in SVC and IVC). There is a clear difference in the tissue oxygenation achieved, which is even larger when \( CO \) is higher (0.3 \( \text{L} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \); Figure 4).

**Venous Parameters of Oxygenation**

Venous blood has returned from tissues with which it has recently been in equilibrium; its oxygen saturation\(^{21}\) offers useful information about tissue oxygenation not available from arterial parameters. The present study shows that upper- and lower-body venous saturations may be different and are determined by different factors in the setting of a bidirectional cavopulmonary shunt.

Neither is consistently lower, and thus neither can be used alone as a complete summary of tissue oxygenation. We suggest that attention should be concentrated on whichever of these 2 parts of the systemic circulation is experiencing the greater hypoxia. The variable \( S_{\text{O}_2}\text{min} \) was constructed to reflect this.

A key finding of the present analysis was that when the lower body is responsible for the majority of the oxygen consumption, an equal distribution of flow between upper and lower body optimizes \( S_{\text{O}_2}\text{min} \). In contrast, when the majority of metabolism is in the upper body, a distribution of flow in proportion to metabolic rate is preferable.

When the upper body consumes the majority of oxygen, because it delivers blood to the lungs directly, it is most efficient to match flow to metabolism. However, when the lower body consumes the majority of the oxygen, there has to be a different balance. The lower body needs the oxygen delivery more, yet its delivery of blood to the lungs for oxygen uptake is indirect via the upper body. In this situation, maximizing oxygen delivery is at odds with maximizing oxygen uptake: A balance must be achieved. To minimize tissue hypoxia in any part of the body, our finding is that the optimal balance is 50:50.

**Impact of Growth and Exercise**

Despite its clinical usefulness as an intermediate step toward completion of the Fontan circulation, the Glenn anastomosis is inherently inefficient and becomes increasingly so when
the proportion of lower-body metabolism rises. Growth and maturation are associated with a relative increase in blood flow to the lower body. Although in neonates, SVC flow accounts for 49% of CO, its contribution diminishes to 35% by the age of 6 years. With exercise, lower-body blood flow increases further (due to increased oxygen and metabolic demand) and upper-body blood flow must rise to match this increase in oxygen demand. This, in turn, requires augmented CO and imposes additional strain on the univentricular (and in some patients, morphologically right ventricular) heart. Maintaining an optimal ratio between upper- and lower-body perfusion is, in theory, an alternative and may be most important in patients with limited CO reserve. However, this may not be possible during exercise because of local tissue factors (such as lactate and acidosis) that lead to local vasodilation and a disproportionate increase in lower-body blood flow. Ultimately, therefore, the Glenn circulation becomes inadequate with the growth of the child and increasingly places limits on the level of exercise that can be achieved.

This situation is acutely exacerbated with exercise such as running. The solution is definitive surgical completion of the Fontan circulation. These theoretical findings are confirmed by previous data showing that growth and maturation (repre-
sent by body surface area) are inversely correlated with arterial oxygen saturation.23 Children above the age of 3.9 years were found to be at significantly increased risk for marked postoperative cyanosis, defined as systemic arterial oxygen saturation <75%.

Postoperative Manipulation

Even though creation of a bidirectional cavopulmonary shunt or completion of the Fontan circulation carries a relatively low risk in the current era,9 perioperative management is challenging, and morbidity remains considerable. These patients are especially vulnerable to reduced tissue oxygenation, and optimal perioperative monitoring and management are paramount. A variety of techniques have therefore been developed to manipulate pulmonary blood flow and improve tissue oxygen delivery. It has been reported that controlled hypoventilation improves,24 whereas hyperventilation worsens.13 systemic oxygenation after bidirectional cavopulmonary anastomosis. Hoskote et al10 and Fogel et al11 demonstrated that selectively increasing inspired CO2 tensions improves cerebral blood flow and ameliorates pulmonary and systemic blood flow early after Glenn anastomosis. In addition, it has been shown recently that mild hypercapnia is associated with improved arterial oxygen transport and diminished arterial lactate levels in postoperative patients.25

Our model supports these findings: For any given oxygen consumption and CO2, increasing upper-body perfusion and thereby pulmonary blood flow augments (total) arterial oxygen delivery. This, in turn, may improve tissue oxygenation and reduce blood lactate levels. However, there is a tradeoff in this strategy. Diverting too much blood to the upper body may starve the lower body of oxygen, inducing lower-body tissue hypoxia and lactate release. The experimental data suggest that this does not occur in the early postoperative setting (in which lower-body oxygen consumption may be relatively low) with arterial pCO2 tensions up to 56 mm Hg. Aebi and colleagues26 highlighted the importance of young age (<8 months) on postoperative arterial oxygenation and speculated that elevated pulmonary arterial pressures may account for this association. Indeed, nitric oxide (a pulmonary vasodilator) has been reported to be beneficial in patients with elevated SVC/pulmonary artery pressures, improving arterial oxygenation and systemic perfusion.12,27

Study Limitations

Our model used certain assumptions that made it possible to cover a wide range of combinations of total CO2 flow distribution, and distribution of metabolic rate. This limits its applicability in several situations. For example, if patients have an aortopulmonary shunt or persistent right ventricle–to–pulmonary artery communication, they will have higher pulmonary blood flow, and thus, oxygenation characteristics will not be adequately modeled under our assumptions. Our model also divides the organs of the body purely according to the vena cava into which they drain. This results in a physiological grouping of organs rather than a strictly anatomic grouping. For example, the myocardium, which drains into the coronary sinus, is grouped with the “lower body.” Such a grouping not only makes sense from the quantitative physiology point of view but also in interpreting what happens during exercise, because myocardial oxygen uptake would be expected to rise significantly alongside that of the lower-body vasculature. However, the actual value of coronary sinus saturation may well be lower than the SVC and IVC saturations. In critically ill patients, the degree of depression of coronary sinus saturation may become very important in limiting myocardial function and therefore determining patient stability.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In the present study, we extended previous mathematical modeling work on patients with bidirectional cavopulmonary (“bidirectional Glenn”) anastomosis to assess the potential utility of several descriptors of oxygen status. The main findings were as follows: (1) If the majority of metabolism is in the upper body, then oxygenation is optimized when flow distribution matches metabolic distribution. In contrast, if the majority of metabolism is in the lower body, oxygenation is optimal when flows are equal. (2) Because there is a tradeoff between flow distribution and saturation, it is unwise to concentrate on maximizing oxygen delivery in patients with bidirectional Glenn. Maximizing systemic venous saturations is conceptually different and physiologically preferable for tissue oxygenation. (3) Growth and maturation are associated with a relative increase in blood flow to the lower body and render the Glenn anastomosis increasingly inefficient. Under exercise, lower-body blood flow increases further, and upper-body blood flow must rise to match this increase in oxygen demand. This, in turn, requires augmented cardiac output, which imposes additional strain on the univentricular heart. Although maintaining an optimal ratio between upper- and lower-body perfusion is, in theory, an alternative, this may not be possible during exercise owing to local tissue factors that lead to a disproportionate increase in lower-body blood flow. Ultimately, therefore, the Glenn circulation becomes inadequate with growth and maturation and increasingly limits exercise capacity. The solution is definitive surgical completion of the Fontan circulation.
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