

Plasma renalase as a biomarker of acute kidney injury after cardiac surgery

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Background

Renal ischemia/reperfusion injury is a major cause of acute renal failure. The lack of validated early biomarkers for predicting acute kidney injury (AKI) has hampered our ability to initiate potentially preventive and therapeutic measures in an opportune way. We tested the hypothesis that plasma renalase is an early biomarker for ischemic renal injury after cardiac surgery.

Patients and methods

We prospectively evaluated 40 adult patients who underwent cardiac surgery. Patients were divided into the AKI group and the non-AKI group on the basis of whether they developed postoperative AKI within 48 h after surgery. Plasma renalase levels were measured before surgery and 24 h after surgery. The primary outcome was AKI diagnosed using the Acute Kidney Injury Network criteria.

Results

Twenty-five (62.5%) patients developed AKI after surgery. Plasma renalase decreased significantly from a mean of 1.2 ± 0.46 ng/ml at baseline to 0.9 ± 0.42 ng/ml 24 h after cardiopulmonary bypass, with a mean %change of 27 ± 14.8 in the AKI group. Univariate analysis showed a significant correlation between AKI and the following: %change in plasma renalase, cardiopulmonary bypass time, and aortic cross-clamp time. Receiver operating characteristic curve analysis revealed that for %change in plasma renalase concentrations at 24 h, the area under the curve was 0.9, sensitivity was 0.92, specificity was 0.87, and likelihood ratio was 7.07 for a cutoff value of 9% change.

Conclusion

Plasma renalase %change is more valid compared with renalase before or after procedure and neutrophil gelatinase-associated lipocalin in the prediction of AKI and represents a novel and highly predictive early biomarker for AKI after cardiac surgery.

Keywords:

acute kidney injury, cardiac surgery, renalase

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Introduction

Renal failure is a noteworthy cause of morbidity and mortality after cardiac surgery [1]. Acute kidney injury (AKI) occurs in about 20–40% of patients and is associated with a mortality rate of 8% compared with 0.9% in patients without AKI [2]. AKI requiring hemodialysis in the postoperative period is uncommon (~1–5%); nevertheless, it is associated with a remarkably high mortality rate of 30–60% [3]. AKI increases the risk for ensuing chronic kidney disease and kidney failure, with its associated morbidity and mortality [4].

Pathophysiological mechanisms of cardiac surgery-associated acute kidney injury (CSA-AKI) include decreased renal perfusion, lack of pulsatile flow, oxidative stress, hypothermia, atheroembolism, and inflammation [5]. The main mechanism of injury is thought to be intraoperative ischemia–reperfusion injury (IRI) [6]. Although cardiac surgery [with or without cardiopulmonary bypass (CPB)] causes renal

injury, this injury often remains undetected until several days after surgery because the currently used marker of renal injury [serum creatinine (Cr) level] is unacceptably insensitive [7].

Data from animal studies demonstrate that AKI due to IRI is potentially reversible [8–10], provided that the therapeutic intervention is administered at or soon after the time of injury [11]. A noteworthy explanation behind our inability to find an effective treatment in humans is the lack of real-time sensitive and specific renal biomarkers to permit the early diagnosis of impending ischemic AKI, similar to troponins in acute myocardial disease, and subsequently an unacceptable deferral in commencing any treatment regimens [11].

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Recent research endeavors have distinguished several proteins that may provide the basis for early identification of AKI [12]. New AKI biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), interleukin (IL)-18, and urinary liver-type fatty acid-binding protein (L-FABP) were examined for the most part in pediatric postcardiac surgery patients. In this homogeneous group, these biomarkers displayed excellent performance for AKI prediction and recognition [13–15]. Be that as it may, these biomarkers' accuracy is not good in more heterogeneous cohorts of adult cardiac surgery patients [16]. For example, urinary NGAL and urinary L-FABP failed to demonstrate high sensitivity and specificity in adult postcardiac surgery AKI [17–19].

Renalase is a 38 kDa flavin adenine dinucleotide-dependent amine oxidase synthesized and secreted by the renal proximal tubules [20]. Renalase degrades circulatory catecholamines and regulates blood pressure, which indicates that it plays a critical role in the cardiovascular complications of chronic kidney disease [21]. Recent studies have demonstrated that exogenous renalase exhibits renal protection in a mice model of renal IRI and may offer a new therapeutic tool for the prevention and treatment of AKI [22,23]. In addition, exogenous renalase attenuated renal tubular necrosis and decreased infiltrated leukocytes [22]. On the basis of these animal studies, renalase was suggested as an early biomarker for ischemic AKI [22].

Taking these data into account, we decided to conduct a prospective observational single-center cohort study to test the hypothesis that plasma renalase, as a key player in catecholamine equilibrium, might represent an early biomarker of ischemic AKI in patients undergoing cardiac surgery and to compare the performance of renalase with other novel (plasma NGAL) and routine (serum Cr) renal biomarkers.

Patients and methods

Study population and data collection

Between January 2015 and July 2015, 104 consecutive patients were screened for eligibility, and we prospectively enrolled a cohort of 40 adult patients undergoing cardiac surgery with the use of CPB at Cairo University Hospital (Cairo, Egypt). Procedures included isolated coronary artery bypass grafting, isolated valve surgery, and simultaneous coronary artery bypass grafting and valve surgery. Exclusion criteria included emergency surgery (operation performed within 24 h after cardiac symptoms

commenced), presence of pre-existing renal impairment, having undergone renal transplant, peripheral vascular disease, use of nephrotoxic drugs or contrast material before or during the study period, and age less than 18 years.

The study required no changes to standard clinical practice during operation and intensive care. The postoperative use of vasopressor agents, inotropic medications (dobutamine or milrinone), and furosemide was recorded hourly until patients were discharged from the ICU. Other variables we obtained included age, sex, CPB time, aortic cross-clamp time (AXT), previous heart surgery, and urine output. This study adhered to the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of Cairo University. Written informed consent was obtained from each participant before enrollment.

Biochemical and biomarkers' measurements

Blood samples were collected at baseline and at frequent intervals for 5 days after CPB. We centrifuged samples at 2000 g for 5 min and stored the supernatants in equal volumes at -80°C . Serum Cr was measured at baseline and routinely monitored at least twice a day in the immediate postoperative period, and at least daily after postoperative day 3. Baseline serum Cr was defined as the concentration obtained at hospital admission the day before surgery. Estimated glomerular filtration rate was estimated with the Modification of Diet in Renal Disease (MDRD) Study equation.

NGAL was measured in serum samples (human lipocalin-2/NGAL ELISA; BioVendor, Brno, Czech Republic) 24 h after initiation of CPB using the sandwich enzyme immunoassay method according to manufacturer's instructions. Concentrations of plasma renalase were measured at baseline and 24 h after commencement of CPB. Measurement was carried out using a sandwich monoclonal enzyme-linked immunosorbent assay kit for renalase in human urine and serum (EIAab Science Inc., Wuhan, China). According to data provided by manufacturer, it is characterized by a detection range of 0.78–50 ng/ml, sensitivity of 0.52 ng/ml, an intra-assay coefficient of variation less than 10%, and an interassay coefficient of variation less than 12%.

Outcome measures

The primary outcome variable was development of AKI, defined as an increase in serum Cr level by either more than 50% or more than 0.3 mg/dl (compared with

preoperative values) during the first 48 h after surgery. Other outcomes included absolute and relative increase in serum Cr from baseline to peak value during the first 5 postoperative days, indicating severity of AKI, dose of furosemide to maintain urine output 0.5–1.0 ml/kg/h, requirement for renal replacement therapy, length of stay in intensive care and in hospital, and mortality (in-hospital and at 6 months postoperatively through information from the outpatient department).

Statistical analysis

Statistical Analysis System (SAS institute Inc, Cary, NC, USA), version 9.2 was used for analyses. Continuous variables were presented as the mean value \pm SD, and categorical parameters were expressed as number and percentage. To compare continuous variables, we used a two-sample *t*-test or the Mann–Whitney rank-sum test, and to compare categorical variables we used the χ^2 or Fisher's exact test, as indicated. To measure the sensitivity and specificity for plasma renalase and other markers at different cutoff values, a conventional receiver operating characteristic (ROC) curve was generated for plasma renalase and serum NGAL at 24 h after CPB. We calculated the area under the ROC curve (AUC) to ascertain the quality of plasma renalase and NGAL as biomarkers. All demographic, preoperative, and intraoperative variables were tested in univariate regression analysis for their relationship with the predefined postoperative clinical outcomes (incidence of AKI, length of stay in ICU, and length of stay in hospital). To determine the correlation between variables, the Pearson and Spearman coefficients of correlation were calculated. Univariate and multivariate stepwise logistic regression analyses were undertaken to assess predictors of AKI. *P*-values were two tailed and a *P*-value less than 0.05 was considered statistically significant.

Results

Acute kidney injury

Twenty-five (62.5%) patients developed AKI according to the Acute Kidney Injury Network criteria. Patients who developed postoperative AKI were comparable to the non-AKI group as regards age, sex, BMIs, and preoperative serum Cr, estimated glomerular filtration rate, and left ventricular ejection fraction (LVEF). However, patients who developed AKI showed longer CPB times and AXTs and received postoperative vasopressor/inotropic support more frequently than those without AKI (Table 1). They also stayed longer in the ICU and hospital. One patient in the AKI group

required continuous renal replacement therapy. Two patients in the AKI group died in the hospital.

Serum creatinine after cardiac surgery

Preoperative, peak postoperative, and change in serum Cr levels after cardiac surgery were not statistically different between patients with and those without AKI. Serum Cr levels increased to nonsignificantly greater levels ($P=0.17$) in patients with AKI. %Change in serum Cr levels was statistically different ($P=0.001$) between patients with and those without AKI (Table 1).

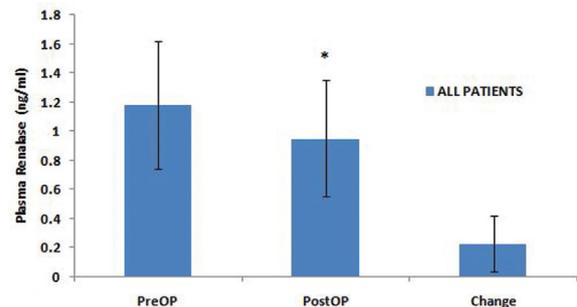
Plasma renalase before and after cardiac surgery

Before surgery, the mean plasma renalase levels in all patients studied was 1.18 \pm 0.44 ng/ml. Plasma renalase level 24 h after surgery was significantly lower compared with preoperative values (0.95 \pm 0.4 vs. 1.18 \pm 0.44; $P<0.0001$, respectively) (Table 2, Fig. 1).

Plasma renalase and acute kidney injury

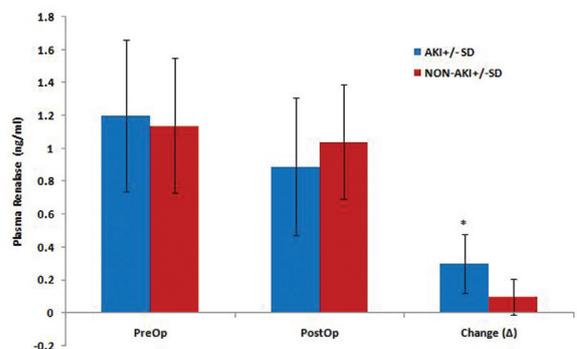
Preoperative plasma renalase levels were similar in patients who later developed AKI and patients without

Figure 1



Plasma renalase levels before (preoperative) and after (postoperative) cardiac surgery and postoperative change in plasma renalase levels (Δ renalase) in all patients (mean \pm SD). * $P<0.0001$ compared with preoperative values.

Figure 2



Plasma renalase levels before (preoperative) and after (postoperative) cardiac surgery (24 h) and postoperative change in plasma renalase levels (Δ renalase) in patients with or without acute kidney injury (AKI) (mean \pm SD). * $P<0.0003$ compared with the non-AKI group.

Table 1 Patient characteristics

	Total (N=40)	AKI [n=25 (62.5%)]	No AKI [n=15 (37.5%)]	P-value
Preoperative				
Sex: male	27 (67.5)	14 (56)	10 (66.6)	0.5
Age (years)	47.67±12.8	47.64±12.7	47.7±13.4	0.98
BMI (kg/m ²)	25.44±2.856	25.83±2.8	24.78±2.9	0.26
Serum creatinine (mg/dl)	0.901±0.22	0.9±0.238	0.9±0.19	0.73
eGFR (ml/min)	89.17±27.9	88.96±32.62	89.5±18.8	0.95
Hypertension	8 (20)	6 (24)	2 (13.33)	0.4
Diabetes mellitus	28 (70)	18 (72)	10 (66.6)	0.72
LVEF<50%	17 (42.5)	11 (44)	6 (40)	0.8
Preoperative medications				
Diuretics	19 (47.5)	12 (48)	7 (46.6)	0.93
ACEI/ARBs	31 (77.5)	20 (80)	11 (73.3)	0.62
Statins	27 (67.5)	18 (72)	9 (60)	0.43
Operation				
CABG with CPB	22 (55)	15 (60)	7 (46.7)	0.4
Single valve	12 (30)	6 (24)	6 (40)	0.3
Multiple valve	4 (10)	2 (8)	2 (13.3)	0.58
CABG+valve	1 (2.5)	1 (4)	0 (0)	0.43
Other	1 (2.5)	1 (4)	0 (0)	0.43
Reoperation (Redo)	2 (5)	2 (8)	0 (0)	0.26
Intraoperative				
Cardiopulmonary bypass time (min)	85±19.39	91.08±21.34	75.06±9.7	0.01*
Aortic cross-clamp time (min)	66.1±16.96	71.4±18.35	57.3±9.5	0.009*
Vasopressor/inotropic support	22 (55)	14 (56)	8 (53)	0.85
High dose of inotropic support	9 (22.5)	6 (24)	3 (20)	0.77
Postoperative				
Vasopressor/inotropic support	26 (65)	20 (80)	6 (40)	0.01*
High dose of inotropic support	10 (25)	9 (36)	1 (6.6)	0.037*
PRBC transfusion	29 (72.5)	20 (80)	9 (60)	0.17
Oliguria (>6h)	26 (65)	18 (72)	6 (40)	0.04*
Furosemide infusion	19 (47.5)	16 (64)	3 (6)	0.0003*
Length of ICU stay (days)	4.95±1.98	5.6±1.9	3.8±1.56	0.004*
Length of hospital stay (days)	14.675±4.8	16.04±5.2	12.4±3	0.018*
Peak serum creatinine (mg/dl)	1.35±0.84	1.5±1.04	1.12±0.18	0.17
Δ Serum creatinine (mg/dl)	0.45±0.733	0.6±0.9	0.2±0.07	0.09
Change serum creatinine (%)	47.7±49.2	62.3±57.3	23.3±9.7	0.001*
Continuous hemodialysis	1 (2.5)	1 (4)	0 (0)	0.43
ICU mortality	3 (7.5)	2 (8)	1 (6.6)	0.87

Values expressed as mean±SD or *n* (%). ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PRBC, packed red blood cells. *Significant.

Table 2 Comparison of biomarkers

	Total (n=40)	AKI [n=25 (62.5%)]	No AKI [n=15 (37.5%)]	P-value
Plasma renalase				
Preoperative (ng/ml)	1.18±0.44	1.204±0.46	1.14±0.41	0.675
Range	0.6–2.2	0.6–2.2	0.7–2.2	
Postoperative(ng/ml)	0.95±0.4	0.89±0.42	1.04±0.35	0.27
Range	0.4–2	0.4–1.8	0.65–2	
Δ Renalase (ng/ml)	0.229±0.189	0.3±0.18	0.099±0.11	0.0003*
Range	0–0.7	0.1–0.7	0–0.4	
Percentage of Δ renalase	19.8±15.67	26.9±14.8	7.92±8.08	<0.0001*
Range	0–63.63	5.3–63.63	0–30	
Serum NGAL				
Postoperative (ng/ml)	1.78±0.3	1.84±0.33	1.69±0.24	0.136
Range	1.1–2.4	1.1–2.4	1.3–2.1	

Values expressed as mean±SD or *n* (%). AKI, acute kidney injury; NGAL, neutrophil gelatinase-associated lipocalin. *Significant.

postoperative AKI (1.204±0.46 vs. 1.14±0.41 ng/ml; $P=0.675$). Patients who subsequently developed AKI displayed a remarkable decrease in plasma renalase at 24 h ($P<0.0001$ vs. baseline; Table 2, Fig. 2). Patients who never developed AKI had a small nonsignificant decrease in plasma renalase 24 h after CPB ($P=0.49$ vs. baseline; Table 2, Fig. 2). The postoperative change in plasma renalase levels (Δ renalase) was significantly different between the two groups (0.3±0.18 vs. 0.099±0.11 ng/ml; $P=0.0003$). Moreover, the percent of Δ renalase was significantly greater in patients who developed AKI compared with patients without postoperative AKI (26.9±14.8 vs. 7.92±8.08%; $P<0.0001$, respectively) (Table 2, Fig. 3).

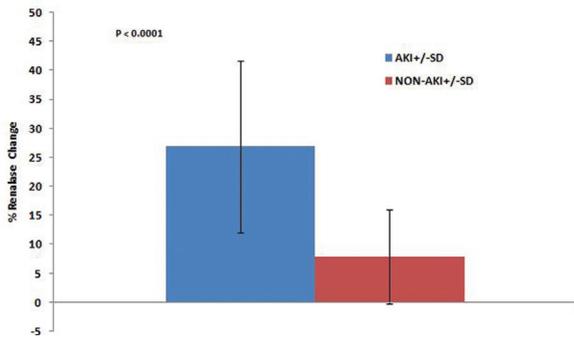
In patients with AKI, univariate linear regression analysis showed that percent of Δ renalase correlated positively with peak Cr ($r=0.446$, $P=0.025$), change in Cr ($r=0.566$, $P=0.003$), %change in Cr ($r=0.69$, $P=0.0001$), Δ renalase ($r=0.762$, $P<0.0001$), NGAL ($r=0.773$, $P<0.0001$), CPB time ($r=0.799$, $P<0.0001$), AXT ($r=0.795$, $P<0.0001$), ICU stay duration ($r=0.724$, $P<0.0001$), and hospital ($r=0.641$, $P=0.0005$) stay duration,

whereas it correlated negatively with LVEF ($r=-0.753$, $P<0.0001$) and postoperative renalase ($r=-0.593$, $P=0.002$). Multivariate linear regression analyses revealed preoperative renalase ($B=-28.7$, $P<0.0001$), postoperative renalase ($B=-6.4$, $P<0.0001$), and Δ renalase ($B=12.9$, $P<0.0001$) as significant independent predictors for increased %change in plasma renalase. Multivariate logistic regression analysis did not show any variable as a significant independent predictor for AKI.

Receiver operating characteristic curves

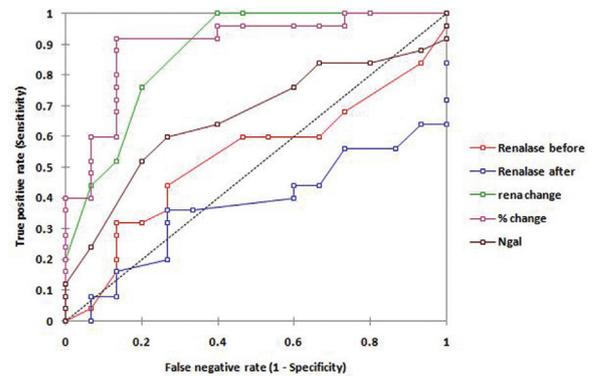
ROC curves were generated to evaluate the ability of plasma renalase to predict AKI. AUCs were low for the absolute renalase levels preoperatively or postoperatively. AUC was highest for the percent of Δ renalase 24 h after surgery [AUC=0.9; 95% confidence interval (CI):

Figure 3



Percentage change in plasma renalase levels after cardiac surgery (24 h) in patients with or without acute kidney injury (AKI) (mean±SD).

Figure 4



Receiver operating characteristic curves for plasma renalase and serum neutrophil gelatinase-associated lipocalin (NGAL) as a predictor of acute kidney injury (AKI). Preoperative renalase [area under the curve (AUC)=0.53; 95% confidence interval (CI): 0.38–0.68; $P=0.687$], plasma renalase 24 h after surgery (AUC=0.375; 95% CI: 0.21–0.54; $P=0.129$), change in renalase (AUC=0.872; 95% CI: 0.81–0.93; $P<0.0001$), %change in plasma renalase (AUC=0.9; 95% CI: 0.81–0.99; $P<0.0001$), and serum NGAL 24 h after surgery (AUC=0.663; 95% CI: 0.53–0.8; $P<0.014$) as a predictor for AKI.

Table 3 Area under the curves for receiver operating characteristics of biomarkers

	AUC	P-value	Cutoff (ng/ml)	Sensitivity (%)	Specificity (%)	PPV	NPV	Accuracy
Plasma renalase								
Preoperative	0.53 (0.38–0.68)	0.687	>1.38	32 (17–52)	87 (60–97)	80 (44.4–97.5)	43.3 (25.5–62.6)	0.525
Postoperative (24 h)	0.375 (0.21–0.54)	0.129	<1.05	36 (20–55)	73 (47–89)	69 (38.6–91)	40.7 (22.4–61)	0.5
Renalase change	0.872 (0.81–0.93)	<0.0001*	>0.08	100 (84–100)	60 (36–80)	80.65 (62.5–92.6)	100 (66.4–100)	0.85
Renalase change (%)	0.9 (0.81–0.99)	<0.0001*	>9	92 (74–99)	87 (61–97.3)	92 (74–99)	87 (60–98)	0.9
Serum NGAL								
Postoperative (24 h)	0.663 (0.53–0.8)	0.014	>1.8	60 (41–77)	73.3 (47.5–89.3)	79 (54.4–94)	52.4 (30–74.3)	0.65

Values in parentheses indicate 95% confidence intervals. Acute renal dysfunction is defined as an increase in serum creatinine level by more than 50% or 0.3 mg/dl (26.52 μmol/l) within 48 h (Acute Kidney Injury Network criteria). AUC, area under the curve; NGAL, neutrophil gelatinase-associated lipocalin; NPV, negative predictive value; PPV, positive predictive value. *Significant.

0.81–0.99; $P < 0.0001$]. The cutoff value at this time (defined as the point on the ROC curve closest to sensitivity=1–specificity=1) was 9% change in plasma renalase level (Fig. 4 and Table 3). AUC of the ROC curve for serum NGAL to predict AKI was 0.663 (95% CI: 0.53–0.8; $P = 0.014$; Fig. 4 and Table 3).

Plasma renalase and cardiopulmonary bypass time/aortic cross-clamp time

Increased duration of aortic cross-clamping or CPB increases the severity of intraoperative renal injury [24], but may not necessarily be detected by an increase in postoperative serum Cr levels. To assess whether we are able to detect this injury using plasma renalase level, we calculated the correlation coefficients between CPB time and AXT with plasma renalase, serum NGAL, and postoperative Cr (peak and change Δ) (Table 4). Plasma renalase levels 24 h after surgery ($P < 0.0001$ for CPB time and AXT), renalase change (Δ renalase) ($P = 0.011$ for CPB time and 0.065 for AXT), and % change in renalase ($P = 0.0001$ for CPB time and AXT) correlated significantly with CPB time/AXT.

Discussion

In this study, patients with AKI displayed a remarkable decrease in plasma renalase at 24 h after CPB, with a significantly different change in plasma renalase levels (Δ renalase) between the two groups. Moreover, the percent of Δ renalase was significantly greater in patients who developed AKI compared with patients without postoperative AKI. In patients with AKI, regression analysis showed that percent of Δ renalase was significantly correlated with peak Cr, change in Cr, %change in Cr, Δ renalase, serum NGAL levels, preoperative LVEF, CPB time, AXT, and ICU and hospital stay durations.

Renalase is a 38 kDa flavin adenine dinucleotide-dependent amine oxidase synthesized and secreted by

the renal proximal tubules and is a key player in catecholamine metabolism [20]. Renalase degrades circulating catecholamines and regulates systemic blood pressure in rodents and humans [25]. Renalase levels are regulated by three key factors: renal function, renal perfusion, and catecholamine levels [26]. Several studies strongly suggest that the kidney is the major source of steady-state renalase secretion to plasma [27,28]. In mice, ischemic AKI led to reduced kidney and plasma renalase levels, with a resultant increase in plasma catecholamine (norepinephrine) levels and exacerbation of renal IRI [22]. Because kidney and plasma renalase levels rapidly decreased after ischemic AKI in mice, it was postulated that urine and plasma renalase may serve as a novel and sensitive biomarker for the early detection of ischemic AKI [22].

Cardiac surgery with CPB is the most common surgical procedure that is associated with a high risk for AKI [29]. Renal injury is frequent after cardiac surgery because of renal hypoperfusion, reperfusion injury, and inflammatory responses [5]. Unfortunately, the currently used marker of renal function (or dysfunction), serum Cr level, is an inappropriately insensitive and late marker of renal dysfunction. Consequently, by the time renal dysfunction is indicated by an increase in serum Cr levels, adequate therapeutic intervention is not possible [30].

In our study, we evaluated the performance of plasma renalase as AKI biomarker in an adult postcardiac surgery cohort. The AUC-ROC value was highest for the percent of Δ renalase at 24 h after surgery (AUC=0.9; 95% CI: 0.81–0.99; $P < 0.0001$) with a sensitivity of 0.92 and specificity of 0.87. The cutoff value at this time was 9% change in plasma renalase level. Compared with renalase, AUC-ROC values for serum NGAL, CPB time, and AXT to predict AKI were 0.663, 0.727, and 0.721, respectively. We

Table 4 Correlation between cardiopulmonary bypass time or aortic cross-clamp time and postoperative creatinine, serum neutrophil gelatinase-associated lipocalin and plasma renalase

	Serum creatinine			Plasma renalase			Serum NGAL
	Peak creatinine	Change in creatinine	Change in creatinine (%)	Postoperative (24 h)	Renalase change	Renalase change (%)	Postoperative (24 h)
CPB time							
Pearson's <i>r</i>	–0.484	0.540	0.909	–0.577	0.206	0.762	0.890
95% CI	–0.609–0.336	0.401–0.655	0.871–0.935	–0.684–0.446	0.030–0.369	0.676–0.827	0.847–0.922
<i>P</i> (two tailed)	0.000*	0.000*	0.000*	0.000*	0.011*	0.000*	0.000*
AXT							
Pearson's <i>r</i>	–0.495	0.543	0.920	–0.610	0.155	0.778	0.884
95% CI	–0.632–0.328	0.385–0.670	0.883–0.946	–0.722–0.468	–0.046–0.344	0.684–0.846	0.830–0.921
<i>P</i> (two tailed)	0.000*	0.000*	0.000*	0.000*	0.065	0.000*	0.000*

AXT, aortic cross-clamp time; CI, confidence interval; CPB, cardiopulmonary bypass; NGAL, neutrophil gelatinase-associated lipocalin. *Significant.

therefore propose that plasma renalase level might be better to detect intraoperative renal injury early after cardiac surgery compared with serum Cr level or serum NGAL.

Our results compare favorably with those obtained for several other biomarkers (urinary, plasma, and serum) of ischemic AKI following cardiac surgery, including kidney injury molecule 1 [31,32], IL-6 [33], IL-8 [33], IL-18 [34], cystatin C [35], *N*-acetyl- β -d-glucosaminidase [32], L-FABP [31], and NGAL [32,34,35].

A meta-analysis evaluating the early postoperative diagnostic performance of biomarkers of CSA-AKI showed that urine biomarkers NGAL, kidney injury molecule 1, and L-FABP exhibited composite AUCs of 0.69–0.72; the composite AUCs for postoperative urine cystatin C, *N*-acetyl- β -d-glucosaminidase, and IL-18 were at least 0.70 [36]. Similarly, the composite AUROCs for postoperative plasma NGAL and cystatin C were less than 0.75 [36]. The meta-analysis concluded that current biomarkers have generally poor and at best modest discrimination for AKI when measured within the first 24 h after cardiac surgery in adults [36].

AKI is characterized by an elevation in plasma catecholamine levels. It has been proposed that, in addition to causing hypertension, excess catecholamines in AKI, through the activation of leukocyte α -adrenergic receptors, may produce an inflammatory response, thus aggravating tissue damage and contributing to multiorgan dysfunction [37]. In addition to regulating blood pressure, renalase may protect against inflammatory tissue injury by metabolizing catecholamines. It has been hypothesized that renalase has cytokine-like characteristics [38]. In mice, renalase deficiency resulted in exacerbated cardiac IRI, and exogenous renalase administration reduced myocardial necrosis and protected against myocardial IRI, which provided a basis for therapeutic strategies for improving cardiomyocyte survival in patients associated with ischemic heart diseases [39]. Interestingly, renalase levels in the blood and kidneys of wild-type mice are decreased following acute renal ischemia. Because the renalase in blood is secreted from the kidneys and is thought to metabolize circulating catecholamines, the excess catecholamines in AKI may be a direct consequence of the concomitant renalase deficiency [22,23]. Notably, the administration of recombinant human renalase to wild-type mice, before induction of renal ischemia, significantly dampens the rise in blood catecholamine levels and blunts the severity of renal injury, with less renal tubular necrosis, inflammation, and apoptosis [22]. Therefore, it has been presumed that

exogenous administration of human recombinant renalase may provide powerful renal protection against ischemic AKI by targeting all three pathways (necrosis, apoptosis, and inflammation) of renal cell injury [22]. The renal protective effects of recombinant renalase are, at least in part, due to increased metabolism of plasma and tissue catecholamines and activation of intracellular signaling cascades (with activation of protein kinase B and the mitogen-activated protein kinase pathway), independent of its ability to degrade catecholamines in addition to contributing to ischemic preconditioning mechanisms [22,40]. Thus, renalase is emerging as a center-stage player in the field of ischemic AKI research, not only as a novel predictive biomarker but also as an innovative therapeutic modality.

This study, as far as we know, is the first study investigating the possible role of plasma renalase in the early diagnosis of ischemic renal injury.

Limitations

First, it is a single-center study, and the number of patients ($n=40$) might be insufficient to determine the reliability and generalizability of plasma renalase.

Second, plasma renalase and serum NGAL were measured at only single time point (24 h) after cardiac surgery. This time point might be relatively late for therapeutic intervention. Further studies with measurement at various time points with regard to a renal insult (i.e. after initiation of CPB) can determine the temporal patterns of change in plasma renalase and would identify the most favorable time point at which measurement of plasma renalase would give the earliest and most accurate prediction of AKI (i.e. the best AUC).

However, within these limitations, we believe our work will stimulate more research on this topic.

Conclusion

Our hypothesis that plasma renalase might represent an early and a more sensitive biomarker of ischemic renal injury compared with serum Cr level or other biomarkers (NGAL) in patients undergoing cardiac surgery was confirmed in this study. The rate of change in plasma renalase from baseline was a more accurate predictor of CSA-AKI compared with the actual absolute values. Our findings provide a conceptual framework for further larger randomized studies in AKI. Plasma renalase levels may serve as a useful biomarker of renal injury in clinical studies investigating renoprotective strategies and allow early identification and treatment of patients at risk. It has been postulated that exogenous administration of

human recombinant renalase may provide powerful renal protection against ischemic AKI and could serve as a preventive and therapeutic agent in ischemic and toxic AKI.

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Conflicts of interest

There are no conflicts of interest.

The study was presented as poster presentation in the mentioned congress but I am not sure that this should be mentioned; it depends on your journal regulations. Presented at the 53rd ERA-EDTA Congress; 21–24 May 2016; Vienna, Austria.

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