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Original Article

Hyperglycaemia is negatively associated with systemic and cerebral oxygen transport in neonates after the Norwood procedure

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Abstract *Objective:* Hyperglycaemia has been identified as a risk factor for adverse outcomes in critically ill patients, including those who have undergone cardiopulmonary bypass. Tight glucose control with insulin therapy has been shown to improve outcomes, but is not common practice for children following cardiopulmonary bypass. We examined the relationship between blood glucose level and systemic and cerebral oxygen transport in a uniform group of neonates after the Norwood procedure. *Methods:* Systemic oxygen consumption was measured using respiratory mass spectrometry in 17 neonates for 72 hours postoperatively. Cardiac output, systemic and total pulmonary vascular resistances – including the Blalock–Taussig shunt, systemic oxygen delivery and oxygen extraction ratio, as well as arterial lactate and glucose, were measured at 2- to 4-hour intervals. Cerebral oxygen saturation was measured by near-infrared spectroscopy. *Results:* Blood glucose levels ranged from 2.8 to 24.6 millimoles per litre. Elevated glucose level showed a significant negative correlation with cardiac output ($p = 0.02$) and cerebral oxygen saturation ($p = 0.03$), and a positive correlation with oxygen extraction ratio ($p = 0.03$). It tended to correlate positively with systemic vascular resistance ($p = 0.09$) and negatively with oxygen delivery ($p = 0.09$), but did not correlate with oxygen consumption ($p = 0.13$). *Conclusions:* Hyperglycaemia is negatively associated with systemic haemodynamics, oxygen transport, and cerebral oxygenation status in neonates after the Norwood procedure. Further study is warranted to examine tight glucose control with insulin therapy on postoperative systemic and cerebral oxygen transport and functional outcomes in neonates after cardiopulmonary bypass.

Keywords: Cardiopulmonary bypass; intensive care; hyperglycaemia; oxygen delivery; oxygen consumption

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HYPERGLYCAEMIA IS A PROMINENT FEATURE IN critical illness, including after cardiopulmonary bypass.[1,2] This is a result of the systemic inflammatory response and complex metabolic and endocrine derangements, which include increased release of catabolic hormones – catecholamines, glucagon, and cortisol – and inhibition of, and resistance to, anabolic hormones – insulin and insulin-like growth factor 1. Hyperglycaemia has long been considered essential for providing fuel to vital organs and interpreted as a beneficial adaptation. However, in recent years, it has been identified as an independent risk factor for adverse outcomes in various critically ill non-diabetic patients, including patients who have had a cardiac infarction or surgery.[3–5] In all, two large randomised, control trials have demonstrated that tight glucose control with insulin therapy is associated with substantial improvement in outcomes of critically ill adults, and is most pronounced after cardiac surgery, reducing the morbidity and mortality by approximately 40%.[6,7] More recently, the beneficial effect was also apparent in paediatric intensive care, where targeting blood glucose to age-adjusted normal fasting concentrations significantly reduced the systemic inflammatory

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response and mortality, despite a relatively high incidence of hypoglycaemia.[8] Conversely, a more recent study by the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation investigators showed increased mortality in critically ill adults treated with tight glucose control.[9]

In children who have undergone cardiopulmonary bypass, it has not been a common practice to treat hyperglycaemia due to concerns of hypoglycaemia and neurologic injury. However, hyperglycaemia has also been associated with poor outcomes in post-cardiopulmonary bypass infants, with increased complications including central nervous system injury, infection, longer intensive care unit stay, and death.[10,11] Given the current controversies involving hyperglycaemia and tight glucose control,[12,13] better identification of risk factors and understanding of the underlying mechanisms are crucial in adequate glucose management in these children. We chose to study neonates undergoing the Norwood procedure, since this group represents a challenging group of patients with often profound systemic haemodynamic instability, oxygen transport imbalance,[14] and significantly reduced cerebral oxygen saturation in the early postoperative period.[15]

Most of the previous clinical studies have focused on observations of the "hard" clinical endpoints of morbidity and mortality. Our group has obtained a physiological understanding of the varied aspects of the Norwood circulation.[14–16] In the present study, we focused on the relationship between elevated blood glucose level and systemic haemodynamics, oxygen transport, and cerebral oxygenation in neonates during the early postoperative period after the Norwood procedure.

Materials and methods

Patients

The Research Ethics Board at the Hospital for Sick Children, Toronto, Canada, approved this study. We obtained consent from the parents of all neonates (n = 17) with hypoplastic left heart syndrome undergoing a classic Norwood procedure with a Blalock–Taussig shunt between April, 2004 and February, 2007. During this time frame, measurements of systemic haemodynamics, oxygen transport, and cerebral oxygen saturation were a routine part of clinical monitoring in our centre. The group consisted of eight patients with aortic and mitral stenosis, nine patients with aortic atresia including three patients with mitral stenosis, and the remaining six patients with mitral atresia, including one patient with total abnormal pulmonary venous connection.

Intraoperative procedures

All patients were intubated with cuffed endotracheal tubes (Microcuff GmbH, Weinheim, Germany). General anaesthesia was maintained with inhaled isoflurane, intravenous fentanyl, and pancuronium bromide. A standard Norwood procedure with a 3.5-millimetre right-modified Blalock–Taussig shunt was performed.[14] Cardioplegia solution consisted of 2:1 blood and crystalloid, the latter including 30 units of insulin and 25 millimoles per litre of glucose (BCD-Vanguard, COBE Cardiacvascular Inc., Mirandola, Italy). A bolus of aprotinin (50,000 kallikrien inhibitor units per kilogram) was given followed by 100,000 kallikrien inhibitor units per 100-millilitre prime. Our protocol was to administer 0.25 milligram per kilogram of phenoxybenzamine at initiation of cardiopulmonary bypass, and milrinone (0.66 microgram per kilogram per minute) and dopamine (5 micrograms per kilogram per minute) before termination of cardiopulmonary bypass. A pulmonary venous line was inserted into the orifice of the right upper pulmonary vein and a central venous catheter was inserted into the superior caval vein.

Postoperative management

Sedation consisted of a continuous intravenous infusion of morphine and lorazepam. Intermittent doses of a muscle relaxant – pancuronium bromide – were given. The oesophageal temperature was maintained between 36°C and 37°C. Time-cycled pressure-control/pressure support ventilation was used with ventilation volume and rate adjusted to control $PaCO_2$ at 45–55 millimetres of mercury. Arterial oxygen saturation was maintained between 70% and 85%, and haemoglobin between 14 and 16 milligrams per decilitre. Vasoactive and inotropic drugs – such as dopamine, milrinone, phenoxybenzamine, and vasopressin – and volume infusions – 5% albumin or packed red blood cells – were administered according to standard protocol.[14] The glucose management protocol was to administer insulin when blood glucose exceeded 15 millimoles per litre. Arterial glucose concentration was measured together with blood gases using a blood gas analyzer (ABL 700, Radiometer Copenhagen, Copenhagen, Denmark)

Methods of measurements

Systemic haemodynamic and oxygen transport variables. Systemic oxygen consumption was measured continuously using an AMIS2000 respiratory mass spectrometer (Innovision A/S, Odense, Denmark). This is a highly sensitive and accurate method for continuous gas analysis, which allows simultaneous measurements of multiple gas

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fractions.[17] Blood samples were taken from the arterial, superior caval vein and pulmonary venous lines to measure blood gases, arterial lactate, and glucose. Correct placement of the superior caval vein and pulmonary venous sampling lines was verified by chest X-ray. Systemic haemodynamics and oxygen transport variables were calculated using the standard equations, including cardiac output, systemic and total pulmonary vascular resistances – including the Blalock–Taussig shunt – systemic oxygen delivery and oxygen extraction ratio.[14] Rate pressure product and cardiac power output, the indirect indicators of estimate myocardial oxygen and adenosine triphosphate consumption, were calculated using the following equations:

$$\text{Rate pressure product (unit)} = \text{heart rate (beats per minute)} \times \text{systolic arterial pressure (millimetres of mercury)}/1000$$

$$\text{Cardiac power output (Watts)} = \text{cardiac output (litres per minute)} \times \text{mean arterial pressure (millimetres of mercury)} \times 0.0022$$

Cerebral oxygen saturation. A near-infrared spectroscopy probe was placed on the patient's forehead to continuously measure cerebral oxygen saturation. The recordings were monitored by a dual-detector device (Somanetics INVOS 5100A, Troy, MI, USA) and recorded at 1-minute intervals.

Study protocol

The study was performed during the first 72 hours after arrival to the intensive care unit. Values of systemic haemodynamic and oxygen transport variables, cerebral oxygen saturation, arterial lactate, and glucose concentrations were collected at 2-hour intervals during the first 24 hours and at 4-hour intervals in the subsequent 48 hours.

Data analysis

Data are expressed as mean (standard deviation). Mixed linear regression analysis for repeated measures was used to determine the nature of any time trend of the measures over the study period. For some measures, various transformations of time – quadratic, logarithmic, and polynomial – were tested regarding the best fit for the time course. In order to reveal the influence of elevated blood glucose on systemic and cerebral oxygen transport variables, the relationship was analysed after temporal justification, that is, between blood glucose and oxygen transport measures after 2 or 4 hours with regard to time. Logarithmic transformation of blood glucose was used for the best fit for correlation with some measures. The strength and trend of correlations are indicated by parameter estimate – or slope – and p-value. All data analysis were performed using SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC, USA). A p-value <0.05 indicated a statistical significance.

Results

Patients

Patients were studied at a mean age of 7 (4) days, a weight of 3.6 (0.5) kilograms, and body surface area of 0.24 (0.03) squared metre. The duration of cardiopulmonary bypass was 130 (31) minutes, aortic cross-clamp 15 (15) minutes, circulatory arrest 15 (15) minutes, and cerebral perfusion 45 (20) minutes. There was no circulatory collapse or death during the study period; however, one patient (Patient 15) required Extra Corporeal Membrane Oxygenation and died on the 25th postoperative day. This was the only patient who received epinephrine after termination of dopamine. The dose of epinephrine in this patient increased from 0.01 to 0.04 microgram per kilogram per minute from 20 to 72 hours. Dopamine (5–10 micrograms per kilogram per minute) was initiated before the termination of cardiopulmonary bypass in all patients. It was discontinued on arrival to the intensive care unit in four patients, within the first 48 hours in 12 patients, and used for the entire study period in the one remaining patient. Milrinone (0.33–0.99 microgram per kilogram per minute) was used in all patients throughout the study period. Phenoxybenzamine (0.5–2.0 milligrams per kilogram per day) was commenced within the first 10 hours and continued for the rest of the study period in 14 patients. Vasopressin (0.0001–0.0008 unit per kilogram per minute) was administered in 11 patients at various times for a duration of 10–60 hours after arrival in the intensive care unit. None of the patients received insulin during the study period. There was no correlation between elevated blood glucose level and the length of mechanical ventilation or intensive care unit stay.

Changes in blood glucose, systemic haemodynamics, oxygen transport, and cerebral oxygen saturation during the study period

A total of 351 arterial glucose measurements were collected. Blood glucose ranged from 2.8 to 24.6 millimoles per litre with 2% of samples (Fig 1; n = 9) less than 4 millimoles per litre, 38% (132) within normal range (4–6 millimoles per litre), and 60%

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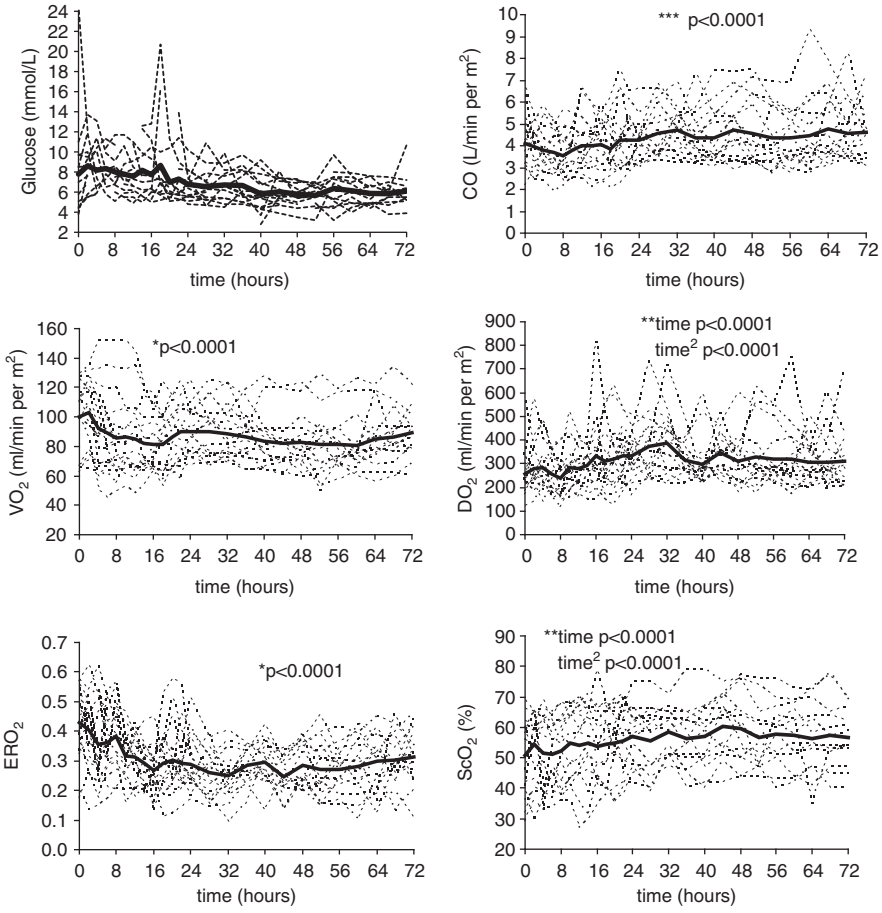

Figure 1.
Individual and mean values of blood glucose, total cardiac output, systemic oxygen delivery, oxygen consumption, oxygen extraction ratio, and cerebral oxygen saturation in 17 neonates during the first 72 hours after the Norwood procedure in the intensive care unit. CO = total cardiac output; DO_2 = systemic oxygen delivery; ERO_2 = oxygen extraction; ScO_2 = cerebral oxygen saturation; VO_2 = oxygen consumption.

(n = 210) > 6 millimoles per litre. There was no hypoglycaemia, defined as less than or equal to 2.2 millimoles per litre.[8] Blood glucose change was significantly related to time after logarithmic transformation. This showed a rapid decrease in the first 40 hours from a mean of 8–6 millimoles per litre ($p < 0.0001$), and remained at that level thereafter. We have previously described the characteristics of the changes in systemic haemodynamics, oxygen transport, and cerebral oxygen saturation.[14,15] In addition, rate pressure product and cardiac power output were significantly related to time after quadratic transformation, being initially low in the first 18–20 hours, followed by a gradual increase for the remaining 52 hours (parameter estimate = 0.22 and 0.00002, respectively, $p < 0.0001$ for both).

The patient who died (Patient 15) had a mean glucose level of 6.3 (1.7) millimoles per litre over 72 hours. This patient initially had the lowest measured oxygen consumption (50–60 millilitres per minute per squared metre) and oxygen extraction ratio (<0.20) among all patients in the first 6 hours, and then subsequently the highest oxygen consumption (120 millilitres per minute per squared metre) from 36 to 72 hours, during which the dose of epinephrine was increased from 0.01 to 0.04 microgram per kilogram per minute.

Correlations between elevated blood glucose level and 2–4-hour later measurements of systemic haemodynamics, oxygen transport, and cerebral oxygen saturation

Logarithmic transformation of blood glucose level showed a positive correlation with heart rate ($p = 0.007$) and systemic vascular resistance ($p = 0.09$). It did not significantly correlate with systemic arterial pressure or rate pressure product ($p = 0.25$ and 0.27, respectively; Tables 1 and 2, Fig 2). It significantly and negatively correlated in a linear manner with cardiac output and cardiac power output ($p = 0.02$ for both), and positively with

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Table 1. Statistical results of the relationship between blood glucose as the independent variable and 2- or 4-hour later measurements of systemic haemodynamics, oxygen transport, cerebral oxygen saturation as the dependent variables with regard to time.

Dependent variables	Intercept	Parameter estimate for time (p-value)	Parameter estimate for glucose (p-value)
Heart rate (beats/min)	146	−0.002 (<0.0001)*	6.5 (0.007)***
SAP (mmHg)	72	0.002 (<0.0001)*	−1.7 (0.25)***
DAP (mmHg)	35	0.0002 (0.06)*	−0.94 (0.17)***
MAP (mmHg)	41	0.0008 (<0.0001)*	−0.47 (0.59)***
SVR (wood unit × m^2)	15.5	−0.0004 (0.85)*	2.5 (0.09)***
tPVR (wood unit × m^2)	17	−0.0002 (0.21)*	1.1 (0.12)***
Qp (L/min per m^2)	2.4	0.0001 (<0.0001)*	−0.21 (0.10)***
Qs (L/min per m^2)	2.4	0.00002 (0.54)*	−0.24 (0.14)***
CO (L/min per m^2)	4.7	0.0001 (<0.0001)*	−0.33 (0.02)***
RPP (unit)	109	0.17 (0.0004)*	−75 (0.03)
CPO (Watts)	0.45	0.00002 (<0.0001)*	−0.009 (0.01)
DO_2 (ml/min per m^2)	336	0.002 (0.66)*	−4.2 (0.09)
VO_2 (ml/min per m^2)	107	−3.7 (<0.0001)**	−4.8 (0.13)***
ERO_2	0.23	6.2E−6 (0.01)*	0.05 (0.03)
Lactate (mmol/L)	3.1	−0.5 (<0.0001)**	0.21 (0.09)***
Dopamine (μg/min per kg)	4.3	−1.0 (<0.0001)**	0.11(0.74)***
Milrinone (μg/min per kg)	0.78	−6.1E−6 (0.244)*	−0.008 (0.42)***
Phenoxybenzamine (mg/day per kg)	1.0	0.0001 (<0.0001)	−0.03 (0.013)
Vasopressin (unit/min per kg)	0.0001	−1.1E−6 (<0.0001)	−1.0E−4 (0.63)***

CO = total cardiac output; CPO = cardiac power output; DO_2 = systemic oxygen delivery; ERO_2 = oxygen extraction ratio; MAP, MVP, and MPVP = arterial, superior caval vein and pulmonary venous mean pressures, respectively; Qp = pulmonary blood flow; Qs = systemic blood flow; RPP = = rate pressure product; SAP, DAP and MAP = systolic, diastolic and mean arterial pressure, respectively; ScO_2 = cerebral oxygen saturation; SVR = systemic vascular resistance; tPVR = total pulmonary vascular resistance including the Blalock–Taussig shunt; VO_2 = systemic oxygen consumption

*Data were entered after quadratic transformation of time

**After logarithmic transformation of time

***Data were entered after logarithmic transformation of blood glucose

Table 2. Statistical results of the relationship between cerebral oxygen saturation as the dependent variable and blood glucose, systemic haemodynamics, and oxygen transport as the independent variables with regard to time.

Independent variables	Intercept	Parameter estimate for time (p-value)	Parameter estimate for haemodynamics and oxygen transport (p-value)	Parameter estimate for glucose (p-value)
Blood glucose (mmol/L)	56	0.08 (<0.0001)		−0.50 (0.03)
Blood glucose (mmol/L) + SAP (mmHg)	42	0.05 (0.01)	0.23 (<0.0001)	−0.33 (0.04)
Blood glucose (mmol/L) + DAP (mmHg)	47	0.07 (<0.0001)	0.00 (0.005)	−0.39 (0.01)
Blood glucose (mmol/L) + MAP (mmHg)	42	0.06 (<0.0001)	0.36 (<0.0001)	−0.32 (0.04)
Blood glucose (mmol/L) + SVR (wood unit × m^2)	64	0.08 (<0.0006)	−0.20 (<0.0001)	−0.32 (0.04)
Blood glucose (mmol/L) + tPVR (wood unit × m^2)	58	0.09 (<0.0001)	0.06 (0.60)	−0.46 (0.03)
Blood glucose (mmol/L) + Qp (L/min per m^2)	55	0.08 (<0.0001)	0.34 (0.59)	−0.34 (0.03)
Blood glucose (mmol/L) + Qs (L/min per m^2)	51	0.07 (<0.0001)	2.5 (<0.0001)	−0.31 (0.04)
Blood glucose (mmol/L) + DO_2 (ml/min per m^2)	49	0.07 (<0.0001)	0.02 (<0.0001)	−0.41 (0.03)
Blood glucose (mmol/L) + VO_2 (ml/min per m^2)	64	0.08 (<0.0001)	−0.04 (0.11)*	−0.40 (0.02)
Blood glucose (mmol/L) + ERO_2	65	0.06 (0.0007)	−30.2 (<0.0001)*	−0.30 (0.05)

DO_2 = systemic oxygen delivery; ERO_2 = oxygen extraction ratio; MAP, MVP, and MPVP = arterial, superior caval vein and pulmonary venous mean pressures, respectively; Qp = pulmonary blood flow; Qs = systemic blood flow; SAP, DAP and MAP = systolic, diastolic and mean arterial pressure, respectively; ScO_2 = cerebral oxygen saturation; SVR = systemic vascular resistance; tPVR = total pulmonary vascular resistance including the Blalock–Taussig shunt; VO_2 = systemic oxygen consumption

All data were entered after quadratic transformation of time

*Data were entered after logarithmic transformation

oxygen extraction ratio ($p = 0.03$), and trended towards a positive correlation with arterial lactate ($p = 0.09$) and negatively with oxygen delivery ($p = 0.09$). It also did not significantly correlate with oxygen consumption after logarithmic transformation ($p = 0.13$). Finally, it negatively correlated

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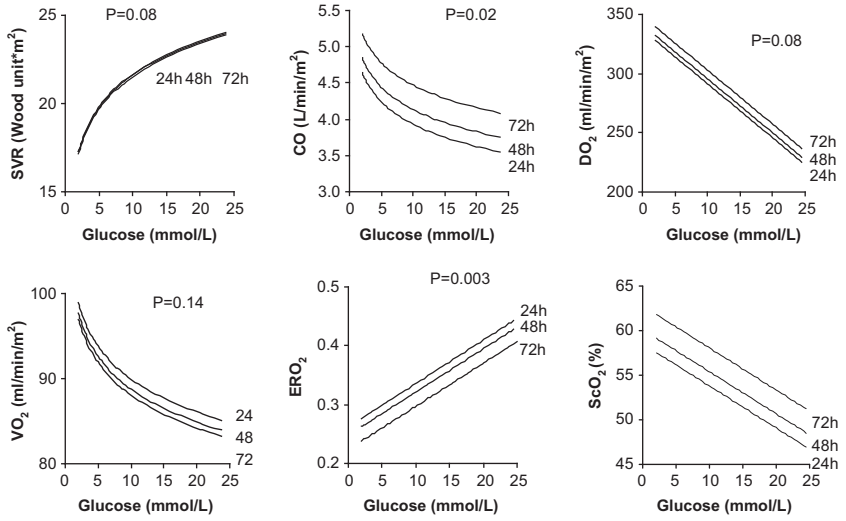

Figure 2.
Representative regression lines of the predictive model of the correlations at 24, 48, and 72 hours between blood glucose, main variables of systemic haemodynamics and oxygen transport including systemic vascular resistance, cardiac output, systemic oxygen delivery, oxygen consumption, oxygen extraction, and cerebral oxygen saturation in 17 neonates after the Norwood procedure in the intensive care unit. CO = total cardiac output; DO_2 = systemic oxygen delivery; ERO_2 = oxygen extraction; ScO_2 = cerebral oxygen saturation; SVR = systemic vascular resistance; VO_2 = oxygen consumption.

with the dose of phenoxybenzamine ($p = 0.013$), but did not correlate with the dose of dopamine ($p = 0.74$), milrinone ($p = 0.42$), or vasopressin ($p = 0.9$).

Elevated blood glucose showed a significant negative correlation with cerebral oxygen saturation ($p = 0.01$). In turn, cerebral oxygen saturation significantly correlated with all systemic haemodynamic and oxygen transport variables except for total pulmonary vascular resistance, as shown in our previous report.[15] Further regression analysis was performed to include each of the systemic haemodynamics and oxygen transport variables with blood glucose, and the statistical significance of the correlation between elevated blood glucose level and cerebral oxygen saturation remained.

Discussion

This study demonstrates a negative relationship between hyperglycaemia and systemic haemodynamics, oxygen transport, and cerebral oxygenation in neonates during the early postoperative period following the Norwood procedure. Our data show a significant negative correlation of elevated blood glucose level with cardiac output, cardiac power output, and cerebral oxygen saturation; a positive correlation with oxygen extraction ratio; and a trend towards a positive correlation with systemic vascular resistance and a negative correlation with oxygen delivery. Following the Norwood procedure, patients represent a high-risk group, and the elevated blood glucose levels observed in our patients reflect the most common practice in the care of children after cardiopulmonary bypass.

Hyperglycaemia affects cellular function in virtually all organ systems including both the central nervous system and cardiovascular system. During critical illness, pro-inflammatory cytokines upregulate glucose transporters, resulting in increased glycolysis, superoxide, and nitric oxide production. The interaction between nitric oxide and superoxides results in peroxynitrite formation that inhibits mitochondrial function and adenosine triphosphate production, thereby disturbing cellular energy metabolism and increasing susceptibility to cell death.[18]

The present study focuses on the relationship between hyperglycaemia and systemic haemodynamics, oxygen transport, and cerebral oxygenation in neonates after cardiopulmonary bypass. The study was not originally designed to identify a cause-and-effect relationship, and it is a known finding that cardiovascular dysfunction may result in hyperglycaemia; however, we analysed blood glucose levels in correlation with oxygen transport, which was measured 2 or 4 hours later, thereby assessing the consequences of changes in blood glucose levels. Indeed, evidence from adult studies and animal experiments supports the notion that hyperglycaemia has adverse effects on systemic haemodynamics, oxygen transport, and cerebral oxygenation.

Our data showed a significant negative correlation between elevated blood glucose levels and

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cardiac output and oxygen delivery. It has been shown that hyperglycaemia for 2 hours in rat hearts is enough to induce excessive nitric oxide and superoxide production, resulting in apoptosis, mitochondrial dysfunction – with reduced adenosine triphosphate production – and myocardial oxygen consumption.[19] The negative correlation between hyperglycaemia and rate pressure product – indirect indicator of myocardial oxygen consumption – and cardiac power output – the indirect indicator of adenosine triphosphate demand – is in concert with those findings.

Furthermore, hyperglycaemia trended towards a positive correlation with systemic vascular resistance. This might be partly due to the lower doses of vasodilators, such as milrinone and phenoxybenzamine, at higher levels of glucose in our patients, and partly due to a decreased local endothelial nitric oxide production via reduced endothelial nitric oxide synthase activation, resulting in vasoconstriction and reduced tissue oxygen delivery.[20] The exact mechanism requires further exploration.

We found an insignificant trend towards a negative correlation between hyperglycaemia and oxygen consumption. This observation was initially unexpected, since the degree of hyperglycaemia reflects the intensity of the systemic inflammatory response, hypermetabolism, and hypercatabolism, all of which increase oxygen consumption. This negative correlation with systemic oxygen consumption is consistent with the negative correlation with myocardial oxygen consumption as indicated by cardiac power output and rate pressure product. This might be explained by previous observations that hyperglycaemia induces a decrease in mitochondrial function and adenosine triphosphate production, which may be improved by tight glucose control with insulin therapy.[21] It is worth mentioning that the patient who died had initially the lowest oxygen consumption. As such, hyperglycaemia may exert an adverse effect on the overall balance of systemic oxygen transport. While impairing oxygen delivery at the systemic and tissue levels, it may simultaneously impair cellular utilisation of oxygen, that is, causes cytopathic hypoxia.

Cerebral oxygen saturation significantly decreases in neonates during the early postoperative period after the Norwood procedure, and the degree is influenced by almost all systemic haemodynamic and oxygen transport variables.[15] In the present study, we found a direct negative relationship between hyperglycaemia and cerebral oxygen saturation, the same mechanism as the effect of hyperglycaemia on systemic oxygen transport; that is, the interactions of cytokines, nitric oxide, and superoxide, may be applied to cerebral oxygen transport impairment.[22] In addition, it has been shown that brief and mild hyperglycaemia may cause blood–brain barrier disruption and accelerate brain injury.[23] Clinical studies have shown that hyperglycaemia is associated with worse mid- and long-term neurological outcomes in post-cardiopulmonary bypass patients.[24] Despite the fact that a recent study failed to identify such an association in infants after complete repair of two-ventricle cardiac defects,[13] hyperglycaemia should be an important matter of concern and investigation in those with complex cardiac defects requiring neonatal surgery. Poor neurodevelopmental and functional outcome is an important morbidity in this group of children, affecting about 70% of school-aged children exceeding cardiovascular morbidity.[25]

Limitations

The present study used post-hoc analysis of data obtained from a prospective study in a relatively small number of neonates with specific and vulnerable physiology after cardiopulmonary bypass. It was not initially designed to identify a cause-and-effect relationship between hyperglycaemia and systemic and cerebral oxygen transport. We analysed blood glucose levels in comparison with oxygen transport, which was measured 2 or 4 hours later in order to test the consequences of hyperglycaemia. The relationship can be best evaluated by randomised controlled clinical trials of tight glucose control in neonates following cardiopulmonary bypass. None of our patients received insulin treatment, and thus the potential effects of insulin cannot be addressed in the present study. Furthermore, there are considerable variations in perioperative management protocols between institutions, such as the use of phenoxybenzamine and vasopressin, which might vary to some extent, the correlations identified in our group of patients. Lastly, the normal range of blood glucose in neonates is still unclear[8,10] and there remain controversies regarding tight glucose control with insulin therapy because of the increased risks of mortality related to hypoglycaemia.[10,12] Further studies are warranted to examine the advantages and/or disadvantages of tight glucose control with insulin therapy in neonates and children following cardiopulmonary bypass.

Conclusion

Hyperglycaemia negatively correlates with systemic haemodynamics, oxygen transport, and cerebral oxygenation status in neonates after the Norwood procedure. Randomised clinical trials of glucose control with insulin therapy are warranted to

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identify the cause-and-effect relationship and provide important information regarding appropriate glucose management strategies in order to improve systemic and cerebral oxygen transport and clinical outcomes in neonates after cardiopulmonary bypass.

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