Validity of the LaFarge equation for estimation of oxygen consumption in ventilated children with congenital heart disease younger than 3 years—A revisit

Jennifer Rutledge, MD,[a] Andrew Bush, MD,[b] Lara Shekerdemian, MD,[c] Ingram Schulze-Neick, MD, PhD,[d] Daniel Penny, MD, PhD,[c] Sally Cai, MS,[e] and Jia Li, MD, PhD[a] ***Alberta and Ontario, Canada; London, United Kingdom; and Melbourne, Australia***

Background The LaFarge equation is the most commonly used equation to estimate oxygen consumption (Vo_2) in patients of all ages with congenital heart disease, although it was generated in patients older than 3 years. We sought to determine the validity of the LaFarge equation in estimating Vo_2 in children younger than 3 years undergoing cardiac catheterization with general anesthesia.

Methods Vo_2 was measured directly using respiratory mass spectrometry in 75 sedated, paralyzed, and mechanically ventilated children in the pediatric cardiac catheterization laboratory. Age ranged from 0.13 to 24 years; 40 children being younger than 3 years. Estimated values for Vo_2 were calculated using the LaFarge equation for all patients. The agreement between measured and estimated Vo_2 was evaluated by the bias and limits of agreement in the 2 age groups. Regression analysis was used to analyze the influence of age on the agreement.

Results A failure of agreement between measured and estimated Vo_2 was noted in both groups of children. As compared to the older group of patients, the agreement was significantly poorer in children younger than 3 years, with a significantly greater overestimation introduced by the LaFarge equation (11% ± 21% vs 53% ± 52%, $P < .0001$).

Conclusion The LaFarge equation introduces significant error in the estimation of Vo_2 in ventilated patients with congenital heart disease of all ages, particularly in children younger than 3 years. (Am Heart J 2010;160:109-14.)

The accurate hemodynamic assessment of patients with congenital heart disease is a fundamental part of the work of the cardiac catheterization laboratory. The direct Fick principle remains the gold standard for calculation of hemodynamic indices in which oxygen consumption (Vo_2) must be known.[1] Although techniques for metabolic monitoring using indirect calorimetry or respiratory mass spectrometry are available for the measurement of Vo_2,[2-4] it is still common practice to estimate Vo_2 values from tables or published predictive equations. Considerable errors introduced by using assumed Vo_2 have been reported.[5-8] We have previously examined the validity of 4 equations in estimating Vo_2 by comparison with directly measured Vo_2 by respiratory mass spectrometry and found poor agreement in all.[8] Among these, the LaFarge equation,[9] the most commonly used equation, gave the closest estimation with the least bias and limits of agreement. However, our previous study excluded patients whose ages fell outside the range originally used to generate the LaFarge equation, that is, younger than 3 years. Despite the LaFarge equation was restricted to patients between 3 and 40 years of age, it is applied in patients of all ages undergoing cardiac catheterization. With advances in surgical techniques and perioperative management, increasing numbers of patients with complex congenital heart defects undergo cardiac surgery at a younger age. This has resulted in an increasing need for diagnostic cardiac catheterization in children younger than 3 years, often with the single goal of accurate evaluation of systemic and pulmonary blood flows and vascular resistances, particularly pulmonary vascular resistance.

From the [a]Division of Pediatric Cardiology, Stollery Children's Hospital, Edmonton, Alberta, Canada, [b]Department of Pediatric Respiratory Medicine, Imperial School of Medicine at National Heart and Lung Institute, Royal Brompton Hospital, Sydney Street, London, United Kingdom, [c]Departments of Cardiology and Intensive Care, The Royal Children's Hospital, Melbourne, Australia, [d]Pulmonary Hypertension in Children, Cardiac Unit, Great Ormond Street Hospital, London, United Kingdom, and [e]Data Center, Congenital Heart Surgeons' Society, Toronto, Ontario, Canada.

Submitted February 12, 2010; accepted April 5, 2010.

Reprint requests: Jia Li, MD, PhD, Division of Pediatric Cardiology, Stollery Children's Hospital Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada T6G 2B7.

E-mail: jia.li@albertahealthservices.ca

doi:10.1016/j.ahj.2010.04.003

If Vo_2 needs to be measured at all, then accuracy is vital.[10,11] A discrepancy between estimated and measured Vo_2 will translate directly into an equivalent percentage underestimation or overestimation of blood flow and vascular resistance. Any error in hemodynamic assessment may significantly mislead surgical and other clinical treatment strategies. Therefore, we revisited our previous data to examine the validity of the LaFarge equation with emphasis on children less than 3 years of age with congenital heart disease undergoing cardiac catheterization.

Methods

A total of 75 patients with congenital heart disease (age range 0.13-24 years) were studied under general anesthesia during cardiac catheterization in the period between 1996 and 2001. These patients all underwent hemodynamic monitoring with Vo_2 measurement for other clinical studies approved by the ethics committee of the Royal Brompton Hospital or Great Ormond Street Hospital, London, United Kingdom,[12-15] and conform to the Declaration of Helsinki. The original clinical studies investigated pharmacologic and ventilatory interventions on cardiac output and pulmonary vascular resistance in children with various congenital heart defects before and after surgical repair.[12-15] The Vo_2 measurements were performed at baseline, before any intervention and are used in the present study. Patients were divided into 2 groups according to age <3 years (n = 40) or ≥3 years (n = 35). Patient diagnoses and demographics in the 2 groups are shown in Table I.

The technique to measure Vo_2 was described in our previous report.[16] Briefly, all patients were sedated and paralyzed with continuous intravenous infusions of propofol and vecuronium. Patients were intubated with a cuffed endotracheal tube (Mallinckrodt Medical, Northampton, United Kingdom) to rule out any respiratory gas leaks. An Amis 2000 quadrupole respiratory mass spectrometer (Innovision A/S, Odense, Denmark) was adapted for use in ventilated patients as described elsewhere.[16,17] Vo_2 was measured continuously using the mixed expirate argon dilution method that allows the mass spectrometer alone to measure metabolic gas exchange and ventilation volume.[1] This requires analysis of inspired and expired gases, together with the collection of all expired gas. This is a sensitive and accurate method for continuous gas analysis that allows simultaneous measurements of multiple gas fractions within a mixture.[2,18-20]

The estimated Vo_2 values were calculated from the equation published by LaFarge[2] for the entire group of patients of all ages as follows:

$$\text{males}: VO_2\ (\text{mL/min/m}^2) = 138.1 - (11.49\ \log_e \text{age}) + (0.378\ \text{HR}) \text{ and}$$

$$\text{females}: VO_2\ (\text{mL/min/m}^2) = 138.1 - (17.04\ \log_e \text{age}) + (0.378\ \text{HR}),$$

where age is in years and HR indicates heart rate in beats/min.

Statistical analysis

The agreement between estimated and measured Vo_2 was analyzed using the method of Bland and Altman[21] for comparison of 2 methods estimating the same quantity. The bias is the mean of the difference of measured minus estimated Vo_2 values; this represents the systematic error. Limits of agreement are the bias ± 2 SD; this represents the random error. The method was applied to the group as a whole and then separately to the group of <3 years and the group ≥3 years. A bias of near zero indicates close agreement, as would narrow limits of agreement. The difference between estimated and measured Vo_2 was also expressed as percentage of the measured Vo_2. Unpaired *t* test was used to compare the absolute and percentage differences between the 2 groups. Regression analysis was used to evaluate the influence of age on the values of estimated Vo_2, measured Vo_2, and the differences between estimated and measured Vo_2. Parameter estimate indicates the slope of change of Vo_2 values per year of age. A P value < .05 was considered significant.

The original clinical study was supported by the British Heart Foundation, and the creation of the article was supported by the principle investigator's (J.L.) start-up award.

Table I. Diagnoses in 2 groups of patients of <3 and ≥3 years old

	No. of patients	
Diagnosis	**Patients 3 y old**	**Patients 3 y old**
AP window	0	1
ASD	5	5
ASD VSD	1	0
AVSD	12	2
Cardiomyopathy	0	1
DORV, PAPVD	0	1
Fontan	1	7
MV disease	2	2
Mustard/senning	1	2
PDA	5	5
Pulmonary HT	0	2
ToF	2	3
VSD	12	4
Total	40	35

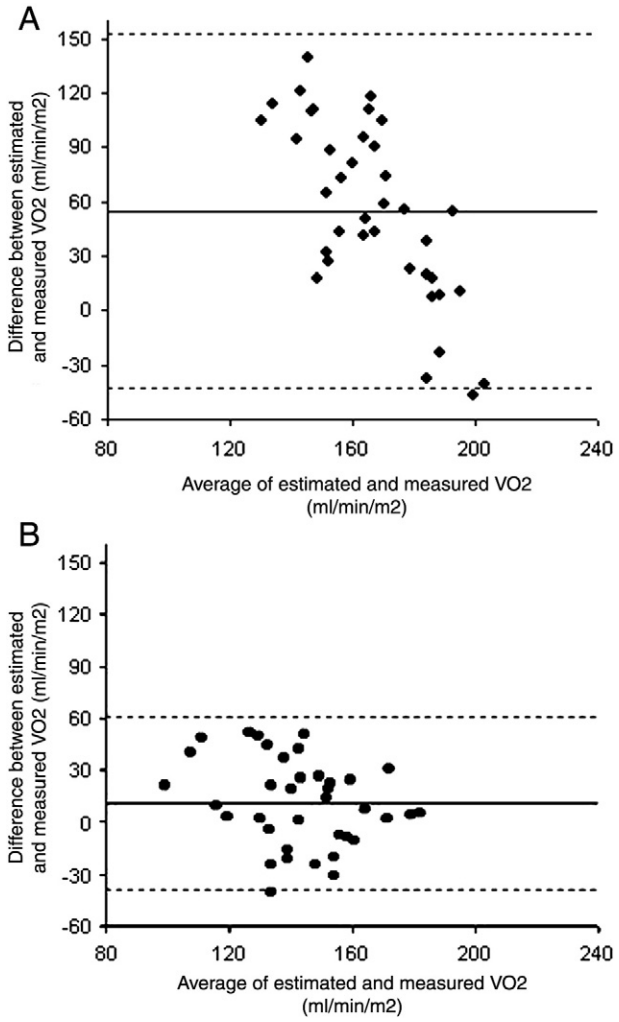
AP, Aortopulmonary; *ASD*, atrial septal defect; *VSD*, ventricular septal defect; *AVSD*, atrioventricular septal defect; *DORV*, double outlet right ventricle; *PAPVD*, partial anomalous pulmonary venous drainage; *MV*, mitral valve; *PDA*, patent ductus arteriosus; *HT*, hypertension; *ToF*, tetralogy of Fallot.

Results

For the entire group, Vo_2 was overestimated by the LaFarge equation, with a bias of 33 mL/kg/m^2, that is, by 33%. The limits of agreement were widely spread from −56 to +123 mL/kg per square meter. Further analysis was performed in the 2 groups of patients of <3 and ≥3 years. Estimation was significantly poorer in the group <3 years with a bias of 55 mL/kg per square meter, as compared to the older group with a bias of 11 mL/kg per square meter. The limits of agreements were −42 to +153 mL/kg/m^2 for children <3 years versus −39 to +61 mL/kg/m^2 for those 3 years (Figure 1, *A* and *B*).

Further analyses were performed to examine the trends of estimated and measured Vo_2 in relation to age.

Figure 1



Agreement of measured and estimated Vo_2 (mL/min) and indexed Vo_2 (mL/min per square meter) in patients <3 years old (**A**, n = 40) and ≥3 years old (**B**, n = 35) undergoing cardiac catheterization.

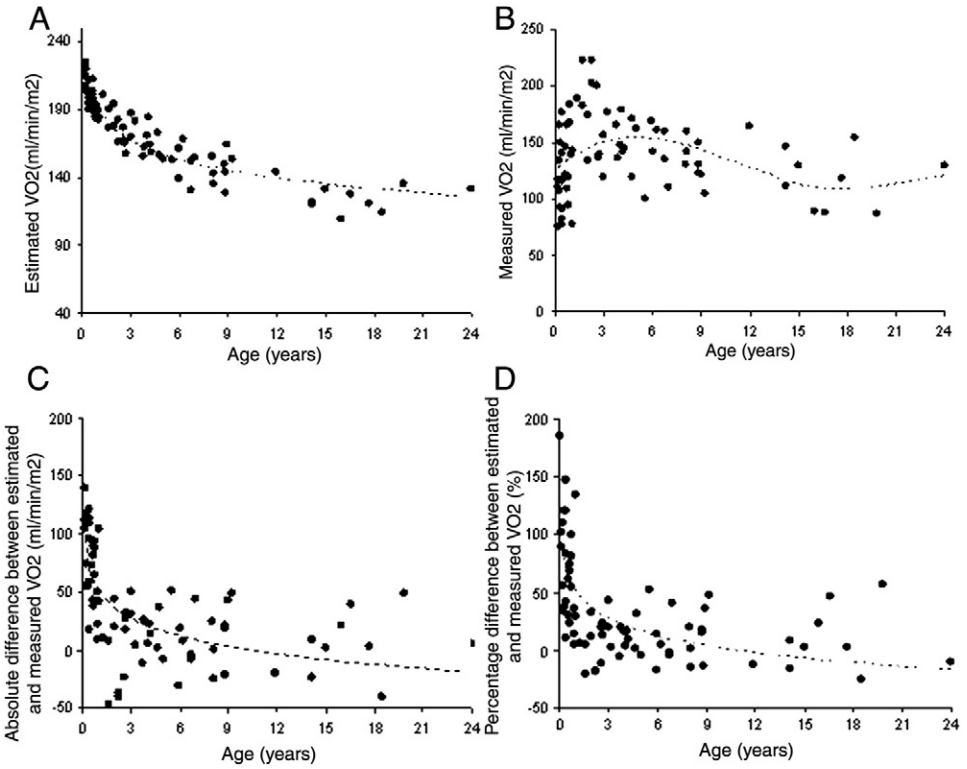
Estimated Vo_2, as presented in the LaFarge equation itself, used a logarithmic transformation of age (parameter estimate = −20, $P < .0001$), whereby there was a rapid decrease from age 0 to 3 years, followed by a slower decrease thereafter (Figure 2A). Measured Vo_2, on the other hand, followed a polynomial trend in relation to age; there was a rapid increase in about the first 3 to 4 years (parameter estimate = 12.7, $P = .002$) followed by a small decrease until approximately age 16 (parameter estimate = −1.63, $P = .001$) and a smaller increase thereafter (parameter estimate = .044, $P = .002$) (Figure 2, *B*). As a result, the difference between estimated and measured Vo_2, as expressed by both the absolute value and percentage of measured Vo_2, showed a logarithmic trend with a rapid decrease from age 0 to 3 years, followed by a small decrease thereafter (parameter estimate = −22, $P < .0001$ for the absolute difference; parameter estimate = −21, $P < .0001$ for the percentage difference) (Figure 2, *C* and *D*). The mean absolute and percentage difference was 55 ± 48 mL/min/m^2 and 53% ± 52%, respectively, in children <3 years old; they were 11 ± 25 mL/min/m^2 and 11% ± 21%, respectively, in children 3 years ($P < .0001$ for both).

Discussion

We report that the LaFarge equation led to significantly poorer estimation of Vo_2 when applied to children younger than to 3 years with congenital heart defects undergoing cardiac catheterization, as compared to those older than 3 years, with a significantly wider range of limits of agreement and greater overestimation. We have shown that the LaFarge equation introduced an overestimation of Vo_2 in children younger than 3 years of 53%, as compared to 11% in the older group, as well as a greater random error in individual patients as indicated by the much poorer agreement in the younger group of children. The age effect is attributed by 2 factors; firstly, the logarithmic nature in the LaFarge equation, and secondly, by a markedly lower directly measured Vo_2 in the younger group.

The LaFarge equation was originally generated from a cohort of 879 patients who were mostly children, studied between 1961 and 1966.[9] It was validated by the traditional Douglas Bag method to measure Vo_2. The past half century has seen significant progress in pediatric cardiology and cardiovascular surgery as well as technology to measure Vo_2. Although the LaFarge equation provides the closest estimation of Vo_2 among all the predictive equations[8] and remains the most commonly used in cardiac laboratories, it has a number of limitations in clinical practice. One of the main factors contributing to the poor agreement between LaFarge's estimated Vo_2 and our directly measured Vo_2 is in the use of conscious sedation with spontaneous ventilation in LaFarge's study population, whereas we (and many others) use general anesthesia and mechanical ventilation during cardiac catheterization. The latter approach alone can reduce Vo_2 by up to 20% to 30%.[22-24] In addition, the Douglas Bag method, used to generate the LaFarge equation, brings with it limitations including the lack of measurement of carbon dioxide concentrations in respiratory gases and an assumed respiratory quotient.[9] A fixed respiratory quotient is not valid in cardiac patients with varied hemodynamics and unpredictable nutritional status.[25] In our patients, Vo_2 was measured with consideration of carbon dioxide concentrations in the respiratory gases by respiratory mass spectrometry.

Figure 2



The trends of estimated V_{O_2} (**A**) and measured (**B**) and their difference in absolute values (**C**) and percentage of measured V_{O_2} (**D**) in relation to age in 75 patients undergoing cardiac catheterization.

Most importantly, the derivation of the LaFarge equation was from patients aged between 3 and 40 years. Despite this fact, the equation is commonly applied to patients of all ages. Some studies have examined the impact of age on estimated V_{O_2} by the LaFarge equation by excluding patients younger than 3 years[7] or by comparing age groups of younger or older than 60 years.[5] However, its validity has not been previously explored in children younger than 3 years. Looking closely into the LaFarge equation, the logarithmic transformation of age intrinsically results in a faster increase in V_{O_2} as age decreases, particularly within the first 3 years of life, as shown clearly in our data (Figure 2, *A*). In our patients, the estimated V_{O_2} was the highest in the youngest patient (0.13 years). Estimated V_{O_2} then decreased in the first 3 years, followed by a small decrease at older ages. Interestingly, in our study, measured V_{O_2} showed almost exactly the opposite trend and was the lowest in the youngest patients and then quickly increased in the first 3 or 4 years. A lower measured V_{O_2} in children younger than 3 years has also been reported by others.[26] The mechanism remains unclear but may be related to body composition—in particular "fat mass" that is higher in younger children[27,28] and V_{O_2} in fat mass is about 20 times less than that in fat-free mass.[28]

Errors in V_{O_2} will result in errors of the same magnitude in the calculation of systemic and pulmonary blood flow and ultimately errors in calculations of systemic and pulmonary vascular resistances. The most consistent patient population undergoing diagnostic catheterization continues to be the single-ventricle patient where catheterization is performed to specifically evaluate the pulmonary artery architecture, pressure, and vascular resistance. Numerous investigators have shown that elevated pulmonary vascular resistance is a risk factor for poor outcome,[29-31] emphasizing the need for accurate hemodynamic assessment. Although most patients can be risk stratified for Fontan completion fairly easily based on clinical, echocardiographic, magnetic resonance imaging, or catheterization criteria, it is the borderline patient in which accurate hemodynamic assessment is critical. Shanahan et al[32] reported that all formulas used to estimate V_{O_2} lead to underestimation of the true indexed pulmonary vascular resistance, to an extent that could significantly influence clinical decision making. This is supported by our data. A mean of 50% underestimation of

pulmonary vascular resistance can be introduced when using LaFarge equation in children younger than 3 years old.

Limitations

Because of the designs of the original research projects, only one patient in the group of children younger than 3 years had a functional single ventricle undergoing the Fontan procedure. There may be some degree of difference in Vo_2 in patients with functional single-ventricle physiology as compared to those with a biventricular circulation due to differences in cardiovascular work and hemodynamic and metabolic status.[33-35] Our data cannot therefore directly address this relationship, although any differences are unlikely to be significant enough to affect the information obtained from the current study.

Conclusion

The LaFarge equation induces a significantly poorer estimation of Vo_2 when used in children younger than 3 years as compared to older patients, with greater overestimation and random errors in individual errors. Direct measurement of Vo_2 rather than its estimation is necessary in children with congenital heart disease undergoing cardiac catheterization, particularly in those younger than 3 years.

Acknowledgements

We thank Dr Andrew Redington for his support over the course of these studies of Vo_2 measurement.

Disclosures

Conflict of interest: none declared.

References

1. Fick A. Über die Messung des Blutquantums in der Herzventrikeln. Sitzungsberichte der physikalisch-medicinischen Gesellschaftzu Würzburg: Stahelschen Universitats-Buch Kunsthandlung; 1870. p. XVI-XVII.
2. Davies NJ, Denison DM. The measurement of metabolic gas exchange and minute volume by mass spectrometry alone. Respir Physiol 1979;36:261-7.
3. Takala J, Keinanen O, Vaisanen P, et al. Measurement of gas exchange in intensive care: laboratory and clinical validation of a new device. Crit Care Med 1989;17:1041-7.
4. Weyland W, Weyland A, Fritz U, et al. A new paediatric metabolic monitor. Intensive Care Med 1994;20:51-7.
5. Wolf A, Pollman MJ, Trindade PT, et al. Use of assumed versus measured oxygen consumption for the determination of cardiac output using the Fick principle. Catheter Cardiovasc Diagn 1998;43:372-80.
6. Fakler U, Pauli C, Hennig M, et al. Assumed oxygen consumption frequently results in large errors in determination of cardiac output. J Thorac Cardiovasc Surg 2005;130:272-6.
7. Schmitz A, Kretschmar O, Knirsch W, et al. Comparison of calculated with measured oxygen consumption in children undergoing cardiac catheterization. Pediatr Cardiol 2008;29:1054-8.
8. Li J, Bush A, Schulze-Neick I, et al. Measured versus estimated consumption in ventilated patients with congenital heart disease: the validity of four equations. Crit Care Med 2003;31:1235-40.
9. LaFarge CG, Miettinen OS. The estimation of oxygen consumption. Cardiovasc Res 1970;4:23-30.
10. Laitinen PO, Rasanen J. Measured versus predicted oxygen consumption in children with congenital heart disease. Heart 1998; 80:601-5.
11. Kendrick AH, West J, Papouchado M, et al. Direct Fick cardiac output: are assumed values of oxygen consumption acceptable? Eur Heart J 1988;9:337-42.
12. Shekerdemian LS, Bush A, Shore DF, et al. Cardiopulmonary interactions after Fontan operations: augmentation of cardiac output using negative pressure ventilation. Circulation 1997;96:3934-42.
13. Shekerdemian LS, Bush A, Lincoln C, et al. Cardiopulmonary interactions in healthy children and children after simple cardiac surgery: the effects of positive and negative pressure ventilation. Heart 1997;78:587-93.
14. Schulze-Neick I, Hartenstein P, Li J, et al. Intravenous sildenafil is a potent pulmonary vasodilator in children with congenital heart disease. Circulation 2003;108(Suppl 1):II167-73.
15. Schulze-Neick I, Penny DJ, Rigby ML, et al. L-arginine and substance P reverse the pulmonary endothelial dysfunction caused by congenital heart surgery. Circulation 1999;100:749-55.
16. Li J, Bush A, Schulze-Neick I, et al. Measured versus estimated oxygen consumption in ventilated patients with congenital heart disease: the validity of predictive equations. Crit Care Med 2003;31:1235-40.
17. Li J, Zhang G, McCrindle BW, et al. Profiles of hemodynamics and oxygen transport derived by using continuous measured oxygen consumption after the Norwood procedure. J Thorac Cardiovasc Surg 2007;133:441-8.
18. Heneghan CP, Gillbe CE, Branthwaite MA. Measurement of metabolic gas exchange during anaesthesia. A method using mass spectrometry. Br J Anaesth 1981;53:73-6.
19. Gillbe CE, Heneghan CP, Branthwaite MA. Respiratory mass spectrometry during general anaesthesia. Br J Anaesth 1981;53:103-9.
20. Roberta MJ, Boustred ML, Hinds CJ. A multipatient mass spectrometer based system for the measurement of metabolic gas exchange in artificially ventilated intensive care patients. Intensive Care Med 1983;9:339-43.
21. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurements. Lancet 1986;1:307-10.
22. Nisbet HI, Dobbinson TL, Thomas TA, et al. Oxygen uptake in ventilated children during methoxyflurane anesthesia. Can Anaesth Soc J 1973;20:334-46.
23. Westenskow DR, Jordan WS. Changes in oxygen consumption induced by fentanyl and thiopentone during balanced anesthesia. Can Anaesth Soc J 1978;25:18-21.
24. Shibutani K, Komatsu T, Kubal K, et al. Critical levels of oxygen delivery in anesthetized man. Crit Care Med 1983;11:640-3.
25. Lindahl SG. Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery. Br J Anaesth 1989;62:70-6.
26. Lundell BP, Casas ML, Wallgren CG. Oxygen consumption in infants and children during heart catheterization. Pediatr Cardiol 1996;17: 207-13.
27. Fomon SJ, Haschke F, Ziegler EE, et al. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 1982;35 (Suppl 5):1169-75.

28. Moukarzel AA, Salas JS, Goulet OJ, et al. Estimate of specific energy expenditure of fat-free mass and fat mass in children receiving total parenteral nutrition. J Med Liban 2003;51:206-10.
29. Gentles TL, Mayer Jr JE, Gauvreau K, et al. Fontan operation in five hundred consecutive patients: factors influencing early and late outcome. J Thorac Cardiovasc Surg 1997;114:376-91.
30. Gentles TL, Gauvreau K, Mayer Jr JE, et al. Functional outcome after the Fontan operation: factors influencing late morbidity. J Thorac Cardiovasc Surg 1997;114:392-403.
31. Mair DD, Hagler DJ, Puga FJ, et al. Fontan operation in 176 patients with tricuspid atresia, results with a proposed new index for patient selection. Circulation 1990;82:164-9.
32. Shanahan CL, Wilson NJ, Gentles TL, et al. The influence of measured versus assumed uptake of oxygen in assessing pulmonary vascular resistance in patients with a bidirectional Glenn anastomosis. Cardiol Young 2003;13:137-42.
33. Kennaird DL. Oxygen consumption and evaporative water loss in infants with congenital heart disease. Arch Dis Child 1976;51: 34-41.
34. Krauss AN, Auld PA. Metabolic rate of neonates with congenital heart disease. Arch Dis Child 1975;50:539-41.
35. Huse DM, Feldt RH, Nelson RA, et al. Infants with congenital heart disease. Food intake, body weight, and energy metabolism. Am J Dis Child 1975;129:65-9.