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Elevated preoperative serum asymmetrical dimethylarginine (ADMA) is associated with poor outcomes after pediatric cardiac surgery

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Abstract *Purpose:* Asymmetrical dimethylarginine (ADMA), an endogenous competitive inhibitor of nitric oxide synthase, is elevated in vascular pathologies such as hypertension and chronic kidney disease. Children undergoing cardiac surgery are at high risk of poor hemodynamic and renal outcomes secondary to cardiopulmonary bypass (CPB). This study tested the hypothesis that elevated preoperative ADMA levels are associated with overall worse clinical outcomes after pediatric CPB. *Methods:* This was a prospective, observational study of 100 patients aged from 2 weeks to 18 years who underwent cardiac surgery involving CPB. Serum ADMA levels were obtained preoperatively and on postoperative days zero through four. Clinical outcomes measured included acute kidney injury (AKI) by pRIFLE criteria, low cardiac output syndrome (LCOS), length of mechanical ventilation, hospital and ICU length of stay, unplanned reoperation, and mortality. *Results:* The 29 patients with an elevated preoperative ADMA were more likely to have prolonged mechanical ventilation, increased ICU and hospital length of stay, unplanned reoperation, and LCOS than those with a normal preoperative level. ADMA levels inversely correlated with estimated glomerular filtration rate (eGFR), but did not differ between patients with and without AKI after CPB. Preoperative ADMA levels correlated with hospital length of stay ($r_s = 0.289$), ICU length of stay ($r_s = 0.308$), and length of mechanical ventilation ($r_s = 0.402$); [all $p < 0.05$]. ADMA levels before surgery had good predictive power for prolonged mechanical ventilation (AUC-ROC 0.809; 95 % CI 0.704, 0.914; $p < 0.001$). *Conclusions:* Patients with elevated ADMA before surgery were more likely to have prolonged mechanical ventilation, develop LCOS, require an extended length of stay, and require reoperation. ADMA levels inversely correlated with eGFR, but did not predict AKI. Preoperative serum ADMA appears to identify pediatric cardiac surgery patients at risk of poor postoperative outcomes following CPB.

Keywords ADMA · Cardiopulmonary bypass · Pediatric intensive care unit · Acute kidney injury · Prolonged mechanical ventilation

Introduction

Asymmetrical dimethylarginine (ADMA) is a competitive inhibitor of nitric oxide synthase (NOS) and blocks production of the potent vasodilator nitric oxide (NO). ADMA is pathologically elevated in disease states with underlying endothelial dysfunction including hypertension, atherosclerosis, coronary artery disease, sepsis, chronic pulmonary hypertension, and chronic kidney disease (CKD) [1–4]. While ADMA is emerging as an important biomarker in critically ill adults [3, 5–8], to date there are few published studies examining ADMA levels in critically ill children [9].

Elevations of ADMA in CKD are thought to be both a cause and a result of kidney dysfunction. Impaired renal function leads to ADMA accumulation as it is cleared by the kidneys and decreased renal function leads to diminished levels of its breakdown enzyme, dimethylarginine dimethylaminohydrolase (DDAH-I) [1, 6]. In animal models, elevated ADMA causes direct glomerular damage, renovascular fibrosis, loss of renal autoregulation, and impaired ability of the kidney to react to oxidative stress [10–12]. As a result, ADMA is elevated in pediatric patients at all stages of CKD [13]. The dynamics of ADMA in acute kidney injury (AKI) have not been described.

High ADMA levels have been independently associated with increased mortality in adults with CKD [3, 5, 6], with multiorgan failure [14], and after myocardial infarction [15]. Pediatric patients who undergo cardiac surgery experience significant cardiovascular and endothelial stress during cardiopulmonary bypass (CPB) and are therefore at increased risk of AKI and cardiovascular compromise. A multicenter study of over 300 pediatric cardiac surgery patients found that 42 % developed AKI after CPB and 8 % developed low cardiac output syndrome (LCOS) or required extracorporeal membrane oxygenation [16]. Elevated ADMA levels can contribute to disruptions in normal endothelial function. Therefore, patients with elevations before CPB may be at risk of worse outcomes after surgery including fluid overload, AKI, pulmonary vascular reactivity or hemodynamic instability. ADMA levels have not been investigated in this population and the link between renal dysfunction and cardiovascular outcomes as predicted by ADMA in adults has not been thoroughly investigated in children.

We hypothesized that elevated preoperative ADMA levels in the pediatric cardiac surgery patient are associated with poorer clinical outcomes after CPB, including AKI, extended length of mechanical ventilation, extended ICU and hospital length of stay, LCOS, unplanned reoperation, and mortality.

Materials and methods

Participants

The study was approved by the Institutional Review Board of Children's Memorial Hospital in Chicago, IL. After informed consent had been obtained, 100 patients aged from 2 weeks to 18 years undergoing cardiovascular surgery requiring CPB were enrolled from August 2009 to July 2010. The only exclusion criterion was preoperative renal replacement therapy. All operations were performed at a tertiary care children's hospital by the same surgical team. ADMA results were not available to the clinical team and did not influence care.

Data collection

Baseline demographic data collected included age on the day of surgery, sex, height, weight, type of congenital heart lesion, and baseline renal function. Surgical variables measured included renal near-infrared regional spectroscopy (NIRS) during CPB, blood pressure on CPB, CPB time and aortic cross-clamp time, Risk Adjustment for Congenital Heart Surgery (RACHS-1) score [17], and urine output on CPB. Postoperative variables recorded were peak weight gain (as a percentage of preoperative weight), fluid balance in the first 24 h, peak inotrope score [18], lowest daily urine output (any postoperative day 0 through 4), use of inhaled NO, and highest daily dose of furosemide (Sanofi Aventis, Chattanooga, TN).

Serum samples were obtained for determination of ADMA, blood urea nitrogen, cystatin C and creatinine levels at the following time-points: preoperatively on the day of surgery, immediately upon arrival to the ICU after surgery, 8 h postoperatively and every morning for the first 4 days after surgery.

Laboratory methods

Samples were processed and stored at −70 °C. ADMA levels were measured using high-performance tandem mass spectroscopy LC/MS/MS method [19]. Serum creatinine values were obtained using an isotope dilution/mass spectrometry, traceable enzymatic assay. Blood urea nitrogen was measured on a standard chemistry analyzer and cystatin C levels were measured using the Beckman PETIA, particle enhancing turbidimetry immunoassay (Gentian, Moss, Norway) and run on a chemical analyzer.

Statistical analysis

Based upon normative pediatric data [19, 20], patients were dichotomized to an elevated ADMA group or

normal ADMA group using a serum cut-off level of 0.8 μM/L, which is above the 95th percentile for age. Baseline, surgical, and postoperative variables were compared between the groups. Outcomes measured were AKI, length of mechanical ventilation, ICU and hospital length of stay, unplanned reoperation during the first four postoperative days, LCOS, and mortality. LCOS was defined as a systemic ventricular ejection fraction less than 45 % estimated by echocardiography (in patients whose systemic ventricular ejection fraction was normal before surgery). AKI was defined using pediatric-modified RIFLE criteria with "failure" as >75 % decrease in estimated glomerular filtration rate (eGFR), "injury" as >50 % decrease in eGFR, and "risk" as >25 % decrease in eGFR. Estimated GFR was calculated at all time-points by the updated Schwartz equation, which includes blood urea nitrogen, serum creatinine, serum cystatin C, height, and sex [21].

Continuous data are presented as medians with interquartile ranges (IQR 1–3) or as means with standard deviation (SD) for parametric data. Dichotomous and continuous variables were compared using the Mann-Whitney *U* test for paired comparisons and the Kruskal-Wallis test for multiple comparisons, and associations between two continuous variables were examined using Spearman's correlation. To calculate the sensitivity and specificity of ADMA for an outcome, receiver-operating characteristic (ROC) curve analysis was performed using the area under the ROC curve (AUC-ROC) to determine predictive value.

Variables were chosen for inclusion in the multivariate analysis if their p value was <0.2 in univariate comparison and if they were independent of variables already included. Weight, weight gain, lowest daily urine output, and maximum daily furosemide dose were not included because of interdependence and relation to age. Lowest blood pressure on CPB and lowest NIRS reading on CPB were also dependent on patient age or the presence of a cyanotic lesion, and were excluded from the analysis.

Significance was set at a p value of <0.05. All statistical calculations were performed using SPSS software, version 12.0 (SPSS Inc., Chicago, IL).

Results

Elevated preoperative ADMA levels and secondary outcomes

To determine the outcomes associated with elevation in ADMA greater than normal for age, we dichotomized the study population according to the preoperative ADMA level. At the preoperative baseline, 29 patients (29 %) had an ADMA level greater than 0.8 μM/L. Table 1 shows the characteristics of the patients with an elevated baseline ADMA. The baseline differences between the groups had to do with variables dependent on age including weight and baseline eGFR. There was no difference in the percentage of cyanotic heart lesions nor the complexity of the operations performed in each group.

An elevated preoperative ADMA level was associated with a worse clinical outcome in every parameter measured except for AKI (Table 2). There was no mortality in this study population. The median length of mechanical ventilation in this cohort was 1 day (IQR 1–1) and 76 % of patients were intubated for 1 day or less. As a result of these data, prolonged mechanical ventilation was defined for this study cohort as longer than 2 days. An elevated preoperative ADMA level had good predictability for prolonged mechanical ventilation (AUC-ROC 0.809, 95 % CI 0.714, 0.904; $p < 0.001$). The ideal point on this ROC curve was a serum ADMA level of 0.75 μM/L with 78 % sensitivity and 74 % specificity, and a negative predictive value of 94 % for prolonged mechanical ventilation.

Preoperative ADMA levels correlated with hospital length of stay ($r_s = 0.289$, $p = 0.004$), ICU length of stay ($r_s = 0.308$, $p = 0.002$), and length of mechanical ventilation ($r_s = 0.402$, $p < 0.001$). In the multivariate analysis adjusting for age, baseline eGFR, CPB time, fluid balance, peak inotrope score, and preoperative ADMA, only preoperative ADMA level and peak inotrope score were independently associated with hospital length of stay. Using logistic regression including the same variables, only preoperative ADMA level (odds ratio 452.9; 95 % CI 7.9, >999; $p = 0.003$), CPB time (odds ratio 1.03; 95 % CI 1.01, 1.05; $p = 0.002$), and peak inotrope score (odds ratio 1.27; 95 % CI 1.01, 1.59; $p = 0.042$) carried independent risk for prolonged mechanical ventilation.

Multivariate analysis was not performed for LCOS or unplanned reoperation, as too few patients developed these outcomes. Multivariate analysis was not performed for ICU length of stay as this is an outcome affected by multiple hospital system factors unrelated to clinical outcome.

ADMA levels in AKI

Five patients developed "injury" (>50 % loss of eGFR), and 30 developed "risk" (>25 % loss of eGFR) according to pRIFLE criteria. No patients developed "failure." There was no significant difference between pre- or postoperative ADMA levels among patients in the category "risk," "injury" or "none." Median serum ADMA values in each group are presented in Table 3. Patients with an elevated preoperative ADMA level were not more likely to develop AKI than patients with a normal preoperative ADMA level ($p = 0.228$).

Table 1 Characteristics of patients with and without an elevated preoperative ADMA level

	Elevated preoperative ADMA ($n = 29$)	Normal preoperative ADMA ($n = 71$)	p value
Age (months)	4 (4–6.5)	61 (21–144)	<0.001[a]
Male	18 (62 %)	37 (52 %)	0.364[b]
Weight (kg)	5.8 (5.0–6.8)	16.6 (9.7–38.6)	<0.001[a]
Baseline eGFR (ml/min/1.73 m^2)	70 (62.5–83)	98 (85–109)	<0.001[a]
Cyanotic lesion	12 (41 %)	33 (46 %)	0.642[b]
RACHS-1 score			
1–2	14 (48 %)	36 (51 %)	0.826[b]
3–6	15 (52 %)	35 (49 %)	
Bypass time (min)	131 (79–166)	95 (64–140)	0.074[a]
Aortic cross-clamp time (min)	79 (52–107)	59 (25–82)	0.064[a]
Low blood pressure on bypass	35 (30–40)	40 (30–45)	0.114[a]
Low renal NIRS on bypass	76 (60–81)	79 (68–87)	0.062[a]
Fluid balance in first 24 h after surgery (ml/kg)	51 (31.6–78.2)	29.3 (8.4–42.9)	0.009[a]
Lowest daily urine output (ml/kg/h)	1.82 (1.38–2.40)	1.33 (1–1.77)	0.001[a]
Maximum furosemide dose (mg/kg/day)	3.97 (3.45–5.48)	2.28 (1.15–3.48)	<0.001[a]
Peak inotrope score	10.5 (10.5–14.8)	10.5 (7.5–12.5)	0.018[a]
Peak weight gain (%)	7.8 (2.95–13.2)	2.8 (0.0–5.7)	0.001[a]
Percent decrease in eGFR	14.9 (1.9–29.9)	16.3 (5.9–30.2)	0.57[a]

Values are medians (IQR 1–3) or number (%)
[a] p values obtained using the Mann–Whitney U test
[b] p values obtained using Chi-squared comparisons

Table 2 Outcomes in patients with and without an elevated preoperative ADMA level

	Elevated preoperative ADMA[a] ($n = 29$)	Normal preoperative ADMA ($n = 71$)	p value
Length of mechanical ventilation (days)	1 (1–5)	1 (1–1)	<0.001[d]
Prolonged mechanical ventilation[b]	12 (41.3 %)	6 (8 %)	<0.001[e]
Length of intensive care stay (days)	7 (5.5–10.5)	6 (4–7)	0.013[d]
Length of hospital stay (days)	8 (6.5–12.5)	7 (5–9)	0.02[d]
Need for unplanned reoperation	3 (10 %)	1 (1 %)	0.039[e]
Low cardiac output syndrome	3 (10 %)	1 (1 %)	0.039[e]
pRIFLE category[c]			
"None"	18 (62 %)	47 (66 %)	0.228[e]
"Risk"	11 (38 %)	19 (27 %)	
"Injury"	0 (0)	5 (7 %)	

Values are medians (IQR 1–3) or number (%)
[a] Defined as >0.8 μM/L
[b] More than 2 days
[c] "Risk" >25 % loss of eGFR, "Injury" >50 % loss of eGFR
[d] p values obtained using the Mann–Whitney U test
[e] p values obtained using Chi-squared comparisons

Relationship between ADMA and eGFR

In the seven patients (7 %) with preoperative eGFR <60 ml/min/1.73 m^2, preoperative ADMA levels were greater than in those with a baseline eGFR ≥60 ml/min/1.73 m^2 (0.96 μM/L, IQR 0.72–1.19, vs. 0.66 μM/L, IQR 0.57–0.83; $p = 0.008$). In all patients, preoperative ADMA levels were inversely correlated with baseline eGFR ($r = -0.443$, $p < 0.001$). The correlation between serum ADMA and eGFR persisted immediately after surgery ($r_s = -0.385$, $p < 0.001$), through 8 h after surgery ($r_s = -0.335$, $p = 0.001$), through postoperative day 1 ($r_s = -0.387$, $p < 0.001$), and through postoperative day 2 ($r_s = -0.231$, $p = 0.021$). The peak ADMA level correlated with the lowest eGFR ($r_s = -0.447$, $p < 0.001$). Figure 1 shows the trends in ADMA levels in each pRIFLE category and the changes in eGFR in each group over the study period.

Discussion

To our knowledge, this is the first pediatric study to identify ADMA as a potential preoperative biomarker for postoperative outcomes, and to report the dynamic

Table 3 Median serum ADMA levels (μM/L) at all study time points in relation to pRIFLE category. Values are medians (IQR 1–3)

Time point	pRIFLE category[a]			*p* value[b]
	"None" ($n = 65$)	"Risk" ($n = 30$)	"Injury" ($n = 5$)	
Preoperative	0.68 (0.58–0.88)	0.74 (0.56–0.94)	0.70 (0.64–0.75)	0.782
Postoperative day				
0 (0 h)	0.7 (0.58–0.90)	0.83 (0.65–1.09)	0.82 (0.79–0.89)	0.193
0 (8 h)	0.59 (0.47–0.74)	0.59 (0.48–0.70)	0.67 (0.64–0.77)	0.334
1	0.51 (0.45–0.61)	0.55 (0.48–0.63)	0.58 (0.52–0.70)	0.279
2	0.45 (0.39–0.53)	0.49 (0.43–0.57)	0.59 (0.43–0.62)	0.205
3	0.54 (0.46–0.63)	0.53 (0.47–0.73)	0.66 (0.39–0.66)	0.697
4	0.65 (0.56–0.75)	0.62 (0.55–0.68)	0.62 (0.46–0.78)	0.438

[a] "Risk" >25 % loss of eGFR, "Injury" >50 % loss of eGFR

[b] Obtained using the Kruskal-Wallis test comparing the ADMA levels between categories

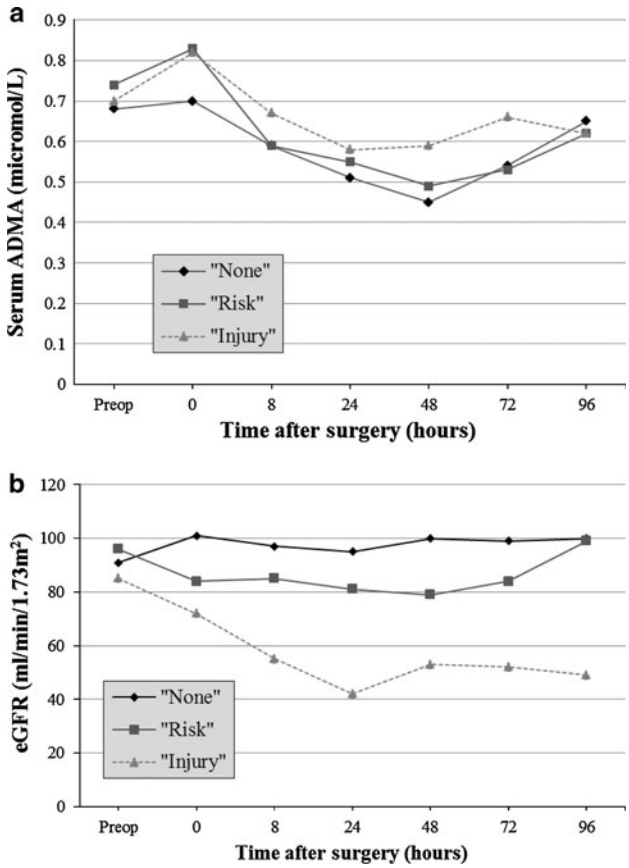

Fig. 1 **a** Median serum ADMA levels throughout the study period in patients in each pRIFLE category: "None," "Risk" (>25 % loss in eGFR), and "Injury" (>50 % loss in eGFR). **b** Concomitant median eGFR in each pRIFLE category

changes of ADMA in AKI after CPB in this population. Elevated preoperative serum ADMA levels were able to identify patients at risk of prolonged mechanical ventilation and extended length of stay. This association is plausible given that elevations in ADMA block protective NOS activity and NO production which in turn may worsen endothelial dysfunction in the face of injury and inflammation from CPB. Elevated ADMA also causes endothelial NOS to shift from NO production to free radical generation, resulting in cytokine release and increased oxidative stress on the endothelium perpetuating a vicious cycle of inflammation and tissue damage [22]. Preoperative elevations in ADMA may exaggerate the impact CPB has on the systemic vasculature, thereby enhancing the risk of pulmonary vascular reactivity, systemic inflammatory response, capillary leak, and edema. All of these effects may serve to lengthen dependence on mechanical ventilation and extend length of stay. Data have shown that fluid overload in children with respiratory failure [23] and pediatric patients undergoing cardiac surgery [24] carries independent risk of prolonged mechanical ventilation and mortality. Pathologic elevations in ADMA may be contributing to this effect or could portend these outcomes.

If validated, ADMA could be added to a growing list of biomarkers with the potential to identify high-risk pediatric candidates for cardiac surgery. Similar to ADMA, cardiac fatty acid-binding protein [25], B-type natriuretic peptide [26] and its precursor NT-proXNP [27], S-100 [28], IL-6, IL-8 [29, 30], cystatin C, and neutrophil gelatinase-associated lipocalin [31, 32] have all shown prognostic or diagnostic potential to identify patients at risk of poor cardiac, neurologic or renal outcomes after CPB.

ADMA levels are elevated in chronic renal dysfunction in adults with end-stage renal disease [7], in adults and children with CKD [2, 13, 33], and in kidney transplant recipients [34]. We did not find a significant association between ADMA levels and AKI after CPB. This may have been due to the small number of patients who developed "injury," and "failure" or less likely because ADMA levels do not rise in the first 4 days of AKI. The inverse association between eGFR and ADMA levels shown in this study points toward the former. However, our small sample size limited the statistical ability to definitively relate ADMA levels with AKI.

Animal and clinical studies have provided conflicting evidence of ADMA as either a marker or mediator of renal dysfunction, or both. As seen in CKD [35], and as a trend seen in Fig. 1 although not statistically significant, our data suggest that ADMA rises before eGFR falls. This implicates extra-renal effects which increase ADMA and subsequently cause a decrease in renal function. It is known that DDAH is inactivated by the type of oxidative stress caused by CPB [36]. Extended CPB and aortic cross-clamp times could lead to suppression of DDAH and allow serum levels of ADMA to rise. And as animal models have shown, elevated ADMA could in turn cause renovascular insult and glomerular damage [10–12]. Recent pediatric studies have confirmed that extended CPB times and aortic cross-clamp times are associated with higher rates of AKI [16, 37]. We found that median aortic cross-clamp times were longer in patients with AKI than those without (115 min, IQR 26–82, vs. 56 min, IQR 26–86; $p = 0.029$) as were median CPB times (163 min, IQR 120–242, vs. 99 min, IQR 64–137; $p = 0.029$). Further investigation into ADMA levels around CPB or in other types of oxidative stress would help elucidate the relationship between DDAH activity, ADMA, and kidney function.

This study had a number of limitations. It was a small, single-center trial of a select patient population which cannot be generalized to other pediatric critical care patients. AKI was not determined using a gold standard reference for kidney function.

We chose a threshold value for serum ADMA above the 95th percentile for age to avoid any confounding age-dependent physiologic variances in ADMA values. Despite this, patients with elevated preoperative ADMA were markedly younger than those with normal values. As there was no difference between groups in the number of cyanotic lesions or the number of patients with higher RACHS-1 scores, it seems unlikely that the complexity of the cardiac lesion was the sole reason. Conversely, the timing of earlier corrective or palliative cardiac surgery could imply more severe cardiac disease. Although a multivariate analysis was performed to adjust for age, larger studies with age-specific subsets are needed to validate these results. We have no concrete explanation for the age differences reported here.

Conclusion

Preoperative ADMA levels were elevated in pediatric cardiac surgery patients who develop prolonged mechanical ventilation and extended length of stay. Although not predictive of AKI, ADMA levels rise before eGFR falls in the perioperative period. Larger, multi-center trials investigating preoperative ADMA levels as predictors of poor cardiovascular, and hemodynamic and renal outcomes in children after CPB are warranted.

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Conflicts of interest None.

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