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 ($P < .0001$). Mg^{2+} 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)

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 Ca²⁺ load.⁸ On the other hand, Mg²⁺ inhibits Ca²⁺ 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 Ca²⁺-induced injury and Mg²⁺ protection on myocardial function have directed the use of a cardioplegic solution with relatively low or zero Ca²⁺ and high Mg²⁺ during CPB.¹¹ Post-CPB management strategies remain to be defined. Therefore, this study aimed to examine the relationship between plasma-ionized Ca²⁺ and Mg²⁺ 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 m², median 0.24 m²) 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 intramedial 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 MgSO₄ 41.5 mmol/L and 0 Ca²⁺). 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 Ca²⁺ and Mg²⁺ management. One patient had Mg²⁺ supplementation in the study period. Ca²⁺ was administered in all but 1 of the patients. Depending on the clinician's judgment in response to lower Ca²⁺ levels, Ca²⁺ 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.

VO₂ 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 Ca²⁺, 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), DO₂, and oxygen extraction ratio (ERO₂).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}

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

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

FIGURE 1. Changes in plasma Ca^{2+} and Mg^{2+} concentrations in 17 neonates during the first 72 hours after the Norwood procedure. Ca^{2+} change was significantly related to time after quadratic transformation with a rapid decrease in the first 8 hours ($P_{\text{time}} = .0008$), followed by a gradual increase thereafter ($P_{\text{time}^2} = 0.0006$). Mg^{2+} change was significantly related to time after logarithmic transformation, rapidly decreasing in the first 40 hours and then slowly decreasing thereafter ($P < .0001$). ICU, Intensive care unit.

Plasma Ca^{2+} and Mg^{2+} concentrations. Ca^{2+} concentration was measured with an ion selective electrode with a Radiometer 800 (Radiometer Medical ApS, Brønshøj, Denmark). Mg^{2+} concentration was measured using the Beckman UniCel DxC system (Beckman Coulter Inc, Brea, Calif) by forming chromagen with change in absorption at 520 nm proportional to Mg^{2+} concentration.

Study Protocol

Postoperative study parameters were recorded prospectively during the first 72 hours after a patient's arrival in the intensive care unit. Values of hemodynamic and oxygen transport variables including plasma Ca^{2+} concentrations were collected at 2-hour intervals during the first 24 hours and at 4-hour intervals in hours 25 to 72. Sampling was avoided if a change in sedation, analgesia, ventilation, or hemodynamic management was made within 15 minutes. Mg^{2+} concentration was measured at 2- to 8-hour intervals in the 72-hour study period because of varied practice among individual clinicians.

Data Analysis

Post hoc analysis was performed to analyze the data collected in a prospective study. Data are expressed as mean $\pm$ standard deviation. Mixed linear regression analysis for repeated measures was used to determine the nature of any time trend of the measures over the 72-hour study period. For some measures, various transformations of time (logarithmic and polynomial) were tested regarding the best fit for the time course. Correlations between the variables were also sought using mixed linear regression analysis for repeated measures. Logarithmic transformation of Mg^{2+} (LogMg) was made in the correlation analysis. The extent of correlation was indicated by parameter estimate and P value. All data analyses were performed with SAS statistical software version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Patients

There was no cardiovascular collapse or death during the study period. All neonates survived to hospital discharge except for 1 who died of cardiac failure on POD 25. Complete data sets of systemic hemodynamics and oxygen

transport were obtained in all 17 neonates for 72 hours except for 1 who was weaned from mechanical ventilation at 48 hours as reported previously.¹²

Changes in Ca^{2+} , Mg^{2+} , and Systemic Hemodynamics: Oxygen Transport During the Study Period

A total of 316 Ca^{2+} and 193 Mg^{2+} measurements were collected. Ca^{2+} ranged from 0.62 to 1.59 meq/L, and Mg^{2+} ranged from 0.51 to 2.09 meq/L. The change in Ca^{2+} was significantly related to time after quadratic transformation. It showed a rapid decrease from 1.08 ± 0.13 meq/L to 0.98 ± 0.10 meq/L in the first 8 hours ($P = .0008$), followed by a gradual increase thereafter to 1.10 ± 0.21 meq/L ($P = .0006$) at 72 hours (Figure 1). Mg^{2+} change was significantly related to time after logarithmic transformation, rapidly decreasing from 1.62 ± 0.25 $\mu\text{g/L}$ to 0.90 ± 0.15 $\mu\text{g/L}$ in the first 40 hours and further slowly decreasing thereafter to 0.64 ± 0.13 $\mu\text{g/L}$ at 72 hours ($P < .0001$) (Figure 1). The characteristics of the changes in systemic hemodynamic and oxygen transport variables have been described (Figure 2).^{1,12} In addition, RPP and CPO were significantly related to time after quadratic transformation, being initially low in the first 18 to 20 hours, followed by a gradual increase for the remaining 52 hours (parameter estimate = 0.22 and 0.00002, respectively, $P < .0001$ for both).

Correlations Between Ca^{2+} and Mg^{2+} and Systemic Hemodynamics: Oxygen Transport During the Study Period

Statistical results are shown in Table 1. LogMg showed a negative correlation with heart rate ($P = .05$). LogMg

FIGURE 2. Changes in systemic hemodynamics and oxygen transport in 17 neonates during the first 72 hours after the Norwood procedure. CO, Cardiac output; CPO, cardiac power output; DO₂, systemic oxygen delivery; ERO₂, oxygen extraction ratio; RPP, rate pressure product; SAP, arterial systolic pressure; SVR, systemic vascular resistance; VO₂, systemic oxygen consumption.

correlated positively with CO ($P = .008$), DO₂ ($P = .08$), and CPO ($P = .01$), and negatively with VO₂ ($P = .08$), ERO₂ ($P = .04$), RPP ($P = .01$), and lactate ($P < .0001$). LogMg showed trends of negative correlation with systolic mean arterial pressures, SVR, and PVR, although statistically insignificant ($P = .14-.22$ for all). No significant correlations were found with other variables. Ca²⁺ showed opposite trends to the correlations of Mg²⁺ with hemodynamic and oxygen transport variables but did not achieve statistical significance except for lactate ($P = .006$). Further analysis to include RPP showed a greater positive correlation of LogMg with CPO (estimate parameter 0.18, $P = .001$ for LogMg). Additional correlation analyses were performed to include inotropes and vasoactive agents (dopamine, vasopressin, milrinone, and phenoxybenzamine). The correlation trends between LogMg and Ca²⁺ and oxygen transport parameters remained the same. The correlation trends between the doses of inotropes and vasoactive agents and systemic hemodynamics and oxygen transport were similar to those in our previous report.^{4,12} There was no significant correlation between the volumes

of blood or albumin infusion with the levels of Ca²⁺ and Mg²⁺ ($P > .10$ for all).

DISCUSSION

This study demonstrates that in the current undefined clinical management of Ca²⁺ and Mg²⁺ levels, Mg²⁺ has significant positive correlations with CO and DO₂, and negative correlations with heart rate, VO₂, ERO₂, and lactate in patients after the Norwood procedure. At any given RPP, Mg²⁺ has a significant and positive correlation with CPO. Ca²⁺ has the opposite trends without achieving statistical significance. Our data indicate that Mg²⁺ has beneficial effects on myocardial energetics and systemic oxygen transport during the early postoperative period in neonates after the Norwood procedure, whereas Ca²⁺ may be harmful.

The harmful effects of Ca²⁺ on cardiovascular function after ischemia–reperfusion injury including CPB have been well recognized. Animal experiments have shown that increased intracellular Ca²⁺ after ischemia–reperfusion accelerates adenosine triphosphate breakdown,

TABLE 1. Statistical results of the correlations between Mg^{2+} and Ca^{2+} and systemic and myocardial oxygen transport oxygen transport variables

Dependent variables	Ca^{2+}		$*Mg^{2+}$	
	Parameter estimate	P value	Parameter estimate	P value
Heart rate (beats/min)	6.0	.47	−10	.05
MAP (mm Hg)	5.0	.2	−3.2	.2
SVR (Wood units/m ²)	3.0	.6	−3.3	.10
tPVR (Wood units/m ²)	3.0	.47	−3.7	.17
CO (L/min/m ²)	0.35	.6	1.64	.008
CPO (watt)	0.1117	.2	0.148	.01
RPP (units)	1.8	.15	−1.8	.01
VO ₂ (mL/min/m ²)	12.4	.4	−17.9	.08
DO ₂ (mL/min/m ²)	−12.4	.9	110	.08
ERO ₂	0.07	.4	−0.11	.04
Lactate (mmol/L)	1.4	.007	−1.1	<.0001

MAP, Mean arterial pressure; SVR, systemic vascular resistance; tPVR, total pulmonary vascular resistance including the Blalock–Taussig shunt; CO, cardiac output; CPO, cardiac power output; RPP, rate pressure product; VO₂, systemic oxygen consumption; DO₂, systemic oxygen delivery; ERO₂, oxygen extraction ratio. *Logarithmic transformation was made of Mg^{2+} to analyze the correlations.

unnecessarily increases contractility and myocardial oxygen consumption,⁵ and causes irreversible myocardial injury.¹⁵ In clinical studies, higher doses of Ca^{2+} administration were associated with increased cardiac and other organ dysfunction,^{6,15} longer intensive care unit and hospital stays and mortality in patients undergoing cardiopulmonary resuscitation,¹⁶ and CPB in children.¹⁷

Mg^{2+} competes with Ca^{2+} for binding sites in the body, thereby exerting beneficial effects.¹⁸ In terms of cardiovascular system, Mg^{2+} attenuates intracellular Ca^{2+} overloading after ischemia–reperfusion by inhibiting the Ca^{2+} channels and increasing mitochondrial and sarcoplasmic reticulum Ca^{2+} uptake.¹⁸ Therefore, use of relatively low or zero Ca^{2+} cardioplegic solutions and maintenance of normal Mg^{2+} levels during and after heart surgery have been shown to improve myocardial functional recovery with increased CO in adults.¹⁹ Furthermore, Mg^{2+} plays an essential role in the maintenance of resting membrane potential to decrease spontaneous sinus node rate, thereby allowing more diastolic filling to increase CO.²⁰ These reports are in concordance with our data of the negative correlations of Mg^{2+} with heart rate and positive correlation with CO. In addition to the cardiac effect, Mg^{2+} also exerts a systemic and pulmonary vasodilatory effect to reduce SVR and PVR resulting from enhanced production and release of potent vasodilators, such as prostacyclin from endothelium,²¹ in addition to the inhibition of cellular Ca^{2+} entry.^{9,18} Lower systemic and pulmonary arterial pressures and resistances have been observed in patients after Mg^{2+} infusion during coronary artery bypass or with congestive heart failure.^{22,23} Likewise, our data showed trends of negative correlation of Mg^{2+} with arterial pressure, SVR, and PVR,

although without achieving statistical significance. This might be due to the routine use of the vasodilator phenoxybenzamine. Nonetheless, the potential vasodilatory effects of Mg^{2+} to some degree may have contributed to the beneficial effects on CO and DO₂ in our patients.

The finding of the negative correlations of Mg^{2+} with VO₂ in critically ill patients is new and in part might be due to the reduced myocardial oxygen consumption as indicated by the negative correlation of Mg^{2+} with RPP. Mg^{2+} may decrease VO₂ in skeletal muscles by inhibiting catecholamine release and metabolism.²⁴ As a result of the increased DO₂ and decreased VO₂, Mg^{2+} showed a beneficial effect on the overall balance of systemic oxygen transport as indicated by its significant negative correlations with ERO₂ and arterial lactate levels.

We further examined the effects of Mg^{2+} on myocardial energetic using CPO and RPP. CPO represents cardiac power, whereas RPP is an indirect measure of myocardial oxygen consumption.^{13,14} It has been suggested that the ability to increase CPO on stimulation is a good descriptor of myocardial functional reserve.²⁵ Our data showed a negative correlation between Mg^{2+} and RPP and a positive correlation with CPO. Of note, the analysis of the interrelationship among Mg^{2+} , RPP, and CPO demonstrated that at any given RPP, Mg^{2+} was associated with relatively greater CPO, an indication of improved efficiency of myocardial energetics. Therefore, Mg^{2+} may exert beneficial effects on the balance of systemic and myocardial oxygen transport in neonates after the Norwood procedure, in contrast with Ca^{2+} . However, none of our patients except one was given supplemental Mg^{2+} , but almost all the patients received Ca^{2+} infusion. Our practice represents the worldwide common practice. Our data suggest that management strategies should be refined to maintain relatively high Mg^{2+} and low Ca^{2+} levels to improve systemic and myocardial oxygen transport and functional outcomes.

Limitations

There are several limitations in our study. First, the hemodynamic and oxygen transport data obtained from this relatively small group of patients have been repeatedly used to examine other aspects of the Norwood physiology.^{1,4,12} This may have introduced the potential bias in the data across these reports. Second, the hemodynamic and oxygen transport parameters were mostly calculated using VO₂, according to the direct Fick principle that would induce a certain degree of mathematic coupling in their relationships. Our present study did not examine the relationship between VO₂ and DO₂. Finally, post hoc analysis was performed in the data collected from a prospective study. The correlation results indicate the trends of Mg^{2+} and Ca^{2+} in our clinical practice in relation with systemic and myocardial oxygen transport variables.

Better refinement of optimal levels of Mg^{2+} and Ca^{2+} is warranted and can be obtained by randomized clinical trials with controlled Mg^{2+} and Ca^{2+} levels in patients post-CPB.

CONCLUSIONS

Plasma Mg^{2+} may exert favorable effects on myocardial energetics and systemic oxygen transport in neonates after the Norwood procedure, whereas Ca^{2+} might be harmful. Maintaining a relatively high level of Mg^{2+} and a low level of Ca^{2+} may promote the efficiency of myocardial work and improve the balance of systemic and myocardial oxygen transport in neonates post-CPB. This information may have important implications in the postoperative management of children post-CPB.

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