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Research Article

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

Introduction: Functionally univentricular parallel circulation represents one of the highest-risk circulatory physiologies for humans. With the arterial saturation linked to both the pulmonary venous and systemic venous saturations and total cardiac output being the sum of systemic and pulmonary blood flow, this circulation is truly unique. Maintaining adequate oxygen delivery is important, and oxygen extraction has been demonstrated to be associated with outcomes. This study aimed to characterize relationships between various hemodynamic parameters and oxygen extraction in this circulation.

Methods: Data from the pre-Glenn catheterization in children with functionally univentricular parallel circulation were utilized to determine relationships between various hemodynamic parameters and oxygen extraction. Oxygen extraction was calculated using the superior caval vein saturation.

Results: Data from 45 catheterizations across 45 unique patients were included in these analyses. Higher systemic blood flow, higher total cardiac output, lower pulmonary to systemic blood flow ratio, higher hemoglobin, and lower systemic vascular resistance were found to be associated with lower oxygen extraction.

Conclusion: Catheterization data demonstrate that a variety of hemodynamic parameters are associated with oxygen extraction. These may be clinically monitored and utilized to help augment oxygen extraction.

Introduction

Parallel circulation represents a unique physiologic state in children with functionally univentricular circulation. 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 circulation linked with respect to saturation, but also 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 must occur with a concurrent change in the other circulation 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 consumption and systemic oxygen delivery. There is a paucity of data on how different hemodynamic parameters impact systemic oxygen delivery, particularly the oxygen extraction ratio. The primary aim of this

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study was to utilize pre-Glenn catheterization to determine the association of different hemodynamic variables with oxygen extraction ratio. Secondary aims included determining the association of hemodynamic variables with superior caval vein saturation and pulmonary to systemic blood flow ratio.

Methods

Study design and patient identification

This was a single-center, retrospective study using data from catheterization in patients with parallel circulation before 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.

Patients who underwent a Glenn procedure were identified using our institutional pediatric cardiothoracic surgery database. These patients were then identified as either having had a catheterization before their Glenn procedure or not. Patients with parallel circulation who underwent a Glenn procedure and underwent a catheterization before 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 before the Glenn procedure or those who died before their Glenn procedure were excluded. Patients with incomplete catheterization data were also excluded. Additionally, patients with venovenous collaterals or other anomalies that could spuriously alter the superior caval vein saturation were 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 pulmonary to systemic blood flow ratio.

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 and pulse pressure. The following saturation variables were identified as those of interest: superior caval vein saturation, systemic arterial saturation (descending aorta saturation), and pulmonary vein saturation. The following laboratory data were identified as of interest: hemoglobin and N-terminal-brain-natriuretic peptide.

The following values were calculated using the 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 superior caval vein saturation. In most instances, a pulmonary vein saturation was directly obtained, although in some cases this was not the case. 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 superior caval vein 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 oxygen extraction ratio is higher than the arteriovenous oxygen difference. 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 numbers. For instance, if the systemic arterial saturation is 80% and the superior caval vein saturation is 60% the arteriovenous difference will be reported as 20 and the oxygen extraction ratio as 25%.

Statistical analyses

Data for all variables were assessed for normal 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 the oxygen extraction ratio after the initial correlation analyses. Oxygen extraction ratio was used as the dependent variable, while superior caval vein saturation, pulmonary to systemic blood flow ratio, 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.

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Receiver operator curve analyses were then conducted for variables with a p-value of less than 0.20 from the Mann-Whitney U test. The presence of an oxygen extraction ratio of over 35% was used as the state variable, and the predictors used were hemoglobin, superior caval vein saturation, total cardiac output, systemic blood flow, pulmonary to systemic blood flow ratio, and systemic vascular resistance. The area under the curves was 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 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 superior caval vein saturation and pulmonary to systemic blood flow ratio 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 superior caval vein saturation or pulmonary to systemic blood flow ratio 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 a 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.

Clinical approach

All catheterizations were done with the use of intubation, mechanical ventilation, and general anesthesia. Anesthetic induction varied but was generally done using an intravenous induction and then maintenance with intravenous agents. Generally, fentanyl, dexmedetomidine, and ketamine or propofol were utilized. Neuromuscular blockade in the form of rocuronium was utilized for these patients as well. Mechanical ventilation was utilized with a pressure control approach. Oxygen saturations were maintained between 75% and 85% while the partial pressure of carbon dioxide was maintained between 35 and 45 mmHg.

Results

Cohort characteristics

A total of 45 patients were included in the final analyses. The median age at cath was three months, while the median weight at cath was 5.25 kg. The most frequent principle cardiac diagnosis in these patients was hypoplastic left heart syndrome, which was noted in 24 (53%) of 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 superior caval vein 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), pulmonary to systemic blood flow ratio (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). Thus, oxygen extraction ratio significantly increases as superior caval vein saturation decreases, as systemic blood flow decreases, as total cardiac output decreases, as pulmonary to systemic blood flow ratio 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), superior caval vein saturation (beta coefficient = -0.67, p < 0.01). And pulmonary to systemic blood flow ratio (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 superior caval vein saturation by 1 was associated with a decrease in oxygen extraction ratio by 0.67, and every increase in pulmonary to systemic blood flow ratio 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).

Oxygen extraction ratio of over 35%: A total of 12 (26%) of patients had an oxygen extraction ratio of over 35%. Median values and p-values for the two groups are presented in Table 2. Superior caval vein saturation, systemic blood flow, cardiac

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.

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output, and systemic vascular resistance were significantly different between the two groups. In those with an oxygen extraction ratio of over 35%, superior caval vein 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, superior caval vein 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: superior caval vein saturation 49.00%, systemic blood flow 2.62 L/min, total cardiac output 5.6 L/min, pulmonary to systemic blood flow ratio 1.03, systemic vascular resistance 15.69 woods units.

A composite score was calculated by assigning one point for each of the following: 1) superior caval vein 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) pulmonary to systemic blood flow ratio less than 1.03; 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 caval vein saturation: Regression analysis with superior caval vein saturation as the dependent variable demonstrated that the following variables were significantly associated with superior caval vein 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 superior caval vein saturation by 1.03, every increase in the systemic blood flow by 1 L/min was associated with an increase in the superior caval vein saturation by 4.85, and every increase in hemoglobin by 1mg/dl was associated with an increase in the superior caval vein saturation by 0.89. The R-squared value for this model was 0.74. No significant linearity was noted in the model (Table 2).

Receiver operator curve analysis for systemic arterial saturation to predict a superior caval vein saturation of less than 49.00% found a systemic arterial saturation of less than 75.50% to be associated with a superior caval vein saturation of less than 49.00% (area under the curve 0.68). Receiver operator curve analysis for hemoglobin to predict a superior caval vein saturation of less than 49.00% found that a hemoglobin of less than 12.6 g/dl was found to be associated with a superior caval vein saturation of less than 49.00% (area under the curve 0.61).

Pulmonary to systemic blood flow ratio: Regression analysis with pulmonary to systemic blood flow ratio as the dependent variable demonstrated that the following variables were significantly associated with pulmonary to systemic blood flow ratio: 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 pulmonary to systemic blood flow ratio by 0.08, every increase in pulmonary vascular resistance by 1 wood unit was associated with a decrease in pulmonary to systemic blood flow ratio by 0.27, every increase in pulse pressure by 1 was associated with a decrease in the pulmonary to systemic blood flow ratio by 0.01, and every increase in hemoglobin by 1mg/dl was associated with a decrease in pulmonary to systemic blood flow ratio by 0.13 (Table 3).

Receiver operator curve analysis for hemoglobin to predict pulmonary to systemic blood flow ratio 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 pulmonary to systemic blood flow ratio 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 pulmonary to systemic blood flow ratio greater than 1.03 (area under the curve 0.57).

Discussion

This study demonstrates the correlations and associations between several hemodynamic parameters in children with

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 1mg/dl increase in hemoglobin

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

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parallel circulation. Factors significantly associated with the oxygen extraction ratio were identified as systemic blood flow, superior caval vein saturation, and the pulmonary to systemic blood flow ratio. Factors significantly associated with superior caval vein saturation were found to be systemic blood flow, systemic arterial saturation, and hemoglobin. Factors significantly associated with the pulmonary to systemic blood flow ratio were found to be systemic vascular resistance, hemoglobin, pulmonary vascular resistance, and pulse pressure. Higher systemic blood flow, higher superior caval vein saturation, lower pulmonary to systemic blood flow ratio, lower systemic vascular resistance, higher systemic arterial saturation, higher hemoglobin, lower pulmonary vascular resistance, and higher pulse pressure were significantly associated with a more ideal physiologic state.

More specifically, these analyses were able to identify some cutoff points that may be helpful in general clinical practice. Systemic blood flow of greater than 2.62 L/min, total cardiac output of greater than 5.60 L/min, pulmonary to systemic blood flow ratio of less than 1.03, systemic arterial saturation of greater than 75.50%, superior caval vein saturation of 49.00, hemoglobin greater than 12.5 g/dl, and systemic vascular resistance less than 15.69 woods units (Table 4).

Parallel circulation represents a unique circulation in which the total cardiac output is 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 about flow and saturation [1].

The circulatory system exists for being able to circulate oxygen. Blood and hemoglobin simply act as the transportation system for oxygen, and the heart is the pump that offers flow to the 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 itself. Blood pressure is the product of cardiac output and systemic vascular resistance, and maintenance of blood pressure in and of itself is not directly linked to oxygen delivery, although if mean arterial blood pressure is maintained or increased by simply increasing cardiac output while either decreasing systemic vascular resistance or maintaining it, then it can be an indicator of better systemic oxygen balance.

Table 4: Proposed clinical targets for hemodynamic variables found to be associated directly or indirectly with the 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

The arteriovenous oxygen difference, or the oxygen extraction ratio, requires simultaneous monitoring of the systemic arterial and systemic venous saturation. Monitoring of the systemic venous saturation and 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 outcomes [6,7].

The superior caval vein saturation was noted to have an independent association with the oxygen extraction ratio. The oxygen extraction ratio decreased as the superior caval vein saturation increased. This makes intuitive sense as the increase in the superior caval vein 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 superior caval vein saturation of over 49.0% seems to help optimize systemic oxygen balance.

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

Systemic blood flow was also noted to have an independent association with the oxygen extraction ratio. The oxygen extraction ratio decreased as the systemic blood flow increased. Maintaining systemic blood flow greater than 2.62 L/min seems to help optimize systemic oxygen balance. Increasing systemic blood flow mediates increased systemic oxygen delivery, and this likely leads to the subsequent decrease in the oxygen extraction ratio.

The systemic arterial saturation was noted to have an independent association with the superior caval vein saturation. The superior caval vein saturation increased as the systemic arterial saturation increased. This likely represents an increase in systemic oxygen content, which then if the arteriovenous difference is maintained, will lead to a higher systemic arterial

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saturation in the subsequent cardiac cycle. The notion that increased oxygen is inherently harmful in parallel circulation has been demonstrated to, in fact, be false, and while increased oxygen may be detrimental, this can easily be monitored by following the venous saturation as the fraction of inspired oxygen is increased [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 increased fraction of inspired oxygen may have passed a situation-specific threshold in which it has negatively impacted systemic oxygen balance. 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 such increase in oxygen extraction ratio is usually seen at any point 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 75.5% seems to help optimize systemic oxygen balance.

Hemoglobin level was noted to have an independent association with superior caval vein saturation as well as pulmonary to systemic blood flow ratio. The superior caval vein saturation increased as the hemoglobin level increased, and the pulmonary to systemic blood flow ratio decreased as the hemoglobin level increased. Increasing hemoglobin increases oxygen content and, subsequently, oxygen delivery if cardiac output is maintained or increased. If oxygen delivery increases, then the superior caval vein saturation also increases in the absence of an increased arteriovenous oxygen difference. In parallel circulation, the interdependence of the systemic arterial saturation on the systemic venous saturation makes this a particularly important tool. In the setting of fully septated, biventricular circulation, the systemic arterial saturation can be maintained near 100% even in the setting of widening arteriovenous oxygen difference as long as the pulmonary venous saturation can be maintained near 100%. However, in the setting of parallel circulation, where the systemic arterial saturation is a weighted average of the pulmonary venous saturation and the systemic venous saturation, a decrease in either the systemic venous saturation or the pulmonary venous saturation, while keeping oxygen extraction the same, will lead to an obligate decrease in arterial saturation. Maintaining a hemoglobin of over 12.5 g/dl seems to help optimize systemic oxygen balance. Previous studies have demonstrated a similar hemoglobin cutoff [12,13]. The benefit of hemoglobin may be secondary not only to the increased oxygen content but also due to the rheologic effects of packed red blood cell transfusion and the effects of additional viscosity. Lister and colleagues demonstrated that packed red blood cell transfusions decreased the pulmonary to systemic blood flow ratio 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 themselves are beyond the scope of this manuscript, but it should be noted that packed red blood cell transfusions are not without documented risks [15]. One such risk is that increased frequency of packed red blood cell transfusions is associated with increased HLA antibodies, which may complicate cardiac transplantation if needed in the future.

Systemic vascular resistance was noted to have an association with the pulmonary to systemic blood flow ratio, with higher systemic vascular resistance being associated with a greater oxygen extraction ratio. This association has been previously described and is relatively intuitive. If systemic vascular resistance increases but myocardial contractility remains the same, stroke volume and cardiac output will subsequently fall. If systemic vascular resistance increases and myocardial contractility increases to maintain a similar cardiac output, myocardial oxygen consumption will have to increase. In the first scenario, the decrease in stroke volume and cardiac output 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].

Along with systemic vascular resistance, systemic blood flow was also noted to have an association with the pulmonary to systemic blood flow ratio, with lower systemic blood flow being associated with a lower pulmonary to systemic blood flow ratio. 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, epinephrine, dopamine, or calcium [20]. The effects of these vasoactive agents, apart from their effects on contractility, must be taken into consideration as well as these agents can actually increase systemic vascular resistance and subsequently myocardial oxygen consumption [21,22].

Pulmonary vascular resistance was also noted to have an association with pulmonary to systemic blood flow ratio, with higher pulmonary vascular resistance being associated with a lower pulmonary to systemic blood flow ratio. This is fairly intuitive as the pulmonary to systemic blood flow ratio is related to the pulmonary vascular resistance to systemic vascular resistance ratio.

Lastly, pulse pressure was noted to have an association with the pulmonary to systemic blood flow ratio, with higher pulse pressure being associated with a lower pulmonary to systemic blood flow ratio. This is particularly of note as many use the pulse pressure as a surrogate marker of the pulmonary to systemic blood flow ratio. Anecdotally, most associate a high pulse pressure with a higher pulmonary to systemic blood flow ratio, 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 form of steal from the systemic circulation can also contribute, it must be

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kept in mind that systemic flow does seem to mediate the pulse pressure more nonetheless. A vast majority of children in this study had right ventricle to pulmonary artery conduits (Sano modification) to provide pulmonary blood flow. As these fill in systole, 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 pulmonary to systemic blood flow ratio 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.

These analyses demonstrate some physiologic associations present in the setting of parallel circulation. There have been very few studies that have focused on the physiologic associations in the setting of parallel circulation in a similar manner. The values identified by these analyses 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 is a unique circulation with a greater inherent risk of systemic venous desaturation and subsequently 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 when utilizing this data, as the data might not apply as is to a free-breathing patient who is not on any 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, superior caval vein saturation, and pulmonary to systemic blood flow ratio. Superior caval vein saturation is further associated with systemic arterial saturation and hemoglobin, while the pulmonary to systemic blood flow ratio 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.

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