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Accurate Measurement of Systemic Oxygen Consumption in Ventilated Children with Congenital Heart Disease

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1. Introduction

Measuring systemic oxygen consumption (VO_2) is a fundamental part of hemodynamic and oxygen transport assessment when using the Fick principle. This measure is pivotal for children with congenital heart disease, at cardiac catheterization and in the Intensive Care Unit (ICU) after cardiopulmonary bypass surgery (CPB). According to the direct Fick principle (Fick, 1870), VO_2 may be combined with the difference between arterial and venous oxygen content, and the pressure gradient, to allow the calculation of each parameter of systemic hemodynamics and oxygen transport. Parameters that may be calculated include systemic and pulmonary blood flows (Qs and Qp) and resistances (SVR and PVR), systemic oxygen delivery (DO_2), and oxygen extraction ratio (ERO_2). Importantly, these parameters can be derived in a variety of simple or complex circulations in congenital heart defects before and after surgical repair or palliation, including *1)* biventricular circulation with or without left to right or right to left shunt (Li, Hoschtitzky et al. 2004; Li, Schulze-Neick et al. 2000; Schulze-Neick, Li et al. 2001; Schulze-Neick, Li et al. 2002), *2)* functionally single ventricular circulation such as hypoplastic left heart syndrome before and after the Norwood procedure (Li, Zhang et al. 2006; Li, Zhang et al. 2006; Li, Zhang et al. 2007; Li, Zhang et al. 2007; Li, Zhang et al. 2008), and *3)* one-and-a-half ventricular circulation such as after the bidirectional cavopulmonary shunt operation (Hoskote, Li et al. 2004; Li, Hoskote et al. 2005).

If VO_2 needs to be measured, then accuracy of the measurement cannot be overemphasized (Kendrick, West et al. 1988; Laitinen and Rasanen 1998; Shanahan, Wilson et al. 2003). Any error in VO_2 measurement will translate directly into an equivalent magnitude of under-estimation or over-estimation of hemodynamics and oxygen transport parameters, which may misdirect surgical and clinical treatment strategies. Prognostic cardiac catheterization is often used for evaluation of systemic and pulmonary blood flows and vascular resistances, particularly pulmonary vascular resistance, in patients with primary or secondary pulmonary hypertension, and in patients with functionally single ventricular abnormalities undergoing staged surgical palliations. In this latter group, elevated pulmonary vascular resistance is a risk factor for poor outcome (Gentles, Gauvreau et al. 1997; Gentles, Mayer et al. 1997; Mair, Hagler et al. 1990), emphasizing the need for accurate hemodynamic assessment before staged palliations.

In ICU patients, the importance of the accurate measurement of VO_2 has been increasingly realized in the past decade or two. Significant alterations in systemic oxygen transport and the contribution of VO_2 in the impaired balance of oxygen transport during the early postoperative period after CPB are now better understood (Chiara, Giomarelli et al. 1987; Li, Hoschtitzky et al. 2004; Li, Schulze-Neick et al. 2000; Li, Zhang et al. 2007; Li, Zhang et al. 2007; Oudemans-van Straaten, Jansen et al. 1996). VO_2 has its own meaning in the balance of oxygen transport, which has been largely ignored. A hypermetabolic response with increased VO_2 occurs in patients after CPB, due mainly to *1)* a systemic inflammatory response (Li, Hoschtitzky et al. 2004; Oudemans-van Straaten, Jansen et al. 1996), *2)* rewarming from hypothermic CPB and fever (Li, Hoschtitzky et al. 2004; Li, Schulze-Neick et al. 2000), and *3)* the use of inotropes (Li, Zhang et al. 2006). The increase in VO_2 is an important contributor to the imbalance of oxygen transport in the early postoperative period, when cardiac function and oxygen delivery are depressed due to myocardial injury by surgery and ischemia-reperfusion (Li, Zhang et al. 2006; Li, Zhang et al. 2007; Wernovsky, Wypij et al. 1995). VO_2 varies greatly between patients and within individual patients over time. Variation in VO_2 results from varied circulatory, metabolic, and hormonal responses to CPB (Li, Hoschtitzky et al. 2004; Oudemans-van Straaten, Jansen et al. 1996), from patient body temperature (Li, Hoschtitzky et al. 2004; Li, Schulze-Neick et al. 2000;), and from pharmacological (Li, Zhang et al. 2006) and ventilator manipulations (Li, Hoskote et al. 2005; Li, Zhang et al. 2008) (please see section 4 for details). In this dynamic milieu, continuous or repeated monitoring of VO_2 is necessary to reflect changes over time.

Accurate measurement of VO_2 allows precise assessment of systemic hemodynamics and oxygen transport parameters in varied circulations after complete repair or palliations (Li, Hoschtitzky et al. 2004; Li, Hoskote et al. 2005; Li, Schulze-Neick et al. 2000; Li, Zhang et al. 2006; Li, Zhang et al. 2006; Li, Zhang et al. 2007; Li, Zhang et al. 2007; Li, Zhang et al. 2008; Schulze-Neick, Li et al. 2001; Schulze-Neick, Li et al. 2002). Actual measurements are superior to the indirect indicators, such as blood pressure and arterial and venous oxygen saturations that are most commonly used in postoperative management. Superiority of actual measurements is seen particularly clearly after the Norwood procedure, when profound hemodynamic instability and oxygen transport imbalance occurs. Furthermore, actual measurements of hemodynamics and oxygen transport parameters are fundamental to bedside physiological research on factors affecting the imbalance of oxygen transport, research aimed at improving the management of critically ill children. With direct and continuous measurement of VO_2 using state-of-the-art technique respiratory mass spectrometry, we have conducted extensive studies in neonates after the Norwood procedure (Li, Zhang et al. 2006; Li, Zhang et al. 2006; Li, Zhang et al. 2007; Li, Zhang et al. 2007; Li, Zhang et al. 2008; Li, Zhang et al. 2008; Li, Zhang et al. 2008; Li, Zhang et al. 2008). We use the Norwood circulation and physiology in this Chapter as a model to understand oxygen transport and the factors affecting oxygen kinetics in children after CPB.

The objectives of this chapter are two-fold. 1) To review the currently available techniques of VO_2 measurement, including published predictive equations and indirect Fick principle using themodilution, their advantages and disadvantages, with special emphasis on respiratory mass spectrometry to assess VO_2 in children undergoing cardiac cauterization and after CPB in the ICU. 2) Using the Norwood physiology as the model to introduce the concept of oxygen transport and further emphasize the importance of direct and continuous

measurement of VO_2 in both clinical care and research in children with congenital heart disease before and after CPB.

2. The inaccurate techniques for measurement of VO_2

2.1 The inaccuracies of predictive equations

Although techniques for metabolic monitoring using indirect calorimetry or respiratory mass spectrometry are available for the direct measurement of VO_2, it is still common practice to estimate VO_2 values from tables or published predictive equations (LaFarge and Miettinen 1970; Lindahl 1989; Lundell, Casas et al. 1996; Wessel, Rorem et al. 1969). Despite attempts to improve the accuracy of estimated VO_2 values, large discrepancies are still observed between measured and estimated values (Laitinen and Rasanen 1998; Shanahan, Wilson et al. 2003; Wolf, Pollman et al. 1998). Such discrepancies present challenges in the clinical application of predictive equations e.g., in the catheterization laboratory setting, because subsequent hemodynamic calculations will be impaired. In ICU patients during the early postoperative period after CPB, estimation of VO_2 is even further exposed to inaccuracies due to significant variability of VO_2 between and within patients over time (Li, Zhang et al. 2006; Li, Zhang et al. 2006; Li, Zhang et al. 2007; Li, Zhang et al. 2008). Furthermore, estimating VO_2 by predictive equations gives a single value for a given patient and makes no provision for the dynamic patient milieu that is inevitable in the early post-operative period (Li, Zhang et al. 2006; Li, Zhang et al. 2006; Li, Zhang et al. 2007; Li, Zhang et al. 2008).

We have compared results from four commonly used equations for estimating VO_2 (LaFarge and Miettinen 1970; Lindahl 1989; Lundell, Casas et al. 1996; Wessel, Rorem et al. 1969) against VO_2 measured directly by respiratory mass spectrometry. Both the equations and the direct measurements were applied to children with congenital heart defects, during cardiac catherization and in the ICU after CPB. We found poor agreement between the direct measurements and all estimated values, especially in children younger than 3 years of age and in the ICU patients (Li, Bush et al. 2003; Rutledge, Bush et al. 2010).

2.1.1 VO_2 values during cardiac catheterization versus in the ICU after CPB

In patients undergoing cardiac catheterization, there is a general *over-estimation* of VO_2 introduced by the equations (Figure 1) (Li, Bush et al. 2003). The conditions of conscious sedation with spontaneous ventilation were used to generate the predictive equations decades ago. In contrast in current practice, general anesthesia and mechanical ventilation are used in most children undergoing cardiac catheterization. General anesthesia and muscle relaxants with mechanical ventilation may decrease the cardiopulmonary work and metabolic rate, resulting in a reduction in VO_2 of up to 20 to 30%.(Nisbet, Dobbinson et al. 1973; Westenskow, Jordan et al. 1978)

In the ICU patients, a general *under-estimation* of VO_2 is introduced by the equations, with very poor agreement to actual measurements, as the equations were generated in preoperative patients undergoing cardiac catheterization (Li, Bush et al. 2003). After CPB, VO_2 is significantly increased and highly variable between patients and within each patient (Figure 2) (Li, Zhang et al. 2006; Li, Zhang et al. 2007; Li, Zhang et al. 2008). Thus, the direct measurement of VO_2 is essential for these patients; continuous or repeated measurements are also essential to reflect the dynamic changes in these patients that occur over time.
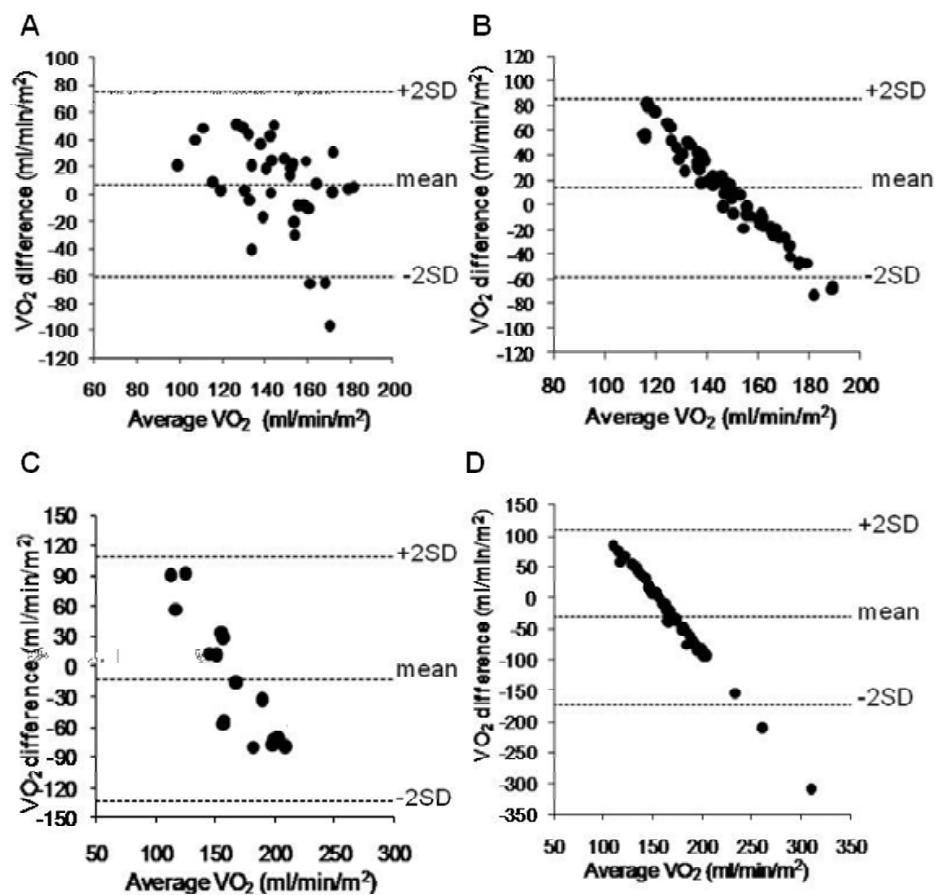
Fig. 1. Agreement of measured and estimated VO₂. Measured VO₂ minus estimated VO₂ is plotted against average VO₂; in patients undergoing cardiac catheterization, (A) using the LaFarge equation and (B) the Wessel equation; and after cardiac surgery in the ICU, (C) using the LaFarge equation and (D) the Wessel equation .
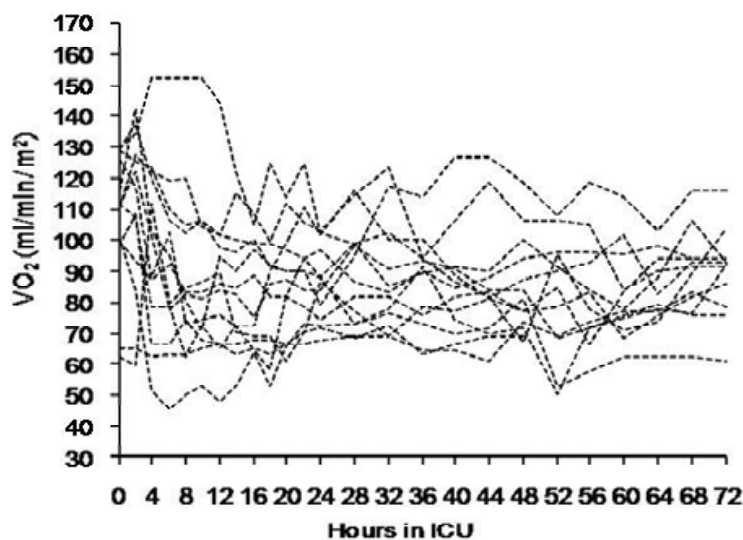

Fig. 2. Measured VO₂ by respiratory mass spectrometry in 14 neonates in the first 72 hours after the Norwood procedure

2.1.2 VO$_2$ values in patients > 3 years old versus ≤ 3 years old

Of the equations we tested initially, the LaFarge equation is the most commonly used and gives the closest estimation to measured results with the lowest bias and limits of agreement (Li, Bush et al. 2003). However, despite the fact that the LaFarge equation was generated and intended for use in patients between 3 and 40 years of age, it is applied in patients of all ages. With advances in surgical techniques and perioperative management, increasing numbers of younger patients with complex congenital heart defects, such as functionally single ventricular abnormalities, undergo cardiac surgery. This in turn increases the need for diagnostic cardiac catheterization in children younger than 3 years, often with the single goal of accurately evaluating pulmonary vascular resistance.

Our initial study, comparing measured and estimated VO$_2$, excluded patients whose ages fell outside the range used in the derivation of LaFarge equation, that is, younger than 3 years. We revisited the data to compare estimates of VO$_2$ in patients younger than 3 years to the earlier data from patients older than 3 years of age. Estimations were significantly poorer in the group younger than 3 years, with a bias of 55 mL/min/m², compared to a bias of 11 mL/min/m² in the older group. The limits of agreements were -42 to +153 mL/min/m² for children < 3 years versus -39 to +61 mL/kg/m² for those ≥ 3 years (Figure 3) (Rutledge, Bush et al. 2010)
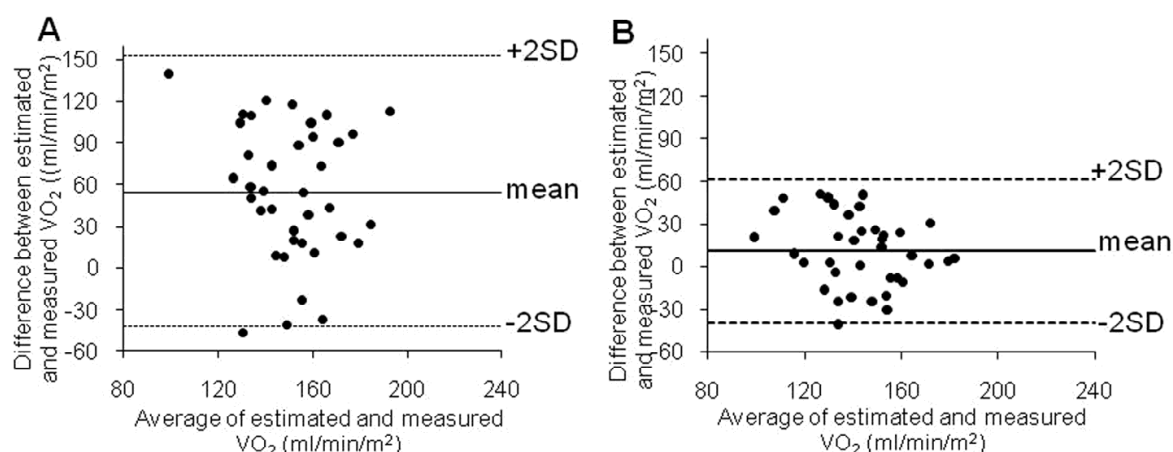

Fig. 3. Agreement of measured and estimated VO$_2$ during cardiac catheterization in patients (A) < 3 years old and (B) > 3 years old.

The LaFarge equation (LaFarge and Miettinen 1970) includes a logarithmic transformation of age for male patients (equation 1) and for female patients (equation 2).

$$VO_2 \ (mL/min/m^2) = 138.1 \text{-} (11.49 \times logeage) + (0.378 \times heart\ rate) \tag{1}$$

$$VO_2 \ (mL/min/m^2) = 138.1 \text{-} (17.04 \times logeage) + (0.378 \times heart\ rate) \tag{2}$$

The logarithmic transformation of age intrinsically results in a faster increase in estimated VO$_2$ as age decreases, particularly within the first 3 years of life (Figure 4A). Interestingly, the directly measured VO$_2$ has almost exactly the opposite trend, being lowest in the youngest patients and quickly increasing in the first 3 to 4 years (Figure 4B). As a result, the errors of estimated VO$_2$ are dramatically related to age (Figure 4C). The reasons for lower VO$_2$ in younger children remain unclear, but body composition may be a factor. In

particular, 'fat mass' is relatively higher in younger children (Fomon, Haschke et al. 1982; Moukarzel, Salas et al. 2003) and VO$_2$ in fat mass is about 20 times lower than in muscular mass (Moukarzel, Salas et al. 2003).

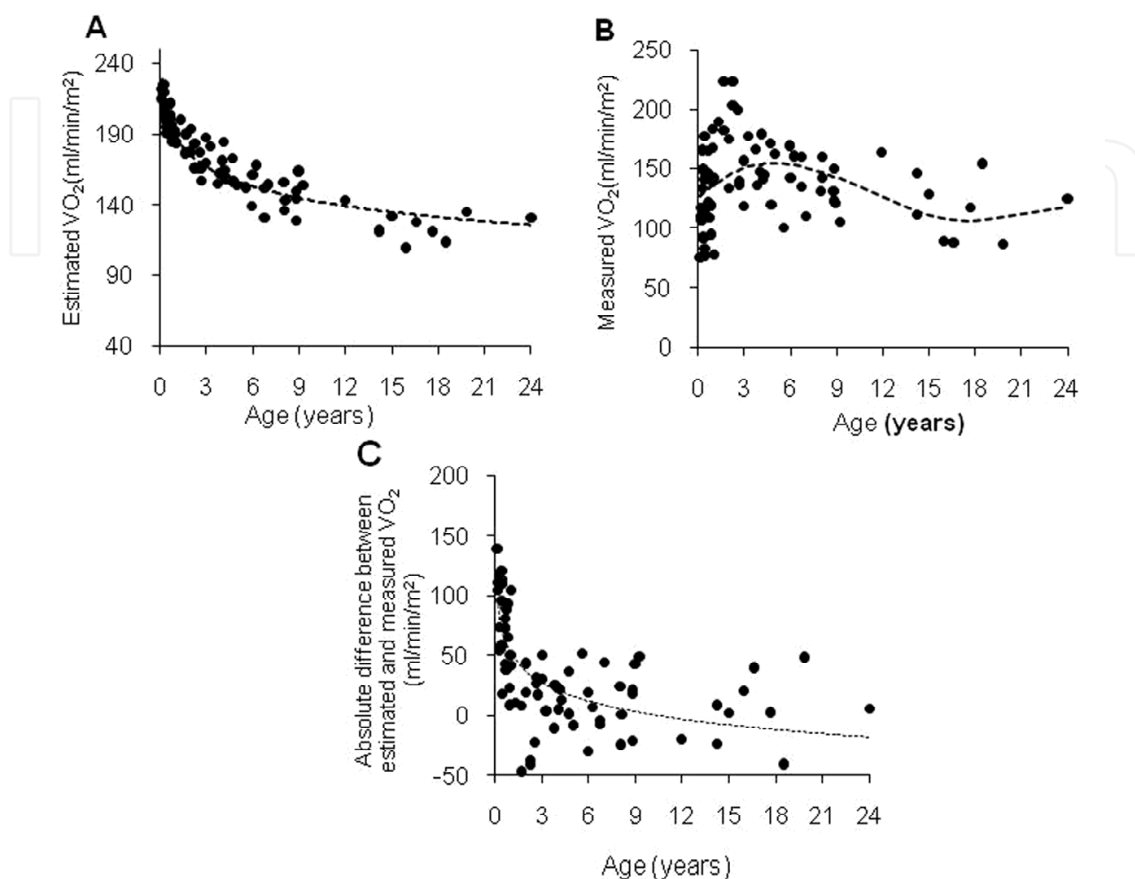Fig. 4. The trends in relation to age of (A) estimated VO$_2$, (B) measured VO$_2$, and (C) their difference, in 75 patients undergoing cardiac catheterization.

We conclude that estimation of VO$_2$ is unacceptably inaccurate for clinical decision-making and research. Direct measurement of VO$_2$ is appropriate for young children with congenital heart defects undergoing cardiac catheterization and in the ICU after CPB. Direct and continuous measurement of VO$_2$ is essential, particularly in those younger than 3 years and in the early postoperative period after CPB.

2.2 Inadequacy of the reverse Fick method
VO$_2$ can also be calculated by the reverse Fick method from the cardiac output, directly measured by the thermodilution technique, for example. This method has obvious limitations for clinical application in patients with congenital heart defects. First, the calculation is clearly intermittent. Second, the presence of intracardiac shunting and tricuspid regurgitation can significantly affect the accuracy of the calculation. Most important, certain complex circulations preclude the use of the thermodilution technique (e.g., after the Norwood procedure, bidirectional caval pulmonary shunt, or the Fontan operation), because of anatomical (e.g., parallel systemic and pulmonary circulations) and methodological (e.g., inadequate mixing) limitations.

3. Direct measurement of VO$_2$ using respiratory mass spectrometry

The concept of mass spectrometry (measuring fractional proportions of substances in a mixture, according to their molecular mass-charge ratios) was first introduced at the end of the 19th century. The recruitment of mass spectrometry into respiratory physiology in the 1940s, and its subsequent refinement over the decades, has established a 'state-of-the-art' method for measuring VO$_2$ using highly accurate and rapid multiple gas analysis. The mixed expirate method (Davies and Denison 1979) enabled use of the mass spectrometer alone to measure metabolic gas exchange and ventilation volume. This technique has been used widely to measure VO$_2$ in a broad spectrum of clinical and experimental conditions. We have adapted the method to continuously measure VO$_2$ with a variety of pediatric ventilators and anesthesia ventilators before, during, and after CPB, using the AMIS 2000 Medical Respiratory Mass Spectrometer System (Innovision A/C Odense, Denmark). Our combination of techniques and equipment makes respiratory mass spectrometry a unique and powerful tool in multiple settings: in the cardiac catheterization laboratory (Schulze-Neick, Li et al. 2002 ; Shekerdemian, Bush et al. 1997; Shekerdemian, Bush et al. 1997), in the operating room (Li, Stokoe et al. 2004), and in the ICU (Li, Hoschtitzky et al. 2004; Li, Schulze-Neick et al. 2000; Li, Zhang et al. 2006; Li, Zhang et al. 2006; Li, Zhang et al. 2007; Li, Zhang et al. 2007; Li, Zhang et al. 2008; Schulze-Neick, Li et al. 2001).

3.1 Principles of mass spectrometry

Mass spectrometers analyze substances in the gas phase by performing a sequence of five operations: *1)* accept and vaporize a minute controlled quantity of sample; *2)* reduce the sample vapor to a very low pressure; *3)* ionize a representative part of the vapor; *4)* separate the ionized particles produced, according to their mass-to-charge ratio; and *5)* read the abundance of particles at specific values of the mass-to-charge ratio.

3.2 Hardware design

Features of a mass spectrometer are outlined in Figure 5.

A Teflon capillary tubing (A) with an internal diameter 0.3 mm and a length of 3 to 6 m provides the gas transport from the sampling site (B) to the vacuum system. There are three sample inlets, one for the on-line continuous monitoring of O$_2$ and CO$_2$ fractional concentrations, the other two for the inspiratory and expiratory gas sampling. The gas sample at atmospheric pressure is drawn at a sampling rate of 10 to 20 mL/min down the tubing (A), passing through the three static electro-magnetic valves (C), which are selected in turn as appropriate to the sequence of gas analysis needed for the metabolic calculations. The sample is drawn by the inlet rotary vacuum pump (D) into the sample chamber (E), and all but a small fraction of it is pumped away continuously at the low-pressure end of the inlet tubing. The turbo molecular pump (F), supported by a second backing rotary pump (G), provides a very high vacuum environment of around 5×10^{-7} mBar in the dispersion chamber (H), housing ionization chamber (I), mass filter (J), and ion detector (K). Thus, the high vacuum provided by the turbo molecular pump draws the remaining gas sample through the molecular leak (L) into the ionization chamber, where the gas molecules are ionized. The ions are focused into a tight beam, enter the aperture of the quadrupole mass filter, and are separated by the quadrupole mass filter (J). The use of appropriate voltages in this field allows only ions of a definite mass interval to pass and reach the ion detector (K),

suppressing the inevitable 'noise' which would otherwise be created by the contaminants that cross the mass filter as a result of scatter. The ions are then collected and pre-amplified in a current-voltage pre-amplifier prior to signal processing. The resulting signal is therefore made as pure as possible before being amplified by the secondary electron multiplier (SEM). Amplification enables a higher sensitivity and faster operation. The resulting output of the detection unit is proportional to the ion current, which in turn is proportional to the partial pressure of the gas species. (Pressures indicated are at normal operating conditions).
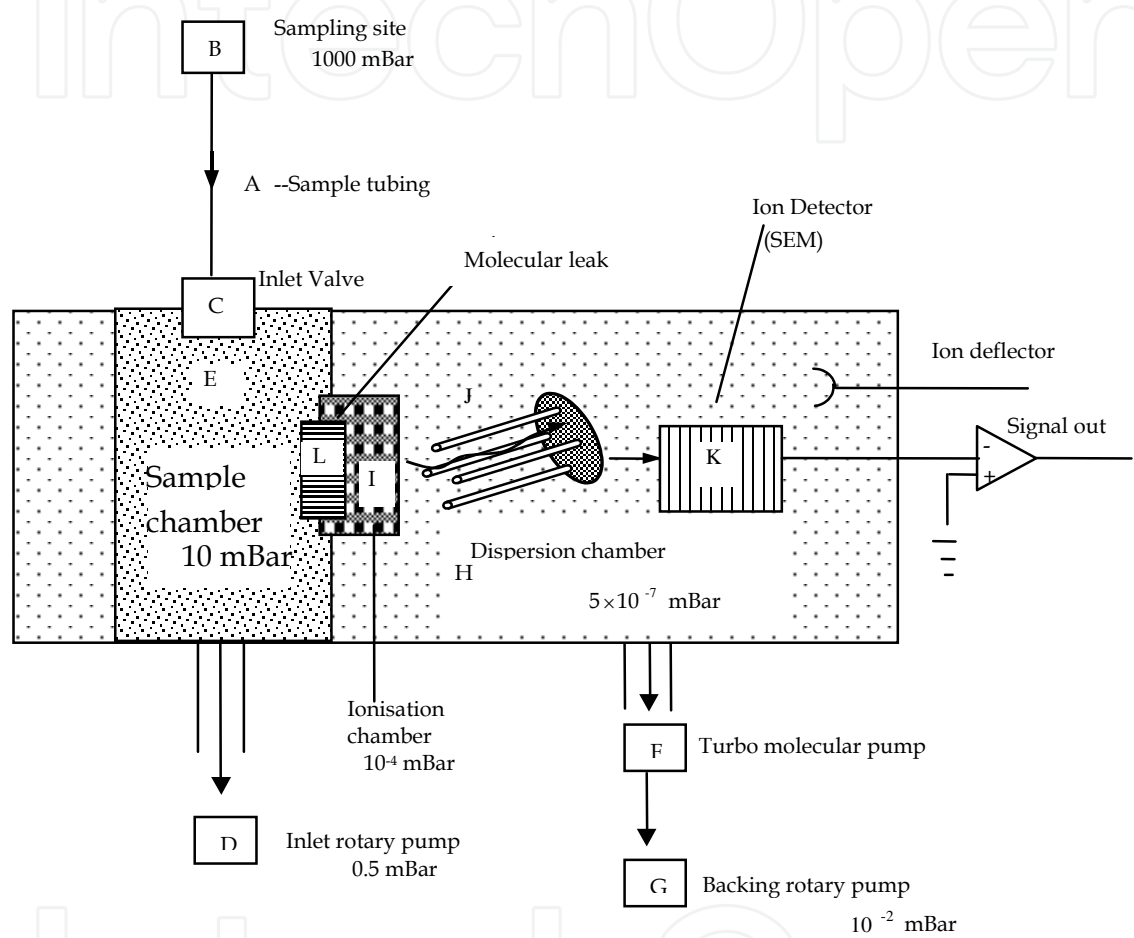

Fig. 5. Design of AMIS 2000 respiratory mass spectrometer.

3.3 The measurement of VO$_2$

The mass spectrometer measures metabolic gas exchange by the 'inert gas dilution method'. 'A known mass flow of a marker gas is injected into expired gas upstream of a mixing box, and the resulting gas composition downstream used to deduce the mass flows of all its components' (Davies and Denison 1979). VO$_2$ is then calculated every 30 seconds as:

$$VO_2 \text{ (STPD)} = V_{Tr} \text{ (STPD)} \bullet [F_{IO2} \bullet (1 - F_{MCO2} - F_{MTr}) - F_{MO2} \bullet (1 - F_{ICO2} - F_{ITr})] / D \qquad (3)$$

$D = F_{MTr} \bullet (1 - F_{IO2} - F_{ICO2}) - F_{Itr} \bullet (1 - F_{MO2} - F_{MCO2})$

V_{Tr} = added flow of indicator gas (tracer, Argon)

$F_{IO2}, F_{ICO2}, F_{Itr}$ = constant fractional concentrations of O$_2$, CO$_2$ and tracer gas in inspired air

F_{MO2}, F_{MCO2}, $F_{MTr:}$ = measured fractional concentrations of O_2, CO_2 and tracer gas at the outlet of the mixing chamber
STPD = Standard temperature and pressure dry.

3.4 Setup of respiratory mass spectrometer in the cardiac catheterization laboratory with anesthesia ventilators

Accurate measurement of minute ventilation relies on the complete collection of expired gas and therefore a leak-free circuit. Ideally, patients are intubated with cuffed endotracheal tubes. Precise VO_2 measurement requires a steady-state period, thus patients are sedated and paralyzed to obviate the confounding effects of movement, agitation, and pain on VO_2. We have adapted the AMIS2000 respiratory mass spectrometer in the cardiac catheterization laboratory to anesthesia ventilators with a partial rebreathing system (Figure 6).
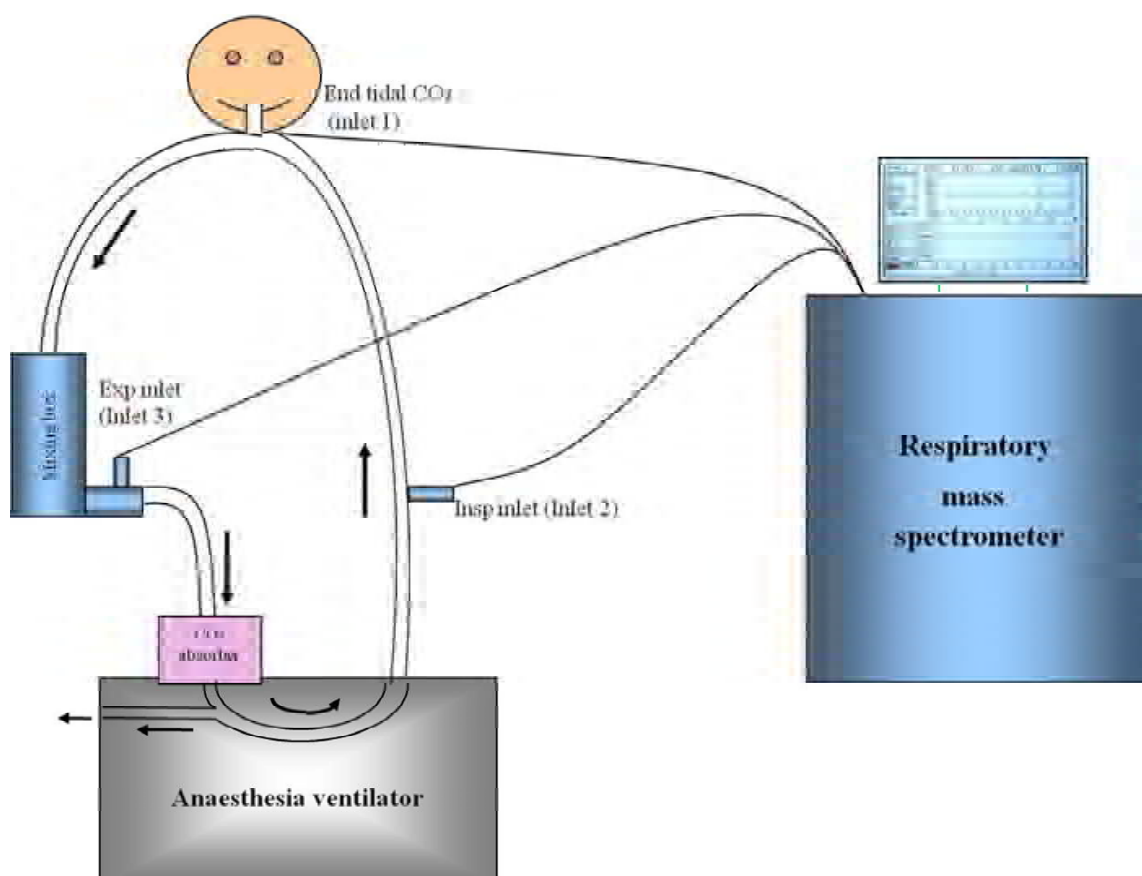

Fig. 6. The setup of the AMIS2000 respiratory mass spectrometer sampling inlets, mixing box, and the circuit of the anesthesia ventilator in the cardiac catheterization laboratory.

Most children undergoing cardiac catheterization are paralyzed and mechanically ventilated by an anesthesia ventilator with a partial rebreathing system, whereby the exhaled gas is re-circulated via a CO_2 absorber and fresh gas mixture is continuously supplied. The mixing box is inserted in the expiratory limb of the ventilator circuit to collect the expired gas. Inlet 1 is placed at the mouth piece close to the endotracheal tube, for continuous on-line monitoring of breath-to-breath oxygen and carbon dioxide fractional concentrations. This checks that the steady state had not been perturbed. Another two inlets are used for the measurement of VO_2. Inlet 2, which is placed in the inspiratory limb of the ventilator circuit, samples inspiratory gas; Inlet 3 samples the 'effluent' mixed expirate from the distal end of the mixing box.

3.5 Setup of respiratory mass spectrometer in the ICU with pediatric ventilators

We have also adapted the AMIS2000 respiratory mass spectrometer in the ICU to various pediatric ventilators with continuous flow (Figure 7). Pediatric ventilators in the ICU use continuous flow to supply fresh gas throughout the breathing cycle. This avoids increasing the amount of work required to trigger spontaneous breathing. In a setup different from the anesthesia ventilator, the mixing box is connected to the exit port of the pediatric ventilator to collect the expired gas, and is also connected to an 'expiratory' inlet (Inlet 3). The expiratory inlet allows sampling of the 'effluent' mixed expirate from the distal end of the mixing box. Inlets 1 and 2 are placed at the mouth piece and in the inspiratory limb respectively, in the same way as in the anesthesia ventilator.
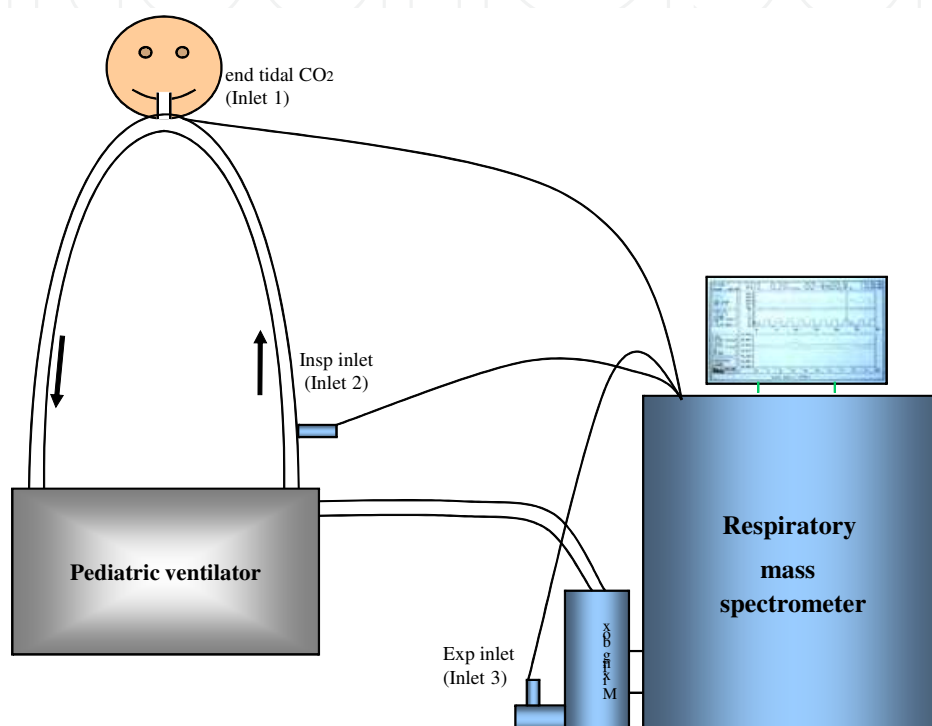

Fig. 7. The setup of the AMIS2000 respiratory mass spectrometer sampling inlets, mixing box, and the circuit of the pediatric ventilator in the ICU.

3.6 Clinical applications of respiratory mass spectrometry in the ICU

Respiratory mass spectrometers were first produced for commercial applications in the late 1980s. The reported precision of the mass spectrometer was as low as 5% in spontaneous breathing at rest or during exercise. The precision increases in paralyzed and ventilated patients. Precision was further improved by avoiding the use of flow sensors. Versatility of the respiratory mass spectrometer is greatly increased by the use of long sampling probes up to 30 meters(Davies and Denison 1979). Long probes allow the study of subjects who otherwise might be inaccessible due to the size of the equipment, such as patients undergoing cardiac catheterization, intensive care, or surgery, where space at the bedside is severely limited. Long probes also enable simultaneous events to be examined sequentially, and permit a single mass spectrometer to be shared between several patients or laboratories. Respiratory mass spectrometers have become valuable clinical research tools. Our adaptation of the respiratory mass spectrometer to pediatric ventilators has allowed us to extensively study systemic hemodynamics and oxygen transport, and the factors affecting them, before and after cardiac

surgery in children with congenital heart defects (Li, Hoschtitzky et al. 2004; Li, Hoskote et al. 2005; Li, Schulze-Neick et al. 2000; Li, Zhang et al. 2006; Li, Zhang et al. 2006; Li, Zhang et al. 2007; Li, Zhang et al. 2007; Li, Zhang et al. 2008; Zhang 2008; Zhang, Holtby et al. 2008).

The importance of oxygen transport is increasingly appreciated in the care of critically ill patients, particularly after CPB (Gilbert, Haupt et al. 1986; Haupt, Gilbert et al. 1985; Hoffman, Ghanayem et al. 2000; Li, Hoschtitzky et al. 2004; Li, Hoskote et al. 2005; Li, Schulze-Neick et al. 2000; Li, Zhang et al. 2006; Li, Zhang et al. 2006; Li, Zhang et al. 2007; Li, Zhang et al. 2007; Li, Zhang et al. 2008; Oudemans-van Straaten, Jansen et al. 1996; Powers, Mannal et al. 1973; Tweddell, Hoffman et al. 1999; Zhang 2008; Zhang, Holtby et al. 2008). The fundamental requirement of ICU management is to match systemic oxygen delivery (DO_2) to VO_2, to sustain cellular metabolism and end-organ function. Many patients requiring ICU support have reduced DO_2, usually as a result of decreased myocardial function. However, in many patients the reduced cardiac output and DO_2 are further compounded by secondary abnormalities of VO_2 that amplify the deficiency of DO_2 and contribute to the overall imbalance of oxygen transport. This combination is seen in many situations such as sepsis and trauma (Gilbert, Haupt et al. 1986; Haupt, Gilbert et al. 1985; Powers, Mannal et al. 1973), but is a consistent feature of cardiac surgery (Hoffman, Ghanayem et al. 2000; Li, Hoschtitzky et al. 2004; Li, Schulze-Neick et al. 2000; Li, Zhang et al. 2007).

Most children experience a phase of reduced cardiac output during the first few hours after CPB (Hoffman, Ghanayem et al. 2000; Li, Zhang et al. 2007; Wernovsky, Wypij et al. 1995). At the same time, VO_2 is increased and highly dynamic in relation to central body temperature (Li, Hoschtitzky et al. 2004; Li, Schulze-Neick et al. 2000), the systemic inflammatory response (Li, Hoschtitzky et al. 2004; Oudemans-van Straaten, Jansen et al. 1996), pharmacological manipulations (Hayes, Timmins et al. 1994; Li, Zhang et al. 2006), and ventilatory manipulations (Li, Hoskote et al. 2005; Li, Zhang et al. 2008). VO_2 is an important constituent in the balance of oxygen transport, but has been largely ignored in ICU management. Traditional management of these patients has focused on augmenting myocardial performance through the use of inotropes, for example, to enhance cardiac output and DO_2. However, inotropic agents may not effectively enhance cardiac output in the presence of myocardial injury, and may paradoxically stimulate systemic and myocardial oxygen consumption, offsetting any gains in DO_2 (Fowler, Alderman et al. 1984; Hayes, Timmins et al. 1994; Li, Zhang et al. 2006). An alternative (and in some ways more rational) approach to improving the balance of oxygen transport may be to decrease VO_2. For example, the use of skeletal muscle paralysis and assisted ventilation is a standard therapy directed at reducing metabolic demands. These simple maneuvers may reduce VO_2 by up to 20 to 30% (Nisbet, Dobbinson et al. 1973; Westenskow, Jordan et al. 1978). Similarly, profound reductions in VO_2 may be achieved simply by controlling central body temperature. We have shown in infants after cardiac surgery, for example, that central pyrexia increases VO_2 by approximately 11% per degree Celsius (Li, Schulze-Neick et al. 2000). Therefore, in the current conceptualization of oxygen transport, emphasis should shift beyond cardiac output and oxygen delivery to the balance between DO_2 and VO_2.

4. Calculation of oxygen transport parameters using directly measured VO_2

4.1 The Fick principle

The Fick principle states that 'The total uptake or release of any substance by an organ is the product of blood flow to the organ and the arteriovenous concentration difference of the substance.' (Fick 1870).

The Fick principle implies that if the flow in a system cannot be measured directly, then it can be measured using an indicator, provided that the indicator is removed at a known rate. Fick described the theory of a method to calculate cardiac output but never actually measured it himself. He argued: 'It is astonishing that no one has arrived at the following obvious method by which the amount of blood ejected by the ventricle of the heart with each systole may be determined directly, at least in animals. One measures how much oxygen an animal absorbs from the air in a given time. During the experiment one obtains a sample of arterial and venous blood; in both the oxygen content is measured. The difference in oxygen content tells how much oxygen each cubic centimeter of blood takes up in its passage through the lungs. As one knows the total quantity of oxygen absorbed in a given time one can calculate how many cubic centimeters of blood passed through the lungs in this time.' (Vandam and Fox 1998).

Verification of the Fick principle in humans was initially accomplished in 1930, through the daring exploits of Baumann and Grollman at a time when cardiac catheterization had yet to be established as a clinical tool. They obtained samples of mixed venous blood by inserting a spinal tap needle just to the right of the sternum; the needle entered the right ventricular chamber by puncturing its wall (Grollman 1932).

The direct Fick principle using VO_2 is one of the oldest methods of measuring systemic and pulmonary blood flows, but nonetheless remains the gold standard. It can be used in simple biventricular and varied complex circulations in congenital heart defects, before or after surgical repair palliations. Relevant equations are provided in the following sections.

4.2 In normal circulation

The direct Fick method measures cardiac output (CO, which is systemic blood flow, Qs, and is equal to pulmonary blood flow, Qp) with VO_2 according to the following equation:

$$CO = VO_2 / (CaO_2 - CvO_2) \tag{4}$$

where CaO_2 and CvO_2 are arterial and the mixed venous oxygen contents, respectively. Then:

$$SVR = (MaP - MsvcP)/CO \tag{5}$$

$$PVR = (MpaP - MpvP)/CO \tag{6}$$

$$DO_2 = CO \times CaO_2 \tag{7}$$

$$ERO_2 = VO_2 / DO_2 \tag{8}$$

where MaP, MsvcP, MpaP, and MpvP are mean systemic arterial, superior vena cava, pulmonary arterial, and pulmonary venous pressures; CaO_2 is systemic arterial oxygen content.

4.3 In biventricular circulation with shunt

In a biventricular circulation, the left to right, right to left, or bidirectional shunt may be present at the atrial, ventricular, or great vessel levels, such as in atrial septal defect, ventricular septal defect, patent arterial duct, or tetrology of Fallot.

$$Qs = VO_2 / (CaO_2 - CvO_2) \tag{9}$$

$$Qp = VO_2 / (CpvO_2 - CpaO_2) \tag{10}$$

$$SVR = (MaP - MsvcP)/Qs \qquad (11)$$

$$PVR = (MpaP - MpvP)/Qp \qquad (12)$$

$$DO_2 = CO \times CaO_2 \qquad (13)$$

where CaO_2, CvO_2, and $CpvO_2$ are systemic arterial and venous, and pulmonary venous oxygen contents; and MaP, MvP, and MpvP are mean systemic arterial, venous, and pulmonary venous pressures. ERO_2 is calculated as in the normal circulation (Equation 8).

4.4 In one-and-a-half ventricular circulation: Bidirectional cavopulmonary shunt

In bidirectional cavopulmonary shunt circulation, the blood from the superior vena cava is directed to the pulmonary arteries, passing through the pulmonary circulation (Qp) and becomes oxygenated before it reaches the systemic circulation. Once in the systemic circulation, the blood from the superior vena cava mixes with systemic venous blood from the inferior vena cava (Qivc) to form total cardiac output (CO). Therefore, as stated by Salim, Case et al. (1995):

$$Qsvc = Qp \qquad (14)$$

$$CO = Qp + Qivc \qquad (15)$$

$$Qp = VO_2 / (CpvO_2 - CsvcO_2) \qquad (16)$$

$$CO = VO_2 \times (CpvO_2 - CivcO_2) / [(CpvO_2 - CsvcO_2) \times (CaO_2 - CivcO_2)] \qquad (17)$$

$$Qivc = CO - Qp \qquad (18)$$

$$SVR = (MaP - MivcP)/Qs \qquad (19)$$

$$PVR = (MsvcP - MpvP)/Qp \qquad (20)$$

where CaO_2, $CivcO_2$, $CsvcO_2$, and $CpvO_2$ are arterial, inferior and superior vena cava and pulmonary venous oxygen contents; MaP, MivcP, MsvcP, and MpvP are mean systemic arterial, inferior and superior vena cava, and pulmonary venous pressures. DO_2 and ERO_2 are calculated as in the normal circulation (Equations 7 & 8).

4.5 In single ventricular circulation: Hypoplastic left heart syndrome and the Norwood circulation

In functionally single ventricular circulation, a single outlet from the heart provides both systemic and pulmonary circulations via an interposed B-T shunt or right ventricle to pulmonary artery shunt. Therefore:

$$CO = Qs + Qp \qquad (21)$$

$$Qs = VO_2 / (CaO_2 - CvO_2) \qquad (22)$$

$$Qp = VO_2 / (CpvO_2 - CaO_2) \qquad (23)$$

$$SVR = (MaP - MsvcP)/Qs \qquad (24)$$

$$\text{'PVR'} = (MaP - MpvP)/Qp \tag{25}$$
$$\text{(including the shunt)}$$

$$DO_2 = Qs \times CaO_2 \tag{26}$$

Where CaO_2, CvO_2 and $CpvO_2$ are systemic arterial, superior vena caval and pulmonary venous oxygen contents; MaP, MsvcP, and MpvP are mean systemic arterial, superior vena cava, and pulmonary venous pressures; 'PVR' is pulmonary vascular resistance including the shunt in the classic Norwood procedure (Li, Zhang et al. 2006; Li, Zhang et al. 2007). ERO_2 is calculated as in the normal circulation (Equation 8).

In this Chapter, the Norwood circulation is used as the model to understand the balance of oxygen transport and the factors affecting it. This is an ideal model to understand the concept of oxygen transport, since the Norwood physiology is characterized by profound hemodynamic instability and oxygen transport imbalance, and represents the most challenging group of children for postoperative management after CPB. Data presented in this chapter were obtained in neonates after the classic Norwood procedure with the Blalock-Taussig shunt, but the basic physiology of the classic Norwood procedure is largely the same as the modified procedure with the right ventricle to pulmonary artery conduit, i.e., a single neonatal ventricle provides the parallel pulmonary and systemic circulations.

5. Improved understanding of the Norwood physiology and postoperative management using direct measurement of VO_2

The Norwood procedure for hypoplastic left heart syndrome, and similar anatomic variants, continues to have significant morbidity, and a mortality rate that ranges from 6% to 25% (Azakie, Merklinger et al. 2001; Gaynor, Mahle et al. 2002; Ohye, Sleeper et al. 2010; Sano, Huang et al. 2009). Despite advances in surgical and postoperative management, these infants have little hemodynamic reserve. Instability following repair is inherent in the neonatal single ventricle supplying parallel pulmonary and systemic circulations, and is compounded by the variable effects of CPB and ischemia and reperfusion injury. Our understanding of the Norwood physiology has been based on theoretical studies using computational models (Barnea, Austin et al. 1994; Migliavacca, Pennati et al. 2001), and on animal models (Kitaichi, Chikugo et al. 2003). Necessarily, these models do not reflect the true functionally single ventricular physiology. In previous studies in humans, arterial superior vena caval oxygen saturations, and their derivations were most commonly used as surrogates of DO_2 (Charpie, Dekeon et al. 2001; Hoffman, Ghanayem et al. 2000; Maher, Pizarro et al. 2003; Tweddell, Hoffman et al. 1999). In some human studies, derived values of pulmonary and systemic blood flows have been obtained, but are based on the key assumption of a fixed VO_2 of 160 or 180 mL/min/m² (Charpie, Dekeon et al. 2001; Hoffman, Ghanayem et al. 2000; Maher, Pizarro et al. 2003; Tweddell, Hoffman et al. 1999). However, as demonstrated above in section 2.1.1 (Figure 2), postoperative VO_2 has wide inter- and intra-patient variability in children (Li, Schulze-Neick et al. 2000; Li, Zhang et al. 2006; Li, Zhang et al. 2007; Li, Zhang et al. 2008). Thus, significant errors may be introduced in the calculation of hemodynamic and oxygen transport indices incorporating fixed values of VO_2. The introduction of such errors has greatly limited our understanding of postoperative hemodynamics and oxygen transport in these patients.

The adaptation of the respiratory mass spectrometer (AMIS2000, Innovision A/S, Demark) to continuously measure VO_2 allows the measurement of actual values for each element of

systemic hemodynamics and oxygen transport. Use of actual values has significantly improved our understanding of the Norwood physiology and its postoperative management.

5.1 Profiles of hemodynamics and oxygen transport after the Norwood procedure

The Norwood physiology is an ideal model for understanding oxygen transport, since it is characterized by profound hemodynamic instability and oxygen transport imbalance (Li, Zhang et al. 2007). Wide, unstable, inter-individual and intra-individual variations in all the elements of hemodynamics and oxygen transport are observed, particularly on the systemic side (including systemic vascular resistant and blood flow). Pulmonary vascular resistance and blood flow are less variable, due to the mechanical limitation of the Blalock-Taussig shunt in the classic Norwood procedure or to the right ventricle to pulmonary artery shunt in the modified Norwood procedure.

5.2 VO_2 and its contribution to the balance of oxygen transport

Previous studies used assumptions for VO_2 of 160 or 180 mL/min/m^2 to calculate hemodynamics (Charpie, Dekeon et al. 2001; Hoffman, Ghanayem et al. 2000; Maher, Pizarro et al. 2003; Tweddell, Hoffman et al. 1999). Those values are much higher than the directly measured VO_2 in our patients, which ranged from 45 to 152 mL/min/m^2 (Figure 8).
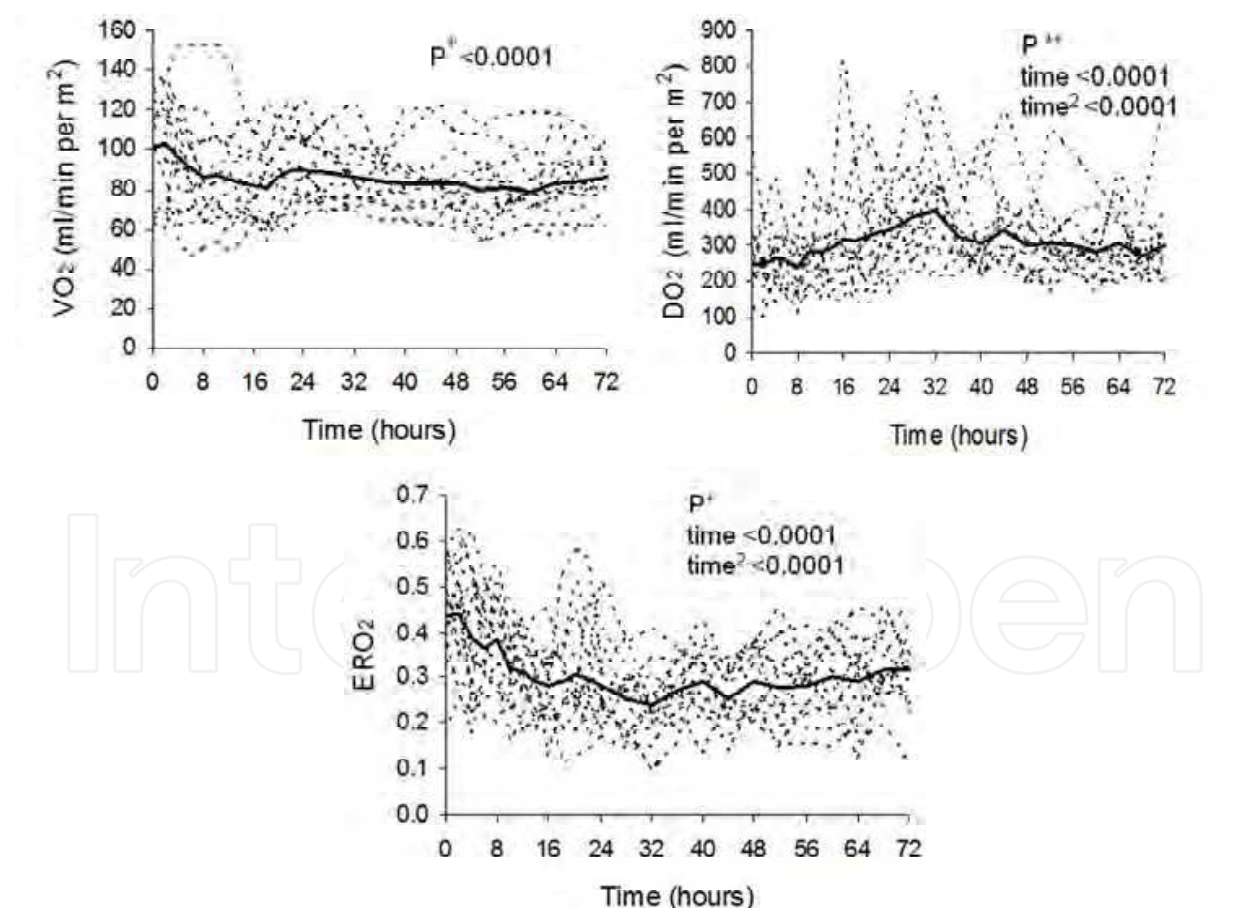

Fig. 8. The changes in oxygen consumption (VO_2), oxygen delivery (DO_2) and oxygen extraction ration (ERO_2) in neonates in the first 72 hours after the Norwood procedure. Dotted lines indicate individual patients; solid line indicates the mean.

An overestimation of VO_2 leads to a direct proportional change in the estimates for the calculated variables. For example, an assumed VO_2 of 170 mL/min/m², compared with the measured mean VO_2 on arrival in ICU of 101 mL/min/m², leads to a 68% overestimation of total CO, Qp, and Qs, and a 68% underestimation of PVR and SVR. Even more important, VO_2 is highly variable both between and within individual patients over time. Using a single assumed VO_2 makes no provision for the highly dynamic patient milieu that is inherent in the Norwood physiology.

VO_2 increases immediately after the Norwood procedure, mainly due to the systemic inflammatory response (Li, Hoschtitzky et al. 2004; Oudemans-van Straaten, Jansen et al. 1996), re-warming from hypothermic CPB and fever (Li, Hoschtitzky et al. 2004; Li, Schulze-Neick et al. 2000), and the use of inotropes (Li, Zhang et al. 2006). After arrival of the patient in the ICU, VO_2 decreases rapidly in the first 24 hours, followed by a slower decrease over the following 48 hours. In the first 24 hours, CO, Qs, and DO_2 are the variables most decreased. However, during the critical first 24-hour period, the balance of VO_2 and DO_2 improves significantly, as indicated by the rapid decrease in ERO_2 (Figure 8). The observed improvement in balance results primarily from a decrease in VO_2, rather than DO_2 as previously reported. After 24 hours, DO_2 became the primary contributor to the balance of oxygen transport.

5.3 Optimizing oxygen delivery

Historically, the postoperative management strategy for patients after the Norwood procedure was directed at diminishing Qp by increasing PVR, in order to increase Qs and DO_2. Analysis of our data reveals that SVR is far more important in determining Qs and DO_2 than is PVR. This indicates that both the systemic and pulmonary vascular compartments have variable resistance, but the systemic circulation has a more profound effect on DO_2, whereas the pulmonary compartment is relatively fixed with the mechanical limitation of the shunt. Interestingly, increases in SaO_2 and PaO_2 have only a weak positive correlation with Qp, implying that relative hypoxia to increase PVR and reduce Qp yields little benefit to DO_2. Our data also show that hemoglobin is an important contributor to DO_2, with a tight correlation between DO_2 and hemoglobin values. Therefore, treatment strategies should be designed to improve DO_2 and its balance with VO_2. Specifically, management strategies to maintain a high hemoglobin value, a low VO_2, and a relatively low and stable SVR appear to be rational.

5.4 Factors that affect the balance of oxygen transport

Direct measurements of VO_2 have allowed us to study the complex effects of some routine treatments on oxygen transport. Some routine treatments used in an effort to improve the balance of oxygen transport in fact have adverse effects.

5.4.1 Catecholamines

Catecholamines, such as dopamine, epinephrine, and norepiphrine, are commonly used in patients after CPB to augment cardiac contractility and DO_2 (Kawamura, Minamikawa et al. 1980; Merin, Bitran et al. 1977; Rosenblum and Frieden 1972). Catecholamines also stimulate VO_2 through their effects on myocardial work and metabolic rate (Cori and Buchwald 1930; Ensinger, Weichel et al. 1993; Maxwell, Crompton et al. 1985). If the increase in DO_2 is greater than the increase in VO_2, catecholamines will improve the overall balance of oxygen

transport and tissue oxygenation. Some reports indicate favorable responses to catecholamine treatment in adults and older children after cardiac surgery (Kawamura, Minamikawa et al. 1980; Merin, Bitran et al. 1977; Rosenblum and Frieden 1972). In neonates, however, catecholamines have additional thermogenic actions through their effects on brown adipose tissue, resulting in an exaggerated increase in VO_2 (Maxwell, Crompton et al. 1985; Penny, Sano et al. 2001; Sell, Deshaies et al. 2004). Furthermore, neonatal hearts are known to have limited reserves to increase cardiac contractility. The reserves might become marginal in a Norwood circulation, with the injured single right ventricle providing parallel pulmonary and systemic circulations. In these patients, efforts to improve DO_2 by catecholamines are more likely to be associated with predominately adverse effects. As we have reported, terminating a moderate dose of dopamine (5 µg/kg/min) was not associated with any significant changes in CO or DO_2, but with a significant decrease in heart rate and rate-pressure product, an indirect indicator of myocardial oxygen consumption (Li, Zhang et al. 2006). VO_2 also decreased by 16±14 mL/min/m^2, representing a change of 20±11%. Terminating dopamine resulted overall in an improvement of the balance of oxygen transport, as indicated by the significant decrease in ERO_2 (Figure 10). Therefore, a moderate dose of dopamine induces predominantly an increase in VO_2, adversely affecting the VO_2–DO_2 relationship. Figure 11 shows examples of on-line VO_2 monitoring before and after dopamine termination.
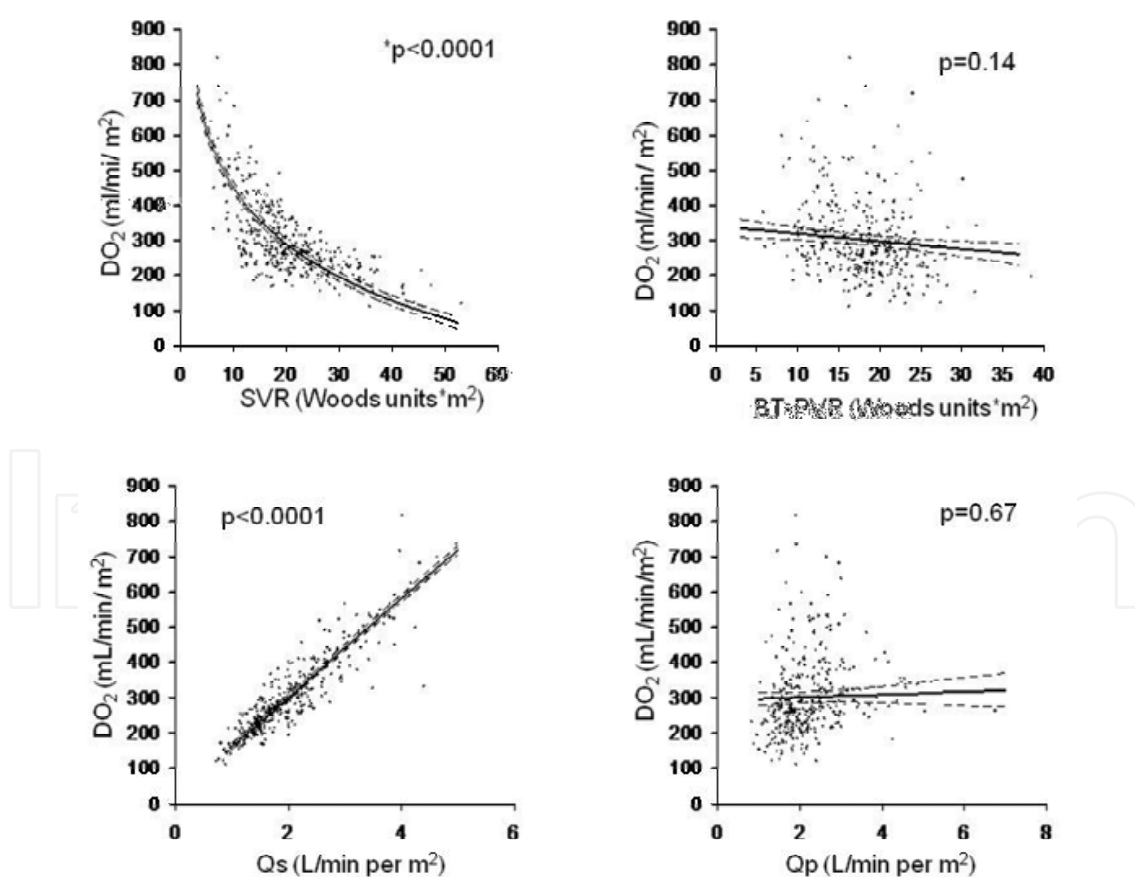

Fig. 9. Correlations between oxygen delivery (DO_2) and systemic vascular resistance (SVR), systemic blood flow (Qs), total pulmonary vascular resistance including the B-T shunt (BT-PVR), and pulmonary blood flow (Qp).
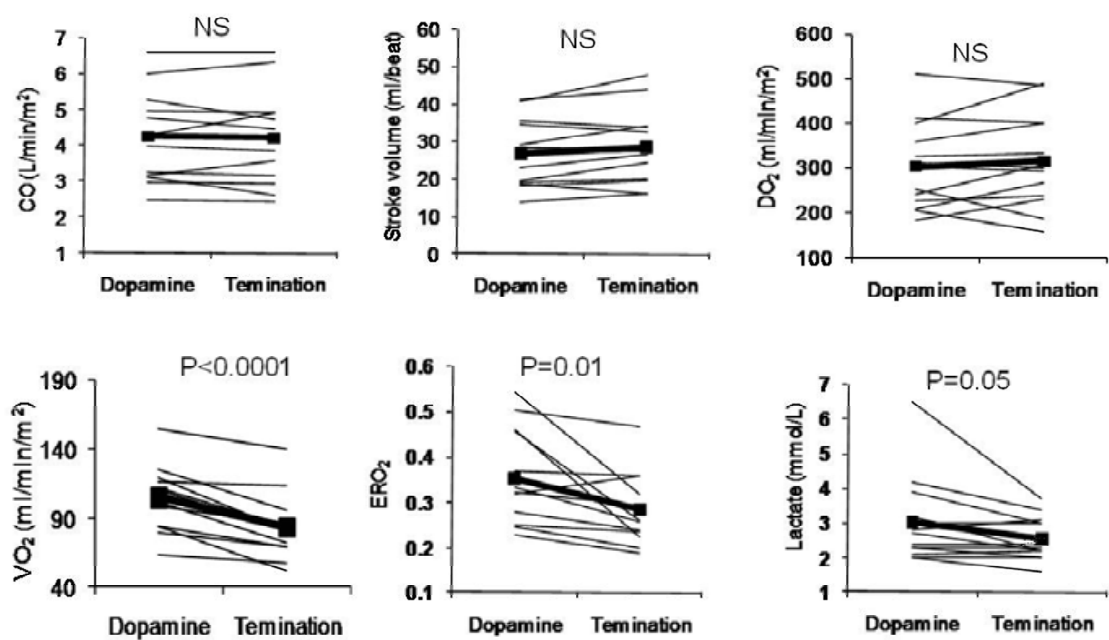
Fig. 10. The individual (thin line) and mean (bold line) changes in systemic hemodynamics and oxygen transport before and after termination of dopamine following the Norwood procedure.
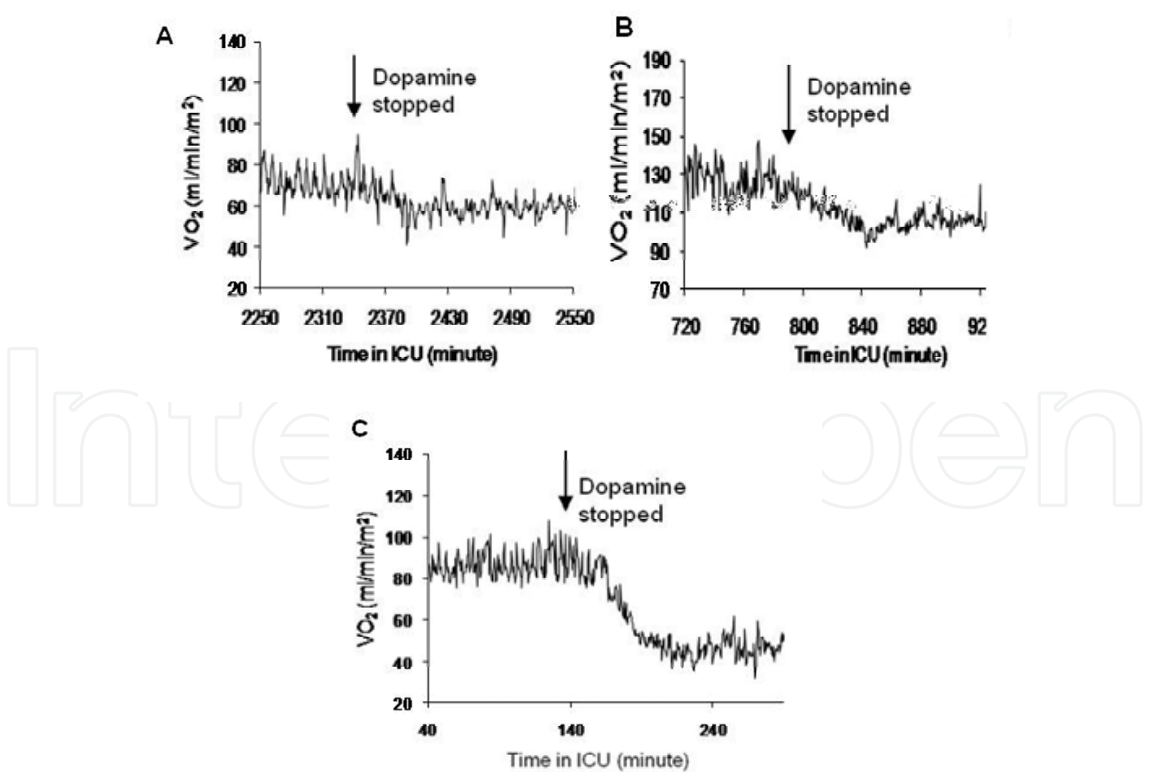

Fig. 11. Examples of the on-line measurement of oxygen consumption (VO_2) in three patients showing rapid and (A) small, (B) moderate, and (C) large decreases in VO_2 after terminating dopamine.

5.4.2 CO_2

CO_2 has been suggested as a factor increasing DO_2 in neonates both before and after the Norwood procedure (Bradley, Simsic et al. 2001; Mora, Pizarro et al. 1994). Consequently, it is a common practice to maintain a relatively high arterial CO_2 tension ($PaCO_2$), primarily by hypoventilation. The potent pulmonary vasoconstrictive effect of CO_2 was believed to decrease pulmonary blood flow (Qp), thereby increasing Qs (Mora, Pizarro et al. 1994). We studied the effect of stepwise increases in $PaCO_2$ from 40 to 50 to 60 mmHg, and found complex effects of CO_2 on systemic and regional oxygen transport (Li, Zhang et al. 2008). Moderate hypercapnia increases Qs as a result of its effect on SVR, rather than via PVR as previously proposed. The increase in systemic blood flow is primarily a consequence of increased cerebral blood flow that compromises splanchnic circulation. Moderate hypercapnia also decreases VO_2 and stimulates the release of catecholamines. The decrease in VO_2 improves the balance of oxygen transport, but the increase in catecholamines may be undesirable (Figures 12). Clinically, CO_2 should be used with caution when the aim is to improve oxygen delivery.
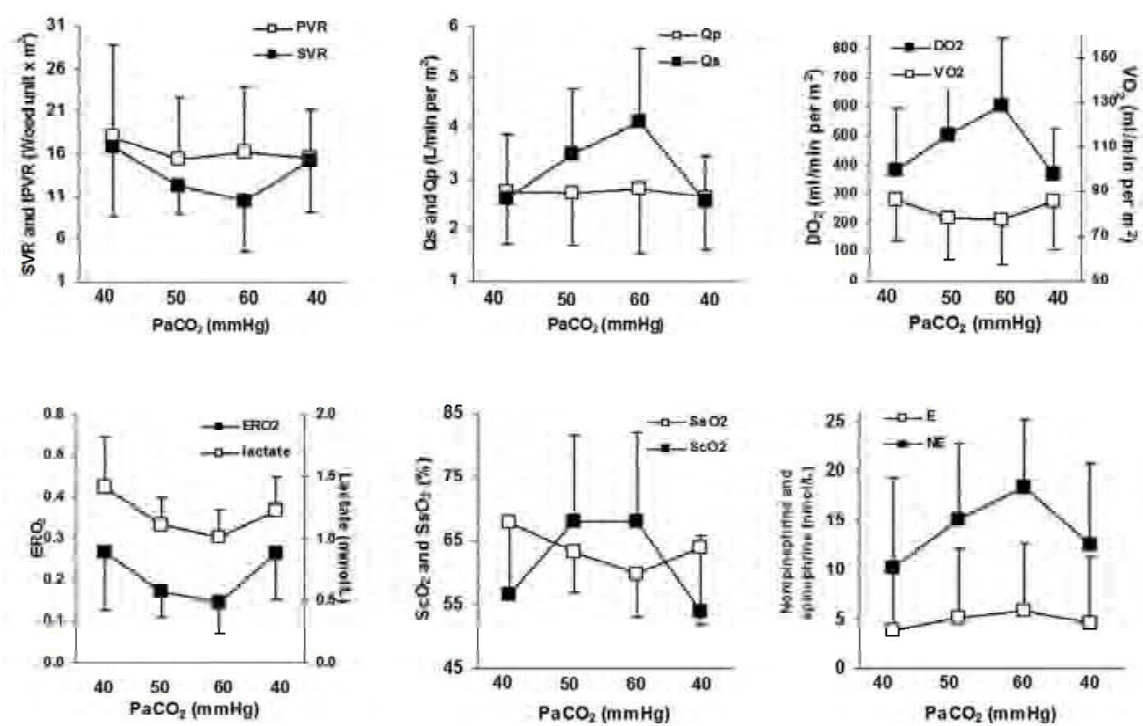

Fig. 12. During stepwise increases in $PaCO_2$ from 40 to 50 to 60 mmHg and after termination of CO_2, changes in systemic and total pulmonary vascular resistances (SVR and PVR), systemic and pulmonary blood flow (Qp and Qs), oxygen consumption and delivery (VO_2 and DO_2), oxygen extraction ration (ERO_2), and lactate, cerebral and splanchnic oxygen saturations (ScO_2 and SsO_2) and in epinephrine and norepinephrine.

5.4.3 Hyperglycemia

Hyperglycemia has been identified as a risk factor for adverse outcomes in critically ill patients, including those after CPB. Tight glucose control with insulin therapy has been shown to improve outcomes, but is not common practice for children following CPB. In our

data, elevated glucose level showed negative correlations with CO and DO_2, and positive correlations with SVR and ERO_2 (Figure 13) (Zhang 2008). Therefore, hyperglycemia is
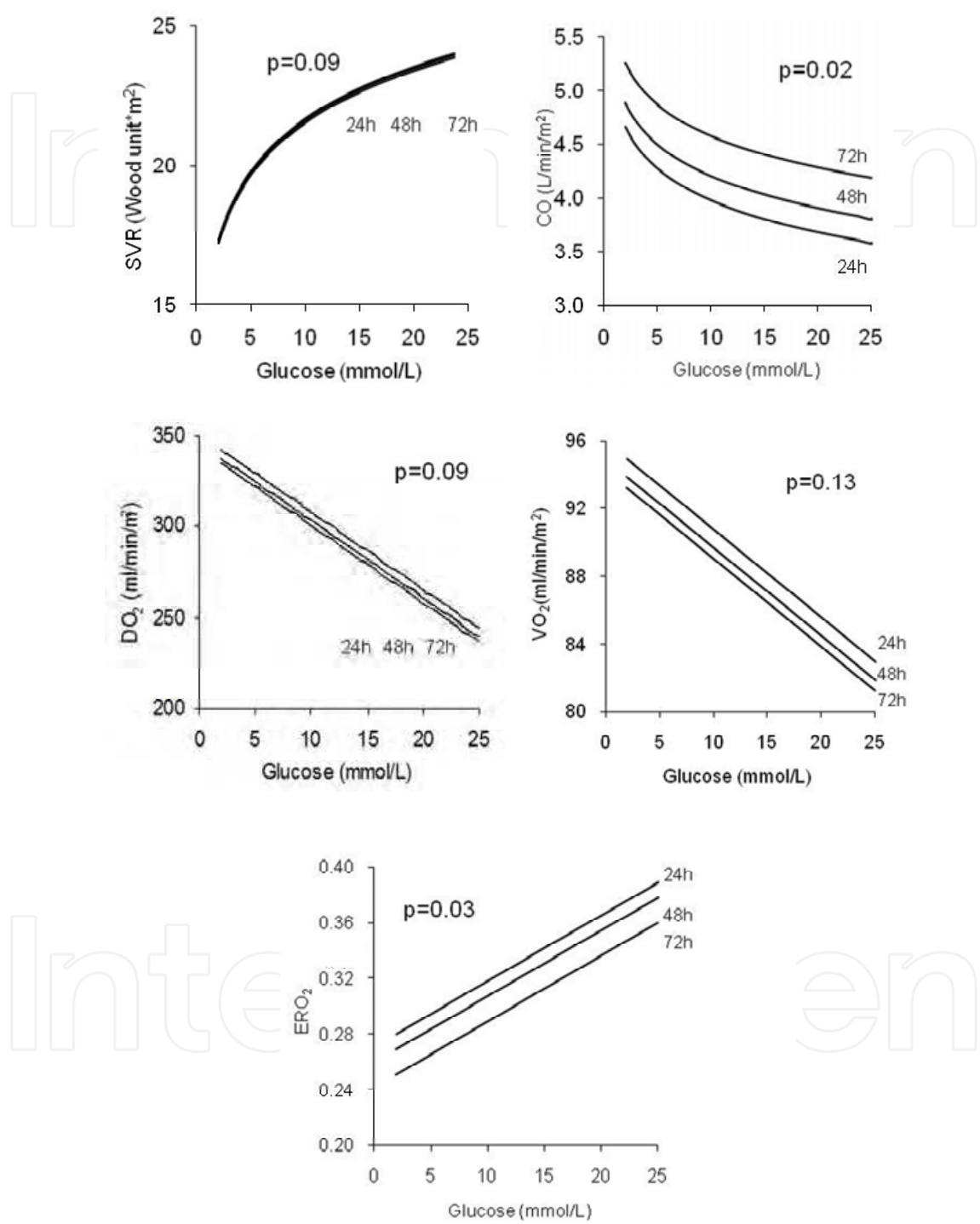

Fig. 13. Representative regression lines for the model predicting correlations between blood glucose and systemic vascular resistance (SVR), cardiac output (CO), systemic oxygen delivery (DO_2), oxygen consumption (VO_2), and oxygen extraction (ERO_2), at 24, 48, and 72 hours after the Norwood procedure for 17 neonates in the ICU.

negatively associated with systemic hemodynamics and oxygen transport status. Randomized clinical trials of glucose control with insulin therapy are warranted to identify the cause-and-effect relationship and to provide important information regarding appropriate glucose management strategies for children following CPB.

5.4.4 Other factors
To date, we have found a few factors in current routine postoperative management that have varied effects on oxygen transport. Further investigations are required to identify other factors in clinical management with favourable or adverse effects, and to design new treatment strategies to improve postoperative oxygen transport and clinical outcomes.

6. Conclusion

The predictive equations currently in use are unacceptable to measure VO_2 in ventilated children with congenital heart disease, particularly in those younger than 3 years of age, and in the early postoperative period after CPB. Direct, continuous, and precise measurement of VO_2 is fundamental for accurate assessments of hemodynamics and oxygen transport in children undergoing cardiac catheterization and in the ICU after cardiac surgery. Respiratory mass spectrometry is the 'state-of-the-art' method, allowing highly sensitive and precise measurement of VO_2. Measured VO_2 and the Fick principle allow the calculation of each parameter of systemic hemodynamic and oxygen transport, in varied circulations in congenital heart defects, both before and after complete surgical repair or palliation. These actual measurements are not only useful in clinical management, but important for bedside physiological studies on the balance of systemic oxygen transport in children after CPB. Some routine treatments in current use are intended to improve the balance of oxygen transport, but may actually worsen it. When considering clinical management of unbalanced oxygen transport, clinicians should choose therapies that address both decreased DO_2 and increased VO_2. ICU management strategies need to be refined to optimize the balance of systemic oxygen transport in children with congenital heart defects undergoing cardiac surgery. The resultant improved clinical outcomes in the early postoperative period and at long term follow-up will improve the quality of life for these vulnerable children.

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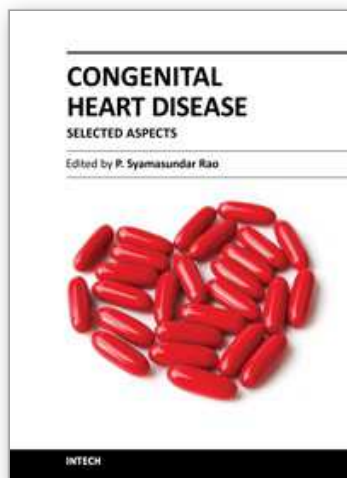
Congenital Heart Disease - Selected Aspects

Edited by Prof. P. Syamasundar Rao

There are significant advances in the understanding of the molecular mechanisms of cardiac development and the etiology of congenital heart disease (CHD). However, these have not yet evolved to such a degree so as to be useful in preventing CHD at this time. Developments such as early detection of the neonates with serious heart disease and their rapid transport to tertiary care centers, availability of highly sensitive noninvasive diagnostic tools, advances in neonatal care and anesthesia, progress in transcatheter interventional procedures and extension of complicated surgical procedures to the neonate and infant have advanced to such a degree that almost all congenital cardiac defects can be diagnosed and "corrected". Treatment of the majority of acyanotic and simpler cyanotic heart defects with currently available transcatheter and surgical techniques is feasible, effective and safe. The application of staged total cavo-pulmonary connection (Fontan) has markedly improved the long-term outlook of children who have one functioning ventricle. This book, I hope, will serve as a rich source of information to the physician caring for infants, children and adults with CHD which may help them provide optimal care for their patients.

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