Use of tissue microdialysis to investigate hyperlactataemia following paediatric cardiac surgery

Riad B.M. Hosein, Kevin P. Morris, William J. Brawn, David J. Barron

Abstract

We investigated tissue lactate, pyruvate and lactate/pyruvate (LP) ratio post cardiac surgery and the relationship of cardiac index and oxygen delivery to late onset hyperlactataemia in ICU. It involved a prospective study of 10 children, mean age 4.9 (0.4) years, post-Fontan operation admitted with normo-lactataemia. Tissue lactate, pyruvate and LP ratio were monitored postoperatively every 30 min for 12 h via subcutaneous microdialysis in the abdominal wall. Cardiac index was measured by PICCO at 0, 4, 8 and 12 h. Blood and subcutaneous tissue lactate were strongly correlated (r = 0.87; P = 0.001). Mean (S.D.) blood lactate rose from 2.23 (0.49) to 3.73 (1.16) mmol l$^{-1}$ in the first 5 h after ICU admission (P = 0.008), only one child remaining normal. Microdialysis revealed lactate rising from 3.8 (0.83) to 5.3 (1.6) (P = 0.011), with a parallel pyruvate rise. LP ratio remained below 20, indicating no tissue oxygen debt. Cardiac index increased from 2.83 (0.63) to 3.77 (1.34) l min$^{-1}$ m$^{-2}$ over the same period (P = 0.05), with a corresponding increase in oxygen delivery from 4556 (1094) to 6076 (2322) ml min$^{-1}$ l$^{-1}$ (P = 0.04). Tissue microdialysis provides near-continuous measurement of tissue lactate and pyruvate, post cardiac surgery. Blood lactate rise post-Fontan is mirrored by tissue lactate and pyruvate concentrations, and not associated with a low or falling cardiac index or with tissue oxygen debt.

Keywords: Late onset hyperlactataemia; Fontan; Microdialysis

1. Introduction

Hyperlactataemia is common in cardiac surgery [1–3]. Hyperlactataemia may result from tissue hypoxia in situations of relative oxygen debt, as in low cardiac output states. However, hyperlactataemia may arise independently of tissue hypoperfusion [4, 5], as such lactate is not always a reliable indicator of tissue hypoxia [5].

Early-onset hyperlactataemia (EOH), present on ICU admission following cardiac surgery, has consistently shown to be associated with increased morbidity and mortality in children and adults [3, 6–8]. In contrast to EOH, we have observed that older children admitted postoperatively with a low blood lactate level commonly develop a late rise in blood lactate within the subsequent 12 h [9]. Maillet et al. suggested this late increase in blood lactate, termed late-onset hyperlactataemia (LOH), to be a benign finding. In a retrospective study we found no evidence that LOH was attributable to tissue hypoperfusion or associated with adverse clinical outcomes in children after cardiac surgery [9]. A strong association between LOH and hyperglycaemia raised the possibility of epinephrine-driven accelerated glycolysis as the underlying mechanism.

The aim of this study was to explore the feasibility of tissue microdialysis to investigate changes in subcutaneous tissue lactate, pyruvate and lactate:pyruvate (LP) ratio in a group of children developing LOH, and to determine whether a rise in blood and tissue lactate was associated with a reduction in cardiac index and oxygen delivery, or an increase in endogenous catecholamine level.

2. Patients/methods

We studied a group undergoing the Fontan operation as we previously observed that 44% of this patient group returned from theatre with a normal lactate but developed a late rise in lactate [9]. Between March 2006 and February 2007, 15 patients agreed to participate. Four were not studied because they developed EOH (admission lactate 3 mmol l$^{-1}$). The fifth was excluded for problems of PICCO line insertion. The Research Department and Ethics Committee approved this study. Written parental consent was obtained.

Microdialysis and PICCO catheters were placed on ICU if admission blood lactate was normal (< 3 mmol l$^{-1}$). Microdialysis samples were collected 1 h after insertion to avoid placement trauma on metabolite measurements. Time 0 was taken as one hour post-ICU admission. Microdialysis
samples were collected at half-hourly intervals for 12 h and the catheter removed after the last reading. Cardiac output, oxygen delivery, arterial and central venous blood gases, adrenaline, noradrenaline and cortisol were measured at 0, 4, 8 and 12 h, in addition to routine ICU measurements and observations.

2.1. Microdialysis

A 1 mm CMA 60 microdialysis catheter (CMA, Solna, Sweden) in the subcutaneous tissue in the anterior abdominal wall. Microdialysate fluid (containing Na\(^+\) 147 mmol l\(^{-1}\), K\(^+\) 4 mmol l\(^{-1}\), Ca\(^{2+}\) 2.3 mmol l\(^{-1}\), Cl\(^-\) 156 mmol l\(^{-1}\), with a pH of 6 and an Osmolality of 290 mosm kg\(^{-1}\)) was infused continuously at a rate of 0.3 \(\mu\)l min\(^{-1}\) through the catheter by a CMA106 microdialysis pump and was collected into microvials, allowing measurement via enzymatic analysis using the CMA ISCUS analyser.

Cardiac output was measured using a femoral artery thermodilution technique (PICCO). A pre-existing femoral arterial line was exchanged for the PICCO catheter. TriPLICATE measurements were made at 0, 4, 8 and 12 h, using a bolus of 5 ml cold (<10 °C) saline into the central venous line. The catheter was removed prior to ICU discharge.

2.2. Operative technique

All cases underwent a fenestrated extra cardiac Fontan operation (total cavo pulmonary connection). Patients were cooled to 32 °C on a cardiopulmonary bypass circuit primed with one unit of packed red cells, one unit of fresh frozen plasma, 2500 U heparin, 5 ml of CaCl\(_2\) 2.5 mmol l\(^{-1}\), 20 ml of 8.4% sodium bicarbonate, Plasmalyte\(^\text{®}\) containing Na 140 mmol l\(^{-1}\), K\(^+\) 5 mmol l\(^{-1}\), Mg 1.5 mmol l\(^{-1}\), Cl\(^-\) 98 mmol l\(^{-1}\), acetate 27 mmol l\(^{-1}\), and gluconate 23 mmol l\(^{-1}\) (Baxter Healthcare Norfolk, UK), 20% mannitol and 20 mg kg\(^{-1}\) of methyl prednisolone.

Postoperatively all patients returned from the theatre with inotropic support of dobutamine of 10 \(\mu\)g kg\(^{-1}\) min\(^{-1}\).

2.3. Analysis

Results are expressed as mean and standard deviation, or median and range where appropriate. Pearson correlation and/or the Wilcoxon signed rank test were used to assess trends and changes in variables over time using the Minitab 14 statistical package. A \(P\)-value of 0.05 was considered statistically significant.

3. Results

Patient demographics are shown in Table 1. Six of the patients had morphological right systemic ventricles and four morphological left ventricles. Mean (S.D.) age was 4.9 (0.4) years, weight 17.0 (3.0) kg, height 105.3 (5.1) cm and cardiopulmonary bypass time was 69.9 (16.3) min, no cardiopлегic arrest required.

All patients had uncomplicated clinical courses, extubated within 10 h of ICU admission and returned to the ward the following day.

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RV, right ventricle; LV, left ventricle; TS, tricuspid stenosis; TA, tricuspid atresia; PS, pulmonary stenosis; HLHS, hypoplastic left heart syndrome; DIIV, double inlet left ventricle; TGA, transposition of the arteries; CoA, coarctation of the aorta; Hypo Arch; Hypoplastic Arch; CPB, cardiopulmonary bypass.

3.1. Blood lactate levels

Nine patients (90%) patients developed LOH. Mean lactate increased from 2.23 (0.49) to 3.73 (1.16) mmol l\(^{-1}\) in the first 5 h (\(P=0.008\)) after returning from theatre. Eight of the nine patients who showed elevated lactate had their blood lactate return to below 3 within 12 h, with the 9th patient after 16 h (Fig. 1). A negative correlation was found between the duration of cardiopulmonary bypass and the change in blood lactate concentration in the first 4 h, with shorter bypass associated with a greater rise in lactate (\(r=0.831; P=0.003\)) as well as tissue lactate (\(r=0.781; P=0.001\)) (Fig. 2). Lactate levels in the prime were poorly correlated to the lactate rise postoperatively.

3.2. Microdialysis

Tissue lactate mirrored blood lactate (Fig. 2). A strong correlation existed between tissue and blood lactate concentrations (\(r=0.870; P=0.001\)). Tissue lactate was consistently higher than the corresponding blood lactate. A median rise of tissue lactate from 3.8 (range 2.9–5.6) to

![Fig. 1. Box plot showing progression of blood lactate of the group over study period.](https://academic.oup.com/icvts/article-abstract/7/3/384/672242)
5.3 (2.7–8.0) compared to blood lactate 2.8 (range 1.9–4.1) to 4.1 (1.7–5.0) μmol l⁻¹ during the first 4 h.

Pyruvate showed similar trends to tissue lactate with a median rise from 235.4 (range 180.3–511.6) to 369.9 (171.0–480.0) μmol l⁻¹ during the first 4 h. The LP ratio
remained between 10–20 during the study (Fig. 2). Generally lactate and pyruvate peaked between 4–8 h after surgery.

Tissue and blood glucose correlated well (r=0.85; P=0.004). However, no significant correlation existed between tissue glucose and tissue lactate level, nor between blood lactate and blood glucose (P=0.445).

Glycerol was consistently above 200 μmol l⁻¹ (Fig. 3b), with a median rise from 697.2 (575.2–1021.6) to 700.1 (range 374.1–1011.4) mmol l⁻¹ during the first 4 h. Nonetheless there was no significant correlation amongst the stress hormones and glycerol.

3.3. Cardiac index

Cardiac index (CI) rose postoperatively from a mean of 2.83 (0.63) to 3.77 (1.34) l min⁻¹ m⁻² over the first 4 h (P=0.05) (Fig. 3a).

Echocardiography demonstrated good ventricular function in all patients.

Mean oxygen delivery rose from 4556 (1094) to 6076 (2322) ml O₂ min⁻¹ (P=0.04) over the first 4 h (Fig. 3a).

We demonstrated no significant increase in oxygen extraction to coincide with the lactate rise over the first 4 h (median increase 1% (range −7 to +21.3%) (P=0.262).

Core and peripheral temperature increased after surgery, with gap reduction over the first 4 h. Mean urine output remained 1 ml kg⁻¹ h⁻¹ throughout.

The mean PA pressures at 0, 4, 8 and 12 h were 15.8 (3.6), 15.6 (3.5), 15.6 (3.5) and 13.6 (2.2), respectively, and these were not correlated with lactate levels or CI.

Patients required filling in the form of 4.5% Human Albumin Solution with negligible lactate levels with no patients requiring blood or FFP.

3.4. Hormonal assays

Adrenaline, cortisol and noradrenaline were elevated (Fig. 3b). No significant correlation existed between catechol-amine or cortisol levels and blood or tissue lactate concentration. All patients returned on dobutamine of 10 μg kg⁻¹ min⁻¹ with no escalations. Five reduced their support to 5 μg kg⁻¹ min⁻¹ by the time of extubation and all by study's termination.

4. Discussion

This study demonstrated the feasibility of microdialysis to provide near-continuous measurement of tissue metabolites. Tissue and blood lactate correlated postoperatively. Microdialysis is a novel and viable technique for real time, in vivo measurements of markers of cell injury and metabolites in the interstitial compartment and involves inserting a semi-permeable membrane (catheter) into the investigated tissue. The membrane is perfused with a perfusate by a low-flow pump. The perfusate equilibrates with the tissue fluid outside the membrane, osmotic pressure being the driving force. Metabolites from the extra-cellular fluid diffuse through the membrane and are carried out of the catheter to a microvial which is transferred to an analyser. We focused on patients who returned from surgery with a low lactate concentration. Nine of 10 patients developed a late rise in blood lactate to >3 mmol l⁻¹, a threshold which Maillet et al. described as LOH in adults [3]. Tissue
lactate rise mirrored a rise in tissue pyruvate, LP ratio remained unchanged and below 20 at a time that lactate was increasing. In ischaemia the LP ratio would be higher [10].

Clinical examination did not suggest poor oxygen delivery. Their blood pressures and urinary output were stable and echocardiographic findings demonstrated good ventricular function in all patients. They also warmed adequately and were quickly weaned from mechanical ventilation with no complications.

PiCCO is attractive combining the reliability of thermo-dilution without needing additional invasive monitoring beyond a central venous line and arterial line. Cardiac index increased when blood and tissue lactate increased. Oxygen extraction remained within normal physiological limits. This would suggest another mechanism for LOH excluding oxygen delivery failure and tissue ischaemia.

What other mechanism could be responsible? Glucose and lactate metabolism are inter-dependent and hyperglycemia has been implicated in previous studies investigating late-onset hyperlactataemia in adults [3]. Normally, increased glycolysis results in increased production of pyruvate which sequentially initiates an increase in Krebs cycle activity and greater energy production. Lactate is created by the reaction of pyruvate with NADH, and increases in parallel in this situation such that LP ratio remains low. Catecholamines have been implicated as a trigger for increased substrate for lactate and pyruvate production through glycolysis [12, 13]. We previously demonstrated a strong correlation between glucose and lactate in children developing LOH [9]. However, this study was unable to demonstrate a significant relationship between catecholamine and lactate concentration, or between glucose and lactate concentration to support this.

An alternative mechanism would be ‘washout’ of lactate, formed in the tissues during cardiopulmonary bypass as a result of tissue hypoxia, coinciding with rewarming and reperfusion. Although the timing of maximal re-warming coincided with a lactate rise, a number of factors contradict this mechanism. The longest bypass runs would have the greatest reservoir of lactate and show the greatest increase, whereas the opposite was in fact the case. Lactate rise was accompanied by a parallel increase in pyruvate, with an LP ratio <20, implying no ischaemia at the time of ‘washed out’. Thirdly, we found no significant correlation between change in temperature or temperature gap and rise in lactate.

Interstitial glycerol concentration in the subcutaneous adipose tissue is a marker for the intracellular lipolytic rate [14]. Glycerol measured in the subcutaneous tissue has been shown to be a surrogate marker of the stress response and originates from fat breakdown into free fatty acids and glycerol. This is controlled by sympathetic nerves in adipose tissue indicating stress [15]. No significant correlation was found between glycerol and tissue lactate. Therefore we cannot conclude that the stress response was responsible for the LOH.

The liver is a major organ of lactate metabolism [11]. Only routine liver function tests (alanine transferase, aspartate transferase, bilirubin and clotting screen) were measured postoperatively. All results were within normal limits. Bypass prime lactate was unlikely to have contributed to the late lactate rise as a large prime lactate load would be expected to result in an increase in lactate peroperatively and on admission to PICU, which was not evident.

5. Limitations

There are some limitations of this study. Only 10 patients were studied, making it difficult to confirm a mechanism to explain LOH. Blood samples and cardiac output measurements were taken at four fixed time-points, with the potential of missing changes between these times, particularly for short half-life substances such as catecholamines. The start of microdialysis was delayed by inserting the microdialysis catheter only after return to ICU, resulting in loss of data for the immediate postoperative period.

6. Conclusion

Tissue microdialysis is feasible and allows monitoring of tissue lactate, pyruvate and other metabolites. We found good correlation between tissue and blood lactate, suggesting that microdialysis may be valuable in investigating hyperlactataemia after cardiac surgery. LOH is common in children who have undergone the Fontan operation, often developing between 0–4 h postoperatively. The blood and tissue lactate rise are accompanied by a parallel increase in tissue pyruvate, with no change in LP ratio, increase in cardiac index and normal oxygen extraction would suggest a non-ischaemic mechanism for lactate rise. Further studies are needed to elucidate the mechanism.

Acknowledgments

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References


Conference discussion

Mr. V. Tsang (London, UK): I have to admit that I’m no metabolic expert, nor do I have a lot of experience with the microdialysis catheter, but I will address your paper in terms of principles. I can understand the attractiveness of this subcutaneous microdialysis catheter monitoring the metabolic status continuously on the intensive care unit. It is very important for patients with low cardiac output and high lactate. In your study you observed your dataset from children who exhibited a low blood lactate in the ICU following cardiac surgery with no evidence of low cardiac output. Why did you do the opposite, in practical terms?

Dr. Hosein: This was envisaged to be part of a larger study looking specifically at elucidating the mechanism for late-onset hyperlactataemia. This was just a feasibility study to see if we could have looked at the tissue microdialysis in kids after surgery because this hasn’t been done before. So that was the initial aim of our study.

Mr. Tsang: I would be very tempted to look at your microdialysis catheter data in patients with low cardiac output and high lactate. Do you have any data at all?

Dr. Hosein: Not at this point. This was only looking at patients with late-onset hyperlactataemia.

Mr. Tsang: You have no patients with low cardiac output and high lactate?

Dr. Hosein: Not in this study, no.

Mr. Tsang: Do you have any data in terms of explaining the hypothesis you made that late-onset hyperlactaemia related to high catecholamine levels or cortisol levels?

Dr. Hosein: The stress response in this study was markedly elevated. However, we don’t have any data to compare the normal stress response of hormones in a standard surgical patient. This was all de novo. So we don’t have data on other patients, but what we can say is that the stress response was quite marked in these patients. What it actually shows is that this late-onset hyperlactatemia, because it’s unrelated to low cardiac output, was probably driven by the stress response of surgery.

Dr. Tsang: My final point, in your conclusion you said the increase in blood lactate mirrored by an increase in subcutaneous tissue lactate and is not associated with a low cardiac output. Why would you not say the increase in blood lactate mirrored by an increase in subcutaneous tissue lactate which is associated with a corresponding increase in cardiac output?

Dr. Hosein: Sorry?

Mr. Tsang: What I’m trying to say is that in your conclusion you used a double-negative which can be misleading. That is, a high lactate is not associated with a low cardiac output. How can you address the discrepancy of a high lactate with an increase in cardiac output or a normal cardiac output?

Dr. Hosein: Well, what we were fearful of in patients with late-onset hyperlactataemia was that there would possibly be a hidden low cardiac output state which we hadn’t identified. That was what we were actually quite sceptical about, and we wanted to prove beyond a reasonable doubt that there was not a low cardiac output state in these patients. I think we have managed to do that in the sense that patients warmed up very well, their urinary output was absolutely fine throughout this study and their objective cardiac output measurements were all normal. The only thing that pointed towards a low cardiac output state was a blood lactate level that rose. Now, if one of my patients at 3:00 in the morning develops a lactate of 4, 5, but they warm up peripherally, their urine output is absolutely fine, their echo postoperatively shows reasonable ventricular function, then I’m not concerned. I think that’s what we tried to show.

Dr. L.H. Edmunds (Philadelphia, Pennsylvania): Does the change in lactate at 4 h correlate with any changes in temperature, and did you try to see what the correlation coefficient was for temperature and lactate? As an addendum, do you think you should remind us all about the buffering capacity of blood when the lactate levels are so low?

Dr. Hosein: I’ll address the first question as much as I can. The correlation between temperature rise and blood lactate was actually an R value of 75, so it did correlate quite strongly with temperature change, yes, it did.

Dr. A. Corno (Liverpool, UK): You have already excluded the patient with low cardiac output as a reason for a late rising lactate level. The other variable unknown is the modality of conduction of cardiopulmonary bypass in terms of normal or low-flow versus high-flow, hypothermia versus normothermia, and low hemoglobin values versus normal values. In your study, despite you didn’t have any period of aortic cross-clamp, you have used hypothermia. Can you give us at least the details about the flow and hemoglobin you used in your study?

Dr. Hosein: I believe hemoglobin levels were about 10 to 12 throughout our study actually. We compared the priming lactate levels within the blood prime as well as the lactate levels when the patient first came back as well as the difference in lactate between 4 h and the time of arrival and they didn’t correlate at all actually.

Dr. Corno: And the flow was?

Dr. Hosein: I’m not sure what the flow was.