Estimating intracardiac and extracardiac shunting in the setting of complex congenital heart disease

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ABSTRACT

Complex congenital heart disease (CHD) is associated with significant morbidity worldwide. Managing hypoxemia in these populations can be difficult, particularly in the setting of cyanotic CHD. However, the presence of additional extracardiac shunts secondary to acute respiratory disease can be very challenging to manage. Before understanding how to deal with hypoxemia in patients with dual shunts, one needs to understand the physiology and diagnosis related to the individual shunts and apply this knowledge to the patient as a whole.

Keywords: Congenital heart disease, pulmonary, shunts

CLINICAL VIGNETTE

A 10-month-old child with a history of hypoplastic left heart syndrome, who has undergone a bidirectional cavopulmonary anastomosis four months earlier, presents with a three-day history of cough, rhinorrhea, and increased respiratory rate. As part of the initial assessment of the child, the pulse oximeter is noted to read a saturation of 65% on room air and the child appears to have some perioral cyanosis as well as mild respiratory distress. Following the institution of oxygen therapy, the saturation increases to 75%, with some resolution of the respiratory distress.

In the setting of a child with cyanotic congenital heart disease with a pulmonary-to-systemic blood flow ratio of less than 1:1, presenting with an intercurrent lower respiratory illness, who may also have pulmonary arteriovenous collaterals, the cause of the respiratory distress and worsening hypoxemia can be multifactorial. The underlying anatomy and circulatory physiology results in increased systemic venous admixture as a result of inferior caval blood being directed into the systemic circulation, and pulmonary venous blood returning to the systemic venous circulation, via collateral circulation. Furthermore, the superadded respiratory illness will result in more desaturated blood returning to the heart from the pulmonary veins, due to worsening ventilation and perfusion mismatch. In determining the contribution of the respective shunts, one must understand the underlying physiologic principles and apply that knowledge in a comprehensive manner to properly manage the child's hypoxemia.

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INTRODUCTION

While surgical techniques for congenital heart disease (CHD) have led to improved survival,[1] late deaths related to respiratory infections continue to be a major burden for these patients.[2] In children with cyanotic CHD and intracardiac shunting, the additional impact of pulmonary disease, with acute worsening of gas exchange and oxygenation can be poorly tolerated, resulting in even greater morbidity.[3] Specifically, patients with underlying CHD, who develop severe lower respiratory tract infections, are at risk for prolonged hospital stays, longer duration of mechanical ventilation, and death.[4,5] This burden is not limited to developed countries, as lower respiratory infections related to respiratory syncytial virus and bacterial pneumonia account for significant morbidity and mortality worldwide,[6,7] and account for more than half of all hospital admissions of patients with congenital heart disease with a secondary respiratory illness.[8] The respiratory syncytial virus is responsible for a majority of cases of bronchiolitis in infants and young children and can present with a spectrum of respiratory symptoms, from mild to

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life-threatening or even fatal.[9] Young infants with critical CHD, particularly those with large unoperated septal defects or palliated single ventricle physiology, are at particular risk. While immunoprophylaxis with palivizumab and improvements in acute care have improved the disease course for some patients, these interventions are not universally available and may not always be effective. Thus, acute respiratory disease remains a significant burden for infants with complex CHD.[3,10]

Typically, the main focus of management in patients with CHD, who are hospitalized with respiratory illness, is to optimize their lung function and to ensure adequate systemic cardiac output and oxygen delivery to the tissues. A prerequisite for this is that there is sufficient pulmonary blood flow to the ventilated portions of the lungs, with minimal intrapulmonary shunting or 'dead space' ventilation. In stable patients with cyanotic CHD, who do not have significant lung disease, the degree of hypoxemia typically reflects an intracardiac shunt, with the assumption that the intrapulmonary shunt remains relatively constant. However, in children with CHD and concomitant parenchymal pulmonary disease, the relative contributions of an existing intracardiac shunt and superadded extracardiac shunting too, can be difficult to quantify. In this setting, the systemic circulation receives two sources of deoxygenated blood: One comes in the form of a systemic venous admixture returning to the heart from the systemic veins or directly from the pulmonary artery, and the other comes in the form of a pulmonary venous admixture returning to the heart from the pulmonary veins. The contribution of desaturated blood from the respective circulations depends on the total blood flow of each circulation, which in turn, determines the amount of systemic cardiac output and hypoxemia.

Intracardiac shunting

Cyanosis resulting from intracardiac shunting generally results from the mixing of oxygenated pulmonary venous blood with the systemic venous admixture. This is almost always due to an anatomical cardiac defect that is either unoperated, or has been surgically palliated. Though the specific types and associated properties of congenital heart defects and their surgical interventions are beyond the scope of this review, the physiological determination of shunts relies on the basic principles of the ratios of systemic and pulmonary blood flow.

In addition to intracardiac right-to-left shunts in the setting of cardiac defects and surgical palliation, which generally result in varying degrees of arterial hypoxemia, physiological right-to-left shunts also exist in normal healthy subjects. The most important of these are Thebesian veins, which drain the capillary beds of the myocardium directly into the left side of the heart. However, they only account for approximately 0.3% of the cardiac output in healthy humans, and do not result in clinically significant cyanosis or hypoxemia. Instead, cyanosis and hypoxemia that is cardiac in origin is almost always secondary to congenital heart defects with mixing of systemic and pulmonary blood flows.

The estimation of shunts

In the intact circulation without an intracardiac shunt, the total amount of blood ejected from the right side of the heart into the pulmonary circulation is equal to that ejected from the left side of the heart into the systemic circulation. The pulmonary blood flow (Qp), is therefore, equal to the systemic blood flow (Qs) and the ratio of these two circuits (Qp:Qs) is equal to one. When a communication, for example, a septal defect, exists between the two circuits, with a pressure difference across that communication, the result is shunting of blood from one circuit to the other. The ratio of Qp:Qs either becomes greater than or less than one, depending on the direction of the shunt. The accurate quantification of blood flow to the respective circulations and calculation of the magnitude of an intracardiac shunt requires the simultaneous measurement of oxygen saturations in the systemic and pulmonary circulations. This ratio of Qp to Qs is derived from the shunt fraction (Qs/Qt) calculation that examines the ratio of the oxygen carrying capacity of blood in various circulations:

$$Qs/Qt = (CcO_2 - CaO_2)/(CcO_2 - CvO_2) \quad (1)$$

In this equation, CaO_2, CvO_2, and CcO_2 represent the oxygen content of the arterial, mixed venous, and pulmonary capillary systems, respectively. The oxygen content of the each of the circulations can be determined by the following relationship between hemoglobin (Hgb), oxygen saturation (Sat), and partial pressure of oxygen (PO_2):

$$CO_2 = (1.34 \times Sat \times Hgb) - (PO_2 \times 0.003) \quad (2)$$

Given that the hemoglobin is a fixed number across all circulations in the body and the partial pressure of dissolved oxygen is negligible in most instances, when this equation for the individual circulations is extrapolated into the shunt fraction expressed in Equation 1, it can be simplified to a ratio of the respective oxygen saturations:

$$Qp:Qs = (SaO_2 - SvO_2)/(SpvO_2 - SpaO_2) \quad (3)$$

Where SaO_2 is the systemic arterial oxygen saturation, SvO_2 is the central venous oxygen saturation, $SpvO_2$ is the pulmonary venous oxygen saturation, and $SpaO_2$ is the pulmonary arterial oxygen saturation. Although this equation does not quantify flows (which would additionally require the measurement of systemic and pulmonary cardiac outputs), Qp:Qs will approximate the direction and magnitude of the shunting that is occurring, i.e., left to right (greater than one) or right to left (less than one).

The measurement of pulmonary and systemic flows

The estimated shunt ratios provide clinicians with important physiologic information, and the elements of this calculation, such as the systemic venous oxygen saturation, provide indirect markers of the systemic oxygen delivery and the degree of oxygen extraction. However, the shunt ratio does not quantify the systemic or pulmonary blood flow. The accurate quantification of blood flow within the cardiovascular system requires more invasive techniques that can be performed in the Intensive Care Unit or the gold standard direct Fick method – more typically performed in the catheterization laboratory.

The direct measurement of cardiac output using dilution methods, such as, thermodilution or indicator dilution techniques, typically requires the flow measurements to be done in circulations in a series with little to no shunt. The presence of a significant intracardiac shunt, therefore, renders these techniques almost useless. The direct Fick method provides an accurate measure of relative flows to the systemic and pulmonary circulations. When the oxygen consumption (VO_2) and oxygen content of arterial (CaO_2) and central venous (CvO_2) blood are estimated or measured, these values can be arranged into the following relationship, demonstrated by the Fick equation, to determine the cardiac output (Q):

$$Q = \frac{VO_2}{CaO_2 - CvO_2} \quad (4)$$

While the direct Fick method is the most accurate method of determining flow, its applicability is limited by the need for blood sampling from multiple sites and for the measurement of oxygen consumption. We have previously shown that predictive equations or assumed values do not accurately estimate oxygen consumption in the CHD population, particularly in the setting of critical illness.[11] The accurate measurement of systemic and pulmonary flow using the direct Fick method, therefore, requires the direct measurement of oxygen consumption, with collection of the expired respiratory gas. This is in general limited to the setting of anesthesia – in the catheterization laboratory, or in the context of physiological research in the Intensive Care Unit.[12]

Non-invasive methods of measuring Qp and Qs have become more popular as technology has evolved. Nuclear imaging techniques using first-pass radionuclide angiocardiography were some of the first non-invasive techniques to be employed for measuring flows and shunts, although there were some issues with imprecision in measuring the level of the shunt.[13,14] Doppler echocardiography has also been used to estimate Qp and Qs in patients with CHD.[15,16] More recently, magnetic resonance imaging has been increasingly used to quantify flows and volumes in CHD, with good correlation with oximetric techniques.[17] However, this requires either general anesthesia or breath-holding, which may preclude its application for some patients.

Extracardiac shunting

In the intensive care setting, clinically important extracardiac right-to-left shunting is usually a result of pulmonary disease. However, physiologic extracardiac shunts also exist in healthy individuals. The most important of these are the bronchial veins that drain a portion of the blood delivered by the bronchial arteries to supply oxygen to the main airway structures. The deep bronchial veins that drain the larger airway structures allow for some physiological shunting, in that, they carry deoxygenated blood from the bronchial capillaries to the pulmonary veins, creating a venous admixture.[18] Similar to the Thebesian veins, the proportion of cardiac output sequestered by these veins is less than 1% in healthy individuals. Likewise, minor areas of atelectasis occurring in healthy subjects alongside the different properties of the zones of the lungs, can be areas of stable physiological shunting, with the minimal overall contribution to venous admixture and arterial oxygenation.[19] These zones of the lungs, termed as the 'three West zones', relate to the distribution of ventilation and blood flow within the lungs.[20] The differential distribution of ventilation and perfusion creates different areas within the lungs where there is a variable, albeit minimal, degree of ventilation/perfusion mismatch.[21,22]

Pathological extracardiac shunts

Extracardiac pathological shunts most commonly occur in the form of parenchymal lung disease, such as, bronchiolitis and pneumonia. In the simplest of terms, these forms of shunting occur when deoxygenated blood from the systemic venous system bypasses the functional terminal respiratory units in the lungs and is unable to become oxygenated during that cardiac cycle, creating a gradient between the partial pressure of oxygen within the alveoli and arterial blood. Ventilation-perfusion mismatch can be particularly problematic in infants with CHD that is associated with either increased or reduced pulmonary blood flow. This can result in the worsening of cyanosis and arterial hypoxemia, and in turn, exacerbate additional factors such as pulmonary hypertension, and may further worsen the clinical picture.

Patients with CHD, and particularly those who have undergone single ventricle surgical palliation, are also at risk for important additional extracardiac shunts at the baseline, which can become exaggerated in the presence of respiratory illness. Examples of these extracardiac shunts include pulmonary arteriovenous fistulae and venovenous collaterals, which are most typically seen following a single ventricle palliation with a cavopulmonary connection (Glenn or Fontan circulation), or aortopulmonary collaterals, which often

coexist with cyanotic CHD. The exact cause of pulmonary arteriovenous fistulae in the setting of a superior cavopulmonary connection is uncertain, but may be due to recirculating hepatic factors.[23] Pulmonary arteriovenous fistulae are particularly common in patients with a superior cavopulmonary connection and are estimated to affect 60% of the patients by echocardiography[24] or more by other imaging techniques. Their contribution to the overall degree of cyanosis at rest is significant; with an additional right-to-left shunt burden of 30% or more in the most severe cases. The prevalence and impact of pulmonary arteriovenous fistulae on hypoxemia is greatest in patients whose pulmonary blood flow is derived solely from the cavopulmonary anastomosis, and less common in patients with anterograde pulsatile pulmonary flow.[25] Venovenous collaterals from the superior to the inferior vena cava occur in over 20% of the patients who have undergone cavopulmonary anastomosis. This results in 'recirculation' of systemic venous blood to the systemic arterial circulation, thus bypassing the lungs completely, and therefore, worsening the degree of arterial hypoxemia. Venovenous collaterals require interventions such as coil occlusion in about 30% of the patients.[26]

Differentiating the source of extracardiac shunts

The simplest means of examining an extracardiac shunt that is pulmonary in nature is by determining the alveolar-arterial gradient (A–a gradient) of the partial pressure of oxygen. The A-a gradient is the difference between the arterial partial pressure of oxygen and the alveolar partial pressure of oxygen. Its determination requires an arterial blood gas, knowledge of the concentration of inspired oxygen, and some basic assumptions. These basic assumptions arise from the alveolar air equation (below) that allows for an estimation of the alveolar PO_2 based on the principles that alveolar and arterial PCO_2 are approximately equal and that the exchange ratio of oxygen consumption to carbon dioxide production is roughly fixed.[27]

$$\text{A-a gradient} = PAO_2 - PaO_2 \quad (5)$$

When expressed mathematically, alveolar PO_2 can be determined by the following equation:

$$\text{Alveolar } PO_2\ (PAO_2) = FiO_2\ (pATM - pH_2O) - PaCO_2/R \quad (6)$$

Where FiO_2 is the inspired oxygen fraction, pATM is the atmospheric pressure (usually 760 mmHg), pH_2O is the water pressure (usually 47 mmHg), $PaCO_2$ is the arterial partial pressure of carbon dioxide and R is the respiratory exchange ratio (usually 0.8).

If the A-a gradient is greater than 12, a significant and pathological extracardiac pulmonary shunt is said to be present. Likewise, if Equation 1 is applied, a shunt fraction of greater than 5% indicates a significant shunt. More specifically, with regard to shunts in normal individuals, an increasing inspired oxygen fraction leads to linear increases in PaO_2. However, if a significant shunt exists, the linear correlation between these parameters becomes reduced to the point where increases in FiO_2 lead to no further increases in PaO_2.[28] The utility of using the A-a gradient in the diagnosis of extracardiac versus intracardiac shunts has been a long-time practice.[29] In this regard, by supplying a patient with 100% oxygen for approximately 20 minutes, one can increase the PAO_2 enough, so that the measured arterial saturation and PaO_2 likewise increase if the disease process is pulmonary in origin. The effects of increased alveolar PO_2 on arterial PO_2 will not occur if the cause of hypoxemia is cardiac in nature. However, this test can lead to a missed diagnosis of intracardiac shunts[30] and with the advent of more sophisticated imaging techniques, has little role in the current diagnosis of extracardiac shunts. Instead, the current diagnosis of extracardiac shunts can be done via similar techniques used in the diagnosis of intracardiac shunts; namely imaging, in the form of radionuclide scan, computed tomography with angiography or cardiac catheterization.

Determination of extracardiac shunting in complex congenital heart disease

When children with complex CHD present with an additional respiratory illness, changes in the flow patterns of both the systemic and pulmonary circulations may be altered dramatically and affect the degree of hypoxemia. These changes are often a consequence of alterations in the pulmonary vascular resistance relating to local lung volumes and pressures that have direct effects on vascular size[31] or changes in the vascular reactivity, secondary to reduced diffusion of oxygen into vessels causing hypoxic vasoconstriction – the so-called von Euler-Liljestrand effect.[32] Within the spectrum of acute lung injury, these local changes can be quite dynamic, as adjacent alveoli as well as lung zones can have different physiological properties through the presence of atelectasis and variable lung inflation.[33] Because of the dynamic properties, management of these patients can likewise be dynamic. While conventional catheterization has its role in the diagnosis and management of shunts, and bedside, echocardiography can provide useful information in the setting of hemodynamic monitoring in respiratory pathology,[34] these tools only provide temporary snapshots into the current state of the disease. Instead, real-time diagnostic tools are needed to provide information that changes as quickly as the disease process does. Historically, pulmonary artery catheters were regarded as necessary tools in the bedside determination of cardiac output and oxygen consumption.[35] However, in more recent times, these catheters have fallen out of favor in light of central

venous catheters placed in the superior vena caval and right atrial junction, that are easier to place in pediatric patients and provide similar data.[36] Newer technologies such as continuous central venous saturation monitors can provide continuous real time data that the bedside physician can use to monitor cardiac output.[37] These catheters, along with the standard arterial catheters that provide hemodynamic and oxygenation data, can provide the bedside physician with enough data to safely manage patients with complex CHD, who have secondary extracardiac shunts.

Applying shunt estimations

Returning to the patient with a hypoplastic left heart syndrome and a bidirectional cavopulmonary anatomosis, who has presented with hypoxemia and cyanosis, estimations of intra-and extracardiac shunting can be determined by using the formulae listed above. In order to estimate the contribution of intracardiac shunting to the overall hypoxemia, the oxygen saturation must be measured in both the pulmonary and systemic arterial and venous systems.

Assuming the patient at the time of previous catheterization did not have any known intra-pulmonary shunts, a measured SaO_2 of 86%, SvO_2 of 61%, $SpaO_2$ of 65%, and an $SpvO_2$ of 100% inserted into Equation 3 would calculate an estimated Qp:Qs of 0.7:1 at baseline, related to the bidirectional cavopulmonary anatomosis (which is typically associated with a Qp:Qs of less than 1).

$$Qp:Qs = (0.86 - 0.61)/(1.0 - 0.65) = 0.7/1 \quad (7)$$

The delineation of shunt fractions in the presence of an *additional* intrapulmonary shunt related either to pulmonary arteriovenous malformations, parenchymal lung disease, or both, requires the determination of the respective oxygen contents of each circulation. Let us assume that we obtain an arterial blood gas after 20 minutes on 100% oxygen and receive the following information: PaO_2 of 41 mmHg, SaO_2 of 75%, $PaCO_2$ of 40 mmHg, and Hgb of 14 g/dl. If this patient had a peripherally inserted central venous catheter, we could likewise obtain central venous blood gas with the following values: $PcvO_2$ of 28 mmHg, SvO_2 of 50%, and $PcvCO_2$ of 45 mmHg. Before solving the CO_2 of the arterial and mixed venous circulations, we must estimate the oxygen content of the pulmonary capillary circulation (CcO_2). First we must determine the PAO_2 (alveolar partial pressure of oxygen). Inserting the arterial blood gases values into Equation 6 will give us an estimated PAO_2 of 663 mmHg.

$$PAO_2 = 1.0\ (760 - 47) - 40/0.8 = 663\ mmHg \quad (8)$$

Assuming that 20 minutes of 100% oxygen saturated the intrapulmonary hemoglobin to 100%, we can insert a Saturation of 100% and a PO_2 of 663 mmHg into Equation 2 and get a pulmonary capillary CcO_2 of 20.75 ml O_2/dl blood.

$$CcO_2 = (1.34 \times 1.0 \times 14) - (663 \times 0.003) = 20.75\ ml\ O_2/dl\ blood \quad (9)$$

Next we solve CaO_2 and CvO_2 by putting in the previous values measured on the blood gases. and obtain a value of 13.95 ml O_2/dl blood and 9.3 ml O_2/dl blood for CaO_2 and CvO_2, respectively.

$$CaO_2 = (1.34 \times 0.75 \times 14) - (41 \times 0.003) = 13.95\ ml\ O_2/dl\ blood \quad (10)$$

$$CvO_2 = (1.34 \times 0.5 \times 14) - (28 \times 0.003) = 9.3\ ml\ O_2/dl\ blood \quad (11)$$

Lastly, these estimates of the oxygen carrying capacity are entered into Equation 1 and a shunt fraction of 59% is calculated.

$$Qs/Qt = (20.75 - 13.95)/(20.75 - 9.3) \times 100 = 59\% \quad (12)$$

Knowing that our baseline shunt determined by the Qp:Qs ratio is approximately 30%, we can say that the patient has a significantly increased degree of shunted deoxygenated blood that is related to an extracardiac issue, namely an arteriovenous malformation or lung disease. Thus, by applying the aforementioned equations with values obtained on blood gases after supplying 100% oxygen, the relative degrees of intracardiac and extracardiac shunts can be estimated.

CONCLUSIONS

Complex CHD is associated with significant morbidity not only related to the CHD itself, but also due to the added disease burden presented by acute respiratory disease and by abnormal vascular connections. These result in extracardiac and typically intrapulmonary shunts, which can be particularly problematic to patients with cyanosis and altered pulmonary blood flow at the baseline. Due to these increased risks, it is necessary for physicians taking care of patients with complex CHD to have a good understanding of the importance of intracardiac and extracardiac shunts that can occurs in these patients and how to distinguish between them.

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