A practical method of measuring oxygen consumption in children with complex mixing circulations by the use of thermodilution cardiac output studies

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Objective: We describe a method to measure oxygen consumption (VO_2) and pulmonary vascular resistive index (PVRI) based on thermodilution cardiac output in patients with complex mixing circulations. We apply this method to patients with a bidirectional cavopulmonary anastomosis (BDCPA). We compare our measured VO_2 with a predicted VO_2 based on a formula using height and weight.

Methods: We reviewed data based on cardiac catheterization and thermodilution cardiac output in a series of 25 catheterizations in patients with BDCPA. We used this data to measure VO_2 and PVRI, and looked for a correlation between the predicted and measured VO_2 . We also assessed whether any other hemodynamic parameter correlated with measured VO_2 .

Results: There was no significant correlation between the predicted and the measured VO_2 (correlation coefficient = -0.258 , $P = .21$). We did find a significant correlation in the difference between the measured and predicted VO_2 against the measured VO_2 such that at a lower measured VO_2 the predictive formula tended to overestimate VO_2 and at a higher VO_2 the formula underestimated VO_2 (correlation coefficient = 0.963 , $P < .0001$). Body surface area did not correlate with measured VO_2 (correlation coefficient = 0.28 , $P < .16$). Mixed venous oxygen content showed a weak negative correlation with VO_2 (correlation coefficient = -0.54 , $P = .005$).

Conclusions: An assessment of PVRI that is based on a predicted VO_2 is unreliable in this patient population. No hemodynamic parameter correlated well with VO_2 . The use of a measured VO_2 is necessary in determining PVRI in these patients. (J Thorac Cardiovasc Surg 2013;146:1179-84)

The assessment of pulmonary blood flow and pulmonary vascular resistance (PVR) in complex mixing circulations is challenging. Still, this assessment remains an important aspect in risk stratification prior to staged surgical palliation via bidirectional cavopulmonary anastomosis (BDCPA) and the Fontan procedure. Typically, this assessment is done by combining cardiac catheterization data with the use of a predicted oxygen consumption (VO_2) from one of several predictive formulas because methods of direct measurement of VO_2 are complicated and require expensive equipment and operator expertise.

We report a previously undescribed method of calculating PVR and VO_2 . We compare this measured VO_2 with a standard predicted VO_2 based on the formula described by Krovets and Goldbloom.¹ We demonstrate how we can calculate PVR based on thermodilution cardiac output

studies in patients with BDCPA. This method can be used in many complex mixing circulations to calculate flows and resistances in the systemic or pulmonary vascular beds. We examined hemodynamic parameters that might predict VO_2 in BDCPA.

METHODS

Assessing the Pulmonary Vascular Resistive Index (PVRI)

Assessment of PVR in a normal circulation is based on the application of Ohm's law:

$$\text{PVR} = \Delta P / Q_P,$$

where R is resistance, ΔP is the mean transpulmonary pressure gradient, and Q_P is pulmonary blood flow.

Pressure is obtained by direct measurement. Pulmonary blood flow equals VO_2 divided by the difference in oxygen content please insert " (cO_2) " in the pulmonary veins and in the main pulmonary artery:

$$Q_P = \text{VO}_2 / (\text{cO}_2 \text{ PV} - \text{cO}_2 \text{ PA}),$$

where cO_2 is the content of oxygen, PV is the pulmonary vein, and PA is the pulmonary artery.

VO_2 can be measured using indirect calorimetry with a Douglas bag, or with tandem mass spectrometry. These methods measure the inspired and expired oxygen content directly, but they are time-consuming, and many centers do not have tandem mass spectrometry to perform such measurements. Oxygen consumption can also be predicted using one of a number of formulas, including those by Lafarge and Miettinen,² Lundell and

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Abbreviations and Acronyms

Ao	= aortic
APC	= aortopulmonary collateral
BDCPA	= bidirectional cavopulmonary anastomosis
BSA	= body surface area
cO ₂	= content of oxygen
ΔP	= mean transpulmonary pressure gradient
IVC	= inferior vena cava
MRI	= magnetic resonance imaging
RA	= right atrium
PA	= pulmonary artery
PV	= pulmonary vein
PVR	= pulmonary vascular resistance
PVRI	= pulmonary vascular resistive index
Q _P	= pulmonary blood flow
Q _S	= cardiac output
Q _V	= systemic ventricular output
SVC	= superior vena cava
VcO ₂	= minute oxygen delivery
VO ₂	= oxygen consumption

colleagues,³ Lindahl,⁴ Wessel and associates,⁵ and Krovetz and Goldbloom.¹ A predictive formula for VO₂ does not require complex measurements, which makes them an attractive solution for obtaining VO₂. However, it has been shown that these formulas are unreliable when compared with measured VO₂ in children with congenital heart defects.

Laitinen and Rasanen,⁶ who compared the formulas by Lindahl,⁴ Wessel and associates,⁵ Lundell and colleagues,³ against indirect calorimetry, and Li and coworkers,⁷ who compared the same formulas as well as the formula published by Lafarge and Miettinen² against respiratory mass spectrometry in children with congenital heart disease found the predictive formulas to be unreliable. In the latter study, the predictive formulas were found to overestimate lower and underestimate higher indexed VO₂. Likewise, Shanahan and colleagues⁸ compared the predictive formulas by Lindahl,⁴ Lundell and colleagues,³ and Lafarge and Miettinen² against indirect calorimetry in 35 patients with a BDCPA. They found that the formulas overestimated VO₂ in their patients and led to an underestimation of PVR, resulting in errors in risk stratification for these patients.

Minute Oxygen Delivery

The search for a simple, noninvasive measurement of cardiac output is ongoing.⁹ Invasive measurement by thermodilution studies are possible and require little additional time or expense for patients who are undergoing planned cardiac catheterization. Thermodilution-derived measurements of cardiac output have generally been found to have good agreement compared with Fick-derived measurements of cardiac output.⁹⁻¹¹

In simple circulations without intracardiac shunts, it is possible to measure cardiac output with thermodilution studies. In this case, pulmonary blood flow is equal to cardiac output (Q_P = Q_S); therefore, Q_P is measured directly and PVR can be solved without measuring VO₂. In this circumstance, VO₂ can be calculated using the Fick principle:

$$VO_2 = Q_P \times (cO_{2\text{ PV}} - cO_{2\text{ PA}})$$

In BDCPA, it is possible to measure systemic ventricular output (Q_V) using thermodilution cardiac output studies, but Q_V is not equal to Q_P. To

resolve this problem, we introduce the concept of minute oxygen delivery (VcO₂).

Oxygen contents and saturations are not additive. In the case of a BDCPA, it is not possible to calculate the aortic (Ao) cO₂ or saturation based on the oxygen contents and saturations in the right atrium (RA) and PVs. Oxygen content in the aorta depends on both the flow and the cO₂ from each of the sources. If we multiply the cO₂ in a vessel (measured in mL/L) by the flow through the vessel (measured in L/min), we obtain the VcO₂ through the vessel (measured in mL O₂/min). We designate this minute oxygen delivery as VcO₂.

Therefore, in a BDCPA, where U is upper body, L is lower body, Q_{EP} is effective pulmonary blood flow, x is the thermodilution measurement.

$$VcO_{2\text{ Ao}} = VcO_{2\text{ PV}} + VcO_{2\text{ RA}}$$

$$Q_V = Q_U + Q_L$$

$$Q_U = Q_{EP}$$

$$Q_V = Q_{EP} + Q_L$$

$$Q_L = Q_V - Q_{EP}$$

$$Q_V = x$$

$$Q_V \times cO_{2\text{ Ao}} = Q_{EP} \times cO_{2\text{ PV}} + Q_L \times cO_{2\text{ RA}}$$

$$Q_V \times cO_{2\text{ Ao}} = Q_{EP} \times cO_{2\text{ PV}} + (Q_V - Q_{EP}) \times cO_{2\text{ RA}}$$

$$Q_{EP} = \frac{x \times (cO_{2\text{ Ao}} - cO_{2\text{ RA}})}{(cO_{2\text{ PV}} - cO_{2\text{ RA}})}$$

Then,

$$Q_{EP} = \frac{VO_2}{(cO_{2\text{ PV}} - cO_{2\text{ PA}})}$$

$$VO_2 = \frac{x \times (cO_{2\text{ Ao}} - cO_{2\text{ RA}}) \times (cO_{2\text{ PV}} - cO_{2\text{ PA}})}{(cO_{2\text{ PV}} - cO_{2\text{ RA}})}$$

Using this method, certain considerations apply to the collection and interpretation of samples during the cardiac catheterization. There should be no competitive blood flow into the PA, including large aortopulmonary collaterals (APCs) or antegrade flow through a patent pulmonary valve. Right atrial blood sampling should be done near the RA–inferior vena cava (IVC) junction to minimize admixture from the PVs, but still allow adequate mixture of blood from the lower body. The PV sample ideally should contain mixed PV blood, but not contain admixture from the IVC.

Subjects

We gathered data prospectively from cardiac catheterizations done in patients with BDCPA from September 2000 to March 2009. We included data sets from multiple catheterizations in the same patient as long as they were done >12 months apart. We excluded those patients with competitive blood supply from the PA when it had not been ligated, such as patients with tricuspid atresia who still had antegrade flow through the pulmonary valve.

Catheterization Procedure

All catheterizations were done under general anesthesia with mechanical, positive-pressure ventilation. Hemodynamic data were collected at the

beginning of the catheterization followed by thermodilution cardiac output studies and prior to any angiography. A thermodilution catheter was used to inject room-temperature saline into the IVC or RA with the thermistor in the ascending aorta. We repeated injections until we had 3 samples that were within 10%, and used the averaged value for cardiac output.

Measured VO_2 and PVR were determined using the method described earlier. Predicted VO_2 was calculated using the formula by Krovetz and Goldbloom¹:

$$\text{VO}_2 = 1.39 \times \text{Height} + 0.84 \times \text{Weight} - 35.7,$$

where height is measured in centimeters and weight is measured in kilograms.

Data Analysis

We looked for correlation between measured and predicted VO_2 (indexed and nonindexed). We also looked for correlation between the difference in the predicted and measured VO_2 against the measured VO_2 . Last, we looked for correlations between patient variables such as height, weight, and body surface area (BSA) as well as hemodynamic parameters including cO_2 and mean pressures throughout the circulation against the measured VO_2 . We evaluated whether there was a parameter that could be a surrogate for VO_2 measurement with thermodilution cardiac output.

We used the Pearson 2-tailed test to look for correlation coefficients between variables. Results were considered statistically significant if the P value was $<.05$.

This study was done with the approval of the research ethics board at the IWK Health Centre. Because of the nature of the study, the requirement for informed consent was waived.

RESULTS

Twenty-seven catheterizations were included. Two patients were excluded from the analysis because of competitive pulmonary blood flow via a patent pulmonary valve. This left 25 catheterizations from 21 patients. The age range was 1.3 to 10 years of age at the time of cardiac catheterization, with a median age of 2.9 years.

The systemic ventricle was the morphologically right ventricle in 11 patients (52%) and the morphologically left ventricle in 10 patients (48%). The underlying cardiac malformation was pulmonary atresia with intact ventricular septum in 3 patients (14%), double-inlet left ventricle in 7 patients (33%), atrioventricular septal defect in 2 patients (10%), hypoplastic left heart syndrome in 6 patients (29%), and dextrocardia, atrioventricular septal defect with heterotaxy in 3 patients (14%).

Fifteen of 21 patients (67%) had collateralization identified at the time of cardiac catheterization. Nine patients (43%) had APCs and 10 patients (48%) had venovenous collaterals, with 4 patients having both APCs and venovenous collaterals. The majority of these were hemodynamically insignificant or were venovenous and did not contribute to any unmeasured shunt. Two patients underwent coil occlusion of collateral vessels; one was a small, left-sided superior vena cava (SVC) and the other was a large APC off of an internal mammary artery.

We found there was no correlation between the predicted VO_2 and the measured VO_2 (correlation

FIGURE 1. The relationship between the difference in measured and predicted oxygen consumption (VO_2) against predicted VO_2 . No difference would be represented as a horizontal scattering around 0 (Pearson correlation coefficient = 0.96, $P < .001$).

coefficient = -0.26 , $P = .21$). We did find correlation between the difference in the predicted and the measured VO_2 compared with the measured VO_2 (Figure 1). The Krovetz and Goldbloom¹ equation increasingly overestimated VO_2 as the measured VO_2 diminished. An overestimation of VO_2 results in an underestimation in PVR.

There were no hemodynamic parameters that were a good substitute for measuring VO_2 . We did see a weak, but significantly negative, correlation between the cO_2 in the RA and the SVC against the VO_2 (Table 1). We found that as VO_2 increased, the systemic venous cO_2 decreased.

As expected, there is a high correlation between the Krovetz and Goldbloom¹ predicted VO_2 and BSA (correlation coefficient = 0.96, $P < .001$), because this value is calculated from the same parameters as BSA. However, our measured VO_2 from thermodilution cardiac output

TABLE 1. Correlation between hemodynamic parameters and indexed VO_2

Variable	Pearson correlation coefficient (P value)
Q_v	-0.09 (.65)
Q_v , indexed	0.16 (.42)
TcO_2 RA	-0.54 (.005)
TcO_2 PV	-0.37 (.07)
TcO_2 SVC	-0.39 (.049)
TcO_2 Ao	-0.37 (.07)
RAP	-0.02 (.9)
mPAP	0.04 (.85)
V_{EDP}	0.07 (.72)

Q_v , Thermodilution cardiac output; TcO_2 , total content of oxygen; RA, right atrium; PV, pulmonary vein; SVC, superior vena cava; Ao, aorta; mPAP, mean pulmonary arterial pressure; V_{EDP} , ventricular end diastolic pressure.

FIGURE 2. There was no correlation between body surface area and measured oxygen consumption (Pearson correlation coefficient = -0.02 , $P = .211$).

measurement did not correlate with BSA at all (correlation coefficient = 0.28 , $P < .16$; Figure 2).

DISCUSSION

The Fontan operation is the final stage in a series of operations creating a circuit to route systemic venous return passively to the PAs, so a single ventricle provides systemic output. It is used to palliate a number of complex congenital heart defects in which a biventricular circulation cannot be attained.

The Fontan operation is preceded by a BDCPA in which the SVC is connected to the PAs. Choussat and Fontan outlined 10 criteria, which have become known as the 10 Commandments, to ensure a good outcome for the Fontan procedure.¹² These are essentially a mean pulmonary arterial pressure of <15 to 20 mm Hg and a normal PVRI.^{13,14}

There has been controversy over the necessity of cardiac catheterization for risk assessment prior to the Fontan procedure with the availability of magnetic resonance imaging (MRI) to provide good anatomic assessment of cardiac and pulmonary arterial anatomy.^{15,16} However, catheterization remains the only way to assess PVRI, pulmonary arterial pressure, transpulmonary gradient, and ventricular end diastolic pressure, which are all predictive of outcome.

Mair and colleagues¹⁷ developed an index based on PVR and ventricular end diastolic pressure. They evaluated this index as a predictor of mortality in children with tricuspid atresia undergoing the Fontan procedure. They found an index of <4 was associated with an 8% late mortality whereas an index >4 was associated with a late mortality of 39%.

Pizzaro and associates¹⁸ reported the outcomes of their patient population of 107 children aged 11 to 35 months

undergoing the Fontan procedure with both single right and single left ventricular anatomy. They reported a transpulmonary gradient of 7.2 ± 1.5 mm Hg in those who died compared with 5.3 ± 1.9 ($P = .03$) in survivors. Elevated pulmonary arterial pressures also predicted a higher likelihood of Fontan takedown.

Malhotra and coworkers¹⁹ reviewed the results of 52 Fontan procedures in patients with systemic left or right ventricles. They found that an elevated PVRI was predictive of Fontan failure resulting in death, revision or takedown of the Fontan, or cardiac transplant. The PVRI in the group that failed with the Fontan procedure was 2.43 ± 1.01 Woods units, which is significantly higher than the overall group (1.95 ± 1.42 [$P = .007$]). This study was performed in Denver, Colorado, with patients living at high altitudes. Therefore, although the finding of an increased PVRI in this group is important, the specific PVRI probably cannot be generalized to other populations. Other authors have found increased PVR to correlate with longer duration of pleural effusion.²⁰

Our data confirm that using an estimated VO_2 for calculation of PVR introduces error. The majority of our patients had a measured VO_2 that was lower than their predicted VO_2 . Because all our patients were about the same age at the time of their catheterizations, the predicted VO_2 based on the Krovetz and Goldbloom¹ formula tended to be very similar between patients. This explains why there was a nearly linear relationship between the difference in predicted and measure VO_2 versus the measured VO_2 .

As seen in Figure 1, the predicted VO_2 was almost always greater than the measured VO_2 . Because the calculation of PVR is based on pressure divided by flow, and flow is proportional to VO_2 using the Fick principle, an erroneously high VO_2 results in a systematic underestimation of PVR. This has also been shown to be the case in other studies that have examined the effect of using an estimated VO_2 versus a measured VO_2 .^{6,8}

We also show that there is no hemodynamic parameter that can be substituted for direct measurement of VO_2 . Although there was correlation with cO_2 in the RA and SVC against the indexed-measured VO_2 , this correlation probably tells us more about how the body responds in low cardiac output situations. Again, using the Fick principle ($VO_2 = Qv \times (cO_{2Ao} - cO_{2SV})$) a decrease in cO_{2SV} represents more oxygen extraction. If cardiac output is relatively fixed, the only way to increase VO_2 is to increase oxygen extraction at the tissue level, resulting in a lower venous O_2 .

We did not find correlation between the measured VO_2 and BSA, as was present when we looked at the Krovetz and Goldbloom¹ prediction of VO_2 against BSA. Prediction of VO_2 based on height and weight is clearly oversimplified because it is influenced by other variables. Li and colleagues²¹ demonstrated that increases arterial in arterial partial pressure of carbon dioxide ($Paco_2$) from 35 to 55 mm Hg resulted in

a significant decrease in VO_2 from 146 mL/min/m^2 to 126 mL/min/m^2 in postoperative BDCPA patients.

The formula by Lafarge and Miettinen² attempts to compensate for some of those variables with the incorporation of heart rate into its predictive formula. We did not record heart rate prospectively at the time of our data acquisition, and its retrospective assessment is not possible because heart rate can vary significantly, even under general anesthesia. However, this formula has been shown to underestimate VO_2 when evaluated in this patient population.⁸

The results of our comparison of a measured VO_2 by thermodilution cardiac output to a predicted VO_2 by Krovetz and Goldbloom¹ were similar to the results of a comparison by Li and colleagues⁷ between measured VO_2 by respiratory mass spectrometry with 4 predictive formulas (Lindahl,⁴ Wessel and associates,⁵ Lundell and colleagues,³ and Lafarge and Miettinen²). Their study was performed in ventilated children with congenital heart disease. Both studies demonstrate that the predictive formulas tend to overestimate lower VO_2 and underestimate higher VO_2 (Figure 1). In our study, we excluded patients with large APCs from our assessment. It is well known that APCs are often present, and it is difficult to quantify APC flow angiographically. Grosse-Wortmann and colleagues²² recently demonstrated the quantification of APC flow by MRI. They found that APC flow contributed as much as 46% of Q_P in patients with a BDCPA as measured by MRI. Although this may seem problematic, our formula derives Q_P based on pulmonary venous cO_2 so that APC flow is accounted for. As such, APC flow is not a concern in assessing Q_P . Potential for error remains, however, if the measured pulmonary venous cO_2 has been altered by flow from a systemic vein to a pulmonary venous connection or regional pulmonary disease.

It should be noted that the thermodilution method must be applied with caution in patients with severe atrioventricular or aortic valve regurgitation. Although some studies have failed to find an effect on thermodilution-derived cardiac output compared with the Fick method in patients with severe tricuspid valve regurgitation,²³ other studies have found that the thermodilution method underestimates cardiac output in this situation.²⁴⁻²⁶ None of our patients had more than moderate valvar regurgitation. However, one must keep in mind that if this method is applied in patients with significant valvar regurgitation, a potential source of error is introduced.

One final potential limitation of this technique is that in these circulations, it is not possible to obtain a pure systemic or pulmonary venous oxygen saturation. We attempted to overcome this with careful positioning of the sampling catheter, as described earlier. Specifically, the pulmonary venous sample was taken from a posterior location in the pulmonary venous atrium, close to the orifice of the PVs, to sample only pulmonary venous return. In our series,

the pulmonary venous saturations were all 95% or more, suggesting little systemic venous contamination. However, contamination of systemic or pulmonary venous samples should be regarded as another potential source of error when using this method.

CONCLUSIONS

The reliance on an estimated VO_2 in the assessment of PVR in patients with BDCPA prior to the Fontan operation provides erroneous results. The method presented for calculating VO_2 is simple and can be done in centers where other methods of measuring VO_2 directly are not readily available, by incorporating thermodilution cardiac output as part of the routine pre-Fontan cardiac catheterization. In this era, there are few instances when the Fontan procedure is not offered on the basis of risk. However, it remains useful to assess patients' risk and to evaluate outcomes in relation to their risk. Because assessing PVR remains one of the primary reasons for cardiac catheterization in this group of patients, this method provides a more precise assessment of PVR and can be used with ease.

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