Cardiology in the Young

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Post-operative acute kidney injury is associated with a biomarker of acute brain injury after paediatric cardiac surgery

Michael Parsons[1], Jason Greenberg[2], Chirag Parikh[1], Jeremiah Brown[3], Devin Parker[3], Jie Zhu[1], Luca Vricella[4] and Allen D. Everett[1]

[1]Department of Pediatrics, The Helen B. Taussig Congenital Heart Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2]Department of Pediatrics, Yale School of Medicine, New Haven, CT, USA; [3]Department of Epidemiology, Dartmouth Geisel School of Medicine, Hanover, NH, USA and [4]Department of Pediatric Cardiac Surgery, University of Chicago School of Medicine, Chicago, IL, USA

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Author for correspondence:
M. Parsons, Johns Hopkins Pediatric Cardiology, Johns Hopkins University, 1800 Orleans St., Room 2201, Baltimore, MD 21287, USA. Tel: (240) 603 9918; Fax: (410) 955 0897; E-mail: mikeresnickparsons@gmail.com

Abstract

Introduction: Children with CHD who undergo cardiopulmonary bypass are at an increased risk of acute kidney injury. This study evaluated the association of end-organ specific injury plasma biomarkers for brain: glial fibrillary acidic protein and heart: Galectin 3, soluble suppression of tumorgenicity 2, and N-terminal pro b-type natriuretic peptide with acute kidney injury in children undergoing cardiopulmonary bypass. *Materials and Methods:* We enrolled consecutive children undergoing cardiac surgery with cardiopulmonary bypass. Blood samples were collected pre-bypass in the operating room and in the immediate post-operative period. Acute kidney injury was defined as a rise of serum creatinine ≥50% from pre-operative baseline within 7 days after surgery. *Results:* Overall, 162 children (mean age 4.05 years, SD 5.28 years) were enrolled. Post-operative acute kidney injury developed in 55 (34%) children. Post-operative plasma glial fibrillary acidic protein levels were significantly higher in patients with acute kidney injury (median 0.154 (inter-quartile range 0.059–0.31) ng/ml) compared to those without acute kidney injury (median 0.056 (inter-quartile range 0.001–0.125) ng/ml) ($p = 0.043$). After adjustment for age, weight, and The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery category, each natural log increase in post-operative glial fibrillary acidic protein was significantly associated with a higher risk for subsequent acute kidney injury (adjusted odds ratio glial fibrillary acidic protein 1.25; 95% confidence interval 1.01−1.59). Pre/post-operative levels of galectin 3, soluble suppression of tumorgenicity 2, and N-terminal pro b-type natriuretic peptide did not significantly differ between patients with and without acute kidney injury. *Conclusions:* Higher plasma glial fibrillary acidic protein levels measured in the immediate post-operative period were independently associated with subsequent acute kidney injury in children after cardiopulmonary bypass. Elevated glial fibrillary acidic protein likely reflects intraoperative brain injury which may occur in the context of acute kidney injury-associated end-organ dysfunction.

CHD represents approximately one-third of all major congenital anomalies, with an estimated 1.35 million newborns affected every year.[1] Cardiovascular malformations account for about 50% of the deaths due to birth defects in the first year of life.[2] Approximately 25% of infants with CHD require immediate intervention such as surgery with cardiopulmonary bypass.[3] Acute kidney injury is a common complication of paediatric cardiac surgery, occurring in 42% of patients in a multicentre prospective study.[4] In that series, patients with acute kidney injury were more likely to remain on mechanical ventilation for a longer period of time and had longer ICU and overall hospital stays.[4] Beyond the initial morbidity and mortality associated with acute kidney injury following cardiac surgery, studies have demonstrated an association between acute kidney injury and the development of chronic kidney disease.[5,6]

Significant advances have been made in the identification of circulating molecules that reflect end-organ injury and function, but more research is needed to identify specific biomarkers and their individual correlations. Determining the relationships between biomarkers and signs of end-organ damage after cardiopulmonary bypass will better allow clinicians to identify patients at risk for adverse secondary outcomes and potentially guide post-operative management to better accommodate these risks. In particular, the association between acute kidney injury and brain injury is important because it could help identify patients at an increased risk of adverse neurodevelopmental outcomes and guide additional developmental interventions for this population. The biomarkers in this study were chosen based on previous research showing correlations with cardiac or end-organ injury after cardiopulmonary bypass in children.

Glial fibrillary acidic protein is an astrocyte intermediate filament protein that is upregulated in settings of central nervous system injury[7] and has been shown to be predictive of neurologic

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injury in various clinical settings, including after acute stroke[8] and cardiac arrest.[9] In neonatal cardiac surgery with cardiopulmonary bypass, elevated post-operative glial fibrillary acidic protein was associated with a worse neurodevelopmental outcome at 12 months of age,[11,12] and in paediatric intensive care patients undergoing extracorporeal membrane oxygenation, high serum glial fibrillary acidic protein levels have been associated with acute brain injury and death.[12]

Galectin 3 is a β-Galactoside-binding lectin that plays a role in tissue inflammation and fibrosis.[13] Plasma Galectin 3 levels are markedly elevated in patients with heart failure[14] and have been associated with long-term mortality in adults.[15] Elevated post-operative Galectin 3 levels have also been shown to improve clinical models for predicting post-operative acute kidney injury in adults undergoing cardiac surgery.[16]

Soluble suppression of tumorgenicity 2 is a member of the interleukin-1 receptor family. It is induced in mechanically overloaded cardiac myoctyes[17] and can protect cardiac function in response to pressure overload.[18] In patients with symptomatic heart failure, soluble suppression of tumorgenicity 2 levels correlates with disease severity and can predict the onset of symptomatic heart failure in patients with acute myocardial infarction.[19] Post-operative soluble suppression of tumorgenicity 2 levels has also been showed to be associated with post-operative risk of acute kidney injury in adults after coronary artery bypass graft surgery.[20]

N-terminal pro b-type natriuretic peptide is the amino-terminal fragment of B-type natriuretic peptide, which is a neuro-hormone secreted by cardiac myocytes in response to wall stress.[21] In a previous study examining adults undergoing cardiac surgery, higher pre-operative B-type natriuretic peptide levels were associated with an increased risk of post-operative acute kidney injury,[22] and similar studies in children have identified additional biomarkers associated with an increased risk of post-operative acute kidney injury.[23]

The present investigation is a single-centre, prospective, observational study examining the relationship of four biomarkers (glial fibrillary acidic protein, Galectin-3, soluble suppression of tumorgenicity 2, and B-type natriuretic peptide) with post-operative acute kidney injury in children undergoing cardiopulmonary bypass.

Materials and methods

Children less than 18 years old undergoing cardiac surgery with cardiopulmonary bypass at Johns Hopkins Hospital were enrolled between July 2011 and July 2014. No patients were excluded. This study was performed with an Institutional Review Board approved waiver of consent.

Heparinised blood samples were collected pre-cardiopulmonary bypass in the operating room and in the post-operative period immediately after decannulation and prior to transfer from the operating room. Glial fibrillary acidic protein was measured as described previously by enzyme-linked immunosorbent assay.[24–29] An electrochemiluminescent immunosorbent assay was developed to measure B-type natriuretic peptide, Galectin-3, and soluble suppression of tumorgenicity 2 on the 96-well plate Meso Scale Discovery platform (N75YA-1; Meso Scale Discovery, Gaithersburg, Maryland, United States of America). Capture antibody-coated plates were blocked with 5% bovine serum albumin-phosphate-buffered saline complemented with 0.05% TWEEN (Croda International PLC, Snaith, UK; PBS-T) and incubated at room temperature on an orbital shaker (500 rpm) for 60 minutes. Calibrators for B-type natriuretic peptide (MSD C01XX-1), Galectin-3 (R&D 840355), and soluble suppression of tumorgenicity 2 (R&D 840760) were produced using commercially provided diluent (MSD R51BB-3) with concentration ranges of 5000–1.22, 4000–0.98, and 8300–2.03 pg/ml, respectively. Samples were diluted 15× in commercially provided diluent (MSD R51BB-3). Calibrators and 15×-diluted samples were added to the plate and incubated for 2 hours on an orbital shaker (500 rpm) at room temperature and washed three times with 150 µl/well with 1× PBS-T. The detection antibody cocktail for B-type natriuretic peptide (MSD D21JK-1), Galectin-3 (R&D 842759), and soluble suppression of tumorgenicity 2 (R&D 840354) was prepared to 1×, 25 ng/ml, and 200 ng/ml, respectively, in commercially provided diluent (MSD R51BA-5) and supplemented with 0.5 µg/ml SA-Sulfo-tag (MSD R32AD-5). Detection cocktail was added to the plates and incubated at room temperature on an orbital shaker (500 rpm) for 60 minutes, protected from light, and then washed three times with 150 µl of 1× PBS-T to remove unbound detection antibodies. Finally, 150 µl of 1× commercially provided read buffer (MSD R92TC-1) was applied, and the plate was promptly read in an MSD Sector Imager 2400. Inter-plate percent coefficient of variation for seven plates was glial fibrillary acidic protein 11%, Gal-3 13%, B-type natriuretic peptide 13.1%, and soluble suppression of tumorgenicity 2 11.2% using an interassay control.

The main outcome analysed in this study was any acute kidney injury, defined as a rise of serum creatinine ≥50% or 0.3 mg/dl from pre-operative baseline within 7 days after surgery.[30] Surgical complexity was categorised using The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery scores.[31] The acute kidney injury versus non-acute kidney injury groups were compared for need for post-operative dialysis, ICU length of stay, hospital length of stay, mortality, complication rate, and reoperation rate using Pearson's chi-square test for dichotomous characteristics and Student's t-test for continuous variables. Biomarker levels were compared via univariate logistic regressions and a multivariate logistic regression adjusted for age (in days), weight (kg), and The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery category. Statistical analysis was completed with Stata Version 14.2 (StataCorp LLC, College Station, TX, USA).

Results

As shown in Table 1, 162 patients with a mean (±SD) age 4.05 years (±5.28 years) were enrolled over 3 years. Ninety-eight (60%) of the patients were male. Cardiac surgery STAT (The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery) levels were 1–2 in 108 children (67%) and 3–5 in 40 children (25%), 159 with 14 (9%) unknown. Out of the 162 patients enrolled, 55 (34%) patients developed acute kidney injury. On univariate analysis, development of acute kidney injury was not associated with age ($p = 0.214$), gender ($p = 0.927$), or weight less than the 10th percentile for age ($p = 0.657$).

The relationship between intraoperative factors and outcomes by acute kidney injury status is shown in Table 2. The developmental of acute kidney injury was not associated with cardiopulmonary bypass time ($p = 0.539$), cross clamp time ($p = 0.962$), or circulatory arrest time ($p = 0.709$). None of the included patients required dialysis. Patients with acute kidney injury on average had a longer length of hospital stay ($p = 0.081$) and ICU stay ($p = 0.384$), but neither result reached statistical significance. There were three operative deaths: two in the acute kidney injury group and one without acute kidney injury. Rates of complications, re-operations,

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Table 1. Patient characteristics by AKI status

Risk factors	n = 162	No AKI No. (%)	AKI No. (%)	*P* (chi-squared)
Age group				
Neonates	14	9 (64.3)	5 (35.7)	0.214
Infants	68	40 (58.8)	28 (41.2)	
Children	80	58 (72.5)	22 (27.5)	
Gender				
Male	98	65 (66.3)	33 (33.7)	0.927
Female	64	42 (65.6)	22 (34.4)	
Weight				
>10th percentile for each group	148	97 (65.5)	51 (34.4)	0.657
<10th percentile for each group	14	10 (71.4)	4 (28.6)	
Prematurity among neonates and infants				
No	67	38 (56.7)	29 (43.4)	0.236
Yes	15	11 (73.3)	4 (26.7)	
The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery level				
1	69	50 (72.5)	19 (27.5)	0.128
2	39	21 (53.8)	18 (46.2)	
3	15	12 (80.0)	3 (20.0)	
4	15	11 (73.3)	4 (26.7)	
5	10	4 (40.0)	6 (60.0)	
Unknown	14	9 (64.3)	5 (35.7)	
Prior cardiothoracic operation				
No	128	83 (64.8)	45 (35.2)	0.530
Yes	34	24 (70.6)	10 (29.4)	
Any non-cardiac congenital anatomic abnormality				
No	141	90 (63.8)	51 (36.2)	0.122
Yes	21	17 (81.0)	4 (19.0)	
Chromosomal abnormality or syndrome				
No	115	68 (59.1)	47 (40.9)	0.004
Yes	47	39 (83.0)	8 (17.0)	

AKI = acute kidney injury.

peri-operative cardiopulmonary arrest, and post-operative mechanical circulatory support were not significantly different between the two groups.

Table 3 shows median and inter-quartile ranges for all biomarkers, separated by acute kidney injury status. Post-operative glial fibrillary acidic protein levels were significantly higher in patients with acute kidney injury (median 0.154 (inter-quartile range, 0.059–0.31) ng/ml) compared to those without acute kidney injury (median 0.056 (inter-quartile range, 0.001–0.125) ng/ml) ($p = 0.043$). Pre-operative and post-operative Galectin-3, soluble suppression of tumorgenicity 2, and B-type natriuretic peptide did not significantly differ between patients with and without acute kidney injury. To determine if circulating cardiac and brain biomarkers have a relationship with acute kidney injury, we explored pre- and post-operative biomarker values stratified by acute kidney injury status. Using univariate biomarker regressions with any acute kidney injury as the outcome, elevation in post-operative glial fibrillary acidic protein was significantly associated with subsequent acute kidney injury (odds ratio, 1.07; 95% confidence interval 1.00–1.14). There was no significant association between elevation in pre-operative glial fibrillary acidic protein and subsequent acute kidney injury (odds ratio 1.02; 95% confidence interval 0.98–1.07). Pre- and post-operative levels of galectin 3, soluble suppression of tumorgenicity 2, and B-type natriuretic peptide were not significantly associated with post-operative acute kidney injury. Biomarker associations with acute kidney injury status were also adjusted for the clinically relevant covariates of age (in days), weight (kg), and The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery category (Table 4). All biomarkers are listed in log-continuous form. In this adjusted model, post-operative glial fibrillary acidic protein remained significantly associated with acute kidney injury (odds ratio 1.25; 95% confidence interval 1.01–1.59). Soluble suppression of tumorgenicity 2, Galectin3, B-type natriuretic peptide, and pre-operative glial fibrillary acidic protein again did not reach statistical significance.

Discussion

Our study sought to explore the association between pre- and post-operative levels of four brain and heart biomarkers with acute kidney injury in children undergoing cardiac surgery with cardiopulmonary bypass. Of the biomarkers tested, we found post-operative glial fibrillary acidic protein levels to be associated with subsequent development of acute kidney injury.

Abnormal neurodevelopmental outcomes are common in children with CHD,[32] and neurodevelopmental disability is the most common morbidity for survivors of CHD surgery.[33] Significant effort has been spent attempting to identify the mechanisms for cerebral injury after undergoing bypass. Similar to the causes of cerebral injury after bypass surgery, a wide range of mechanisms have been identified as potential causes of acute kidney injury. Mechanisms for cardiac surgery associated acute kidney injury include peri-operative renal ischaemia and reperfusion injury as well as emboli secondary to aortic cannulation and cross-clamping. Cardiopulmonary bypass can also lead to haemolysis and pigment nephropathy, oxidative stress, and inflammation.[34–36] The kidneys are particularly vulnerable to the systemic inflammation seen during bypass, and previous research has linked elevations in post-operative inflammatory cytokines with both a subsequent diagnosis of acute kidney injury and increased mortality.[37] The overall rate of acute kidney injury in our cohort (34%) was consistent with previously published prospective, observations studies of post-cardiac surgery kidney injury.[4] The rate of acute kidney injury did not reach significance across The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery levels.

We demonstrate that higher post-operative plasma glial fibrillary acidic protein was significantly associated with an increased risk of acute kidney injury. The association of glial fibrillary acidic protein levels in the immediate post-operative period and subsequent acute kidney injury reveals multi-organ injury in the presence of acute kidney injury with possibly a common mechanism of injury. Elevations in glial fibrillary acidic protein were present immediately after decannulation and occurred prior to changes in creatinine in the setting of kidney injury. The elevated glial fibrillary acidic protein levels in our cohort suggest the presence of neurologic injury in the intraoperative period[10,11] with long-term neurodevelopmental consequences.

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Table 2. Intraoperative factors and outcomes by AKI status

Characteristics	n (%) or mean ± SD		p
	No AKI	AKI	
N	106	56	
Intraoperative factors			
Use of cardiopulmonary bypass intraoperatively	105 (99.1%)	56 (100.0%)	0.466
Cardiopulmonary bypass time (mean ± SD)	137.3 ± 65.1	144.9 ± 92.1	0.539
Cardiopulmonary bypass time categories			
>60 minutes	92 (87.6%)	51 (91.1%)	0.508
>90 minutes	79 (75.2%)	41 (73.2%)	0.779
>120 minutes	59 (56.2%)	32 (57.1%)	0.908
Cross-clamp time (mean ± SD)	76.4 ± 52.9	76.0 ± 66.5	0.962
Circulatory arrest	6 (5.7%)	4 (7.1%)	0.709
Outcomes			
AKI severity			0.000
AKI with ≥50% and <100% increase in serum creatinine	0 (0.0%)	18 (36.7%)	
AKI with ≥100% increase in serum creatinine	0 (0.0%)	31 (63.3%)	
Post-operative dialysis	0 (0.0%)	0 (0.0%)	
Length of stay in ICU (days) (median, IQR)	3.0 (2.0, 6.0)	3.5 (2.0, 5.0)	0.384
Length of stay in hospital (days) (median, IQR)	6.0 (4.0, 13.0)	7.0 (5.0, 12.5)	0.081
Pre-operative mechanical ventilation	2 (1.9%)	0 (0.0%)	0.301
Mortality – operative death	1 (0.9%)	2 (3.6%)	0.238
Any complication	20 (18.9%)	13 (23.2%)	0.514
Re-operation	4 (3.8%)	0 (0.0%)	0.141
Peri-operative cardiopulmonary arrest	1 (1.3%)	0 (0.0%)	0.492
Post-operative mechanical circulatory support	0 (0.0%)	1 (2.7%)	0.150

AKI = acute kidney injury; IQR = inter-quartile range; SD = standard deviation.

Table 3. Median and IQR biomarker levels by AKI status

Biomarker (ng/ml)	Pre-op versus Post-op	Median (IQR)		Odds ratio (95% confidence interval)	p
		AKI	No AKI		
Soluble suppression of tumorgenicity 2/interleukin-1	Pre-op	2264 (1408–3335)	1945 (1218–4090)	1.01 (0.74–1.38)	0.927
	Post-op	3236 (2218–5965)	3475 (1980–5846)	1.09 (0.75–1.59)	0.638
Galectin 3	Pre-op	16861 (9852–30133)	14934 (8876–19446)	1.33 (0.89–1.99)	0.161
	Post-op	25263 (17176–39812)	24475 (14854–35093)	1.36 (0.88–2.08)	0.163
N-terminal pro b-type natriuretic peptide	Pre-op	565 (216–1678)	388 (191–1546)	1.10 (0.93–1.30)	.269
	Post-op	426 (171–1467)	454 (175–1399)	1.04 (0.87–1.24)	0.682
Glial fibrillary acidic protein	Pre-op	0.001 (0–0.009)	0.001 (0–0.011)	1.02 (0.98–1.07)	0.284
	Post-op	0.154 (0.059–0.31)	0.056 (0.001–0.125)	1.07 (1.00–1.14)	0.043

AKI = acute kidney injury; IQR = inter-quartile range.

The brain and the kidneys are both vulnerable to injury during cardiopulmonary bypass, and there are several common physiologic pathways to explain why damage to these organ systems might occur simultaneously. Both organs are sensitive to the hypoxic damage secondary to systemic hypotension that is commonly seen in the intraoperative and immediate post-operative period. Prolonged low oximetry numbers obtained during cardiac surgery via renal near-infrared spectroscopy have been shown to correlate with subsequent acute kidney injury in infants.[38] Vascular beds in the brain and the kidneys are similarly susceptible to injury from emboli, as aortic cross-clamping will typically occur proximately to the blood supply to both. Other systemic insults with the potential

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Table 4. Biomarkers associations with acute kidney injury adjusted for age (in days), weight (kg), and The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery category

		Adjusted	
	Biomarker	Odds ratio (95% confidence interval)	p Value
Soluble suppression of tumorgenicity 2	Pre-op	0.83 (0.59–1.17)	0.291
	Post-op	0.85 (0.56–1.31)	0.463
Galectin 3	Pre-op	1.26 (0.85–1.86)	0.245
	Post-op	1.31 (0.82–2.10)	0.255
N-terminal pro b-type natriuretic peptide	Pre-op	1.00 (0.83–1.21)	0.964
	Post-op	0.97 (0.80–1.18)	0.774
Glial fibrillary acidic protein	Pre-op	0.92 (0.76–1.11)	0.383
	Post-op	1.25 (1.01–1.59)	0.045

IQR = inter-quartile range; kg = kilogram.

to injure both the brain and the kidney include hyperglycaemia and the diffuse inflammatory response associated with surgery in general and the bypass circuit in particular. The correlation between elevated glial fibrillary acidic protein levels and acute kidney injury in our cohort highlights the presence of multi-organ dysfunction in children after undergoing cardiopulmonary bypass operations and could have important clinical implications regarding the likelihood of additional adverse outcomes.

No statistically significant association was found between pre- or post-operative levels of Galectin 3, soluble suppression of tumorgenicity 2, or B-type natriuretic peptide with acute kidney injury. The odds ratios for pre- and post-operative galectin 3 were 1.33 and 1.36, respectively, but did not reach statistical significance. B-type natriuretic peptide, Galectin-3, and soluble suppression of tumorgenicity 2 have all been associated with severity of heart failure,[15,39,40] and B-type natriuretic peptide has additionally been shown to correlate with mortality after cardiac surgery.[41] The lack of significant association between these biomarkers and subsequent acute kidney injury could suggest that the mechanism of kidney dysfunction is independent of both cardiac stress during bypass and heart failure after bypass. It is also possible that the blood samples were obtained prior to the point at which acute markers of cardiac stress would be most elevated. Galectin-3 in particular plays an important role in cardiac fibrosis and remodelling[42] and may not reflect the acute cardiovascular changes that occur in the immediate pre- and post-operative periods. Another potential explanation for the lack of significance is that our study was under-powered to detect this association with acute kidney injury.

Our study has several limitations. Our cohort consisted of patients undergoing surgery at a single location, which does not account for practice variations across multiple centres or regional differences in patient population. Our study did not include information about neurological injuries noted in the post-operative period, which could be useful clinical information given the noted elevation in glial fibrillary acidic protein. Further studies are needed to evaluate the clinical relevance and potential neurodevelopmental sequelae associated with elevated glial fibrillary acidic protein levels, especially in non-neonatal cardiac surgery.

In summary, we found that post-operative glial fibrillary acidic protein elevation immediately after children undergo cardiopulmonary bypass is associated with subsequent acute kidney injury. This suggests sub-clinical intraoperative brain injury which may occur in the context of acute kidney injury-associated end-organ dysfunction. In addition to post-operative glial fibrillary acidic protein elevation serving as a potentially useful predictor of subsequent acute kidney injury, the presence of acute kidney injury could also serve as a sign of concurrent brain injury and help guide future neurodevelopmental follow-up. Future studies should investigate the role of glial fibrillary acidic protein at later time points after cardiac surgery to study the associations with short- and long-term neurological outcomes.

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Conflicts of Interest. None.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees (Johns Hopkins Institutional Review Board).

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