Factors Associated with Oxygen Extraction Ratio and Pulmonary to Systemic Blood Flow in Parallel Circulation: Insights From Cardiac Catheterization Data

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Abstract

Background

Parallel circulation represents a unique physiologic state in children with functionally univentricular cardiac anatomy characterized by the arterial saturation being a weighted average of the pulmonary venous and systemic venous saturation leaving circulation at increased risk for developing inadequate systemic oxygen delivery. The primary aim of study was to utilize pre-Glenn catheterization data to determine the association of different hemodynamic variables on oxygen extraction ratio. Secondary aims included determining the association of hemodynamic variables on superior vena cava (SVC) saturation and pulmonary to systemic blood flow ratio (Qp:Qs).

Methods

This was a single-center, retrospective study using data from children with parallel circulation prior to Glenn procedure between 2017–2020. Correlation analyses using spearman correlation were conducted between all the variables of interest to survey potential correlations. A linear regression analysis was conducted to model the oxygen extraction ratio using variables noted to have a statistically significant correlation. Receiver operator curve analyses were conducted for variables with a p-value of less than 0.20 and binary variables were created for the predictors that had an area under the curve of greater than 0.70. Separate regression analyses were conducted for each with either SVC saturation or Qp:Qs as dependent variable. Independent variables were identified based on the factors found to have a statistically significant correlation with the dependent variable from the initial spearman correlation analyses.

Results

A total of 45 patients were included in the final analyses. Median oxygen extraction ratio was 32.0% and it significantly increases as SVC saturation decreases, systemic blood flow decreases, total cardiac output decreases, Qp:Qs increases and systemic vascular resistance increases. Regression analyses with oxygen extraction ratio as the dependent variable demonstrated that systemic blood flow, SVC saturation, and Qp:Qs were significantly associated with oxygen extraction ratio. Regression analysis with SVC saturation as the dependent variable demonstrated that systemic arterial saturation, systemic blood flow and hemoglobin were significantly associated with SVC saturation:

Conclusion

Oxygen extraction ratio in parallel circulation is significantly associated with systemic blood flow, SVC saturation, and Qp:Qs. SVC saturation is further associated with systemic arterial saturation and

hemoglobin while Qp:Qs is associated with systemic vascular resistance, pulmonary vascular resistance, and pulse pressure. Understanding of these factors can help guide clinical monitoring and management strategies for this high-risk circulation.

Introduction

Parallel circulation represents a unique physiologic state in children with functionally univentricular cardiac anatomy. This circulation is characterized by the arterial saturation being a weighted average of the pulmonary venous and systemic venous saturation. Due to the general lability of the systemic venous saturation, the arterial saturation also becomes more variable in this circulation. Not only are the systemic and pulmonary circulations linked with respect to saturation but also to flow. Total cardiac output in the setting of parallel circulation is the sum of both the pulmonary and systemic blood flows. An increase in either pulmonary or systemic blood flow can only occur with a concurrent decrease in flow to the alternate system of equal magnitude unless total cardiac output changes [1].

This intricate balance between the two circulations for both saturation and flow leaves children with this circulation at increased risk for developing inadequate systemic oxygen delivery. The adequacy of systemic oxygen delivery is dependent on both systemic oxygen content and systemic oxygen consumption. There is a paucity of data on how different hemodynamic and physiologic parameters impact systemic oxygen delivery, particularly oxygen extraction ratio. The primary aim of this study was to utilize pre-Glenn catheterization data to determine the association of different hemodynamic variables on oxygen extraction ratio. Secondary aims included determining the association of hemodynamic variables on superior vena cava (SVC) saturation and pulmonary to systemic blood flow ratio (Qp:Qs).

Methods

Study design and patient identification

This was a single center, retrospective study using data from catheterization in patients with parallel circulation prior to the Glenn (superior cavopulmonary anastomosis) procedure. Parallel circulation was defined as circulation in which the saturation of blood to the pulmonary and systemic circulations is equal. It should be noted that the majority of patients at this institution undergo right ventricle to pulmonary artery conduits (Sano modification) to provide pulmonary blood flow as opposed to brachiocephalic artery to pulmonary artery shunts (Blalock-Taussig-Thomas shunts).

Patients who underwent a Glenn procedure were identified using our institutional pediatric cardiothoracic surgery database. Patients with parallel circulation who underwent a catheterization prior to their Glenn procedure between July 2017 and July 2020 were included in this study. Patients who required extracorporeal membrane oxygenation at the time of their catheterization prior to the Glenn procedure or those who died prior to their Glenn procedure were excluded. Patients with incomplete catheterization data were also excluded.

Objectives

The primary objective of this study was to determine what hemodynamic and clinical factors significantly impacted the oxygen extraction ratio. Secondary objectives of this study were to determine what hemodynamic and clinical factors significantly impacted systemic blood flow and the Qp:Qs.

Variables of interest

The following pressure variables were identified as those of interest based on previously published data and physiologic principles: right atrial pressure, left atrial pressure, mean pulmonary artery pressure, systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure. The following saturation variables were identified as those of interest: SVC saturation, pulmonary artery saturation, systemic arterial saturation (descending aorta saturation), pulmonary vein saturation. Hemoglobin was identified as a laboratory value of interest.

The following values were calculated using above data: pulmonary blood flow, systemic blood flow, total cardiac output, systemic vascular resistance, pulmonary vascular resistance, arteriovenous oxygen difference, and oxygen extraction ratio.

Pulmonary blood flow was calculated using the Fick equation with the pulmonary artery saturation and pulmonary vein saturation. Systemic blood flow was calculated using the Fick equation with the systemic arterial saturation and the SVC saturation. In most instances a pulmonary vein saturation was directly obtained. In cases where a pulmonary vein saturation was not directly measured, a saturation of 98% was assumed. Total cardiac output was then calculated as the sum of the pulmonary blood flow and the systemic blood flow. Systemic vascular resistance was calculated by dividing the difference between the mean arterial pressure and the right atrial pressure by the systemic blood flow. Pulmonary vascular resistance was calculated by dividing the difference between the mean pulmonary artery pressure and the left atrial pressure by the pulmonary blood flow.

Arteriovenous oxygen difference was calculated by subtracting the SVC saturation from the systemic arterial saturation. The oxygen extraction ratio was calculated by dividing the arteriovenous oxygen difference by the systemic arterial saturation. The oxygen extraction ratio was used for the primary objective of this study as it essentially normalizes the arteriovenous oxygen difference with respect to the arterial saturation. In the setting of fully septated, biventricular circulation where the systemic arterial saturation is 100%, the arteriovenous oxygen difference and the oxygen extraction ratio are equal. In the setting of parallel circulation where the systemic arterial saturation is not 100%, the lower the arterial saturation the greater the difference between the arteriovenous oxygen difference and the oxygen extraction ratio. The numbers reported in this manuscript for both of these values will be the absolute number. For instance, if the systemic arterial saturation is 80% and the SVC saturation is 60% the arteriovenous difference will be reported as 20 and the oxygen extraction ratio as 25%.

Statistical analyses

Data for all variables was assessed for normalcy of distribution using skewness and kurtosis. Correlation analyses using spearman correlation were then conducted between all the variables of interest to initially survey potential correlations.

Next, a linear regression analysis was conducted to model the oxygen extraction ratio using variables noted to have a statistically significant correlation with oxygen extraction ratio after the initial correlation analyses. Oxygen extraction ratio was used as the dependent variable while SVC saturation, Qp:Qs, and total cardiac output were used as the independent variables. The regression analysis was conducted in a stepwise fashion with a p-value of 0.05 used for entry and a p-value of 0.10 used for exclusion.

Next, those with an oxygen extraction ratio of over 35% were identified. This specific cutoff was used as previously published studies have demonstrated an oxygen extraction ratio of over 35% being associated with increased morbidity and mortality. All variables of interest were compared between the two groups. As all variables of interest were continuous variables, a Mann-Whitney-U test was utilized for these comparisons.

Receiver operator curve analyses were then conducted for variables with a p-value of less than 0.20 from the Mann-Whitney-U test. Presence of oxygen extraction ratio of over 35% was used as the state variable and the predictors used were hemoglobin, SVC saturation, total cardiac output, systemic blood flow, Qp:Qs, and systemic vascular resistance. Area under the curves were assessed for each receiver operator curve analysis. Predictors with an area under the curve of greater than 0.70 then had optimal cutoff points identified.

Next, binary variables were created for the predictors that had an area under the curve of greater than 0.70 as described above to identify those who did and did not have values above or below the optimal cutoff points. The number of these variables that for which the optimal cutoff point was exceeded for each patient was calculated. This was considered the composite score. A receiver operator curve analysis was then conducted to determine the utility of the composite score to predict an oxygen extraction ratio of over 35%.

As SVC saturation and Qp:Qs repeatedly were identified as variables significantly associated with oxygen extraction ratio, regression analyses were conducted to determine what factors were significantly associated with them. Separate regression analyses were conducted for each with either SVC saturation or Qp:Qs as the dependent variable. Independent variables were identified based on the factors found to have a statistically significant correlation with the dependent variable from the initial spearman correlation analyses. Regression analyses were conducted as stepwise regressions with a p-value of 0.05 used for entry and p-value of 0.10 used for exclusion.

All statistical analyses were done using SPSS version 23.0. A p-value of less than 0.05 was considered statistically significant. Any use of the word “significant” or “significantly” in the manuscript refers to statistical significance unless explicitly stated otherwise.

Results

Cohort characteristics

A total of 45 patients were included in the final analyses. The median age at catheterization was three months and the median weight was 5.2 kg. The most frequent principle cardiac diagnosis was hypoplastic left heart syndrome which was noted in 24 (53%) patients. Atrioventricular septal defect and double inlet left ventricle were the second most frequent diagnoses in this group with 4 (9%) patients having atrioventricular septal defect and 4 (9%) having double inlet left ventricle.

Median values and correlations

Correlations are outlined in supplemental table 1.

Oxygen extraction ratio

Median oxygen extraction ratio was 32.0%. Significant correlations were found between oxygen extraction ratio and the SVC saturation ($r= -0.72$, $p < 0.01$), systemic blood flow ($r= -0.91$, $p < 0.01$), total cardiac output ($r= -0.69$, $p < 0.01$), Qp:Qs ($r = 0.52$, $p < 0.01$), systemic vascular resistance ($r = 0.84$, $p < 0.01$), and pulmonary to systemic vascular resistance ratio ($r= -0.33$, $p = 0.02$) (supplemental table 1). Phrased in a more clinical context, oxygen extraction ratio significantly increases as SVC saturation decreases, as systemic blood flow decreases, as total cardiac output decreases, as Qp:Qs increases, and as systemic vascular resistance increases.

Regression analyses with oxygen extraction ratio as the dependent variable demonstrated the following variables were significantly associated with oxygen extraction ratio: systemic blood flow (beta coefficient= -3.12, $p < 0.01$), SVC saturation (beta coefficient= -0.67, $p < 0.01$). and Qp:Qs (beta coefficient = 2.85, $p < 0.01$). Phrased in a more clinical context, every increase in systemic blood flow by 1 L/min was associated with a decrease in oxygen extraction ratio by 3.12%, every increase in SVC saturation by 1% was associated with a decrease in oxygen extraction ratio by 0.67%, and every increase in Qp:Qs of 0.1 was associated with an increase in the oxygen extraction ratio by 0.28%. The r-squared value for this model for estimating oxygen extraction ratio was 0.96, indicating that 96% of the value of the oxygen extraction ratio was accounted for by the variables in the model. No significant collinearity was present in the model (Table 1).

Table 1
Results of regression analysis demonstrating the association of hemodynamic variables and oxygen extraction ratio (significant findings only)

	Beta-coefficient	p-value	Interpretation
Systemic blood flow	-3.12	< 0.01	Oxygen extraction ratio decreases by 3.12 with every 1 L/min increase in systemic blood
Superior caval vein saturation	-0.67	< 0.01	Oxygen extraction ratio decreases by 0.67 with every 1 increase in the superior caval vein saturation
Pulmonary to systemic blood flow ratio	2.85	< 0.01	Oxygen extraction ratio increases by 2.85 with every 1 increase in the pulmonary to systemic blood flow ratio

Oxygen extraction ratio of over 35%

A total of 12 (26%) patients had an oxygen extraction ratio of over 35%. SVC saturation, systemic blood flow, cardiac output, and systemic vascular resistance was significantly different between the two groups. In those with an oxygen extraction ratio of over 35%, SVC saturation was lower (44.50% versus 55.00%), systemic blood flow was lower (2.01 L/min versus 3.01 L/min), total cardiac output was lower (4.88 L/min versus 6.99 L/min), and systemic vascular resistance was higher (23.07 woods units versus 12.58 woods units).

Receiver operator curve analyses were done to predict an oxygen extraction ratio of over 35% using the following independent variables: hemoglobin, SVC saturation (area under the curve = 0.33), systemic blood flow (area under the curve = 0.95), total cardiac output (area under the curve = 0.85, systemic to pulmonary blood flow ratio (area under the curve = 0.69, and systemic vascular resistance (area under the curve 0.91). Optimal cut-off points for variables with an area under the curve of greater than 0.70 were identified as follows: SVC saturation 49.00%, systemic blood flow 2.62 L/min, total cardiac output 5.6 L/min, Qp:Qs 1.03, and systemic vascular resistance 15.69 woods units.

A composite score was calculated by assigning one point for each of the following: 1) SVC saturation less than 49.00%; 2) systemic blood flow less than 2.62 L/min; 3) total cardiac output less than 5.6 L/min; 4) Qp:Qs less than 1.03; 5) systemic vascular resistance greater than 15.69 woods units. A composite score of over 2.5 was predictive of having an oxygen extraction ratio of over 35% with an area under the curve of 0.98. Thus, having any three of these risk factors, concurrently, appears to be associated with a significantly increased oxygen extraction ratio.

Superior Vena Cava (SVC) saturation

Regression analysis with SVC saturation as the dependent variable demonstrated that the following variables were significantly associated with SVC saturation: systemic arterial saturation (beta coefficient 1.03, $p < 0.01$), systemic blood flow (beta coefficient 4.85, $p < 0.01$) and hemoglobin (beta coefficient 0.89, $p = 0.02$). Phrased in a more clinical context, every increase in the systemic arterial saturation by 1% was

associated with an increase in the SVC saturation by 1.03%, every increase in the systemic blood flow by 1 L/min was associated with an increase in the SVC saturation by 4.85%, and every increase in hemoglobin by 1mg/dl was associated with an increase in the SVC saturation by 0.89%. The r-squared value for this model was 0.74. No significant linearity was noted in the model (Table 2).

Table 2
Results of regression analysis demonstrating the association of hemodynamic variables and superior caval vein saturation (significant findings only)

	Beta-coefficient	p-value	Interpretation
Systemic arterial saturation	1.03	< 0.01	Superior caval vein saturation increases by 1.03 for every 1 increase in the systemic arterial saturation
Systemic blood flow	4.85	< 0.01	Superior caval vein saturation increases by 4.85 for every 1 L/min increase in systemic blood flow
Hemoglobin	0.89	0.02	Superior caval vein saturation increases by 0.89 for every increase 1mg/dl increase in hemoglobin

Receiver operator curve analysis for systemic arterial saturation to predict a SVC saturation of less than 49.00% (cutoff identified previously in this study) found a systemic arterial saturation of less than 75.50% to be associated with a SVC saturation of less than 49.00% (area under the curve = 0.68). Receiver operator curve analysis for hemoglobin to predict a SVC saturation of less than 49.00% found a hemoglobin of less than 12.6 g/dl was found to be associated with a SVC saturation of less than 49.00% (area under the curve = 0.61).

Pulmonary to systemic blood flow ratio (Qp:Qs)

Regression analysis with Qp:Qs as the dependent variable demonstrated that the following variables were significantly associated with Qp:Qs: systemic vascular resistance (beta coefficient 0.08, $p < 0.01$), pulmonary vascular resistance (beta coefficient − 0.27, $p < 0.01$), pulse pressure (beta coefficient − 0.01, $p = 0.02$), and hemoglobin (beta coefficient − 0.13, $p = 0.03$). Phrased in a more clinical context, every increase in the systemic vascular resistance by 1 wood unit was associated with an increase in the Qp:Qs by 0.08, every increase in pulmonary vascular resistance by 1 wood unit was associated with a decrease in Qp:Qs by 0.27, every increase in pulse pressure by 1 mmHg was associated with a decrease in the Qp:Qs by 0.01, and every increase in hemoglobin by 1mg/dl was associated with a decrease in Qp:Qs by 0.13 (Table 3).

Table 3
Results of regression analysis demonstrating the association of hemodynamic variables and pulmonary to systemic blood flow ratio (significant findings only)

	Beta-coefficient	p-value	Interpretation
Systemic vascular resistance	0.08	< 0.01	Pulmonary to systemic blood flow ratio increases by 0.08 with every 1 woods unit increase in systemic vascular resistance
Pulmonary vascular resistance	-0.27	< 0.01	Pulmonary to systemic blood flow ratio decreases by 0.27 with every 1 woods unit increase in pulmonary vascular resistance
Pulse pressure	-0.01	0.02	Pulmonary to systemic blood flow ratio decreases by 0.01 with every 1 increase in pulse pressure
Hemoglobin	-0.13	0.03	Pulmonary to systemic blood flow ratio decreases by 0.13 with every 1 mg/dl increase in hemoglobin

Receiver operator curve analysis for hemoglobin to predict Qp:Qs of greater than 1.03 (cutoff identified previously in this study) found that a hemoglobin of less than 12.30 g/dl was associated with a Qp:Qs greater than 1.03 (area under the curve = 0.59). Receiver operator curve analysis for pulse pressure found that a pulse pressure of less than 41.50 was associated with a Qp:Qs greater than 1.03 (area under the curve = 0.57).

Discussion

This study demonstrates the correlations and associations between several hemodynamic parameters and oxygen delivery in children with parallel circulation. Factors significantly associated with the oxygen extraction ratio were identified as being systemic blood flow, SVC saturation, and Qp:Qs. Factors significantly associated with SVC saturation were found to be systemic blood flow, systemic arterial saturation, and hemoglobin. Factors significantly associated with Qp:Qs were found to be systemic vascular resistance, hemoglobin, pulmonary vascular resistance, and pulse pressure. Higher systemic blood flow, higher SVC saturation, lower Qp:Qs, lower systemic vascular resistance, higher systemic arterial saturation, higher hemoglobin, lower pulmonary vascular resistance, and higher pulse pressure were significantly associated with improved oxygen delivery.

More specifically, these analyses were able to identify some cutoff points that may be helpful in general clinical practice for improving oxygen delivery: systemic blood flow greater than 2.62 l/min, total cardiac output greater than 5.60 l/min, Qp:Qs less than 1.03, systemic arterial saturation greater than 75.50%, SVC saturation greater than 49.00%, hemoglobin greater than 12.5 g/dl, and systemic vascular resistance less than 15.69 woods units (Table 4).

Table 4
Proposed clinical targets for hemodynamic variables found to be associated directly or indirectly with oxygen extraction ratio

Systemic blood flow	**Greater than 2.62 L/min**
Total cardiac output	Greater than 5.60 L/min
Pulmonary to systemic blood flow ratio	Less than 1.03
Systemic arterial saturation	Greater than 75.5%
Superior caval vein saturation	Greater than 49.0%
Hemoglobin	Greater than 12.5 g/dl
Systemic vascular resistance	Less than 15.69 woods units

Parallel circulation represents a unique circulation in which the total cardiac output gets divided into the pulmonary and systemic circulations. Without an increase in total cardiac output, any increase or decrease in either pulmonary or systemic blood flow must be accompanied by an obligatory change in the opposite direction by an equal magnitude. Additionally, the systemic arterial saturation in this circulation is a weighted average of the pulmonary venous and systemic venous saturations. This direct link of flow and saturation between the pulmonary and systemic circulations makes this circulation potentially more tenuous and requires care to balance the two circulations in regards to flow and saturation [1].

The circulatory system exists for being able to deliver oxygen. Blood and hemoglobin simply act as the transportation system for oxygen, and the heart is the pump that drives forward flow of blood. The heart is normally septated such that the deoxygenated and oxygenated blood pools coming from the systemic venous and pulmonary venous circulations are separated. In parallel circulation, however, this septation is lost. The effect of the mixing of the two blood pools is that the systemic arterial saturation is lower than in a fully septated circulation. The assessment of cardiac output, however, can still be done utilizing the Fick equation, simply understanding that the arteriovenous difference still provides data about the adequacy of systemic oxygen delivery. As always, the adequacy of systemic oxygen delivery can be impaired by either increased oxygen consumption or decreased systemic oxygen delivery. Blood pressure is the product of cardiac output and systemic vascular resistance, and maintenance of blood pressure in and of itself isn't directly linked to oxygen delivery. Even if mean arterial blood pressure is maintained, increasing cardiac output or decreasing systemic vascular resistance or or both can lead to better systemic oxygen delivery.

The arteriovenous oxygen difference or oxygen extraction ratio require simultaneous monitoring of the systemic arterial and systemic venous saturation. Maintaining an adequate systemic venous saturation has been shown to help detect early hemodynamic decline and improve outcomes in those with parallel circulation [2–6]. Monitoring regional near infrared spectroscopy, similarly, has also been demonstrated to help improve outcome [6, 7].

An increase in the SVC saturation was noted to have an independent association with a decrease in the oxygen extraction ratio. This makes intuitive sense as the increase in the SVC saturation in and of itself reflects adequacy of systemic oxygen delivery, reflecting either a decrease in systemic oxygen consumption or an increase in oxygen delivery. Maintaining a SVC saturation of over 49.00% seems to help optimize systemic oxygen delivery.

A decrease in the Qp:Qs was noted to have an independent association with a decrease in the oxygen extraction ratio. A decrease in Qp:Qs without a concomitant change in total cardiac output would imply an increase in systemic blood flow and consequently an increase systemic oxygen delivery. Maintaining a Qp:Qs of less than 1.03 seems to help optimize systemic oxygen balance. This finding is similar to findings in previous studies [3, 8, 9].

An increase in systemic blood flow was noted to have an independent association with a decrease in the oxygen extraction ratio. Maintaining systemic blood flow greater than 2.62 L/min seems to help mediate increased systemic oxygen delivery and likely leads to the subsequent decrease in the oxygen extraction ratio.

An increase in the systemic arterial saturation was noted to have an independent association with an increase in the SVC saturation. This likely represents an increase in systemic oxygen content which then, if the arteriovenous difference is maintained, will lead to a higher systemic arterial saturation in the next cardiac cycle. The notion that increased oxygen is inherently harmful in parallel circulation has been demonstrated to be false, and while increased fraction of inspired oxygen may be detrimental when left unchecked, this can easily be monitored via multiple ways including following the venous saturation [10]. If an increase in the fraction of inspired oxygen leads to a worsening in the oxygen extraction ratio, then this is an indication that the fraction of inspired oxygen delivered to the patient may have passed a situation-specific threshold to negatively impacted systemic oxygen delivery. In the presence of alpha-blockade such as with phenoxybenzamine or phentolamine, systemic arterial saturation and oxygen extraction ratio seem to be linearly correlated, and no increase in oxygen extraction ratio is usually seen with increasing systemic arterial saturation [11]. These concepts support the findings of the current analyses which suggest maintaining a systemic arterial saturation of greater than 75.50% seems to help optimize systemic oxygen balance.

An increase in hemoglobin level was noted to have an independent association with an increase in SVC saturation and a decrease in Qp:Qs. Higher hemoglobin increases oxygen delivery if cardiac output is maintained. If oxygen delivery increases, then the SVC saturation also increases in the absence of increased oxygen extraction. Maintaining a hemoglobin of over 12.5 g/dl seems to help optimize systemic oxygen delivery. Previous studies have demonstrated a similar hemoglobin cutoff [12, 13]. The benefit of hemoglobin may be secondary not only to the increased oxygen delivering capacity but also to the rheological effects of packed red blood cell on circulatory viscosity. Lister and colleagues demonstrated that packed red blood cell transfusion decreased the Qp:Qs in the setting of ventricular septal defects [14]. While the transfusion increased both the pulmonary vascular resistance and the

systemic vascular resistance, the increase in pulmonary vascular resistance was greater. The risks versus benefits of transfusions are beyond the scope of this manuscript, but it should be noted that packed red blood cell transfusion is not without documented risks [15].

An increase in systemic vascular resistance was noted to have an association with an increase in Qp:Qs. This association has been previously described and is relatively intuitive. If systemic vascular resistance increases but myocardial contractility remains the same, effective cardiac output will subsequently fall due to an increased percentage of stroke volume flowing to the pulmonary circuit. If systemic vascular resistance increases and myocardial contractility increases to maintain similar cardiac output, myocardial oxygen consumption will have to increase. In the first scenario the decrease in stroke volume flowing to the systemic circuit will result in lower systemic oxygen delivery, while in the second scenario the increase in myocardial oxygen consumption at an equal cardiac output will also lead to a decrease in systemic oxygen delivery. Thus, maintaining systemic vascular resistance at low levels is important in the setting of parallel circulation and may be achieved by agents such as phenoxybenzamine, phentolamine, sodium nitroprusside, nicardipine, or milrinone [16–19].

An increase in pulmonary vascular resistance was also noted to have an association with a decrease in Qp:Qs. This is fairly intuitive as the Qp:Qs is inversely related to the pulmonary vascular resistance.

Along with systemic vascular resistance, an increase in systemic blood flow was also noted to have an association with a decrease in Qp:Qs. This should come as no surprise as increasing cardiac output while keeping oxygen content the same results in greater systemic oxygen delivery as systemic oxygen delivery is the product of these two. Enhancing total cardiac output can be done by increasing circulating volume or by increasing contractility with agents such as milrinone, low dose epinephrine, or calcium [20]. Apart from their effects on contractility, the vascular effects of these vasoactive agents must be taken into consideration as these agents can increase systemic vascular resistance and subsequently myocardial oxygen consumption [21, 22].

Lastly, a higher pulse pressure was noted to have an association with a lower Qp:Qs. This is particularly of note as many use the pulse pressure as a surrogate marker of Qp:Qs. Anecdotally, most associate a high pulse pressure with higher Qp:Qs assuming that the pulse pressure is widened because of pulmonary steal. This should not be of particular surprise as pulse pressure is directly related to cardiac output. In the setting of parallel circulation this means that pulse pressure is directly related to systemic flow. While some level of steal from the systemic circulation can occur, it must be kept in mind that systemic flow does seem to mediate the pulse pressure more. A vast majority of children in this study had right ventricle to pulmonary artery conduits (Sano modification) to provide pulmonary blood flow. Hence the reduction in diastolic blood pressure due to steal from the systemic circulation in diastole is not present. Thus, while a greater pulse pressure may be associated with increased Qp:Qs in those with Blalock-Taussig-Thomas shunts, this does not seem to be the case in the setting of right ventricle to pulmonary artery conduits.

There have been very few studies that have focused on the hematologic and physiologic associations between parallel circulation and systemic oxygen delivery. The values identified in this study are simply representative of numbers that have resulted from analyses of a group of patients from a single center. What is more important is the underlying physiologic principles rather than the absolute numbers. As parallel circulation has greater inherent risk of systemic venous desaturation and hemodynamic compromise, it is important to elucidate factors associated with a low-risk state in this circulation.

While these analyses are additive to the literature, they are not without their limitations. This is a single center, retrospective study. Due to varying surgical and medical strategies across different institutions, these findings may not be perfectly applicable to other patient cohorts. The physiologic principles should remain the same, although there may be some difference in the actual cutoff values. These should, however, be minimal. The data here are cardiac catheterization data. Thus, the patients were intubated and sedation for the procedure. This must be kept in mind as this data may not be as applicable to a free-breathing patient off all sedatives. Nonetheless, the underlying physiologic principles related to the adequacy of systemic oxygen delivery and its associated factors should not be dramatically different.

Conclusion

Oxygen extraction ratio in parallel circulation is significantly associated with systemic blood flow, SVC saturation, and Qp:Qs. SVC saturation is further associated with systemic arterial saturation and hemoglobin while Qp:Qs is associated with systemic vascular resistance, pulmonary vascular resistance, and pulse pressure. Understanding of these factors can help guide clinical monitoring and management strategies for this high-risk circulation.

Declarations

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Statement of human rights: The Study have been approved by the appropriate institutional ethics committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Availability of Data and Material: All data and materials, as well as software application, support our published claims and comply with field standards.

Author's Contribution

Rohit S. Loomba, Saul Flores and Enrique G. Villarreal contributed to the study conception and design. Material preparation, data collection and analysis were performed by Juan S. Farias and Kristin Jenson. The first draft of the manuscript was written by Joshua Wong and Rohit S. Loomba. Saul Flores and Fabio Savorgnan commented on previous versions of the manuscript. All authors read and approved the final manuscript. Reviewing and editing was done by Enrique G. Villarreal and Rohit S. Loomba.

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