The importance of blood lactate clearance as a predictor of early mortality following the modified Norwood procedure

Bari Murtuza a, Douglas Wall a, Zdenka Reinhardt b, John Stickley a, Oliver Stumper b, Timothy J. Jones a, David J. Barron a,*, William J. Brawn a

a Department of Cardiac Surgery, Birmingham Children’s Hospital, Steelhouse Lane, Birmingham B4 6NH, UK
b Department of Cardiology, Birmingham Children’s Hospital, Steelhouse Lane, Birmingham B4 6NH, UK

Received 31 August 2010; received in revised form 20 January 2011; accepted 24 January 2011; Available online 29 March 2011

Abstract

Objective: Optimisation of Norwood physiology, with focus on systemic perfusion, has beneficial effects on haemodynamic stability and perioperative mortality following the Norwood procedure for hypoplastic left heart syndrome. Early identification of high-risk patients during the postoperative phase might allow for institution of alternative management strategies with the possibility of avoiding poor outcome. Several studies have suggested that arterial blood lactate level, as an index of systemic perfusion and oxygen delivery, can to some extent predict mortality following paediatric cardiac surgery, though these studies have included heterogeneous groups of patients with only few Norwood patients. We sought to determine whether the blood lactate profile could be used to derive a simple, clinically applicable decision algorithm to direct therapy in a pre-emptive manner and perhaps identify patients for elective extracorporeal life support following the Norwood procedure.

Methods: We retrospectively analysed all patients at our institution who had undergone modified Norwood procedures between March 2002 and May 2008. All patients had received right ventricle-pulmonary artery conduits. Patients with systemic-pulmonary shunts were excluded. Outcome measures included 7-day and 30-day mortality. Serial arterial blood lactate measurements were taken in all patients for at least 72 h. Conditional inference tree modelling was used to determine the discriminatory value of the lactate profile and other pre- and intra-operative risk factors in terms of selecting survivors.

Results: As many as 221 patients were included. The 7-day ICU mortality was 26/219 (11.8%) with total 30-day mortality of 35/219 (15.8%). There were 21 interstage deaths. Mortality modelling demonstrated that an inability to clear blood lactate levels to <6.76 mmol l⁻¹ within the first 24 h was highly discriminatory in terms of predicting death within the first 30 days. A total of 11 out of 12 patients in this group died. Other risk factors examined, including weight, ascending aorta size, cardiopulmonary bypass and ischaemic times, were not as predictive in our model.

Conclusion: We have identified minimum blood lactate level within the first 24 h after the Sano–Norwood procedure as a highly discriminatory predictor of perioperative mortality. These patients might benefit from elective institution of early mechanical circulatory support.

© 2011 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Norwood; Hypoplastic left heart; Lactate; Mortality

1. Introduction

Blood lactate levels have been shown to correlate with systemic perfusion and oxygen delivery in a number of settings, including sepsis and following surgery for congenital heart disease [1,2]. Further, a number of studies have shown an important correlation between blood lactate levels and perioperative mortality in paediatric cardiac surgical patients [1—3]. Whilst several risk prediction models have been described in this population, such as the risk adjusted classification for congenital heart surgery (RACHS-1), these have not been specifically designed to direct therapy in an anticipatory manner and the numbers of Norwood patients in these studies have been small [4,5].

Since its introduction, the Norwood procedure has led to a better outcome for patients with hypoplastic left heart syndrome (HLHS) [6,7]. In particular, with continued improvements in perioperative management and refinements in surgical technique, several centres have reported 30-day survival rates of >75% and a growing number of families elect to continue with a pregnancy where an antenatal diagnosis of HLHS has been made [8—11]. One of the most significant technical developments is the Sano modification of the classical Norwood procedure using a right ventricle-pulmonary artery (RV-PA) conduit rather than a systemic-PA shunt [12]. This has purported benefits in terms of limiting diastolic runoff and improving coronary and systemic perfusion [8,10,12]. Good systemic perfusion and optimisation of Norwood physiology, in turn, have a beneficial...
effect on early haemodynamic stability and survival following the stage I procedure for HLHS.

We sought to determine whether the blood lactate profile, as a surrogate for systemic perfusion, would be a good predictor of perioperative mortality following the Norwood procedure. We examined early postoperative arterial blood lactate (LAC) levels as a predictor of 30-day and 7-day mortality. Conditional inference tree modelling (CITM) was used to determine the discriminatory value of the LAC profile, as well as known predictors of mortality such as weight, ascending aorta size, cardiopulmonary bypass (CPB) and ischaemic times, with a view to developing a simple, clinically applicable algorithm that might be used in directing management decisions to improve outcomes.

2. Materials and methods

2.1. Patients

All patients with a hypoplastic left heart were included in the study. A total of 16 patients with a single left-ventricle-dependent circulation was excluded as we wished to include only patients who had undergone the modified Norwood procedure with RV-PA Sano shunts. During the study period, no patient had undergone hybrid procedures with initial bilateral PA banding and maintenance of the arterial duct. All patients had a transthoracic echocardiogram prior to surgery to confirm the diagnosis and cardiac anatomy according to presence of aortic and mitral stenosis/atresia. Scan images were independently assessed by two cardiologists (Oliver Stumper, Zdenka Reinhardt). The distinction between valvar atresia and stenosis was made by assessment of flow using colour flow Doppler imaging on the two-dimensional images. Patients with non-classical HLHS variants such as unbalanced complete atrioventricular septal defects were also included. All patients were operated on at the Birmingham Children’s Hospital, Birmingham, UK, between March 2002 and May 2008. This era represented the time when our institution switched to the Sano modification of the Norwood procedure utilising an RV-PA conduit which was either left or right sided in terms of the pulmonary artery anastomosis. The study was a retrospective review that had been registered with the Institutional Research and Development Board and ethical approval had been waived by the Central Office for Research Ethics Committees due to use of retrospective, anonymised data.

Follow-up data for all patients were collected through patient records and data which had been stored either in written documents or electronically (Heartsuite Database; Systeria Inc., Glasgow, UK). All patients were followed up either at the Birmingham Children’s Hospital or at their local institution within the UK.

2.2. Surgical technique

All patients had been stabilised preoperatively with prostaglandin E1, either on the ward or on the paediatric intensive care unit (ICU). Surgery was performed in all cases at a median of 4 days of age (range: 0–108 days). The conduct of the surgery involved deep hypothermic circulatory arrest (DHCA) with systemic cooling to a nasopharyngeal temperature of 18–22°C with arterial perfusion via a 3.0 mm Gore-Tex® (WL Gore & Associates UK Ltd, Livingstone, Scotland) shunt into the innominate artery as previously reported by our institution [13]. Selective antegrade cerebral perfusion was used for patients. Cold crystalloid cardioplegic solution was employed as a single dose for myocardial protection and aortic arch reconstruction performed using pulmonary homograft patch. The RV-PA connection was constructed using a Gore-Tex® graft which was 5.0 mm for patients ≥2.5 kg and 4.0 mm for patients less than 2.5 kg. Patients were weaned from CPB on a standard inotrope regimen of 0.2–0.5 μg kg⁻¹ min⁻¹ milrinone and 0.01–0.15 μg kg⁻¹ min⁻¹ epinephrine. All patients underwent epicardial echocardiographic assessment of the heart prior and immediately after separation from CPB. Delayed sternal closure was routinely adopted for all patients in the study. Upon arrival in the ICU, target arterial oxygen saturations (SaO₂) were 70–80% with mixed venous oxygenu saturations (SvO₂) of 40–50%. Serial arterial blood LAC levels were measured routinely for all patients until the time of chest closure and for at least 48 h thereafter; sampling interval was at least hourly for the first 6 h after surgery. Whilst blood LAC levels were monitored, we did not use this as a parameter for goal-directed therapy in the management of our patients. Peritoneal dialysis catheters were routinely left on free drainage for all patients after surgery.

2.3. Statistical analysis and mortality modelling

All data were analysed using the statistical software package ‘R’ version 2.4 (R Foundation, Vienna, Austria). Continuous variables are presented as means with the standard deviation (SD) or as medians with the stated range. Comparative univariable analyses were performed using the unpaired t-test or Tukey multiple comparisons of means. Binomial or ordinal data are expressed as percentages, and comparative univariable analyses performed using the two-sided Fisher’s exact test. The Kruskal–Wallis test was used for continuous variables (weight and blood LAC level) as a non-parametric test of group differences. A probability value of <0.05 was taken to represent a statistically significant difference between groups. CITM was used to determine the discriminatory ability of pre- and intra-operative risk factors (weight, ascending aorta size, CPB and ischaemic times) as well as serial blood LAC values, in terms of selecting survivors versus non-survivors within the first 7 or 30 days.

CITM is relatively simple in terms of potential clinical usefulness and ability to predict mortality early with high discriminatory value. This would be important in terms of directing any subsequent intervention which would likely to be unproven in such a high-risk group of patients. CITM methodology uses recursive partitioning and allows one to explore the structure of a dataset and to visualise decision values for prediction of outcome [14]. CITM generates a non-parametric regression tree with the tree type based on outcome variable class and tree ‘growth’ based on statistical stopping rules.
3. Results

3.1. Patient characteristics and intra-operative data

A total of 221 patients was included in the study (135 males and 86 females). Of these, two died in the operating room and were excluded from the mortality modelling analysis (Fig. 1). Antenatal diagnosis was present for 153 patients (69.2%). The mean age of the patients at the time of surgery was 7.66 ± 13.1 days, whilst the mean weight of patients was 3.1 ± 0.6 kg. Of the 221 patients, the assignment to morphologic categories was as follows: aortic stenosis-mitral stenosis (AS-MS), n = 64 (29.0%); aortic atresia-mitral atresia (AA-MS), n = 43 (19.5%); AA-MA, n = 88 (39.8%). For non-classical variants, n = 26 (11.7%). The mean size of the ascending aorta (AscAo) was 3.3 ± 1.5 mm. The smallest AscAo size was associated with the AA-MA morphologic subtype. Other patient characteristics including antenatal diagnosis, impaired RV function, restrictive inter-atrial septum and presence of tricuspid regurgitation are shown in Table 1. The mean CPB time was 117.5 ± 34.8 min; median circulatory arrest time 15.5 min (range: 9–83 min); and mean cross-clamp (CC) time 55.8 ± 17.6 min. We did not find that, in themselves, longer CPB, circulatory arrest or CC times were significantly associated with higher 7-day mortality. The RV-PA shunt was placed to the left side of the Damus connection in 28 patients (12.7%) and to the right side in the other 194 patients. The overall 7-day mortality was 26/221 patients (11.8%), with a 30-day mortality of 35/221 (15.8%).

3.2. Perioperative mortality: patient-related factors

We found that patient weight <2.5 kg was significantly associated with higher 7-day (p = 0.0086; Fig. 2) and 30-day mortality (p = 0.010) compared with patient weight ≥2.5 kg. In assessing the influence of AscAo size, groups were divided into patients with AscAo < 2.5 mm and those with AscAo ≥ 2.5 mm. AscAo < 2.5 mm, however, was not associated with higher 7-day (p = 0.352) or 30-day mortality (p = 0.315).

3.3. Blood LAC profile: 30-day and 7-day mortality

The mean blood lactate on arrival in PICU was 7.3 ± 3.9 mmol l⁻¹. CITM demonstrated that the most specific predictor of 30-day mortality was inability to clear the blood LAC level to <6.76 within the first 24 h (p < 0.001; Fig. 3A); 11/12 (92%) patients within this group died. Importantly, the LAC emerged as the most important predictive factor from amongst all the parameters incorporated into the risk model, that is, weight, ascending aorta size, CPB and ischaemic times as well as LAC values themselves. For patients with a minimum 24-h LAC < 6.76, there were 24/209 deaths within 30 days. Of those who died within this group, minimum SaO₂ < 42.9% at 12 h emerged as the next most important predictor of mortality in the hierarchy of CITM nodes. For patients with SaO₂ > 42.9% at this time, a prolonged CPB time >160 min then discriminated

---

**Table 1.** Preoperative characteristics of patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>&lt;2.5 kg</td>
<td>23</td>
</tr>
<tr>
<td>≥2.5 kg</td>
<td>198</td>
</tr>
<tr>
<td>Ascending aorta size</td>
<td></td>
</tr>
<tr>
<td>&lt;2.5 mm</td>
<td>36</td>
</tr>
<tr>
<td>≥2.5 mm</td>
<td>185</td>
</tr>
<tr>
<td>Morphologic type</td>
<td></td>
</tr>
<tr>
<td>AA-MA</td>
<td>88</td>
</tr>
<tr>
<td>AA-MS</td>
<td>43</td>
</tr>
<tr>
<td>AS-MS</td>
<td>64</td>
</tr>
<tr>
<td>Other</td>
<td>26</td>
</tr>
<tr>
<td>Other features</td>
<td></td>
</tr>
<tr>
<td>TR &gt; mild</td>
<td>37</td>
</tr>
<tr>
<td>Impaired RV function pre-stage</td>
<td>83</td>
</tr>
<tr>
<td>Restrictive IAS</td>
<td>51</td>
</tr>
<tr>
<td>Antenatal diagnosis</td>
<td>153</td>
</tr>
</tbody>
</table>

Fig. 1. Summary of overall patient outcomes. Of the 221 patients, two died in the operating theatre. The majority of perioperative deaths occurred within the first 7 days.

Fig. 2. Patient weight versus 7-day mortality. A lower patient weight emerged as a significant risk factor for 7-day ICU mortality. The thick horizontal lines within the boxes represent median values with 50% of data values included within the boxes — delimited by the upper and lower quartiles. 95% of data points are included within the ‘whiskers’ associated with each box. p value for significance was determined using the Kruskal–Wallis statistic.
most effectively between survivors and non-survivors (Fig. 3A). Minimum 24-h LAC levels also emerged as the most discriminatory factor for survival versus non-survival at 7 days, though the LAC value predicting a poor outcome was >4.73 and only detected 13/28 deaths in this group of patients (Fig. 3B). Similar to findings for the 30-day mortality model, however, low SaO2 and then CPB times emerged as the next two most important discriminatory factors at sequential levels of the tree hierarchy (Fig. 3B). Although SvO2 measurements were used in some patients at various time points, we did not have sufficient data across the entire group for meaningful analysis.

In examining SaO2 and LAC values at 6 h as surrogates for Qp and Qs respectively, no consistent association could be demonstrated between the maximum/minimum 6-h LAC, first LAC and maximum/minimum 6-h SaO2, though there was a slight trend toward lower minimum SaO2 with an increasing maximum 6-h LAC amongst those patients who died within 30 days (Fig. 4).

3.4. Interstage and post-stage II mortality: LAC profile, SaO2

Of the 219 patients admitted to PICU after surgery, there were 186 patients discharged from hospital, with 21 interstage deaths and 165 patients proceeding to stage II (Fig. 1). The overall interstage mortality was thus 21/221 (9.5%). The mean age at the time of stage II was 164.0 ± 60.1 days. The first LAC-level arrival in ICU following stage I was more strongly associated with a higher post-Norwood ICU mortality than with interstage or post-stage II mortality (Fig. 5). Interstage mortality beyond 30 days was not significantly associated with weight <2.5 kg or ascending aorta size <2.5 mm. Three other factors were examined for their association with poorer interstage survival. ICU length of stay (p = 0.0008) as well as number of hours on mechanical ventilation (p = 0.010) was both greater for patients who died during the interstage period compared with survivors. Two or more chest exploration events on ICU also showed a
Fig. 5. First LAC level versus mortality stage. A higher first LAC level on arrival on ICU was associated more strongly with ICU death than Glenn or interstage mortality. This finding was statistically significant (Kruskal–Wallis test).

trend to being more associated with higher interstage mortality, though this was not statistically significant.

4. Discussion

We have presented our 6-year, single-centre experience of 221 patients using the Sano modification of the Norwood procedure in HLHS variants. The overall 7-day mortality was 11.8%, with a 30-day mortality of 15.8%. Patient weight, though not ascending aorta size, emerged as a risk factor for mortality in accordance with previous reports [8,9,15]. Importantly, the blood LAC profile was strongly associated with clinical outcome. Using CITM methodology, we have shown that failure to clear LAC levels to <6.76 within the first 24 h is highly discriminatory in terms of selecting out non-survivors in the first 30 days: 11 of 12 patients in this group died. Elevated LAC levels were also predictive of 7-day mortality. It should be emphasised that CITM identified LAC levels as being more discriminatory than other risk factors interrogated using the model including: weight, ascending aorta size, CPB time, circulatory arrest time and impaired RV function.

4.1. Early mortality and perioperative risk

The overall 30-day mortality of 15.8% in this series compares favourably with other published series from a similar era, with many centres achieving early survival of >75% [9,11,15]. We recently reported the results of 153 patients from our own centre who had undergone the Sano-modified Norwood procedure with a 30-day mortality of 22.2% [10]. Other recent published results have used the classical Norwood procedure in the large majority of patients [9,11,15]. The interstage mortality found here was 8.1%. Recent literature reports interstage mortality rates of 8–15%, though at least centres have reported 0% interstage mortality following introduction of intensive home surveillance programmes [9,11]. The exact causes of interstage mortality have been difficult to elucidate and mortality is often sudden and unexpected. Cardiopulmonary resuscitation post-Norwood procedure, however, has been found in one study to be associated with higher interstage mortality [9]. Sano et al. have identified weight <2.5 kg, gestational age <37 weeks and significant tricuspid regurgitation as being factors associated with overall mortality in their series of 62 modified Norwood patients with a median follow-up of 32 months [8]. Although we do not routinely institute a home surveillance programme as has been described by Furck et al., our interstage mortality with the Sano-modified Norwood patients is <10% [9].

Various scoring systems have been devised to predict preoperative risk of patients undergoing congenital heart surgery, including the RACHS-1 score, with a higher RACHS-1 category being associated with a higher early mortality and length of hospital stay [4]. In addition, several risk factors for mortality have been identified specifically in patients undergoing the Norwood procedure, including patient weight, size of ascending aorta, presence of a genetic syndrome, CPB and cross-clamp times, and morphologic subtype of HLHS [8,9,15]. We found that weight <2.5 kg was associated with reduced 7-day and 30-day survival. This finding has been reported by others, though some groups have not shown that weight is a major risk factor for early mortality [9]. In terms of other preoperative patient-related factors that might have an influence on early outcomes, a number of studies have alluded to the relevance of morphologic subtype of HLHS [8,11]. The distribution of patients across morphologic groups in our series is comparable with previous reports [16]. We did not, however, find that particular classical morphologies were associated with higher perioperative mortality, though non-classical variant morphology was associated with poorer 30-day survival. A detailed analysis of the effect of morphologic subtypes was not undertaken, however, and this is an area for further study.

4.2. Early mortality: importance of blood LAC profile

In addition to finding no significant differences in classical HLHS morphologic subtypes in terms of predicting survival, we, in accordance with others, did not find significant differences in CPB, CC, or DHCA times between survivors and non-survivors [8]. Although most published analyses of Norwood outcomes have focussed on pre- and intra-operative risk factors such as these, few studies have attempted to look for changes in simple biochemical parameters that may identify patients at higher risk following stage I reconstruction for HLHS. Some recent data have emerged for the usefulness of continuous oximetric superior vena cava saturation data in terms of predicting outcome, with a failure to achieve a mixed venous oxygen saturation of >55% within the first 18 h after the Norwood procedure being identified as a risk factor for mortality [17]. Few institutions, however, routinely employ this invasive form of monitoring. By contrast, the arterial blood LAC level is frequently and routinely monitored.

In our series, there were 35/221 (15.8%) deaths within 30 days and 21 interstage deaths, though the majority of deaths
within the first 30 days occurred within 7 days (26/33 patients; 78.8%). Similar findings have been reported by others [1,18]. Indeed, Charpie et al. observed nine deaths/46 patients (19.6%) within 72 h following neonatal repair for complex congenital heart disease [1]. We sought to determine whether the arterial blood LAC profile could in any way highlight patients who were more likely to die within this very early time period. Our finding that maximum LAC levels early on are associated with poorer perioperative survival is perhaps intuitive. More interesting here, however, is the finding that the minimum level to which the LAC level is cleared in the first 24 h is highly discriminatory in terms of predicting 30-day mortality.

In early work, Deshpande and Platt demonstrated an association between elevated blood LAC levels and mortality in neonates who were mechanically ventilated, though none of these patients had undergone cardiac surgery [19]. Looking specifically at cardiac surgical patients, some reports have focussed on the initial LAC level upon arrival in ICU as a predictor of early mortality, though these data have been conflicting. Siegel et al. reported a very high positive predictive value (PPV) of a LAC value of >4.2 mmol l\(^{-1}\) for mortality following cardiac surgery involving CPB [20]. Hatherill et al., however, in their study, found that a LAC level >6 mmol l\(^{-1}\) was more predictive, though with a low PPV of only 32% [2]. Further, in this latter study, only 7.1% of patients had undergone the Norwood procedure. We certainly observed a trend toward higher initial LAC levels in non-survivors, though there was considerable overlap in initial LAC values between survivors and non-survivors. It should also be noted that the initial LAC level is often elevated in neonates that have undergone a period of DHCA or selective perfusion at deep hypothermia and a high initial LAC level in these patients may not be reliable indicators of systemic perfusion or oxygen delivery.

It has been suggested that serial blood LAC measurement is a more reliable method for predicting mortality after CPB in neonates rather than a single initial level. Kalyanaraman et al. reported a good correlation between the total time after surgery where the lactate was >2 mmol l\(^{-1}\), and perioperative mortality, ventilation time and length of stay [3]. This study, however, only included 22 neonates/129 patients and only eight patients in RACHS-1 category 6. Perhaps the most relevant study to date concerning serial LAC values and risk of mortality in the context of the present work is that by Charpie et al., who reported the use of serial LAC measurements in neonates following complex cardiac surgery [1]. Of their patient group, 73.0% had undergone a Norwood stage I repair. They found an increase in LAC level of >0.75 mmol l\(^{-1}\) h\(^{-1}\) to have a PPV of 100% for a poor outcome, defined as death or institution of extracorporeal membrane oxygenation (ECMO).

The studies of Hatherill et al. found the greatest differences in LAC levels between survivors and non-survivors at 0, 6, and 24 h [2]. Importantly, this group also found that the non-survivors group exhibited an increase in LAC levels from 18 to 24 h which was not observed in the survivors group [2]. In measuring the period of time for which the LAC levels were >2 mmol l\(^{-1}\) (defined as LAC-time), Kalyanaraman et al. found LAC times of 24–48 h in RACHS-1 category 4 and 6 patients, and in non-survivors versus survivors in children following CPB surgery [3]. Further, Charpie et al. similarly found the largest increment in blood LAC levels in 3/8 patients with poor outcome (defined as death or need for ECMO) were with within the first 10 h [1]. They also found that the greatest difference in LAC levels for patients with good versus poor outcomes was at 24 h, with all patients in the good outcome group exhibiting a normal LAC level at 24 h [1]. These data are consistent with our own findings that the minimum level to which the lactate is cleared within the first 24 h has the greatest discriminatory value in terms of selecting survivors versus non-survivors. The patients in our study who died within 30 days had impaired ventricular function on ECHO with concurrently impaired high LAC levels, though the ventricular function was not quantitatively assessed. It should be noted, however, that no consistent association between postoperative atrio-ventricular (AV) valve regurgitation and high LAC levels was observed. Further, other mechanical problems such as aortic arch obstruction did not appear to account for the elevated LAC values and no patient in the study population who had evidence of aortic arch obstruction necessitated intervention within the first 30 days.

Importantly, it has been shown that blood LAC levels change in advance of sudden catastrophic changes in patient haemodynamics or other clinical parameters of low cardiac output and, further, that it may be difficult to identify patients with low cardiac output who will survive versus those who will acutely decompensate [1]. This underscores the potential powerful utility of our criterion in terms of the predictive ability of the blood LAC profile and the opportunity provided to closely re-analyse patient haemodynamics and clinical status and to re-focus attention on strategies to optimise Qp:Qs. Although not included in the present series, we have recently had a patient with high LAC levels within 24 h post-modified Norwood procedure in whom chest exploration was performed, with application of a haemostatic clip to partially reduce the lumen of the RV-PA shunt, with subsequent improvement in haemodynamics and fall in LAC. Early identification of such patients with high LAC also allows one to consider a timely intervention such as early, elective ECMO, to modify the universally dismal course of the patient group we have identified. Certainly, very good outcomes have been reported by Ungrleider et al., for routine mechanical circulatory assistance following the Norwood I procedure with 89% survival [21]. Indeed, in this study, increasing lactate was used as an index of worsening tissue hypoperfusion and as a key contributing factor in the decision to institute ECMO. Following commencement of mechanical ventilatory support, the blood LAC levels normalised to <2 mmol l\(^{-1}\) within 1.8 ± 1.1 days of surgery [21]. Others, however, have found that, at best, survival of ECMO patients was only 50%, though in these reports, it was instituted as an emergent measure where the patient could not be separated from CPB or where support had been instituted on the ICU [17].

### 4.3. Qp:Qs and the RV-PA conduit

We investigated the relationship of measured early blood LAC levels as a surrogate for the adequacy of systemic perfusion and the arterial oxygen saturations as a reflection of pulmonary blood flow, although numerous other factors related to mechanical ventilation settings and pharmacolo-
gical manipulation are well known to influence the Qp:Qs ratio [22]. It should be noted, however, that SaO2 and LAC are only indirect indicators of Qp/Qs and data on the SvO2 as well as SaO2 would be useful in this regard [17]. It is interesting to note that we did not find a positive correlation between rising LAC levels and higher SaO2 within the first 6 h after surgery. Charpie et al. have suggested that the differences in Qp:Qs between ECMO and non-ECMO patients following the Norwood procedure are greatest within 6 h of surgery [22]. We found that patients with lower minimum 6-h SaO2 values tended to have higher LAC values (Fig. 4). Whilst it is possible that there was an element of pulmonary stenosis and/or a small shunt size for a given patient, it is important to note two things in this regard. Firstly, we did not find any clear evidence of significant PA stenosis in our patients upon postoperative echocardiography, though it was not possible to make accurate quantitative measurements of branch PA sizes at this stage. Secondly, concerning the effects of length of shunt, we have previously published data showing that, although a right-sided RV-PA shunt is indeed slightly longer than a left-sided one, this was not found to influence either survival at 30 days or growth of the PA confluence or size of branch PAs [10]. Taken together, we suggest that the higher LAC levels associated with lower SaO2 values are more reflective of a low cardiac output rather than small shunt size or pulmonary obstruction.

4.4. Study limitations and conclusions

This study was a retrospective, single-centre study which as such limits the power of the statistical inferences that may be made. Concerning the blood LAC analysis, additional, more detailed assessment of the Qp:Qs ratio and measurement of mixed venous oxygen saturations could help clarify the importance of the blood LAC profile as a predictor of early mortality. Whilst 11/12 patients with lactate >7.67 at 24 h died and tended to have impaired ventricular function on ECHO, no specific correlation could be made between LAC levels and at best semi-quantitative measurements of postoperative RV function. Near infrared spectroscopy (NIRS) was used for intra-operative monitoring in some patients, though not routinely employed on ICU for monitoring, and an association between cerebral or splanchic NIRS values and LAC values could not therefore be determined. This would be an interesting area for further study.

It is possible that a comparative study could be designed to address the potential benefits of interventions such as elective ECMO in the patients identified as being at high risk based on their LAC profile, though this would require careful design and might take some time to accrue a reasonable number of patients with comparable characteristics in the two arms, that is, ECMO versus non-ECMO. Finally, we have not undertaken a detailed study of factors affecting interstage mortality and this, together with a study of interstage interventions (surgical or catheter-based) such as for recoarctation, is an area for further study.

Our findings with this large, single-centre experience of the RV-PA conduit support its use routinely for patients with HLHS and suggest that the reduced diastolic runoff and improved coronary perfusion may be one explanation for the good outcomes we have observed. The importance suggested here of the early blood LAC profile warrants further study and confirmation by other investigators and re-opens the debate as to the role of elective extracorporeal life support in patients following the Norwood procedure for the highest-risk groups of patients as identified here by 24-h minimum LAC levels and how outcomes might compare using this strategy versus the hybrid route in patients identified as high-risk preoperatively.

Acknowledgements

We thank the Cardiology Department (Joe de Giovanni, Paul Miller, Tarak Desai, Ashish Chikermane and Chetan Mehta) and Departments of Anaesthesia and Intensive Care for help with care of all patients and Joe Eurell for assistance in data collection.

References

Appendix A. Conference discussion

Dr G. Steilin (Padova, Italy): First of all, I would like to apologise for the limitation of my discussion since I did not have the chance to read the manuscript in advance.

The monitoring of the serum lactate in the postoperative period is certainly a parameter which has been considered important in many centres. However, we need to consider that some of these patients could have been very sick preoperatively. Therefore the operative result might depend on the preoperative condition. So my first question is, have you correlated your serum lactate level with the preoperative condition as well as with the postoperative condition?

Dr Murtuza: What I can say is indirectly, yes, we included in the risk model a number of preoperative as well as intra-operative parameters. We included the weight of the patient, ascending aortic size, as well as the height of the patient. We also included patients who had significantly impaired RV function, in addition to other intra-operative parameters within the same model: bypass times, cross-clamp times and circulatory arrest times. And despite including all of those factors, we still see that the lactate level emerges as the most specific predictor.

Dr Steilin: Okay, now, the second question: Have you correlated your serum lactate level with other parameters? You said that you correlated it with the aortic bypass time, but have you correlated it with other parameters which are very important in the postoperative period as, for instance, the mixed oxygen saturations, or is the LV function monitored by echocardiography?

Dr Murtuza: Yes. First of all, the model itself takes into account all the complex interactions between all the variables. That is the first thing to say. The second thing is, yes, of course we always assess the haemodynamic and clinical status of the patient. We have not specifically taken values for those parameters and correlated them with the blood lactate level.

The other thing to say is that we did have limited mixed venous oxygen saturation data on some patients, though these were not sufficient to perform a formal analysis.

In this regard, I should just mention that Dr Tweddell’s paper from 2007 showed very nicely that continuous oximetric SVC saturation data in this group of patients demonstrated that, in patients who were unable to achieve an MVO2 of greater than 55% within the first 18 hours, the risk of perioperative mortality was greater. But as I say, we did not have enough data ourselves on the MVO2 in our group of patients.

Dr Steilin: The last question: According to your results, what do you think will be your strategies for those patients that you have selected with the high lactate level and therefore are at high risk of death? Would you leave the chest open postoperatively? Would you leave purse strings in the mediastinum? Would you leave an ECMO running next to the patients? What would you do?

Dr Murtuza: First of all, I should say that all of our patients routinely have their chest left open for delayed chest closure. In the majority of cases, the chest is closed within 48 hours.

The other thing to say is that as a result of this study, there are a number of things to consider. We have found that a lactate value of >6.76 mmol/l at 24 hours identifies a higher-risk group of patients following the Norwood procedure, and an obvious question is what do we do with this information?

I think there are a number of things which I will answer very briefly. The first is that once we have identified a patient as higher risk according to the lactate profile, it enables the whole team to re-focus and reasses the haemodynamics and clinical status of that patient in a very careful manner, and to re-evaluate our strategies for optimizing Qp/Qs. It does raise the question as to whether we should consider, as I mentioned, elective ECMO support for these patients.

And I think the other thing to say is that we have had one patient identified as being in the high-risk group fairly recently, in whom we went back and reduced the diameter of the Sano shunt using haemostatic clips applied externally. Subsequently, the haemodynamics and clinical status of that patient as well as the lactate levels improved very rapidly, and the patient had a favourable 30-day outcome.