The relationship between plasma concentrations of ionized calcium and magnesium with cardiac energetics and systemic oxygen transport in neonates after the Norwood procedure

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Objective: We sought to determine the relationship between plasma calcium and magnesium concentrations with postoperative systemic hemodynamics and oxygen transport in neonates after the Norwood procedure.

Methods: Postoperative systemic oxygen consumption was continuously measured using respiratory mass spectrometry for 72 hours in 17 neonates. Arterial, superior vena caval and pulmonary venous blood gases and pressures, plasma calcium, and lactate levels were measured at 2- to 4-hour intervals to calculate cardiac output, rate pressure product, cardiac power output, systemic oxygen delivery, and oxygen extraction ratio. Plasma magnesium levels were measured at 2- to 8-hour intervals.

Results: Plasma calcium levels decreased in the first 8 hours from 1.08 ± 0.13 mmol/L to 0.98 ± 0.08 mmol/L, followed by an increase to 1.10 ± 0.26 mmol/L at 72 hours ($P < .0001$). Mg2þ change was significantly related to time after logarithmic transformation, rapidly decreasing from 1.62 ± 0.25 mg/L to 0.90 ± 0.15 mg/L in the first 40 hours and further decreasing slowly thereafter to 0.64 ± 0.13 mg/L at 72 hours ($P < .0001$). Plasma magnesium levels had a significant positive correlation with cardiac output ($P = .008$) and cardiac power output ($P = .01$), and a negative correlation with heart rate ($P = .05$). Plasma magnesium levels correlated positively with systemic oxygen delivery and negatively with systemic oxygen consumption ($P = .08$ for both), resulting in significant negative correlations with oxygen extraction ratio ($P = .04$) and lactate levels ($P = .05$). For a given cardiac power output, plasma magnesium showed a significantly negative correlation with rate pressure product ($P = .01$). Plasma calcium levels showed the opposite trend, which was statistically insignificant except for lactate ($P = .007$).

Conclusions: Plasma magnesium may exert favorable effects on myocardial energetics and systemic oxygen transport in neonates after the Norwood procedure, whereas plasma calcium may be harmful. Maintaining a relatively high level of plasma magnesium and a low level of plasma calcium may improve myocardial work efficiency and the balance of systemic and myocardial oxygen transport. (J Thorac Cardiovasc Surg 2012;144:474-9)

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The early postoperative course after the Norwood procedure is characterized by profound systemic hemodynamic instability and oxygen transport imbalance.[1] Systemic oxygen delivery (DO_2) is critically low with limited reserve of myocardial function because of the injured neonatal single ventricle providing parallel pulmonary and systemic circulations.[2] At the same time, systemic oxygen consumption (VO_2) is significantly elevated as a result of systemic inflammatory response to cardiopulmonary bypass (CPB),[3] rewarming, and the use of inotropes.[1] We have reported the adverse effects of fever and dopamine on the VO_2–DO_2 relationship as a result of predominant stimulation of VO_2 over DO_2.[4] Obviously, the major goal and challenge in the postoperative management after the Norwood procedure are to optimize the balance between DO_2 and VO_2 at the minimal expense of myocardial energetics.

Refined balance of plasma Ca^{2+} and Mg^{2+} is considered to be one of the treatment strategies in patients post-CPB. Intracellular hypercalcemia may accelerate adenosine triphosphate breakdown and unnecessarily increases contractility and myocardial oxygen consumption.[5] The elevated intracellular Ca^{2+} after ischemia–reperfusion leads to irreversible cellular injury.[6] On the contrary, clinical studies have suggested that hypocalcemia usually observed post-CPB might not produce any obvious adverse effects.[5,7] Of note, neonatal immature myocytes are more prone to injury because of a reduced capacity to handle the

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Abbreviations and Acronyms

CO = cardiac output
CPB = cardiopulmonary bypass
CPO = cardiac power output
DO_2 = systemic oxygen delivery
ERO_2 = oxygen extraction ratio
LogMg = logarithmic transformation of Mg^{2+}
POD = postoperative day
PVR = pulmonary vascular resistance
RPP = rate pressure product
SVR = systemic vascular resistance
VO_2 = systemic oxygen consumption

intracellular Ca^{2+} load.[8] On the other hand, Mg^{2+} inhibits Ca^{2+} membrane transport and thus prevents its intracellular accumulation.[9] It may also protect the neonatal myocardium against the negative effects of high levels of circulating catecholamines.[10]

The effects of Ca^{2+}-induced injury and Mg^{2+} protection on myocardial function have directed the use of a cardioplegic solution with relatively low or zero Ca^{2+} and high Mg^{2+} during CPB.[11] Post-CPB management strategies remain to be defined. Therefore, this study aimed to examine the relationship between plasma-ionized Ca^{2+} and Mg^{2+} concentrations and systemic hemodynamics and oxygen transport in neonates in the early postoperative period after the Norwood procedure.

PATIENTS AND METHODS

Patients

The institutional research ethics board at the Hospital for Sick Children, Toronto, Ontario, Canada, approved this study. The written informed consent was obtained from the parents of consecutive 17 neonates (14 boys; aged 4–16 days, median 7 days; weighing 2.8–4.2 kg, median 3.5 kg; body surface area 0.18–0.27 m^2, median 0.24 m^2) with hypoplastic left heart syndrome after the Norwood procedure between April 2004 and November 2006. Data from these patients were reported previously on many other aspects of systemic hemodynamics and oxygen transport.[1,4,12]

Operative Procedure

Neonates were intubated with a cuffed endotracheal tube (Microcuff-Heidelberg-Pediatric; Microcuff GmbH, Weinheim, Germany). General anesthesia was maintained with inhaled isoflurane, intravenous fentanyl, and pancuronium bromide. A standard Norwood procedure with regional cerebral circulation was used. All neonates had a 3.5-mm right modified Blalock–Taussig shunt with the distal anastomosis placed centrally on the intramediastinal pulmonary artery. CPB management consisted of a target flow of 125 mL/min/kg and a hematocrit value of 25% to 30% with modified pH-stat blood gas management for uniform cooling (18°C–20°C) at the esophageal site. Cardioplegic solution consisted of 2:1 blood and crystalloid (including $MgSO_4$ 41.5 mmol/L and 0 Ca^{2+}). Selected cerebral perfusion was performed in all neonates at pump flows of 30 to 35 mL/min/kg for 0 to 70 minutes (median, 44 minutes). All neonates received aprotinin 50,000 KIU/kg and methylprednisolone 10 mg/kg before CPB. Phenoxybenzamine 0.25 mg/kg was added to the pump prime. Separation from CPB occurred after initiation of infusions of milrinone (0.66 μg/min/kg) and dopamine (5 μg/min/kg). CPB duration was 66 to 172 minutes (median, 124 minutes), aortic crossclamp duration was 39 to 126 minutes (median, 60 minutes), and circulatory arrest was 1 to 46 minutes (median, 9 minutes). Modified ultrafiltration was used in all neonates immediately after separation from CPB. A pulmonary venous line was inserted into the orifice of the right upper pulmonary vein. The sternal incision was routinely left open in all patients for delayed closure.

Postoperative Critical Care

Infants received time-cycled pressure control/pressure support ventilation. Sedation and analgesia were given as a continuous intravenous infusion of morphine (20–40 μg/kg/h), intermittent injections of lorazepam (0.1 mg/kg), and pancuronium (0.1 mg/kg). Pancuronium was discontinued when the patient achieved satisfactory hemodynamic stability. The central esophageal temperature was monitored continuously and maintained at 36°C to 37°C. Vasoactive agents (milrinone, dopamine, phenoxybenzamine, and vasopressin) and ventilatory settings were adjusted according to the institutional standard protocol to achieve arterial carbon dioxide tension at approximately 45 to 50 mm Hg and pH 7.3 to 7.4, mean arterial blood pressure 40 to 45 mm Hg with systolic arterial pressure in the range of 55 to 65 mm Hg, arterial oxygen saturation 70% to 80%, and superior vena caval saturation of 44% to 55%. Intravenous infusions of 5% albumin 12.5 to 350 mL (median, 75 mL) on postoperative day (POD) 1, 15 to 190 mL (median, 60 mL) on POD 2, and 8 to 190 mL (median, 10 mL) on POD 3 were given to maintain filling pressures of 7 to 10 mm Hg. Blood transfusions in the range of 20 to 132 mL (median, 40 mL) on POD 1, 2 to 69 mL (median, 40 mL) on POD 2, and 30 to 102 mL (median, 30 mL) on POD 3 were given to maintain hemoglobin generally between 14 and 16 mg/dL. There was no standard protocol about the Ca^{2+} and Mg^{2+} management. One patient had Mg^{2+} supplementation in the study period. Ca^{2+} was administered in all but 1 of the patients. Depending on the clinician's judgment in response to lower Ca^{2+} levels, Ca^{2+} administration varied in the range of 1.6 to 11.07 mmol (median, 2.56 mmol) on POD 1, 1.6 to 11.5 mmol (median, 5.6 mmol) on POD 2, and 1.6 to 8.8 mmol (median, 5.3 mmol) on POD 3.

Methods of Measurements

Systemic hemodynamic and oxygen transport variables. VO_2 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 that allows simultaneous measurements of multiple gas fractions.[1] Blood samples were taken from the arterial, superior vena caval, and pulmonary venous lines to measure blood gases, arterial Ca^{2+}, and lactate levels. The chest x-ray verified correct placements of the superior vena caval and pulmonary venous sampling lines. Systemic hemodynamic and oxygen transport variables were calculated using the standard equations, including cardiac output (CO), systemic and total pulmonary vascular resistance (PVR), including the Blalock–Taussig shunt (systemic vascular resistance [SVR] and total peripheral vascular resistance, respectively), systemic and pulmonary blood flows (Qs and Qp, respectively), DO_2, and oxygen extraction ratio (ERO_2).[1] All values were indexed to body surface area as calculated before the operation.

Myocardial energetics. Rate pressure product (RPP) and cardiac power output (CPO), the indirect indicators of myocardial oxygen consumption and cardiac power, respectively, were calculated using the following equations:[13,14]

$$\text{RPP(unit)} = \text{heart rate(beats/min)} \times \text{systolic arterial pressure(mm Hg)}/1000$$

$$\text{CPO(watts)} = \text{CO(L/min)} \times \text{mean arterial pressure(mm Hg)} \times 0.0022$$

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