Usefulness of High Estimated Pulmonary Artery Systolic Pressure to Predict Acute Kidney Injury After Cardiac Valve Operations

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High estimated pulmonary artery systolic pressure (ePASP) has been established as a detrimental predictor for adverse outcomes in patients with chronic kidney disease. However, the relation between preoperative high ePASP and the development of cardiac surgery associated acute kidney injury (CSA-AKI) has not been validated. We performed a retrospective cohort study of adult patients who underwent valve surgery in 2015 at Zhongshan Hospital, Fudan University. Right ventricular systolic pressure, a surrogate for pulmonary systolic pressure, was estimated in the study group of 1056 patients by preoperative echocardiography. CSA-AKI was defined based on the Kidney Disease Improving Global Outcomes criteria. The relation between preoperative ePASP and CSA-AKI was demonstrated with the use of multivariate analysis after adjusting for potential risk factors for CSA-AKI. Of these patients, preoperative ePASP was 44.5 ± 14.9 mm Hg. 401 (38%) patients developed CSA-AKI in which 73 patients (6.9%) suffered from severe AKI (stage II and III). Multivariate analysis showed that preoperative ePASP was independently associated with CSA-AKI (odds ratio per 10 mm Hg increment, 1.099; 95% confidence interval, 1.003 to 1.204; p = 0.042). Preoperative ePASP more than 60 mm Hg was found to be linked with the increasing incidence of AKI by 62% and in-hospital mortality by over 300%, but not linked with severe AKI or renal replacement therapy. In conclusion, an increase in preoperative ePASP was independently and significantly associated with the development of CSA-AKI in patients who underwent valve surgery. Such relation between preoperative ePASP and CSA-AKI could provide a novel therapeutic target against prevention of AKI. **(Am J Cardiol 2019;123:440−445)**

High estimated pulmonary artery systolic pressure (ePASP) measured by transthoracic echocardiography (TTE) has been considered as a detrimental element for cardiovascular risk in patients with chronic kidney disease (CKD) or end stage renal disease (ESRD) who underwent renal replacement therapy (RRT).[1−5] Similarly, in patients who underwent cardiovascular surgery, preoperative PASP measured by TTE or right-sided cardiac catheterization was linked to increased cardiovascular and all-cause mortality.[6−12] Acute kidney injury (AKI) evidently is a prevalent complication after cardiac surgery with an increased morbidity and mortality.[13−15] Considerable risk factors have hitherto been established as predictors for AKI, however, to date, studies investigating the association between preoperative ePASP and the incidence of AKI were scarce. Thus, we sought to explore whether preoperative ePASP measured by echocardiography is an essential predictor for AKI in the cohort of patients who underwent valve operations.

Methods

Patients who received elective valve surgery from January 2015 to December 2015 at Zhongshan Hospital, Fudan University were consecutively enrolled into the study according to the inclusion and exclusion criteria. Demographic data, comorbidities, baseline kidney function, echocardiographic data, and intraoperative parameters were collected retrospectively from the electronic medical records. The institutional review board of Zhongshan Hospital granted permission for study design and data collection and all participants were informed by written consent before the enrollment.

Inclusion criteria for this study were adult patients (age ≥18 years) who underwent valve repair or replacement

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surgery due to degenerative or congenital valvular heart disease during study period. Exclusion criteria were: patients underwent concurrent coronary artery bypass graft; patients who had solitary kidney or underwent RRT or kidney transplantation; patients who had a medical record for chronic obstructive pulmonary disease or atrial fibrillation; patients whose echocardiographic data were not available before surgery.

Echocardiography was performed by experienced physician using a commercially available echocardiographic machine (GE Vingmed Ultrasound, Horten, Norway). Right ventricular systolic pressure (RVSP) was estimated by preoperative TTE and used as a surrogate of ePASP in absence of right ventricular outflow obstruction. Continuous-wave Doppler was utilized to measure maximum jet velocity whereas color flow Doppler identified tricuspid regurgitation flow. RVSP was calculated with the maximal tricuspid regurgitation velocity (Vmax) and utilized the modified Bernoulli's equation:[16] $ePASP = 4 \times (Vmax^2) + \text{right atrial pressure}$. Right atrial pressure was measured by inferior vena cava diameter during respiration.[17,18] ePASP was analyzed as a continuous variable and mild-to-moderate or severe pulmonary hypertension (PH) was defined at cutoff values of 35 mm Hg or 60 mm Hg, respectively.[19]

Baseline serum creatinine was defined as the peak value in 3 months before surgery. Estimated glomerular filtration rate (eGFR) was estimated by Modification of Diet in Renal Disease equation. Postoperative serum creatinine was measured every 24 hours during intensive care unit period. AKI was defined by Kidney Disease Improving Global Outcomes criteria.[20] Subjects were separated into 2 groups according to the occurrence or absence of cardiac surgery associated acute kidney injury (CSA-AKI).

Continuous data were presented as means ± standard deviation or as median (interquartile range) whereas categorical data were shown as numbers (%). Comparisons between subjects with or without AKI were carried out by 2-tailed *t* test, chi-square test, or Fisher's exact test where appropriate. Univariate and multivariate analyses were performed to identify potential risk factors for CSA-AKI. Only factors with p value of <0.10 in univariate analyses or with clinical significance were further entered into multivariate logistic analysis. Multicollinearity was checked as well. ePASP was regarded as continuous data and further interrogated in increments of 10 mm Hg in univariate and multivariate analyses. Logistic analyses were further conducted in patients with the presence of ePASP ≥60 mm Hg versus <60 mm Hg as the predictor of interest for renal complications (CSA-AKI, severe CSA-AKI, and RRT) and in-hospital mortality. Statistical significance was considered as a 2-tailed p value of <0.05. All of the analyses were accomplished using SPSS Statistic (ver. 18.0, SPSS Inc.). The data, analytical methods, and study materials will be available to other researchers for the purposes of reproducing or replicating the procedure.

Results

The mean age of patients was 56.1 ± 11.6 years, and 53.5% (n = 563) of them were male. Baseline serum creatinine was 0.91 ± 0.27 mg/dl with a mean eGFR of 86.2 ± 21.2 ml/min per 1.73m2 (Modification of Diet in Renal Disease). Mean preoperative ePASP measured by echocardiography was 44.5 ± 14.9 mm Hg. PH (ePASP > 35 mm Hg) was presented in 76.5% (n = 808) of patients whereas severe PH (ePASP ≥ 60 mm Hg) was shown in 13.2% (n = 149) patients. Four hundred-one patients (38%) developed CSA-AKI (31.1% and 6.9% in mild and severe AKI, respectively). Sixteen patients (1.52%) received RRT during hospitalization and in-hospital mortality rate was 1.4% (n = 15; Table 1).

Univariate analyses showed occurrence of CSA-AKI was closely related to male gender, age, body mass index, comorbidities, left ventricular ejection fraction, left ventricular end systolic dimension, contrast agent exposure, ePASP, eGFR, serum creatinine, cardiopulmonary bypass and cross-clamp duration (Figure 1; Table 2). Multivariate logistic analyses revealed that male gender, age, body mass index, ePASP and cardiopulmonary bypass duration maintained a statistically significant association with the development of CSA-AKI (Table 3).

Subgroup analyses revealed that ePASP was significantly associated with odds of development of AKI in patients without diabetes, hypertension, coronary artery disease, and cancer as well as in patients with tricuspid valve surgery (Table 4). Nevertheless, such association was abolished in patients with or without previous contrast exposure.

Patients were then separated into 2 groups according to preoperative ePASP values. The incidence of CSA-AKI was nearly 52% higher in patients with ePASP ≥60 mm Hg versus <60 mm Hg (p = 0.022). In-hospital mortality rate in patients with ePASP ≥60 mm Hg was much higher than patients with ePASP <60 mm Hg (p = 0.020). Nevertheless, the incidence of severe AKI and RRT was comparable in patients with or without severe PH (Table 5).

Discussion

Our analysis proposed the presence PH was prevalent (76.5%) in patients who underwent elective valve surgery and ePASP was significantly higher in patients with CSA-AKI. Preoperative ePASP measured by echocardiography was an independent predictor for CSA-AKI even after adjusting for potential risk factors. Importantly, patients with severe PH before valve surgery had a significantly higher incidence of AKI and in-hospital mortality.

PH has been recognized as an essential prognostic factor in patients with severe aortic stenosis (AS) receiving surgical valve replacement.[8,21–23] Zuern et al considered even mild-to-moderate PH (30 mm Hg ≤ PASP ≤ 60 mm Hg) in patients with severe AS for surgical aortic valve replacement might be a significant and independent risk factor for 5-year mortality.[8] Similarly, echocardiographic PASP of ≥50 mm Hg was found to be an essential risk factor for overall and cardiovascular mortality in patients with mitral valve regurgitation.[6] Moreover, preoperative PH in patients with degenerative mitral valve disease resulted in a fourfold higher risk of postoperative 3-year mortality.[24] In our cohort of patients with degenerative or congenital valvular heart disease, we found identically that severe PH (ePASP ≥ 60 mm Hg) estimated by echocardiography was closely related to a higher in-hospital mortality.

Table 1
Demographic and perioperative characteristics in patients with or without acute kidney injury after cardiac valve surgery

	Acute kidney injury Yes N = 401	Acute kidney injury No N = 655	p value
Men	253 (63.1%)	310 (47.3%)	<0.001
Age (years)	57.9 ± 10.2	55.0 ± 12.2	<0.001
Body mass index (kg/m^2)	23.8 ± 3.4	22.7 ± 3.0	<0.001
Comorbidities			
Hypertension	140 (34.9%)	166 (25.3%)	0.001
Diabetes mellitus	28 (7.0%)	32 (4.9%)	0.153
Chronic kidney disease	70 (17.4%)	20 (3.1%)	<0.001
Coronary artery disease	26 (6.5%)	23 (3.5%)	0.026
Cancer	3 (0.7%)	7 (1.1%)	0.602
Previous contrast exposure	241 (60.1%)	357 (54.5)	0.075
New York Heart Association III-IV	304 (75.8%)	458 (74.0%)	0.522
Baseline renal function			
Estimated glomerular filtrate rate	83.7 ± 21.8	87.8 ± 20.7	0.003
Serum creatinine (mg/dl)	0.96 ± 0.32	0.88 ± 0.23	<0.001
Echocardiographic parameters			
Left ventricular ejection fraction	60.4 ± 9.1	61.5 ± 8.2	0.059
Estimated pulmonary artery systolic pressure (mm Hg)	46.0 ± 17.6	43.5 ± 13.0	0.015
Left ventricular end-diastolic dimension (mm)	54.3 ± 9.1	53.6 ± 8.8	0.245
Left ventricular end-systolic dimension (mm)	36.5 ± 8.9	35.6 ± 7.8	0.069
Primary disease			
Mitral stenosis/regurgitation	380 (94.7%)	605 (92.4%)	0.131
Aortic stenosis/regurgitation	301 (75.1%)	475 (72.5%)	0.363
Tricuspid regurgitation	139 (34.7%)	204 (31.1%)	0.236
Surgical type			
Single mitral valve	94 (23.3%)	168 (25.2%)	0.420
Single aortic valve	102 (25.4%)	189 (28.9%)	0.228
Single tricuspid valve	3 (0.7%)	10 (1.5%)	0.265
Mitral valve + tricuspid valve	87 (21.7%)	129 (19.7%)	0.434
Aortic valve + tricuspid valve	4 (1.0%)	3 (0.5%)	0.294
Mitral valve + aortic valve	50 (12.5%)	73 (11.1%)	0.515
Mitral valve + aortic valve + tricuspid valve	61 (15.2%)	83 (12.7%)	0.243
Surgery variables			
Cardiopulmonary bypass duration (minutes)	107.6 ± 41.3	90.5 ± 28.3	<0.001
Cross-clamp duration (minutes)	64.3 ± 27.8	55.7 ± 21.8	<0.001
Postoperative renal function			
Serum creatinine at postoperative day 1 (mg/dl)	1.46 ± 0.53	0.94 ± 0.24	<0.001
Serum creatinine at postoperative day 2 (mg/dl)	1.34 ± 0.80	0.82 ± 0.24	<0.001
Urine output at postoperative 6 hours (ml)	749 ± 543	790 ± 558	0.242
Urine output at postoperative 24 hours (ml)	2073 ± 1338	2086 ± 1043	0.860
Outcomes			
Return to operating room for bleeding	13 (3.2%)	11 (1.7%)	0.098
Length of stay in intensive care unit (days)	2.0 [1.0-4.0]	1.0 [1.0-2.0]	<0.001
Length of stay in hospital (days)	12.0 [10.0-16.0]	11.0 [10.0-14.0]	<0.001
Postsurgery length of stay (days)	8.0 [7.0-10.0]	7.0 [6.0-9.0]	<0.001
In-hospital mortality	13 (3.2%)	2 (0.3%)	<0.001

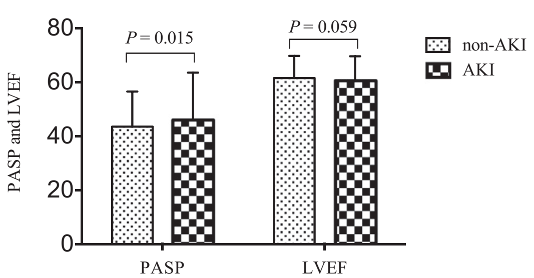

Figure 1. Echocardiographic value of PASP and LVEF in patients with or without AKI. Abbreviations: AKI = acute kidney injury, LVEF = left ventricular ejection fraction, PASP = pulmonary artery systolic pressure.

The relation between PH and kidney dysfunction has been demonstrated profoundly in patients with CKD or ESRD receiving maintenance dialysis.[5,25,26] Recent systematic review and meta-analysis including patients with CKD and ESRD revealed that overall prevalence of PH diagnosed by echocardiography was 23% and PH was related to an increased risk for cardiovascular events and death in such cohort of patients.[4]

Nevertheless, studies illustrating the association between PH and AKI were scarce. David et al found that in patients receiving surgical aortic valve replacement, severe PH (≥60 mm Hg) measured by right-sided heart catheterization

Table 2
Univariate analysis of preoperative and intraoperative predictors of acute kidney injury

Predictor	Odds ratio	95% Confidence interval	p value
Gender (Men)	1.902	1.475−2.453	<0.001
Age (per 10 years increment)	1.255	1.121−1.405	<0.001
Body mass index (per 1 unit increment)	1.111	1.067−1.157	<0.001
Comorbidities (present)			
Hypertension	1.580	1.206−2.071	0.001
Diabetes mellitus	1.461	0.866−2.466	0.155
Chronic kidney disease	5.801	1.199−8.062	0.029
Coronary artery disease	1.905	1.072−3.387	0.028
Cancer	0.698	0.179−2.714	0.604
Previous contrast exposure (present)	0.795	0.618−1.023	0.075
New York Heart Association III-IV (present)	0.910	0.683−1.214	0.522
Echocardiographic parameters			
Left ventricular ejection fraction (per 1 unit increment)	0.986	0.972−1.000	0.053
Estimated pulmonary artery systolic pressure (per 10 mm Hg increment)	1.115	1.026−1.210	0.010
Left ventricular end-diastolic dimension (per 1 mm increment)	1.008	0.994−1.022	0.245
Left ventricular end-systolic dimension (per 1 mm increment)	1.014	0.999−1.030	0.061
Renal function			
Estimated glomerular filtration rate (per 1 unit increment)	0.991	0.985−0.997	0.003
Serum creatinine (per 1 mg/dl increment)	3.243	1.953−5.386	<0.001
Intraoperative variables			
Cardiopulmonary bypass duration (per 1 minute increment)	1.015	1.011−1.019	<0.001
Cross-clamp duration (per 1 minute increment)	1.014	1.009−1.020	<0.001

Table 3
Multivariable analysis of preoperative and intraoperative predictors of acute kidney injury

Predictor	Odds ratio	95% Confidence interval	p value
Gender (men)	1.806	1.343−2.430	<0.001
Age (per 10 years increment)	1.304	1.120−1.517	0.001
Body mass index (per 1 unit increment)	1.108	1.058−1.160	<0.001
Hypertension (present)	0.890	0.643−1.232	0.483
Coronary artery disease (present)	0.794	0.397−1.588	0.515
Previous contrast exposure (present)	1.231	0.899−1.685	0.195
Left ventricular ejection fraction (per 1 unit increment)	0.994	0.973−1.015	0.567
Estimated glomerular filtration rate (per 1 unit increment)	0.998	0.991−1.005	0.649
Estimated pulmonary artery systolic pressure (per 10 mm Hg increment)	1.099	1.003−1.204	0.042
Left ventricular end-systolic dimension (per 1 mm increment)	1.007	0.984−1.030	0.564
Cardiopulmonary bypass duration (per 1 minute increment)	1.014	1.010−1.019	<0.001

was independently associated with postoperative AKI.[7] High RVSP, a surrogate for PASP, was also linked to an increased risk of postoperative acute renal failure in patients who underwent transcatheter aortic valve replacement.[23] Similarly, our study delineated ePASP was a significant risk factor for postoperative AKI in patients who underwent valve surgery even after adjusting for potential risk factors, further designating the relation

Table 4
Subgroup analyses: adjusted association between estimated pulmonary artery systolic pressure and development of postoperative acute kidney injury

Patient cohort	Odds ratio*	95% Confidence interval	p value
Without diabetes mellitus/hypertension/ coronary artery disease/cancer	1.061	0.899−1.253	0.481
With diabetes mellitus/hypertension/ coronary artery disease/cancer	1.119	1.001−1.251	0.049
Without previous contrast exposure	1.116	0.973−1.280	0.117
With previous contrast exposure	1.019	0.979−1.257	0.104
Without tricuspid valve disease	1.032	0.889−1.199	0.676
With tricuspid valve disease	1.157	1.007−1.330	0.040

* represents the change in odds of development of acute kidney injury associated with per one-unit increase in estimated pulmonary artery systolic pressure adjusted for age, gender, body mass index, comorbidities, preoperative contrast exposure, baseline estimated glomerular filtration, left ventricular ejection fraction, left ventricular end-systolic dimension, and cardiopulmonary bypass duration.

Table 5
Postoperative renal outcomes and in-hospital mortality in patients with estimated pulmonary artery systolic pressure ≥60 mm Hg versus those with <60 mm Hg

	Estimated pulmonary artery systolic pressure		p value	Hazard ratio (95% confidence interval)
	≥60 mm Hg	<60 mm Hg		
Acute kidney injury	65 (46.8%)	336 (36.6%)	0.022	1.519 (1.060-2.175)
Severe acute kidney injury	14 (10.1%)	59 (6.4%)	0.115	1.629 (0.883-3.004)
Renal replacement therapy	11 (2.0%)	5 (1.0%)	0.192	2.029 (0.700-5.881)
In-hospital mortality	5 (3.6%)	10 (1.1%)	0.020	3.384 (1.139-10.053)

between PASP (or RVSP) and AKI in the setting of cardiac surgery. Right ventricular dysfunction, especially increased right atrial pressure and central venous pressure, at least partly contribute to the renal congestion and deterioration of kidney function in patients with PH.[27,28] Further, overwhelming neurohormonal activation due to PH may lead to worsening of vascular remodeling of renal circulation which precipitates high risk of AKI after valve operations.[29]

Confirmative diagnosis of PH should be dependent on the findings of increased mean PASP through right-sided heart catheterization rather than through echocardiography. However, as a standard measurement for patients who underwent cardiac surgery, the latter has more appeal for clinical practice due to its noninvasive and convenient profiles. Nozohoor et al proposed a correlation between mean and systolic PASP measured by right-sided heart catheterization and echocardiography in patients with AS.[24] Our study evaluated PASP through preoperative echocardiography and found a strong relation between preoperative PASP and CSA-AKI. It further emphasized the critical role of PASP measured by TTE in the risk stratification of AKI in high-risk patients who underwent cardiac surgery which may contribute to providing a novel therapeutic target against the development of CSA-AKI. Thus, preoperative PASP should not only be considered as a predictor for poor outcome but an essential risk factor for the development of AKI in patients receiving valve surgery.

Our study is the first original article focusing on a thorough relation between preoperative PH and CSA-AKI in a large cohort of patients receiving valve surgery. We proposed the prevalence of PH in patients with valvular heart disease and further demonstrated preoperative PH could be a predictor for CSA-AKI. Our findings cannot only truly benefit for screening risk factors for AKI in patients who underwent valve surgery but also contribute to improving both renal and overall outcomes after cardiac surgery.

However, as a single-center retrospective study, results from our study may confer intrinsic bias of study design. Furthermore, PASP was estimated by echocardiography other than measured by golden standard-right heart catheterization, which may result in difference in measurements between estimated and actual PASP. Hence, further studies should be investigated to evaluate the dynamic role of PH, measured by right-sided heart catheterization, in multicenter AKI cohorts.

In conclusion, an increase in preoperative ePASP was independently and significantly associated with the development of CSA-AKI in patients who underwent valve surgery.

Disclosure

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.10.023.

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