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Original Article

The influence of measured versus assumed uptake of oxygen in assessing pulmonary vascular resistance in patients with a bidirectional Glenn anastomosis

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Abstract *Aims:* To determine the accuracy of data relating to pulmonary vascular resistance data in patients with a bidirectional Glenn anastomosis as calculated using predicted versus measured uptake of oxygen. *Methods:* We studied retrospectively the data from 33 patients with a bidirectional Glenn anastomosis who underwent cardiac catheterisation prior to surgery to complete the Fontan circulation. Their weight ranged from 5.4 to 51.7 kg, and they were aged up to 12 years. Uptake of oxygen was measured using the Deltatrac II metabolic monitor. From the calculated indexed pulmonary vascular resistance, cases were stratified according to the risk of failure of the subsequent Fontan circulation. The six patients with a resistance of greater than 4 Um^2 were deemed at high risk, the six with a resistance from 3 to 4 Um^2 at moderate risk, and the 21 patients with a resistance less than 3 Um^2 at low risk. Uptake of oxygen was also estimated from the predictive formulas of Lindahl, Lundell et al. and LaFarge and Miettinen. The indexed resistance was similarly calculated using these formulas and a comparable stratification of risk made from this data. *Results:* The predicted values for uptake of oxygen were consistently higher than those measured, leading to an underestimation of indexed resistance, with mean difference between −0.62 and −1.57 Um^2. This difference resulted in misclassification of between five and nine of the 12 patients considered at moderate or high risk as being at low-risk. No other haemodynamic data could reliably separate the subjects deemed at low-risk from those considered to be at high-risk. A transpulmonary gradient of greater than 7 mm of mercury was found to be 100 percent specific for elevated indexed resistance, but only 60 percent sensitive. *Conclusions:* In patients with bidirectional Glenn anastomoses, all formulas based on predictive uptake of oxygen lead to underestimation of the true indexed pulmonary vascular resistance, to an extent that could significantly influence clinical decision-making. The transpulmonary gradient is not a reliable surrogate for indexed pulmonary vascular resistance.

Keywords: Cavopulmonary anastomosis; cardiac catheterisation; pulmonary arterial pressure; haemodynamics

Measurement of cardiac output and pulmonary vascular resistance during cardiac catheterisation is an integral part of assessment in patients who have had a bidirectional Glenn anastomosis prior to completion of the Fontan circulation. A normal pulmonary vascular resistance is less than 2 Um^2, and a significantly higher resistance has been shown to be a risk factor for the Fontan procedure.[1–3]

Uptake of oxygen is an essential part of the calculation of pulmonary vascular resistance, which is derived using the Fick principle, relating uptake and delivery of oxygen. The uptake can be measured using a direct calorimetric method, which measures the levels of oxygen and carbon dioxide in the lines from and to the ventilator containing inspired and expired air. It has

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been found in other studies that errors in the determination of pulmonary vascular resistance do occur when using predictive formulas.[4,5] Nevertheless, those working in many centres do not measure the uptake of oxygen, choosing instead to estimate it from predictive formulas based on body surface area or measurements of weight. Since a low resistance is an important prerequisite for a successful Fontan circulation, we sought to assess whether the assumptions made concerning uptake of oxygen led to clinically significant errors in the determination of pulmonary vascular resistance. Our aim, therefore, was to compare pulmonary vascular resistance values calculated from measured and predicted consumption of oxygen in children who had undergone construction of a bidirectional Glenn anastomosis. A secondary aim was to determine if the transpulmonary gradient, or pulmonary arterial pressure, were reliable indicators of pulmonary vascular resistance in this population.

Methods

We studied retrospectively the haemodynamic data obtained during cardiac catheterisation in children with a bidirectional Glenn shunt, in whom the uptake of oxygen had been measured, between 1996 and 2000. We included a total of 33 procedures performed in 30 children, of whom 12 were females and 18 males, with weights ranging from 5.4 to 51.7 kg and a median of 15.4 kg. They were aged from birth to 12 years, with a median of 3.5 years.

Any alternative source of flow of blood to the lungs was assessed using angiography, and 11 patients were found to have no aortopulmonary collateral arteries. Small collateral arteries that required no coiling were seen in 7 patients, while 13 had significant collateral arteries coiled after the haemodynamic calculations had been completed. Three had a remaining band round the pulmonary trunk, two of these also having collateral arteries, and two had a small patent arterial duct, one of these with collateral arteries closed using a coil.

All patients received a general anaesthetic, and were ventilated throughout the procedure with the inspired oxygen fraction maintained between 0.25 and 0.30. The oxygen uptake was measured in each case using the Deltatrac II Metabolic Monitor (Helsinki, Finland), and a stable baseline was achieved prior to collecting data relating to pressures and saturations. A minimum of five minutes of stable readings for uptake of oxygen was averaged for the purposes of the Fick calculations. The maximum variability accepted for stable uptake was 5 ml/min for babies ventilated at less than 3 l/min, and 10 ml/min for children ventilated at between 3 and 12 l/min.

The following haemodynamic data was reviewed and analysed:

- Pulmonary arterial and left atrial pressures. Left atrial pressure was determined either directly in 28 of the 33 of cases, from the pulmonary arterial wedge pressure in three cases, and from pulmonary arterial diastolic pressure in the remaining case. The pulmonary arterial saturations were taken distally, and compared to the saturations in the superior caval vein for evidence of collateral arterial

Table 1. Details of the population used in the derivation of the predicted formulas for Lundell et al., Lindahl, and LaFarge and Miettinen in part A, and the derived formulas in part B.

A. Details of populations

Formulae	Sedation	Patients in study	Age range (years)	Weight (kg)	Factors included in formula
Lundell et al.	Sedated	504	0–36		Weight, height, heart rate, body surface area
Lindahl	Anaesthetised	38	0–7	3.6–25	Weight
LaFarge and Miettinen	Sedated	879	3–40		Age, heart rate

B. Derived formulas

Formulae	Groups	Criteria	Formulae
Lundell et al.	Children	<3 years	$VO_2 = 0.40 \times \text{weight} + 1.91 \times \text{height} + 0.17 \times \text{heart rate}$
	Males	>3 years	$VO_2 = 157.9 \times \text{body surface area} + 0.79 \times \text{heart rate} - 61.8$
	Females	>3 years	$VO_2 = 159.0 \times \text{body surface area} + 0.77 \times \text{heart rate} - 61.6$
Lindahl	Children	<10 kg	$VO_2 = 6.8 \times \text{weight} + 8.0$
	Children	>10 kg	$VO_2 = 4.0 \times \text{weight} + 35.8$
LaFarge and Miettinen	Male		$VO_2 = 138.1 - 11.49 \log_e(\text{age}) + 0.378 (\text{heart rate})$
	Female		$VO_2 = 138.1 - 17.04 \log_e(\text{age}) + 0.378 (\text{heart rate})$

Units of measurement: oxygen uptake (VO_2 ml/min), weight (kg), height (cm), heart rate (bpm), body surface area (m^2), age (years)

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supply. The saturations were averaged for completion of the calculations.
- Pulmonary venous or left atrial saturations.
- Systemic arterial blood gases.
- Pulmonary venous saturation was measured directly in 28 of the 33 cases, and assumed to be 100 percent in the remaining five cases.

Values for haemoglobin, height, weight, sex, and heart rate were all recorded. Cardiac output and pulmonary vascular resistance were calculated using standard formula.

- Cardiac output was calculated by dividing the value for uptake of oxygen by the arteriovenous difference in content of oxygen.
- Pulmonary vascular resistance was obtained by dividing the transpulmonary pressure gradient by the calculated cardiac output.

We used the three predictive formulas derived by Lundell et al.[6] Lindahl[7] and LaFarge and Miettinen,[8] respectively, to estimate the uptake of oxygen for comparison with the uptake measured using the Deltatrac monitor.

Details of the predictive formulas are given in Table 1.

The pulmonary vascular resistance was calculated using the predicted and measured uptakes of oxygen, respectively, indexed against body surface area calculated in units per metre squared. The two results were compared with each other. Patients were further classified into groups at low, moderate and high risk for failure of the Fontan circulation on the basis of the indexed resistance. Those with a resistance of less than 3 Um^2 were considered at low risk, those between 3 and 4 Um^2 at moderate risk, and those with values greater than 4 Um^2 at high risk.

The relationship of indexed pulmonary vascular resistance to mean pulmonary arterial pressure and the transpulmonary gradient was also studied.

Statistical analysis

Measured and predicted uptake of oxygen, and indexed values of pulmonary vascular resistance, were compared using the Bland Altman technique.[9]

Results

Mean differences

Uptake of oxygen: The differences between measured and predicted values are shown in Figure 1.

The formulas used for calculations consistently overestimated uptake. The formula of Lundell et al. showed the greater difference from the measured uptake, ranging from 9.2 to 109.3 ml with a mean of 59.2 ml. The margin of error was shown to increase at higher levels of uptake.

The Lindahl formula showed less scatter, with a range from −19.6 to 57.4 ml, and a mean of 18.9 ml. Using the formula of LaFarge and Miettinen, the discrepancy ranged from −33 to 49.8 ml, with a mean of 23.3 ml.

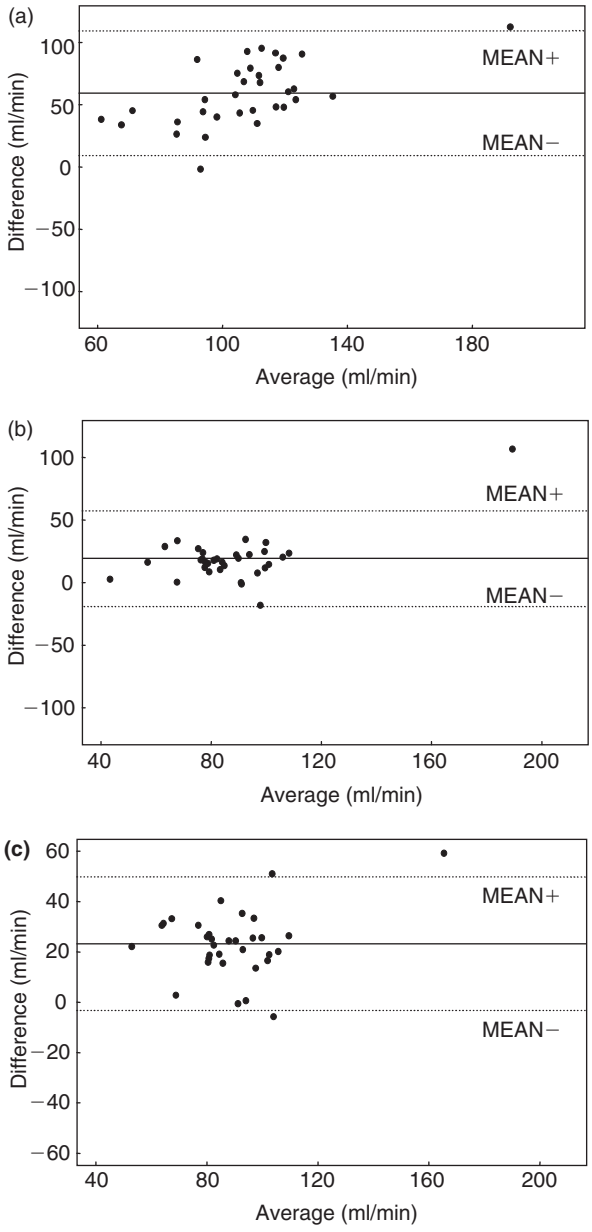

Figure 1.
Bland and Altman plot showing the difference between predicted oxygen uptake using the formulae of Lundell et al. (a), Lindahl (b), and LaFarge and Miettinen (c) minus measured oxygen uptake from 30 patients (33 procedures) with a bidirectional Glenn anastomosis.

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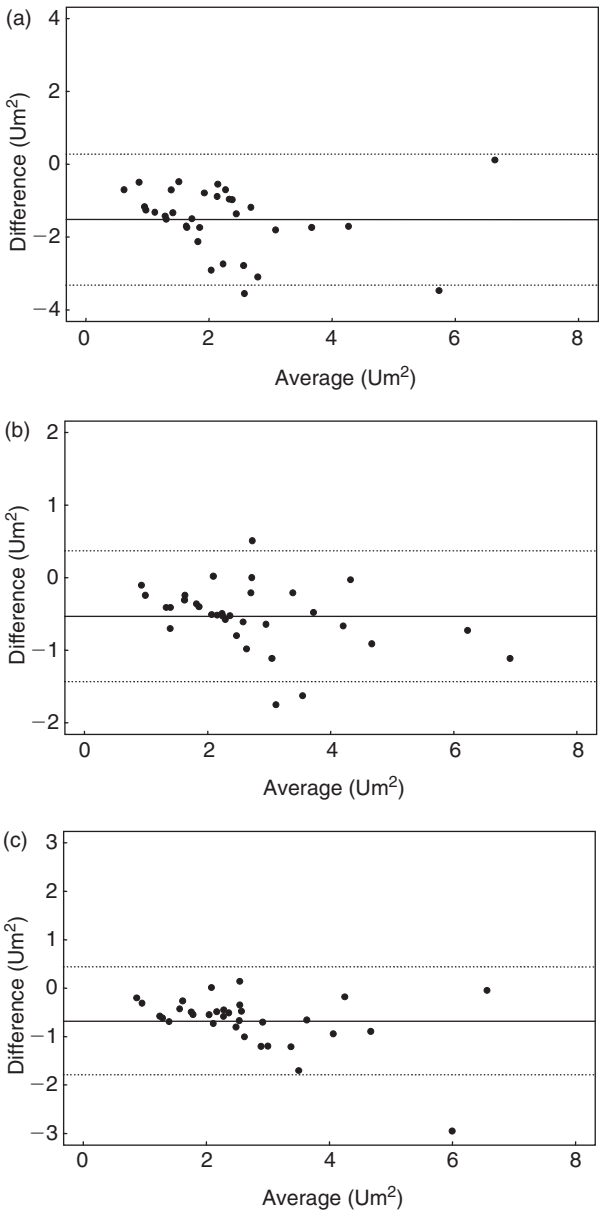

Figure 2.
Bland and Altman plots showing the difference between indexed pulmonary vascular resistance using the predictive formula of Lundell et al. (a), Lindahl (b), and LaFarge and Miettinen (c) minus the indexed pulmonary resistance calculated using measured oxygen uptake in 30 patients (33 procedures) with a bidirectional Glenn shunt. (Units metre squared: Um^2.)

Indexed pulmonary vascular resistance: When the results using predicted values for uptake of oxygen were used to calculate indexed pulmonary vascular resistance (Fig. 2), Bland and Altman plots demonstrated that the predictive formulas lead to significant underestimations compared to those obtained when uptake was measured. The formula of Lundell et al. underestimated the indexed pulmonary vascular resistance by a mean of 1.52 Um^2. The error ranged from +0.28 to −3.32 Um^2 . The Lindahl formula led to an underestimation by a mean of 0.53 Um^2. The error ranged from +0.37 to −1.43. The formula of LaFarge and Miettinen showed a mean underestimation of 0.68 Um^2, with the error ranging from +0.44 to −1.79 Um^2.

Risk stratification based on indexed pulmonary vascular resistance: Patients were then stratified for risk of failure of the Fontan circulation based on their measured indexed pulmonary vascular resistance. Using these values, 21 patients were classified as being at low risk, with an indexed pulmonary vascular resistance less than 3 Um^2, six as being at moderate risk with an indexed pulmonary vascular resistance between 3 and 4 Um^2, and another six as being at high risk, with the indexed pulmonary vascular resistance greater than 4 Um^2.

Comparison was then made to see if any patients would have been misclassified if the indexed pulmonary vascular resistance had been calculated using the formulas to predict uptake of oxygen (Table 2). The formula of Lundell et al. produced the largest change in the classification, with an additional six patients initially considered at moderate risk, and three initially categorised as being at high risk, joining the original 21 patients graded as being at low risk when using measured uptake of oxygen. With this formula, only two patients would now have been graded at high risk for subsequent failure of the Fontan circulation based on the estimated indexed pulmonary vascular resistance.

Taken together, underestimation of the indexed pulmonary vascular resistance using values for uptake of oxygen predicted using the three formulas resulted in the misclassification of between five and nine of the 12 patients considered as being at high or moderate risk when the measured values for uptake of oxygen were used in the calculations.

Relationship of pulmonary arterial pressure and transpulmonary gradient to indexed pulmonary vascular resistance: There was a clear correlation between the transpulmonary gradient, taken as the mean pulmonary arterial pressure minus the mean left atrial pressure, and indexed pulmonary vascular resistance, but with a wide scatter of values (Fig. 3). In the two patients with a transpulmonary gradient of greater than 7 mm of mercury, the indexed pulmonary vascular resistance was elevated, at greater than 6 Um^2. A transpulmonary gradient of greater than, or equal to, 7 mm of mercury was 100 percent specific for an elevation in indexed pulmonary vascular resistance greater than four, but only 60 percent sensitive, being predictive in three of the five patients. The mean pulmonary arterial pressure showed a poor correlation with indexed pulmonary vascular resistance, with a wide scatter seen on the graph.

Table 2. Classification of number of subjects into the level of risk for failure of the Fontan circulation based on indexed pulmonary vascular resistance (PVRI) calculated using measured and predicted uptake of oxygen.

	Risk level		
	Low PVRI < 3 Um^2	Moderate PVRI 3–4 Um^2	High PVRI > 4 Um^2
PVRI using measured oxygen uptake	21	6	6
PVRI using Lindahl	26 (1 high, 4 mod, 21 low)	3 (1 high, 2 mod)	4 (4 high)
PVRI using Lundell et al.	30 (3 high, 6 mod, 21 low)	1 (1 high)	2 (2 high)
PVRI using LaFarge and Miettinen	27 (6 mod, 21 low)	2 (2 high)	4 (4 high)

Units = units metre squared (Um^2)

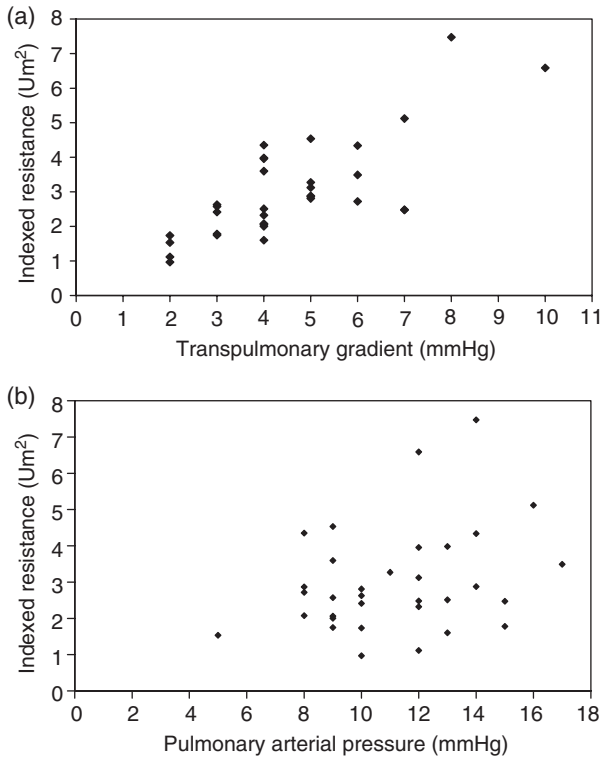

Figure 3.
Scatter plot of the transpulmonary gradient versus the indexed pulmonary vascular resistance (a), and mean pulmonary arterial pressure versus indexed pulmonary resistance (b) for 30 patients with a bidirectional Glenn anastomosis.

Discussion

The haemodynamic boundaries between success and failure of the Fontan circulation are increasingly being tested. Even with perfect bypass and surgical techniques, some patients will experience physiological failure of the Fontan circulation, resulting in emergency take-down or even death. For the majority of cases, the suitability for completion of the circulation after the bidirectional Glenn anastomosis is fairly obvious. It is, however, the borderline cases where the decision whether or not to proceed to complete the Fontan circulation is difficult. In this setting, accurate, reliable haemodynamic data, particularly pulmonary vascular resistance data, are critical.

Our study has now demonstrated that assuming values for the uptake of oxygen will frequently result in underestimation of the pulmonary vascular resistance in patients with a bidirectional Glenn anastomosis. The decision to proceed to complete the Fontan circulation, or to fenestrate a Fontan anastomosis, are influenced by the calculated pulmonary vascular resistance. The study has also shown that pulmonary arterial pressure and the transpulmonary gradient, alone or in combination, do not reliably reflect pulmonary vascular resistance, and vice versa. Pulmonary arterial pressure is also influenced by left atrial pressure, which in turn is influenced by end-diastolic ventricular pressure and atrioventricular valvar regurgitation. Both of these factors may lead to failure of the Fontan circulation, as well as a high pulmonary vascular resistance. This may be why, in some studies, a high pulmonary arterial pressure has been found to be a fairly consistent risk factor for failure of the Fontan circulation.[1] Meaningful haemodynamic assessment depends on accurate measurements of both pulmonary arterial pressure and pulmonary vascular resistance. Aortopulmonary collateral supply is a common occurrence with a bidirectional Glenn anastomosis. The pulmonary arterial saturations were always taken well out into the branch pulmonary arteries, and an average taken for the value of the saturation in the pulmonary arterial bed. The presence of these collateral vessels will inevitably produce some inaccuracy in the estimation of the flow of blood within the lungs, and hence pulmonary vascular resistance. This is difficult to quantify, and is a separate source of error from assumption of uptake of oxygen.

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The study was not designed to relate the haemodynamic data and results to the clinical outcome of our patients, some of whom have subsequently undergone a Fontan repair. The small number of patients with high pulmonary vascular resistance, and other confounding factors for perioperative outcome, made such an analysis inappropriate until a larger cohort is available. The largest series to date, from Boston[1] did show that high preoperative pulmonary vascular resistance was a risk factor for failure of the Fontan circulation, but the majority of their patients had not undergone construction of a bidirectional Glenn anastomosis prior to completion of the Fontan circulation. A separate question, therefore, but of equal importance, is whether high pulmonary vascular resistance in a patient who has survived a bidirectional Glenn anastomosis is indeed a significant risk factor for subsequent failure of the Fontan circulation. The answer is not yet known. Other factors may prove to be of more importance, such as end-diastolic ventricular pressure, the presence of atrioventricular valvar regurgitation, or pulmonary arterial pressure itself. The data from our study does not show which haemodynamic parameter is the best to identify patients at risk of failure. This can only be identified when patients have been followed up subsequent to completion of the Fontan procedure.

If the uptake of oxygen has to be estimated, and not measured, we found that the best agreement was with the Lindahl formula, which was also derived from patients under general anaesthesia. Nevertheless, this still resulted in the significant misclassification of patients in our series from high or moderate to low risk, and we cannot recommend its use.

In summary, failure to measure the uptake of oxygen during cardiac catheterisation of patients with a bidirectional Glenn anastomosis leads to a significant error in the measurement of pulmonary vascular resistance, usually, but not invariably, an underestimation. The error is of a magnitude that could lead to significant errors in clinical decision-making.

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