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Systemic oxygen transport derived by using continuous measured oxygen consumption after the Norwood procedure–an interim review

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Abstract

The balance between systemic O_2 consumption (VO_2) and O_2 delivery (DO_2) is impaired in children after cardiopulmonary bypass surgery, with decreased DO_2 and increased VO_2. The major goal, and the major challenge, of postoperative management has been to match DO_2 to VO_2 in order to sustain cellular metabolism, particularly in neonates after the Norwood procedure. While much effort has been put into augmenting cardiac output and DO_2, VO_2 remains largely ignored. Respiratory mass spectrometry allows the precise and continuous measurement of VO_2. Measured VO_2, using the direct Fick principle, allows for the calculation of each element of systemic O_2 transport in the complex Norwood circulation. The actual measurements of O_2 transport have allowed us, in the past five years or so, to extensively investigate the Norwood physiology in terms of the VO_2–DO_2 relationship and the factors affecting it in clinical treatments. Therefore, the first objective of this article is to introduce the technique of respiratory mass spectrometry and its adaption to measure VO_2 across paediatric ventilators with continuous flow. The second objective is to give an interim review of the main findings in our studies on systemic O_2 transport in 17 neonates in the first 72 h after the Norwood procedure. These findings include the profiles of systemic O_2 transport, the important contribution of VO_2 to the impaired balance of O_2 transport and the complex effects of some routine clinical treatments on the VO_2–DO_2 relationship (including catecholamines, $PaCO_2$, Mg^{2+} and hyperglycaemia, as well as patient-specific anatomical variations). The influence of systemic O_2 transport on cerebral oxygenation is also introduced. This information may help us to refine postoperative management in neonates after the Norwood procedure. Our initial studies mark the end of the beginning, but much is yet explored. Ultimately, the resultant improved systemic and regional O_2 transport in the early postoperative period may have an important impact on long-term outcomes, thereby improving the quality of life for these vulnerable children.

Keywords: Respiratory mass spectrometry • Oxygen transport • The Norwood procedure

INTRODUCTION

The element of O_2 transport has been increasingly appreciated in the care of children with congenital heart defects after cardiopulmonary bypass (CPB) surgery [1–8]. The fundamental requirement of postoperative management is to match systemic O_2 delivery (DO_2) with O_2 consumption (VO_2) in order to sustain cellular metabolism and end-organ function. This is also a major challenge. In most children after CPB, cardiac function and DO_2 are depressed due to myocardial injury by surgery and ischaemia reperfusion [4, 5]. At the same time, VO_2 is increased and highly dynamic [1–4, 9, 10], due to systemic inflammatory response [9, 11], rewarming from hypothermic CPB and fever [1, 9], and pharmacological [2] and ventilatory manipulations [10, 12, 13]. VO_2 constitutes an important component of the imbalance of O_2 transport after CPB and of the effects, beneficial or adverse, of some routine clinical treatments [1–4, 10, 13]. However, in clinical practice, VO_2 remains largely ignored.

The imbalance of O_2 transport is particularly profound in neonates after the Norwood procedure for hypoplastic left heart syndrome and similar anatomical variants [2–4]. Due to this, the Norwood procedure continues to have a significant morbidity and a mortality rate that ranges from 6 to 25% [14–17]. This is inherent in the single ventricle supplying parallel pulmonary and systemic circulations and is compounded by the variable effects of CPB, ischaemia and reperfusion injury, and systemic inflammatory and metabolic response. In the Norwood circulation, the reserve of DO_2 is marginal. On the other hand, the increase in VO_2 is more substantial in neonates because of the greater systemic inflammatory and metabolic responses [18, 19] and the greater stimulation of VO_2 by inotropes [2, 20].

In this dynamic milieu, with significant alterations in the VO_2–DO_2 relationship, indirect indicators of haemodynamics such as heart rate, arterial blood pressure and arterial and venous O_2 saturations are most commonly used to guide postoperative management to optimize the balance of O_2 transport. Their adequacy has been questioned [6]. Although central venous O_2 saturation accurately reflects the overall balance of O_2 transport, it does not discriminate between the contributions of DO_2 and VO_2 [3, 21]. In some clinical reports, derived values of systemic and pulmonary blood flows (Q_s and Q_p) and DO_2 have been

obtained, but these are based on the false assumption of a fixed VO_2 of 160 or 180 ml/(min/m^2) [7, 8, 22, 23].

This situation has changed with the adaptation of the highly sensitive and precise technique of respiratory mass spectrometry to continuously measure VO_2 across paediatric ventilators with continuous flow. Measured VO_2, using the direct Fick principle, allows for the calculation of the actual values for each element of systemic O_2 transport in the Norwood circulation, including Q_s and Q_p and systemic and pulmonary resistances (SVR and PVR), DO_2 and O_2 extraction ratio (ERO_2). In the past five years or so, we have extensively investigated systemic O_2 transport and factors affecting it in routine clinical treatments after the Norwood procedure [2–4, 6, 10, 24–27].

Therefore, the objectives of this article are two fold: first, to introduce the technique of respiratory mass spectrometry and its adaptation to paediatric ventilators to continuously measure VO_2; second, to give an interim review of the main findings from our studies on O_2 transport to serve as 'food for thought' in further exploration of the Norwood physiology.

RESPIRATORY MASS SPECTROMETRY

The introduction of mass spectrometry into respiratory physiology in the 1940s was the basis for the development of the state-of-the-art methods for measuring VO_2 using highly accurate and rapid multiple gas analyses. The reported precision of the earlier methods using the mass spectrometer was as low as 5% in spontaneous breathing at rest or during exercise against a Douglas bag [28]. The precision may increase in paralysed and ventilated patients. We have adapted the method to continuously measure VO_2 with a variety of paediatric ventilators with continuous flow, using the AMIS 2000 Medical Respiratory Mass Spectrometer System (Innovision A/C, Odense, Denmark), making it a unique and powerful research tool in the paediatric intensive care unit (ICU) [1–4, 6, 9, 10, 13, 24–27, 29–33].

Principles of mass spectrometry

Mass spectrometers analyse substances in the gas phase by performing a sequence of five operations: (i) accepting and vaporizing a minute controlled quantity of sample; (ii) reducing the sample vapour to a very low pressure; (iii) ioning a representative part of the vapour; (iv) separating the ionize particles produced, according to their mass-to-charge ratio; and (v) reading the abundance of particles at specific values of the mass-to-charge ratio.

Set-up of the respiratory mass spectrometer with paediatric ventilators

We have adapted the AMIS 2000 respiratory mass spectrometer in the ICU to various paediatric ventilators with continuous flow, such as the Servo 300 and Servo-i (Siemens AG, Munich, Germany) (Fig. 1). The mixing box is connected to the exit port of the paediatric ventilator to collect the expired gas and is also connected to an 'expiratory' inlet (Inlet 3). The expiratory inlet allows for the 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.

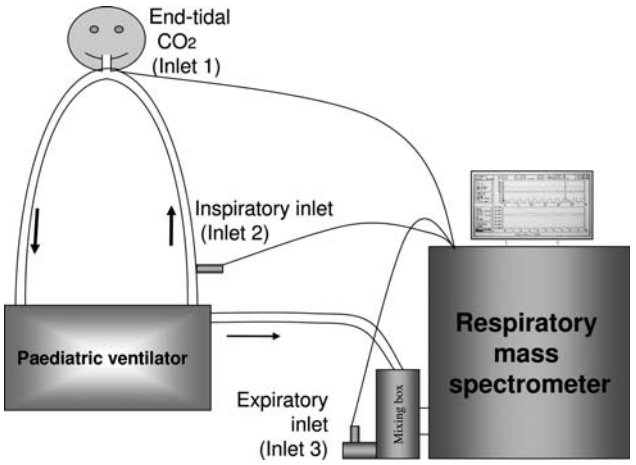

Figure 1: The set-up of the AMIS 2000 respiratory mass spectrometer sampling inlets, the mixing box and the circuit of the paediatric ventilator in the ICU.

Accurate measurement of VO_2 relies on the complete collection of expired gas and thus a leak-free circuit. Patients are, therefore, intubated with a cuffed endotracheal tube (Microcuff-Heidelberg-Pediatric; Microcuff GmbH, Weinheim, Germany). Additionally, patients are usually sedated and paralysed in order to obviate the confounding effects of movement, agitation and pain on VO_2 and to ensure a steady state.

Calculation of O_2 transport parameters using VO_2 in the Norwood circulation

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' [34]. The direct Fick principle using VO_2 is one of the oldest methods used for measuring Q_p and Q_s, but nonetheless remains the gold standard. The equations used for calculating O_2 transport in the Norwood circulation, i.e. single ventricular circulation, are as follows:

$$Q_s = \frac{VO_2}{CaO_2 - CsvcO_2},$$

$$Q_p = \frac{VO_2}{CpvO_2 - CaO_2},$$

$$CO = Q_s + Q_p,$$

$$SVR = \frac{MaP - MsvcP}{Q_s},$$

$$tPVR = \frac{MaP - MpvP}{Q_p\ (\text{including the shunt})},$$

$$DO_2 = Q_s \times CaO_2,$$

$$ERO_2 = \frac{VO_2}{DO_2},$$

where CaO_2 $CsvcO_2$ and $CpvO_2$ are, respectively, the systemic arterial and superior vena caval O_2 contents and MaP, MsvcP and MpvP and pulmonary venous are the mean systemic arterial, superior vena caval and pulmonary venous pressures, respectively.

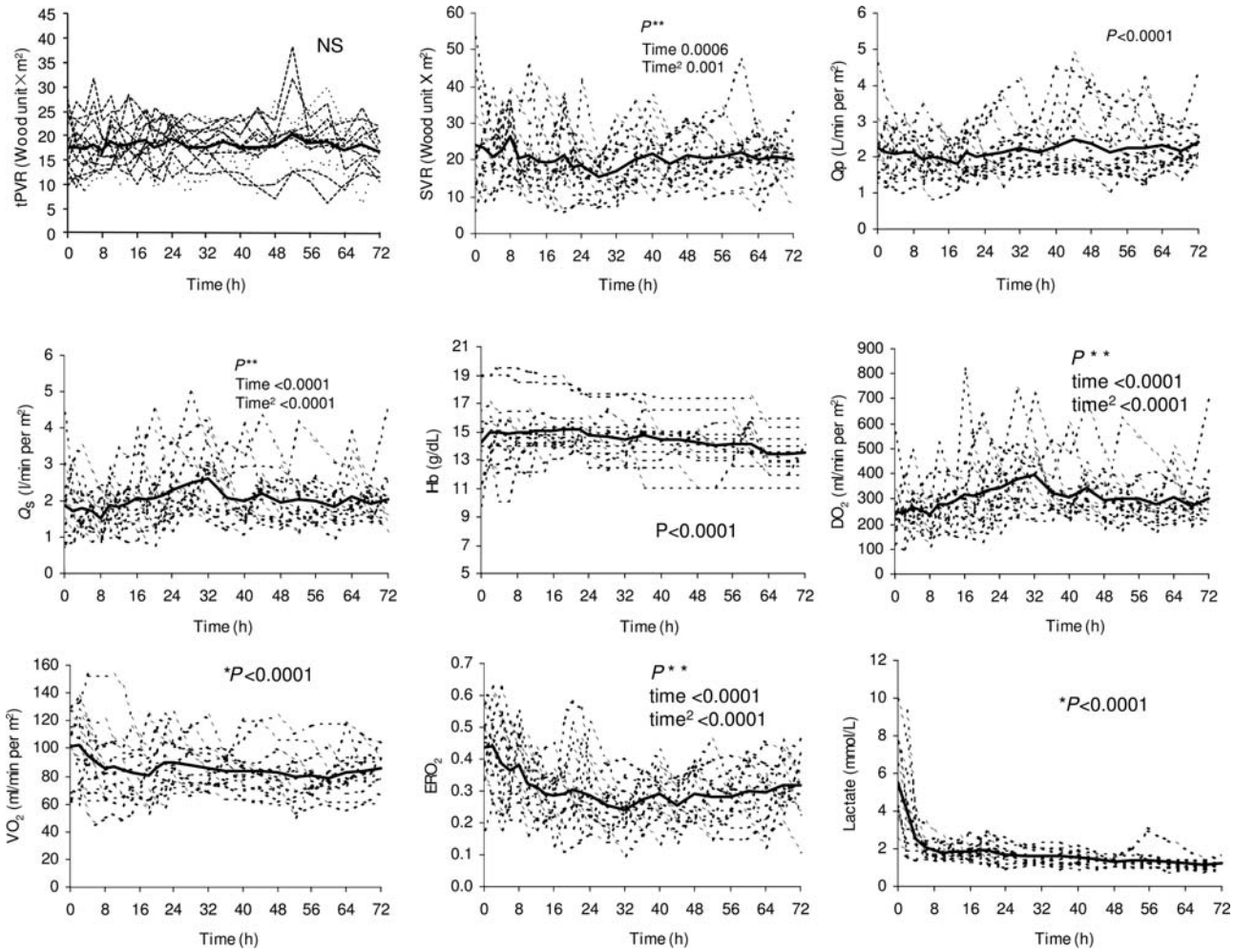

Figure 2: Individual and mean values of systemic O_2 transport parameters. Total pulmonary vascular resistance with the BT shunt (tPVR) and SVR, Q_p, Q_s, haemoglobin (Hb), DO_2, VO_2, ERO_2 and arterial lactate levels during the first 72 h after patient arrival in the ICU.

SYSTEMIC O_2 TRANSPORT AFTER THE NORWOOD PROCEDURE

The actual measurements of systemic O_2 transport parameters have enabled us to examine the alterations in the VO_2–DO_2 relationship after the Norwood procedure and, more importantly, to explore the factors affecting the relationship, beneficial or adverse, in the routine treatments that are used to optimize O_2 transport. The rest of this paper summarizes the main findings from our studies in 17 neonates during the first 72 h after the classical Norwood procedure with the Blalock–Taussig shunt, between April 2004 and November 2006, at the Hospital for Sick Children in Toronto, Ont., Canada. These findings may also be largely applied to the modified Norwood procedure with a right ventricle to the pulmonary artery shunt.

Profiles of systemic O_2 transport after the Norwood procedure

The wide, unstable inter- and intra-individual variations in all the elements of O_2 transport reflect the profound instability of the early postoperative course after the Norwood procedure (Fig. 2) [4]. The variability is particularly greater on the systemic side (including SVR and Q_s). PVR and Q_p are less variable due to the mechanical limitation of the Blalock–Taussig shunt in the classical Norwood procedure or to the right ventricle to the pulmonary artery shunt in the modified Norwood procedure. Over the first 72 h after the Norwood procedure, Q_p, Q_s and DO_2 gradually increase.

VO_2 varies significantly both between and within patients, ranging from 45 to 152 ml/(min/m^2). Note that these measured values are all below the previously assumed values of 160 or 180 ml/(min/m^2) [7, 8, 22, 23]. Overall, VO_2 is high immediately after the Norwood procedure [3, 4]. It decreases rapidly in the first 24 h, followed by a slower decrease over the following 48 h, with a total decrease of about 20%. In the first 24 h, CO, Q_s and DO_2 are the variables that decrease the most. However, during the critical first 24-h period, the balance of VO_2–DO_2 improves significantly, as indicated by the rapid decrease in ERO_2. The observed improvement in balance results primarily from a decrease in VO_2, rather than from any significant improvement in DO_2 as reported previously [7, 23, 35]. This indicates the important contribution of VO_2 to the balance of O_2 transport in the early hours after the Norwood procedure.

Optimizing systemic O_2 delivery

Correlation analyses of DO_2 with other systemic O_2 transport parameters reveal the important factors that contribute to DO_2

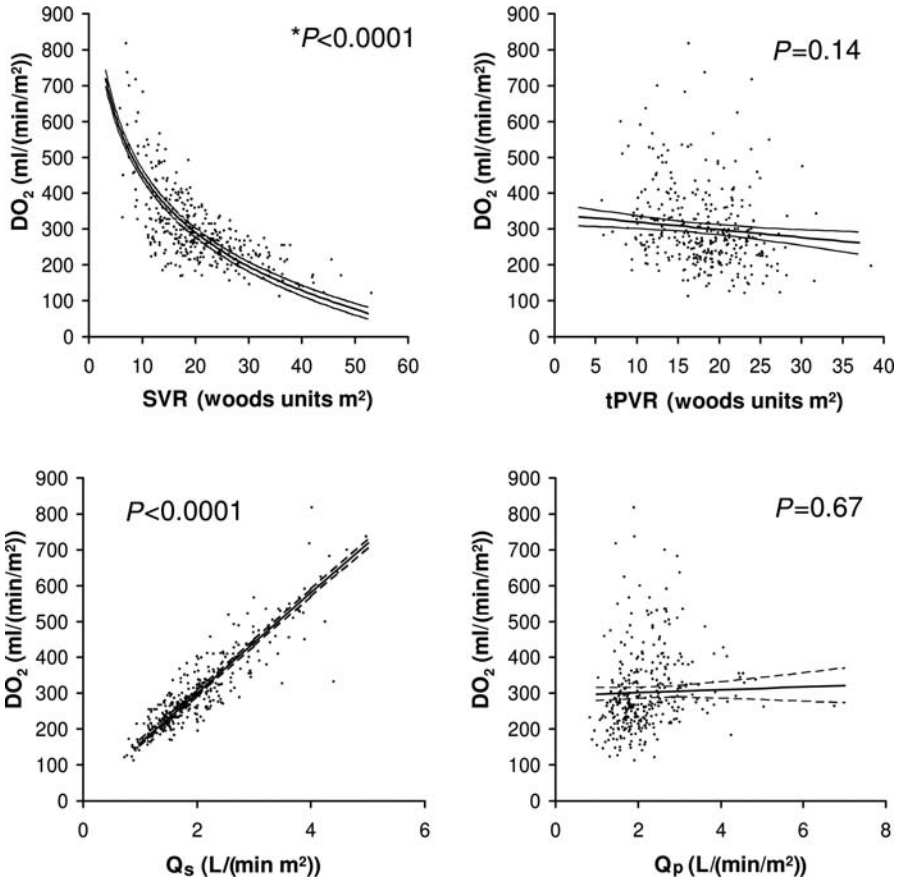

Figure 3: Correlations of systemic DO_2 with SVR, Q_s, total pulmonary vascular resistance including the BT shunt (tPVR) and Q_p in patients during the first 72 h after arrival in the ICU.

in the Norwood circulation [4]. There is a close positive correlation of DO_2 with Q_s and a negative correlation with SVR, but not with Q_p or tPVR (Fig. 3). Furthermore, among the variables of arterial O_2 content, DO_2 is not correlated with SaO_2 and only weakly correlated with PaO_2. Haemoglobin value has a high positive correlation with DO_2. Therefore, clinical management strategies aiming to increase DO_2 should target SVR and Q_s as well as haemoglobin, but not tPVR, Q_p, SaO_2 or PaO_2. The routine use of systemic vasodilators such as phenoxybenzamine and nitroprusside to maintain a relatively low and stable SVR has been shown to improve O_2 transport and postoperative outcomes [8, 36]. In contrast, vasoconstrictors such as vasopressin may have adverse effects on almost all the elements of systemic O_2 transport, including decreases in Q_s, CO and DO_2 as a result of an increase in SVR, leading to an increase in ERO_2 and lactate [27]. Additionally, more attention should be paid to the maintenance of a relatively high level of haemoglobin throughout the prolonged postoperative course [4].

Factors affecting VO_2 and its balance with DO_2

Direct and continuous measurements of VO_2 have allowed us to study the complex effects of clinical treatments on VO_2 itself and its relation with DO_2. Some routine treatments used in an effort to improve the balance of O_2 transport have in fact complex or even adverse effects.

Catecholamines. Catecholamines, such as dopamine, epinephrine and norepinephrine, are commonly used in children after CPB to augment cardiac contractility and DO_2. Catecholamines also stimulate VO_2 through their effects on myocardial work and metabolic rate [37]. If the increase in DO_2 is greater than the increase in VO_2, then catecholamines will improve the overall balance of O_2 transport and tissue oxygenation. In neonates, however, catecholamines have additional thermogenic actions through their effects on brown adipose tissue [38], resulting in an exaggerated increase in VO_2 [20]. Furthermore, neonatal hearts are known to have limited reserves to increase cardiac contractility. The reserves become marginal in a Norwood circulation. In these patients, efforts to improve DO_2 by catecholamines are more likely to be associated with predominately adverse effects. As we have reported [2], terminating a moderate dose of dopamine (5 μg/kg/min) was associated not with any significant changes in CO or DO_2 (Fig. 4A), but with a significant decrease in heart rate and rate pressure product, an indirect indicator of myocardial O_2 consumption. VO_2 also decreased by 16 ± 14 ml/min/m^2, representing a change of $20 \pm 11\%$. The termination of dopamine resulted in an overall improvement of the balance of O_2 transport, as indicated by the significant decrease in ERO_2. In other words, a moderate dose of dopamine induces predominantly an increase in VO_2, adversely affecting the VO_2–DO_2 relationship. Fig. 4B shows an example of on-line VO_2 monitoring before and after dopamine termination.

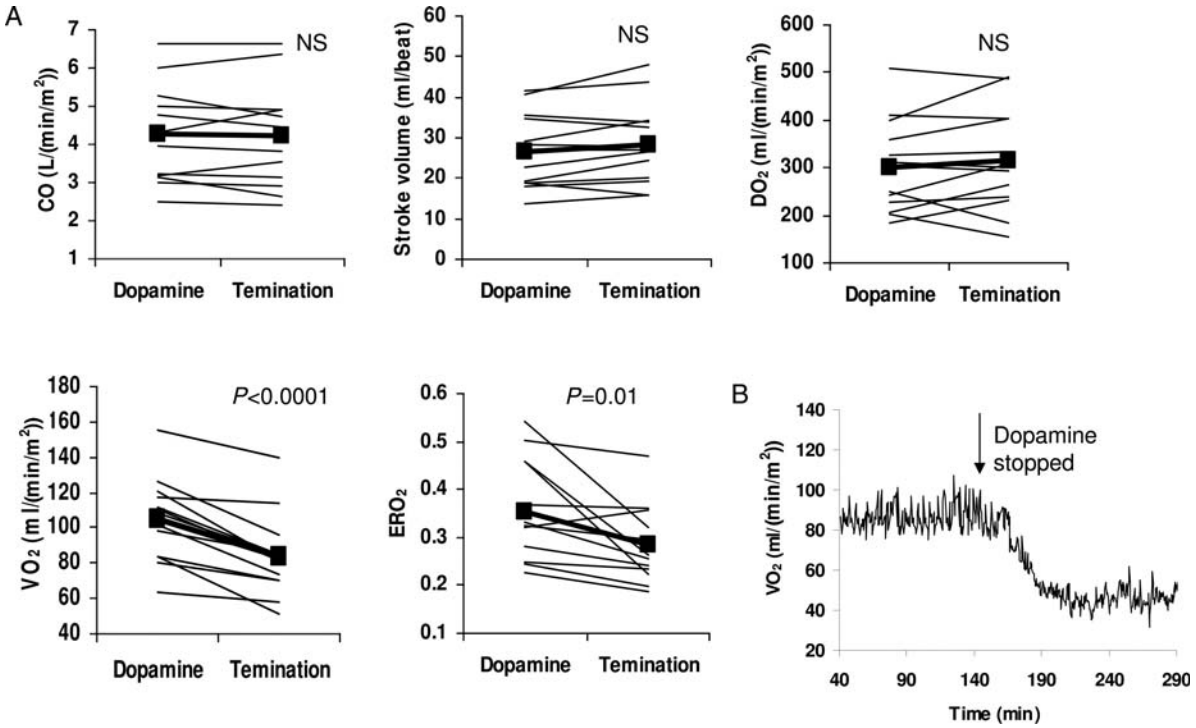

Figure 4: (**A**) The individual (thin line) and mean (bold line with closed squares) changes in systemic O_2 transport before and after termination of dopamine following the Norwood procedure. CO: cardiac output; DO_2: O_2 delivery; ERO_2: O_2 extraction ratio; VO_2: O_2 consumption. (**B**) An example of the on-line measurement of VO_2 showing the rapid decrease in VO_2 after terminating dopamine (7.5 μg/kg/min).

CO_2. CO_2 has been suggested as a factor increasing DO_2 in neonates both before and after the Norwood procedure [39]. 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 Q_p, thereby increasing Q_s. 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 O_2 transport (Fig. 5) [10]. Moderate hypercapnia increases Q_s as a result of its effect on SVR, rather than via PVR as proposed previously [39]. The increase in Q_s is primarily a consequence of increased cerebral blood flow that compromises splanchnic circulation, as indicated by the increase in cerebral O_2 saturation and the decrease in splanchnic O_2 saturation measured by near infrared spectroscopy (Somanetics INVOS 5100A, Troy, MI, USA). Moderate hypercapnia also decreases VO_2 and stimulates the release of catecholamines. The decrease in VO_2 improves the balance of O_2 transport, but the increase in catecholamines may be undesirable. Clinically, CO_2 should be used with caution when the aim is to improve DO_2.

Plasma-ionized calcium and magnesium. The realization of Ca^{2+} injury and Mg^{2+} protection on myocardial function has indicated the use of a cardioplegic solution with low Ca^{2+} and high Mg^{2+} during CPB [40]. However, postoperative management strategies have not been clearly defined. While supplemental Ca^{2+} is commonly used in current practice, little attention is paid to the supplementation of Mg^{2+}. From our data [41], we found that Mg^{2+} shows significant positive correlations with CO and DO_2 and negative correlations with heart rate, VO_2, ERO_2 and lactate after the Norwood procedure. We further examined the effects of Mg^{2+} and Ca^{2+} on myocardial energetics, using cardiac power output and rate pressure product. Cardiac power output represents cardiac power, whereas rate pressure is an indirect measure of myocardial O_2 consumption [22, 23]. At any given unit of rate pressure product, Mg^{2+} has a significant and positive correlation with cardiac power output. Ca^{2+} shows the opposite trend, although without achieving statistical significance. As such, our data indicate the beneficial effects of Mg^{2+} on myocardial energetics and systemic O_2 transport, whereas Ca^{2+} may be potentially harmful. Therefore, maintaining a relatively high level of Mg^{2+} and low level of Ca^{2+} may promote the efficiency of myocardial work and improve the balance of systemic and myocardial O_2 transport.

Hyperglycaemia. Hyperglycaemia has been identified as a risk factor for adverse outcomes in critically ill patients, including patients who have undergone CPB. Tight glucose control with insulin therapy has been shown to improve outcomes [42, 43], but is not a common practice followed for children after CPB. In our patients, blood glucose ranged from 2.8 to 24.6 mmol/l in the first 72 h after the Norwood procedure, with 60% of the measures being >6 mmol/l [33]. Correlation analysis of our data demonstrates a negative association between hyperglycaemia and systemic O_2 transport, with elevated glucose levels being closely and negatively correlated with CO and DO_2 and positively correlated with SVR and ERO_2 (Fig. 6). Our study was not designed to identify the cause-and-effect relationship. Randomized clinical trials of glucose control with insulin therapy are warranted to provide information regarding appropriate glucose management strategies in order to improve O_2 transport and clinical outcomes in neonates after the Norwood procedure and other cardiac surgeries.

Other factors. The Norwood procedure has a large dispersion of case complexity due to a wide spectrum of cardiac and non-cardiac lesions that certainly influence postoperative cardiac function and O_2 transport. The comprehensive Aristotle score,

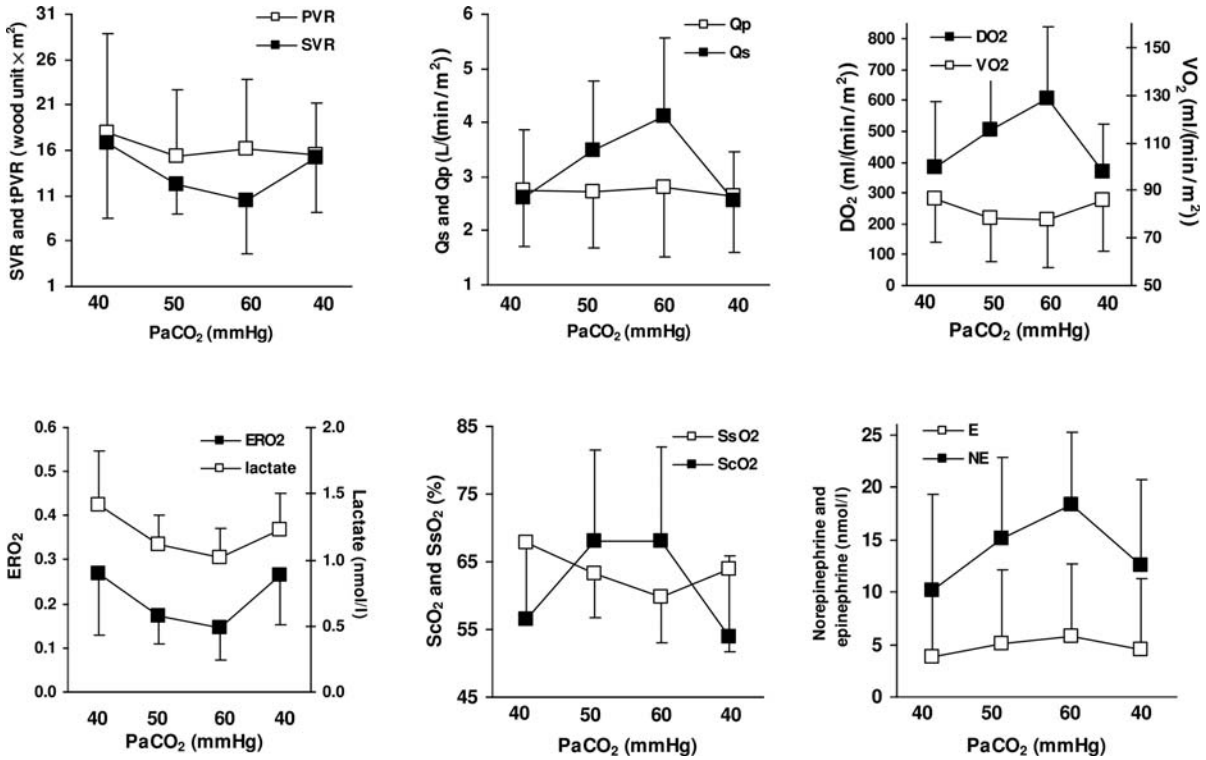

Figure 5: The changes (mean ± SD) in systemic O_2 transport including SVR, total pulmonary vascular resistance (tPVR), Q_p, Q_s, VO_2, DO_2, ERO_2, lactate saturation, ScO_2, SsO_2 and plasma epinephrine and norepinephrine concentration during the stepwise increases in $PaCO_2$ from 40 to 50 to 60 mmHg, and after termination of the additional inspired CO_2 at $PaCO_2$ 40 mmHg.

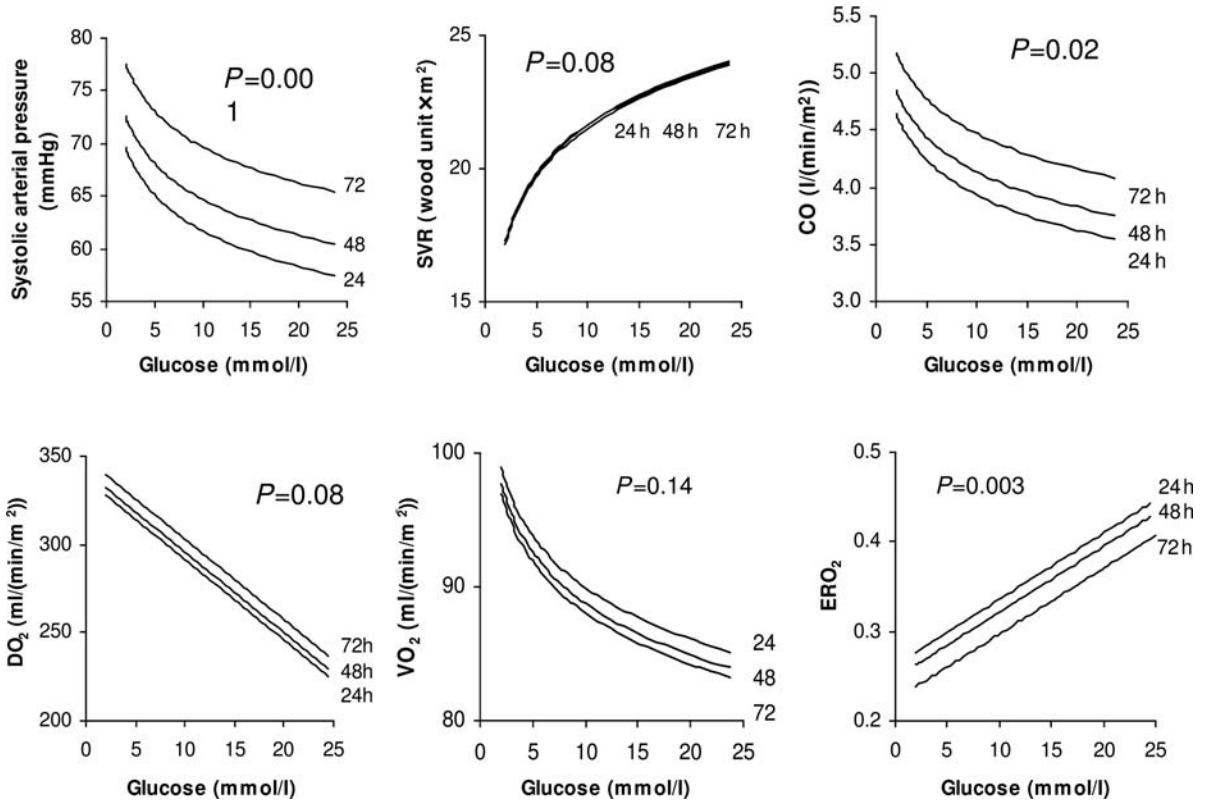

Figure 6: Representative regression lines for the predictive model of the correlations at 24, 48 and 72 h between blood glucose and the main variables of systemic O_2 transport, including systolic arterial pressure, SVR, cardiac output (CO), DO_2, VO_2 and ERO_2 after the Norwood procedure.

as an individualized measure of the complexity, summarizes the specific patient characteristics including the procedure-dependent factors (i.e. anatomical variations and associated procedures) and procedure-independent factors (i.e. clinical status of the patient) [44]. We have used the comprehensive Aristotle score with these specific factors and analysed the correlation with postoperative O_2 transport [25]. Not surprisingly, the comprehensive Aristotle score significantly correlates with CO following the Norwood procedure (Fig. 7). More importantly, our data analysis identified the specific risk factors contributing to a low postoperative CO level after the Norwood procedure, including preoperative myocardial dysfunction, mechanical ventilation to treat cardiorespiratory failure, atrioventricular valve regurgitation and aortic atresia. Therefore, a preoperative estimation of the comprehensive Aristotle score, particularly in association with these specific risk factors, may help to anticipate a high postoperative morbidity with low cardiac output syndrome and promote special prevention strategies.

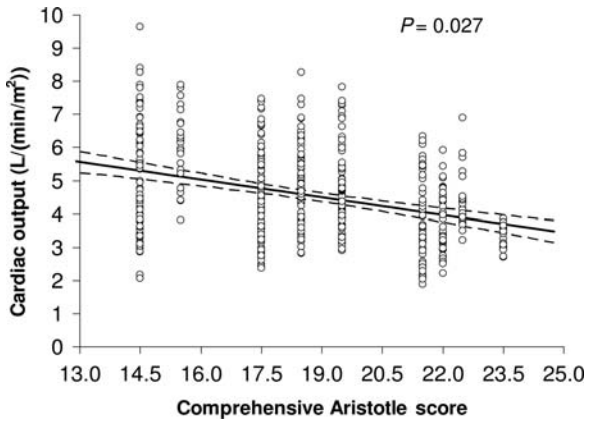

Figure 7: The correlation of the repeatedly measured total cardiac output and the comprehensive Aristotle score in neonates during the first 72 h after the Norwood procedure.

Influence of systemic O_2 transport on cerebral oxygenation. Ischaemic brain injury is a serious and frequent morbidity following the Norwood procedure in both the early postoperative period and the long-term follow-up [45]. Studies on neurological outcomes have largely focused on specific intraoperative risk factors such as pH imbalance and/or deep hypothermic circulatory arrest [46]. Preoperative reduction of cerebral blood flow and ischaemic injury are reported to be most severe in neonates with hypoplastic left heart syndrome [47]. The profound imbalance of systemic O_2 transport may place the cerebral oxygenation at further risk. We used near infrared spectroscopy to measure cerebral O_2 saturation after the Norwood procedure and found a significant reduction in the first 72 h that was particularly noticeable in the first 12 h (Fig. 8) [26]. Correlation analysis of systemic O_2 transport and cerebral O_2 saturation demonstrates that cerebral O_2 saturation is significantly influenced by all the parameters of systemic O_2 transport. As such, interventions to modify systemic O_2 transport may provide further opportunities to reduce the risk of cerebral ischaemia and improve neurodevelopmental outcomes.

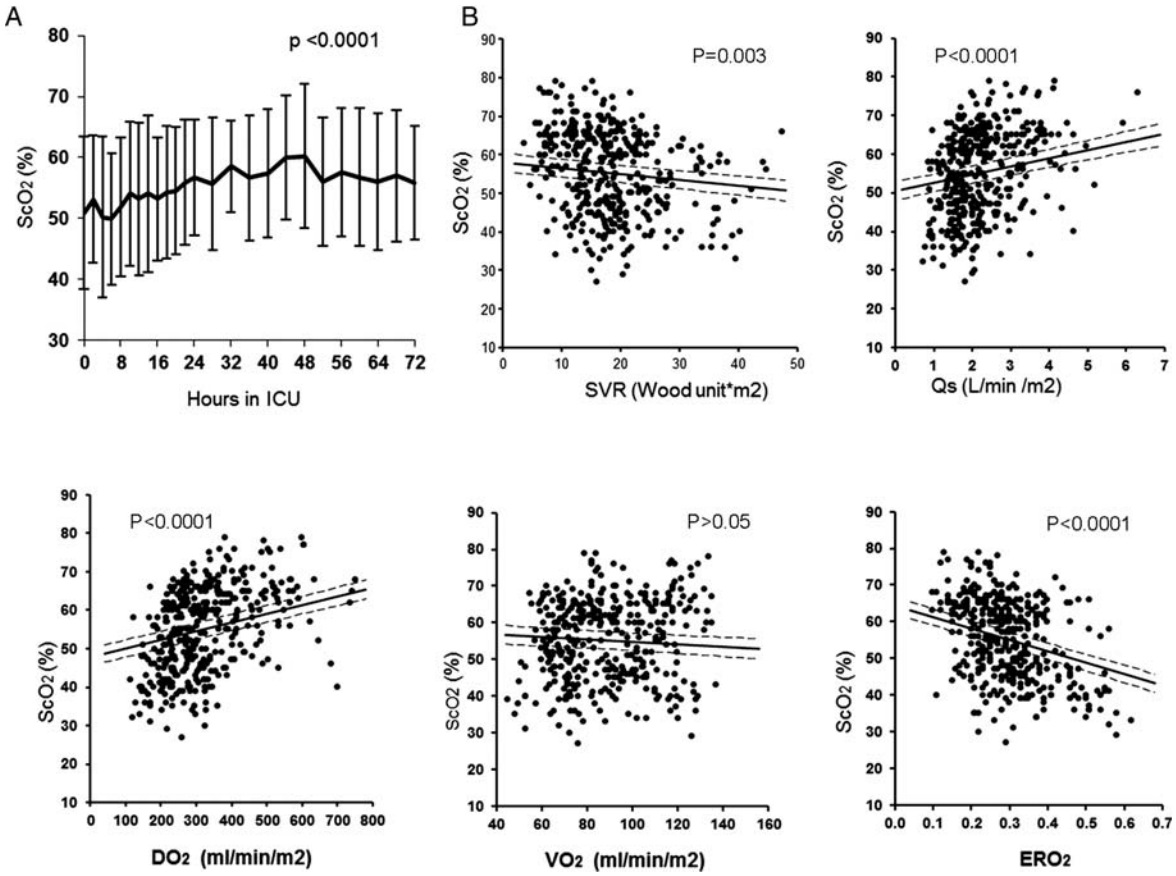

Figure 8: (**A**) Changes (mean ± SD) of ScO_2 during the first 72 h after the Norwood procedure. (**B**) Correlations between ScO_2 and systemic O_2 transport parameters of SVR, Q_s, systemic VO_2, DO_2 and ERO_2 during the first 72 h after the Norwood procedure.

CONCLUSION

Respiratory mass spectrometry is the state-of-the-art method for allowing the precise and continuous measurement of VO_2. Measured VO_2 and the direct Fick principle allow for calculation of the actual values of each element of systemic O_2 transport in the Norwood circulation, which allows analysis of the complex physiology after the Norwood procedure. The important findings to date are summarized in this review. Based on these findings, a number of refined postoperative management strategies may be considered to optimize systemic O_2 transport. The lowering of VO_2 with careful use of inotropes and the maintenance of a high haemoglobin level and a low SVR with vasodilators appear to be rational approaches. Additionally, the maintenance of a moderate $PaCO_2$ level, normal blood glucose, relatively low plasma Ca^{2+} and high Mg^{2+} may promote the balance of systemic O_2 transport. The improvement in systemic O_2 transport may have beneficial effects on cerebral oxygenation. Finally, a preoperative estimation of the comprehensive Aristotle score with specific patient risk factors may help to anticipate a high postoperative morbidity with low cardiac output syndrome and promote special strategies to prevent it. Ultimately, the resultant improved systemic and regional O_2 transport in the early postoperative period may have important impacts on long-term outcomes, thereby improving the quality of life for these vulnerable children. Our initial studies mark the end of the beginning. Much is yet to be explored.

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