



Plasma proteoglycan 4: a novel biomarker for acute lung injury after pediatric cardiac surgery

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Background: Identification of biological molecules related to post cardiopulmonary bypass (CPB) lung injury could help diagnose, predict and potentially impact patient's clinical course after cardiac surgery. Proteoglycan 4 (PRG4) initially identified as potential biomarker for patients with prolonged mechanical ventilation following CPB in a prior study. To further validate these findings, we sought to understand the association of lower plasma PRG4 with prolonged mechanical ventilation and worse lung compliance in a larger cohort of pediatric patients post CPB.

Methods: Retrospective chart review study. Pediatric Cardiac Intensive Care Unit, Tertiary Hospital. Infants <1 year old with tetralogy of Fallot, ventricular septal defect, or atrioventricular septal defect who underwent surgical repair 2012–2020 and had stored plasma samples in our biorepository were screened for inclusion. Patients with mechanical ventilation before surgery were excluded. Patients were divided into quartiles based on postoperative duration of mechanical ventilation (control <25th percentile, study >75th percentile). Preoperative and 48-hour postoperative samples for each cohort (20 patients each) were tested for PRG4 level using enzyme-linked immunosorbent assay (ELISA) technique.

Results: Study group had lower lung compliance, higher mean airway pressure and higher oxygen need postoperative when compared to control group. Plasma PRG4 levels before surgery and 48 hours postoperative were lower in study group compared to control group (P=0.0232 preoperative; P=0.0016 postoperative). Plasma PRG4 levels were compared preoperative to PRG4 levels postoperative in both group, there was no statistically significant difference (study group: P=0.0869; control group: P=0.6500)

Conclusions: Lower levels of plasma PRG4 is associated with longer duration of mechanical ventilation, worse ventilator compliance and higher oxygen requirement after cardiac surgery in our patient population. Further validation of this finding in a larger and more diverse patient population is necessary prior to its application at the bedside.

Keywords: Acute lung injury (ALI); proteoglycan 4 (PRG4); pediatric cardiac surgery; infants; biomarkers

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Introduction

The use of cardiopulmonary bypass (CPB) during surgical repair for infants with heart disease is associated with systemic inflammatory response syndrome (SIRS) and variable end organ injury (1-3). The SIRS response can have significant impact on lung injury, but the extent of the injury varies amongst patients and its mechanism is not fully understood (4,5).

Over the past decade, several plasma and bronchoalveolar lavage biomarkers for lung injury have been investigated and have provided a better understanding of the pathophysiological mechanism of lung injury (6). Although many of these biomarkers are awaiting validation, they have the potential of playing a prognostic and therapeutic role in caring for patients with lung injury (7).

Proteoglycan 4 (PRG4) is a mucin-like glycoprotein originally discovered in synovial fluid, and classically studied as a boundary lubricant, that is present throughout the body at various biointerfaces, tissues, and fluid. Its biological properties in modulating the inflammatory and innate immunologic response have been explored in recent studies (8-11), as well as its ability to modulate smooth muscle cell phenotype during vascular remodeling and intimal calcification (12). In terms of a systemic biomarker, altered levels of serum PRG4 were found to offer prognostic value for adult patients with chronic obstructive pulmonary disease (13).

In a recent pilot study, our group identified PRG4 as

potential biomarker for prolonged mechanical ventilation in infants with complex cardiac surgery using both an unbiased proteomic analysis and enzyme-linked immunosorbent assay (ELISA) testing (14). In order to further validate our findings and to better correlate the PRG4 levels with respiratory and clinical outcomes we analyzed serum PRG4 levels in a larger cohort of infant patients before and after CPB. We hypothesized that decreased PRG4 plasma levels pre and postoperative were associated with longer mechanical ventilation duration, worse lung compliance and increased oxygen requirement after surgery. We present this article in accordance with the STARD reporting checklist (available at <https://tp.amegroups.com/article/view/10.21037/tp-23-194/rc>).

Methods

Patient selection

All patients younger than 6 years old at Children's of Alabama who underwent cardiac surgery were approached for participation in the congenital heart center biorepository under a separate institutional review board (IRB) approval. Our current study was reviewed and approved by the University of Alabama at Birmingham's IRB (approval No. IRB-300003366; approval date February 02, 2022; study title: "Validation of Specific Serum Biomarkers Role as Prognostic Surrogates for Acute Lung Injury after Cardiac Surgery Requiring CPB in Pediatric Patients") and informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Patients who had preoperative and 48-hour postoperative samples in this repository and had surgical repair for tetralogy of Fallot (TOF), ventricular septal defect (VSD) or atrioventricular septal defect (AVSD) at 1 year or younger were included in our study. Patients who required mechanical ventilation before surgery were excluded. We had a total of 86 patients from 2012 to 2020 who met the inclusion criteria and had available samples in the biorepository. We divided our studied patients into quartiles based on duration of mechanical ventilation. We had 21 patients in the control group (<25th percentile of mechanical ventilation duration) and 21 patients in the study

Highlight box

Key findings

- Proteoglycan 4 (PRG4) can be used as a biomarker for acute lung injury after pediatric cardiac surgery.

What is known and what is new?

- Patients with lower serum levels of PRG4 after surgery have lower lung compliance, higher oxygen demand and longer mechanical ventilation duration.

What is the implication, and what should change now?

- There is some evidence of the utility of PRG4 as biomarker for acute lung injury after cardiopulmonary bypass surgery.

group (>75th percentile of mechanical ventilation duration). We randomly selected 20 patients in each group and tested their plasma level for PRG4 at two time points, preoperative and 48-hour postoperative. We did not test the remaining samples of the remaining patients (n=46) who met the inclusion criteria. ELISA testing was conducted, in a blinded matter at the University of Connecticut Health Center under a research collaboration and biological material transfer agreement which was established on Jun 01, 2022 with award number 2025674. The fund of our study allowed us to test only 40 patients for PRG4 (two sample for each patient).

Plasma samples

Blood samples pre- and post-operative were collected by the bedside nurses and stored in heparinized tubes. Samples were handled by centrifugation and plasma was isolated and stored in the heart center biorepository in -80 °C centigrade freezer. One sample (250 µL) at each time point (preoperation and 48-hour postoperation) for each included patient (n=40 patients) was transferred to the University of Connecticut Health Center.

PRG4 ELISA analysis

PRG4 concentration in plasma samples was quantified using a commercially available sandwich ELISA (PRG4 DuoSet ELISA, DY9829-05, R&D Systems, Minneapolis, MN, USA), essentially as per the manufacturers' instruction. The one important deviation was using full-length recombinant human PRG4 (rhPRG4, Lubris LLC, Framingham, MA, USA) (15,16) to generate the standard curve (1–1,000 µg/mL) instead of the supplied PRG4 peptide. Samples were assayed at 1:500 dilution, in technical duplicate, and 96-well plates were read at 450 nm on a microplate reader (i3x, Molecular Devices, San Jose, CA, USA). The plate-based ELISA assay employed here requires an overnight incubation step and then approximately 7 hours of work, which is a typical duration for bench ELISA analysis. However, PRG4 has also been quantified using a homogenous bead-based assay employing the AlphaLISA platform (Molecular Devices, Shelton, CT, USA) (17), which has the potential for high-throughput analysis of clinical samples.

Statistical analysis

Descriptive analyses [means, standard deviations, medians,

interquartile ranges, frequency distributions (%) were used to describe patient demographics, clinical characteristics, clinical outcomes and respiratory variables. Student's *t*-tests and paired *t*-tests were used to compare continuous measures between groups as appropriate. Mann-Whitney *U* test were used to compare non-normal continuous measure and Chi-square, Fisher's exact tests were used to compare categorical variables. Multivariable linear regression was performed for the prolonged mechanical ventilation outcome with adjustment for the weight and age at time of surgery. All hypothesis tests were two-tailed. A *P* value of <0.05 indicated statistical significance. All analyses were performed in SAS (version 9.4, Cary, NC, USA).

Clinical outcomes

The secondary outcomes of our analysis included intensive care unit (ICU) and hospital length of stay (day), duration of inotropic support (hours) rather than vasopressor inotrope score, duration of inotropic support was defined as the total duration of inotropic infusion start (or admission time if they are admitted on inotropic support) to the time of weaning infusion off. Lactate level at admission and creatinine level at post-operative days 1 and 2.

Results

Patient characteristics

Patients in the study group were younger (median 91 days) and had lower weight (mean 4.28 kg) at time of surgery (*Table 1*). There were more males in the control group compared to the study group (55.0% *vs.* 40.0%). The majority (65.0%) of our cohort were White. Only one patient in our cohort had genetic abnormality (trisomy 21 syndrome). There was no statistical difference in regard to CPB and aortic cross clamp time among groups. There were total of 20 patients in our cohort with AVSD (9 in control *vs.* 11 in study), 8 with VSD (7 in control *vs.* 1 in study), and 12 with TOF (4 in control and 8 in study). All our patients are admitted to the cardiac ICU (CICU) intubated and on mechanical ventilation. Patients are extubated after admission whenever they are ready from the respiratory and hemodynamic standpoint.

PRG4 plasma levels

Preoperative and postoperative levels of PRG4 were

Table 1 Patient characteristics

Characteristics	Control (n=20)	Study (n=20)	P value
Age (days)	146 [120, 197]	91 [39, 129]	0.0013
Weight (kg)	5.19±0.98	4.28±1.34	0.0197
Cardiopulmonary bypass (min)	69.5 [55.0, 97.0]	88.5 [67.0, 123.0]	0.1635
Aortic cross clamp (min)	48.5 [36.5, 59.5]	51.5 [45.0, 67.5]	0.6649
Gender, male	11 (55.0)	8 (40.0)	0.3422
Race, White	13 (65.0)	13 (65.0)	0.9900

Data are presented as mean ± standard deviation, median [interquartile range] or n (%).

Table 2 Comparison of mean levels of pre- and post-operative plasma PRG4

Testing period	PRG4 plasma concentration (µg/mL)			P value (control vs. study)
	Control (n=20)	Study (n=20)	Difference (control–study)	
Pre-operative	13.01±7.50	8.15±7.50	4.86±6.49 (0.70, 9.01)	0.0232
Post-operative	12.25±5.97	6.88±3.76	5.37±4.99 (2.18, 8.57)	0.0016
Difference (pre-operative–post operative)	0.76±7.40 (–2.72, 4.23)	1.27±3.16 (–0.20, 2.75)	–	–
P value (pre- vs. post-operative)	0.6500	0.0869	–	–

Data are presented as mean ± standard deviation (95% CI). P values are based on *t*-test or paired *t*-test as appropriate. PRG4, proteoglycan 4; CI, confidence interval.

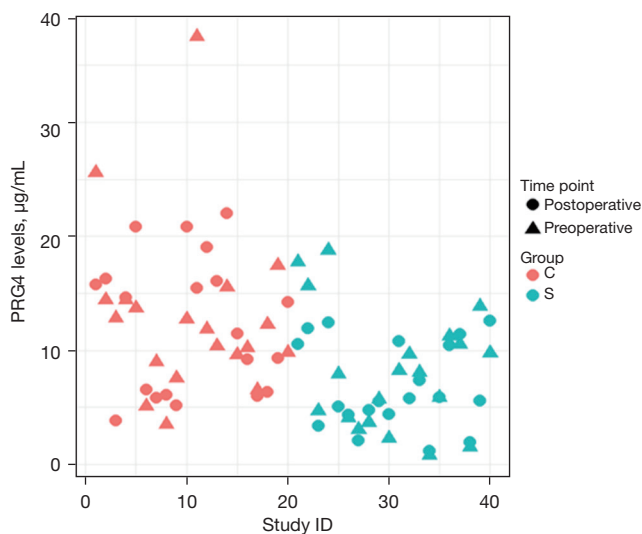


Figure 1 PRG4 levels for all study subjects. Each study subject has two samples; preoperative and postoperative. Group C, control group; Group S, study group. PRG4, proteoglycan 4; ID, identity.

significantly lower in the study group compared to control group (preoperative mean 8.15 vs. 13.01 µg/mL, *P*=0.0232; postoperative mean 6.88 vs. 12.25 µg/mL, *P*=0.0016). There was a trend toward lower levels of PRG4 in postoperative samples in the study group (6.88 vs. 8.15 µg/mL, *P*=0.0869); however, it was not statistically significant (Table 2, Figure 1).

Respiratory variables

The median duration of mechanical ventilation for subjects in the control group was 11.9 vs. 78.5 hours in the study group (*P*<0.0001). Patients in the study group had significantly lower lung compliance (median 2.1 vs. 3.1) and higher mean airway pressure (median of 10 vs. 9) at the admission time to the CICU following surgery (*P*=0.003 and 0.021, respectively). Patients in the control group required less oxygen support at admission time to the CICU and 4 hours after admission. The tidal volume was indifferent among groups and this can be related to the volume control mode of ventilation that is used widely in

Table 3 Ventilatory indices and outcomes for study versus control

Variables	Control (n=20)	Study (n=20)	P value
Admission			
FiO ₂	0.45 [0.40, 0.59]	0.57 [0.46, 0.95]	0.021
PaO ₂ (mmHg)	144 [106, 231]	78 [65, 102]	<0.001
PaO ₂ /FiO ₂ ratio	377.5 [237.8, 475.3]	141.0 [70.7, 243.0]	<0.001
MAP (cmH ₂ O)	9 [8, 9]	10 [9, 11]	0.021
ETCO ₂ (mmHg)	40.5 [36.3, 44.0]	33.0 [30.5, 40.5]	0.017
Tidal volume (mL/kg)	8.1 [7.6, 9.1]	7.8 [7.3, 8.9]	0.424
Lung compliance (mL/mmHg)	3.1 [2.7, 3.8]	2.1 [1.4, 2.7]	0.003
4 hours post-admission			
FiO ₂	0.40 [0.30, 0.48]	0.60 [0.40, 0.83]	0.012
PaO ₂ (mmHg)	117.0 [84.8, 159.5]	82.3 [55.2, 89.2]	<0.001
PaO ₂ /FiO ₂ ratio	330.4 [180.4, 400.8]	143.4 [64.9, 209.2]	<0.001
Length of ventilation (hours)	11.9 [10.1, 12.8]	78.5 [55.6, 145.3]	<0.0001

Data are presented as median [interquartile range]. FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of oxygen in the arterial blood; MAP, mean airway pressure; ETCO₂, end tidal carbon dioxide.

Table 4 Clinical outcomes

Outcome	Control (n=20)	Study (n=20)	P value
Lactate admission (mmol/L)	1.4 [1.2, 1.6]	2.5 [1.8, 3.4]	<0.001
Creatinine POD1 (mg/dL)	0.30 [0.29, 0.39]	0.50 [0.39, 0.60]	<0.001
Creatinine POD2 (mg/dL)	0.26 [0.20, 0.30]	0.40 [0.30, 0.56]	<0.001
Duration of inotropes (hours)	1.0 [1.0, 1.0]	8.5 [4.3, 11.0]	<0.001
CICU LOS (days)	3.0 [2.0, 4.0]	14.5 [8.3, 29.5]	<0.001
HLOS (days)	6.5 [5.0, 7.0]	21.5 [11.0, 36.8]	<0.001

Data are presented as median [interquartile range]. POD, postoperative day; CICU, cardiovascular intensive care unit; LOS, length of stay; HLOS, hospital LOS.

our center and is routinely set at 7 to 8 mL/kg (Table 3).

1.0 hour, median of 2.5 vs. 1.4 mmol/L, P<0.001) (Table 4).

Clinical outcomes

In general, patients in the study group had worse clinical outcomes in comparison to patients in the control group. The CICU length of stay was significantly longer for patients in study group (median of 14.5 vs. 3.0 days, P<0.001). The hospital length of stay was longer for patients in the study group (median of 21.5 vs. 6.5 days, P<0.001). The duration of inotropic support was longer and serum lactate at admission were higher in the study group (8.5 vs.

PRG4 plasma levels as predictor of prolonged mechanical ventilation with adjustment for weight and age

Using logistic regression, we studied the ability of PRG4 plasma levels in predicting prolonged mechanical ventilation as shown in Table 5. For each 1 unit decrease in preoperative PRG4 level, there was 13.7% higher likelihood of prolonged mechanical ventilation [odds ratio: 0.863, 95% confidence interval (CI): 0.751–0.991, P=0.0374]. For each 1 unit decrease in postoperative PRG4 level, there was

Table 5 Pre- and post-operative PRG4 levels as risk factor of prolonged mechanical ventilation before and after adjustment for weight and age

PRG4 levels	Odds ratio	95% CI	P value
Preoperative	0.863	0.751–0.991	0.0374
Adjusted preoperative	0.865	0.745–1.000	0.0580
Postoperative	0.804	0.689–0.939	0.0060
Adjusted postoperative	0.801	0.668–0.960	0.0167

Logistic regression. For each 1 unit decrease in PRG4 level, there is 13.7% and 20% higher chance of having prolonged mechanical ventilation for preoperative and postoperative levels respectively. After adjustment for weight and age, for each 1 unit decrease in postoperative PRG4 levels, there is 20% higher chance of having prolonged mechanical ventilation. PRG4, proteoglycan 4; CI, confidence interval.

20% higher likelihood of prolonged mechanical ventilation (odds ratio 0.804, 95% CI: 0.689–0.939, $P=0.0060$). After adjustment for weight and age, preoperative PRG4 levels were not able to predict prolonged mechanical ventilation (95% CI: 0.745–1.000, $P=0.0580$). However, each one unit decrease in the postoperative PRG4 level, there was 20% higher likelihood of prolonged mechanical ventilation (95% CI: 0.668–0.960, $P=0.0167$) as shown in *Table 5*. The receiver operative curve for postoperative PRG4 level in predicting prolonged mechanical ventilation after adjustment for weight and age is shown in *Figure S1*.

Discussion

Recent evidence suggests a role of PRG4 in regulating the inflammatory response in variable organs including the lung. PRG4 can bind to toll like receptors and mediate the anti-inflammatory response to injury (8,10,18). Additionally, PRG4 may have a critical role in maintaining tissue hemostasis as well. Proteoglycan depositions were found to contribute to lung pathology and variable serum levels were correlated with the disease prognosis for patients with chronic obstructive pulmonary disease (13-19). Recently, PRG4 was found to play a protective role in prevention adhesions after cardiectomy and loss of PRG4 in the pericardial fluids after cardiectomy might had induced adhesion formation (20).

Our prior pilot study suggested a correlation between low PRG4 plasma levels with long mechanical ventilation in pediatric patients following CPB (21). This comparative study between patients with and without prolonged

mechanical ventilation supports the findings of our pilot study as well as correlates lower serum levels of PRG4 with worse lung compliance, higher mean airway pressure and increased need for supplemental oxygen.

In addition, patients with lower PRG4 plasma levels had a longer hospital stay and longer duration of inotropic support. The length of CPB and aortic cross clamp was indifferent among the two groups and there was no difference statistically when we compared the postoperative PRG4 levels to the preoperative levels in both groups. This finding leads us to speculate about the possibility of a lower serum PRG4 level predicting prolonged mechanical ventilation postoperatively. Lower levels of PRG4 in the study group may suggest a native predisposition for adverse lung injury after cardiac surgery rather than the exposure to CPB.

At this stage and as evident in our study, lower levels of PRG4 are correlated with worse clinical and respiratory outcomes. We were limited by the number of patients that had matching cardiac defects and available samples in our study; thus, we were not able to discover the association of longer CPB time with the postoperative levels of PRG4. Our study did not investigate the association of different cardiac lesions with the length of mechanical ventilation. We divided our patients based on the length of mechanical ventilation rather than the cardiac lesion. Thus, we are unable to have any conclusion relating to the association of cardiac defect and PRG4 levels. In addition, we were unable to discover the impact of certain demographic characteristics on the PRG4 levels. Study group had lower postoperative levels of PRG4 compared to preoperative levels, but that was statistically insignificant. The duration of inotropic support was clinically and statistically longer in the study group, due to the retrospective nature of our study, we are unable to determine if this hemodynamic variation is related to acute lung injury or heart failure or both.

Conclusions

Following cardiac surgery, infants with prolonged mechanical ventilation had lower levels of plasma PRG4. Lower levels of PRG4 were associated with worse ventilatory and clinical outcomes. PRG4 level may have prognostic value in regard to acute lung injury for infants with cardiac surgery. We plan to validate our finding and further explore the association of PRG4 levels with worse outcomes in a larger and more diverse group. Testing PRG4 levels in other bodily fluids might shine the light on the pathophysiological role of PRG4 in adverse lung injury.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at <https://tp.amegroups.com/article/view/10.21037/tp-23-194/rc>

Data Sharing Statement: Available at <https://tp.amegroups.com/article/view/10.21037/tp-23-194/dss>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tp.amegroups.com/article/view/10.21037/tp-23-194/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the University of Alabama at Birmingham Institutional Review Board (approval No. IRB-300003366) and individual consent for this retrospective analysis was waived.

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