Intraoperative Evaluation of Renal Resistive Index with Transesophageal Echocardiography for the Assessment of Acute Renal Injury in Patients Undergoing Coronary Artery Bypass Grafting Surgery: A Prospective Observational Study

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ABSTRACT

Background: Acute kidney injury (AKI) is a common complication after on pump coronary artery bypass grafting (CABG) surgery and is associated with a poor prognosis. Postoperative AKI is associated with morbidity, mortality, and increase in length of intensive care unit (ICU) stay and increases the financial burden. Identifying individuals at risk for developing AKI in postoperative period is extremely important to optimize outcomes. The aim of the study is to evaluate the association between the intraoperative transesophageal echocardiography (TEE) derived renal resistive index (RRI) and AKI in patients undergoing on-pump CABG surgery.

Methods: This prospective observational study was conducted in patients more than 18 years of age undergoing elective on pump CABG surgery between July 1, 2018, and December 31, 2019, at a tertiary care center. All preoperative, intraoperative, and postoperative parameters were recorded. TEE measurement was performed in hemodynamically stable patients before the sternum was opened. Postoperative AKI was diagnosed based on the serial measurement of serum creatinine and the monitoring of urine output.

Results: A total of 115 patients were included in our study. Thirty-nine (33.91%) patients had RRI >0.7 while remaining seventy-six (66.08%) patients had RRI <0.7. AKI was diagnosed in 26% (30/115) patients. AKI rates were significantly higher in patients with RRI values exceeding 0.7 with 46.15% (18/39) compared to 15.75% (12/76) in RRI values of less than 0.7. Multivariate analysis revealed that AKI was associated with an increase in RRI and diabetes mellitus. The RRI assessed by receiver operating characteristic (ROC) curve and the area under the curve (AUC) to distinguish between non-AKI and AKI groups were 0.705 (95% CI: 0.588–0.826) for preoperative RRI. The most accurate cut-off value to distinguish non-AKI and AKI groups was a preoperative RRI of 0.68 with a sensitivity of 70% and specificity of 67%.

Conclusions: An increased intraoperative RRI is an independent predictor of AKI in the postoperative period in patients undergoing CABG surgery. The cutoff value of TEE-derived RRI in the intraoperative period should be >0.68 to predict AKI in the postoperative period.

Keywords: Acute kidney injury, coronary artery bypass grafting, renal resistive index, transesophageal echocardiography

INTRODUCTION

The kidney is one of the most vulnerable organs to have insult during cardiac surgery. The incidence of acute kidney injury (AKI) after cardiac surgery ranges between 15% and 30% and requires renal replacement therapy (RRT)

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in 1% to 5% of the cases.[1-3] Postoperative AKI is associated with longer length of ICU and hospital stays, higher hospital cost, and higher morbidity and mortality.[4-7] Multiple factors are responsible for the development of AKI in patients undergoing cardiac surgery. In addition to its limited understanding of the pathophysiology of AKI make it difficult to predict the onset of AKI.[2] The most commonly used method for diagnosing AKI is serial measurements of serum creatinine and monitoring urine output. However, to diagnose AKI after renal insult, it may take up to 48 hours due to their dependency on serum creatinine accumulation.[8,9]

Renal protection is an important measure to improve cardiac surgical outcomes during the perioperative period. Therefore, quick AKI diagnosis through novel biomarkers has become a priority.[8,10] For clinical practice, a biomarker is a single characteristic that can be objectively measured and evaluated as an indicator of the underlying pathogenic process.[11] However, it is associated with certain limitations such as additional cost; poor reliability in some conditions like albuminuria, bilirubin, and methylene blue; and current lack of availability at most clinical centers.

The ultrasound imaging of renal artery flow is highly sensitive and specific in the early detection of AKI.[12,13] However, the transcutaneous ultrasound imaging is not possible to perform in the intraoperative period in patients undergoing cardiac surgery. Transesophageal echocardiography (TEE) is the most widely used imaging modality in intraoperative period to assess the cardiac function in patients undergoing cardiac surgery. However, it can be used to assess renal artery flow to evaluate the renal resistive index (RRI). Intraoperative TEE is a new approach to determining the RRI. It can be measured by placing a sample volume at the arcuate or interlobar arteries of the kidneys and helps in assessing renal function. A threshold RRI of >0.70 is suggestive of decreased renal function.[14,15] Bossard *et al.*[13] in their recent study reported that RRI measured in the postoperative period can predict the onset of AKI if it is more than 0.79 in cardiac surgical patients. They also observed that an RRI of >0.83 can predict the need for dialysis. The role of TEE in the intraoperative period to diagnose AKI remains very less studied.

The aim of our study was to evaluate the association between the intraoperative TEE-derived RRI and AKI in patients undergoing on-pump coronary artery bypass grafting (CABG) surgery.

METHODS

After approval of institutional ethical committee (NK/4551/714), a prospective cohort study was conducted in patients more than 18 years of age undergoing elective on pump CABG surgery between July 1, 2018, and December 31, 2019, at the Postgraduate Institute of Medical Education and Research, Chandigarh, India. Patients who were already on inotropic support, intraaortic balloon pump (IABP) support, deranged renal function test, preoperative atrial fibrillation (AF), and the echocardiographer unable to place a satisfactory pulsed-wave doppler on intrarenal artery were excluded. Written informed consent was obtained 1 day prior to surgery. The trial was registered at Clinical Trial Registry India (NCT025827).

Each patient after inclusion had the following data recorded: age, gender, hypertension, diabetes mellitus, stroke, use of angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) and serum creatinine, surgical procedure, preoperative hemoglobin, the duration of aortic cross-clamping, and cardiopulmonary bypass (CPB).

After attaching standard ASA monitoring, general anesthesia was induced with intravenous fentanyl and propofol, and tracheal intubation was facilitated with vecuronium. For anaesthesia maintenance, isoflurane with intermittent boluses of fentanyl and vecuronium was used. CPB was via a centrifugal pump with nonpulsatile flow, with mild hypothermia, and vasoactive or vasodilatory support as it is necessary to support mean arterial pressures (target 60–80 mmHg).

Transesophageal echocardiography measurements

A comprehensive TEE examination (Philips iE33, Andover, MA) with a multiplane TEE probe (Philips X7-2t) was performed in hemodynamically stable patients without any inotropic support or fluid boluses were given when needed to attain baseline hemodynamics before sternotomy by a TEE certified cardiac anesthesiologist. A method described by Bandyopadhyay and colleagues was used to visualize the left intrarenal artery and blood flow velocity in an intrarenal artery was obtained with pulse wave doppler (PWD).[16] The probe is finely adjusted until a clear image of the left kidney is obtained. Color flow doppler (CFD) with a Nyquist limit of 15–20 cm/s is used to visualize the renal vasculature. Placing a CFD over the mid-portion of the kidney body and varying the probe angle (0–45 degrees) may help visualize branches of the renal artery. Renal arterial flow velocity pattern recorded with PWD has a systolic and diastolic stroke [Figure 1]. The RRI was calculated as the

difference between the highest systolic blood velocity and the lowest diastolic blood velocity divided by the highest systolic blood velocity (vmax systole − vmin diastole/vmax systole). Velocity in interlobar or cortico-medullar arteries was assessed more than three times in left kidney and the RRI was calculated as the average of all values.

All patients underwent CABG intervention. After coming off bypass, all patients were shifted to the cardiac surgical ICU. In the postoperative period, all patients were weaned off from ventilator and inotropic support with the discretion of attending anesthesiologist. The postoperative serum creatinine value was considered the highest value within 48 hours after surgery. Serum creatinine was measured using the Jaffe technique with a normal range of 0.4–1.0 mg/dL for females and 0.6–1.3 mg/dL for males. The occurrence of AKI was defined by the KGIDO network criteria.[17] Postoperative urine production was obtained from the hourly measurements during the cardiac surgery ICU stay.

Statistical analysis

The analysis was conducted using IBM SPSS statistics (version 22.0). The normality of quantitative data was checked by measures of Kolmogorov–Smirnov tests of normality. For skewed data, comparisons for two groups (RRI <0.7 and RRI >0.7) were made by the Mann–Whitney test. For normally distributed data, Student t-test was applied to compare two groups. Categorical variables were reported as counts and percentages. Group comparisons were made with the Chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) curves were calculated to find maximal cut-off values of RRI for AKI. The ROC curve is a plot of sensitivity versus 1-specificity for maximal cut-off values. To find an independent predictor for RRI >0.7, logistic regression

analysis was carried out. Predictors for RRI >0.7 were identified on univariate analysis and the significant ones were subjected to multivariate regression analysis.

RESULTS

A total of 124 patients consented for the study, with 115 patients analyzed and the remaining 9 patients excluded due to inability to correctly place the PWD across the intrarenal artery or poor-quality images [Figure 2].

In total, 115 patients were evaluated in our study. Twenty-five patients were female (22%) and 90 patients were male (78%). Thirty-nine (33.91%) patients had RRI >0.7 while remaining 76 (66.08%) patients had RRI <0.7. Patients on preoperative diuretics, history of diabetes mellitus, high VIS score, and AKI in the postoperative period were more often associated with RRI values exceeding 0.7 ($P < 0.05$). However, remaining preoperative, procedural, and postoperative characteristics were comparable between both the groups ($P > 0.05$) [Table 1].

AKI was diagnosed in 26% (30/115) patients. AKI rates were significantly higher in patients with RRI values exceeding 0.7 with 46.15% (18/39) compared to 15.75% (12/76) in RRI values of less than 0.7. The diagnosis of AKI during ICU stay was based on the urine output and serum creatinine value in patients. In a total of 30 AKI patients, 28 (93.33%) were diagnosed using only the creatinine criteria while the remaining 2 (6.66%) patients were diagnosed using both urine output and serum creatinine criteria. Only one patient received renal replacement therapy within 2 days.

Multivariate analysis (odds ratio, ±95% CI, and P value) was performed to detect independent predictors that are associated with AKI in the postoperative period. Two independent predictors, RRI (OR = 1.26; CI: 1.43 to 8.80; $P = 0.006$) and diabetes mellitus (OR = 1.20; CI: 1.30 to 8.59; $P = 0.012$), were found to be associated with AKI in the postoperative period [Table 2].
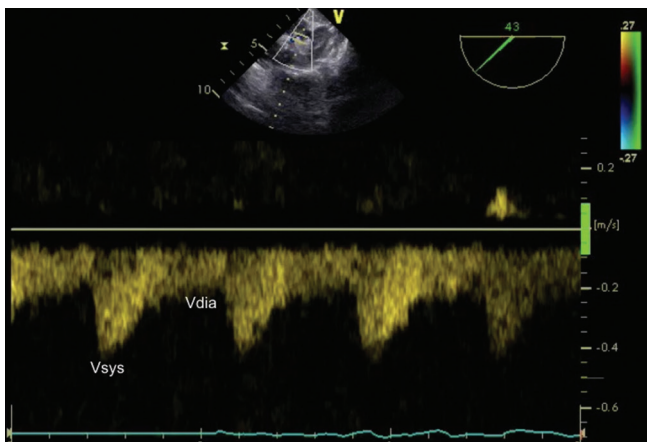
Figure 1: Transesophageal echocardiography showing renal artery blood flow. Vsys = peak systolic velocity; Vdia = trough diastolic velocity
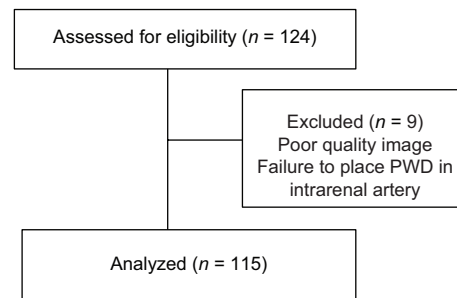
Figure 2: Consort flow diagram

The RRI assessed by ROC curves and the area under the curve (AUC) to distinguish between non-AKI and AKI groups was 0.705 (95% CI: 0.588–0.826) for intraoperative RRI [Figure 3]. The most accurate cut-off value to distinguish non-AKI and AKI groups was a intraoperative RRI of 0.68 with a sensitivity of 70% and a specificity of 67%.

DISCUSSION

In our prospective observational study, we found that elevated preoperative RRI (>0.7) and diabetes mellitus were two independent factors that are significantly associated with AKI in the postoperative period. The risk of AKI in the postoperative period is profound with these even after adjusting for the confounder factors. The incidence of AKI (26%) in the current study was comparable with the previous study done by Parida *et al.*,[3] who found an incidence of AKI between 15% and 30% and RRT of 1%–5%.

The most commonly used method for diagnosing AKI is serial measurements of serum creatinine and monitoring urine output. However, it requires 48 hours post-insult to diagnose AKI due to their dependency on serum creatinine accumulation.[8,9] Therefore, a marker which can detect the early AKI in the postoperative period is of paramount importance. The ultrasound imaging of renal artery flow is highly sensitive and specific in the early detection of AKI.[12,13] Daniel Hertzberg *et al.*,[15] in their prospective study, performed renal ultrasound examination a day prior to cardiac surgery in ward, and the author demonstrated that patients with an elevated preoperative RRI (>0.7) have an increased risk of developing AKI after cardiac surgery and they concluded that in combination with other markers,

the RRI might be a useful tool for detecting patients with an increased risk of developing AKI. Anne D. Cherry *et al.*,[18] in their retrospective study, documented that the RRI obtained intraoperatively in cardiac surgery patients is highly associated with AKI and warrants further evaluation as a promising "earliest" AKI biomarker. These significant findings suggest that RRI assessment should be included in the standard intraoperative TEE exam. In another study conducted in cardiac surgery by Bossard *et al.*,[13] they found that the patients undergoing CABG showed that the postoperative RRI could predict AKI with 85% sensitivity and 94% specificity. To the best of our knowledge, there are only very few studies that have been performed during the intraoperative period using TEE to derive RRI in patients undergoing on-pump CABG surgery. In this prospective study, we found that an increased intraoperative RRI (>0.7) was a marker for an increased risk of developing AKI after on-pump CABG surgery.

RRI has been studied to gain diagnostic and prognostic values in different diseases like an evaluation of renal allograft rejection,[19,20] detection of renal artery stenosis in hypertensive patients,[21,22] assessment of progression in
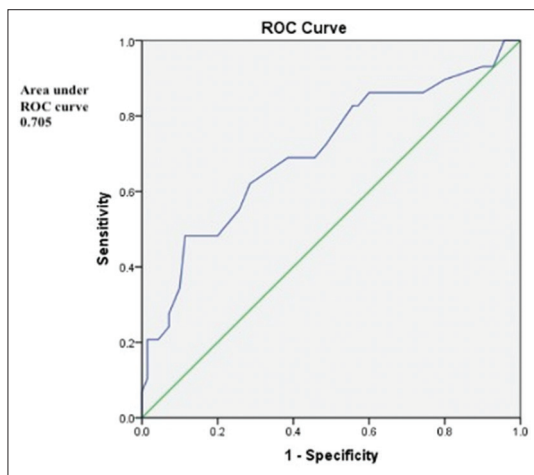
Figure 3: Receiver operating characteristic curve. The cut-off value for the preoperative RRI was obtained at a sensitivity of 70% and a specificity of 67%.

Table 1: Patient's preoperative, intraoperative and postoperative characteristics

Variable	RRI <0.7 *n*=76	RRI >0.7 *n*=39	P
Age at surgery	59.61±9.50	62.63±7.49	0.133
Female (%)	13 (17.10)	12 (30.76)	0.089
Diabetes (%)	15 (19.73)	18 (46.15)	0.005*
Beta blockers (%)	72 (94.73)	36 (92.30)	0.157
Statins (%)	68 (89.47)	30 (76.92)	0.952
ACEI (%)	33 (43.42)	16 (41.02)	0.778
Diuretics (%)	7 (9.21)	13 (33.33)	0.001*
Eltroxin (%)	3 (3.94)	2 (5.12)	0.116
EF >35%	58 (76.31)	31 (79.48)	0.482
EF <35%	18 (23.68)	8 (20.51)	0.387
GLS %	-12.69±3.38	-12.54±2.72	0.856
CPB time (Minutes)	138.34±32.3	141.40±30.21	0.937
AXC time (Minutes)	120.39±26.76	126.30±31.29	0.653
VIS score	5.2±5.5	8.2±7.1	0.044*
Baseline creatinine	0.824±0.209	0.912±0.334	0.278
Postoperative creatinine	0.894±0.209	1.55±0.489	0.016*
AKI (%)	12 (15.78)	18 (46.15)	0.010*
Protein mg/dl	7.06±0.46	7.2±0.63	0.168
Albumin mg/dl	4.2±0.38	4.2±0.41	0.996
Urine output 12 hrs	1527.0±357.8	1517.0±438.8	0.905

ACEI, Angiotensin converting enzyme inhibitor; EF, Ejection fraction; GLS, global longitudinal strain; CPB, cardiopulmonary bypass; AXC, aortic cross clamp; VIS, vasoactive inotropic score; AKI, acute kidney injury

Table 2: Multivariate analysis of predictors of AKI in the postoperative period

	P	Odds ratio	95% CI	
			Upper	Lower
RRI	0.006	1.26	8.80	1.43
DM	0.012	1.20	8.59	1.30

RRI, renal resistive index; DM, diabetes mellitus

chronic kidney disease,[23] and prediction of renal outcomes in critically ill patients.[12,24] RRI has also been used as a predictive value for AKI in other non-cardiac surgeries and in sepsis patients. A study in orthopedic surgery patients showed that a postoperative RRI > 0.70 predicts AKI with 94% sensitivity and 71% specificity.[25] In patients with severe sepsis, the RRI was better at predicting AKI than cystatin C.[26] Another study on intensive care patients on mechanical ventilation showed an association between an increased RRI and persistent AKI.[12]

RRI is mainly affected by renal and extrarenal factors. Renal factors that are responsible for alterations in RRI are vascular compliance and venous pressure. Factors like heart rate, aortic stiffness, and pulse pressure are the extrarenal determinants of the RRI.[27] Pharmacologically induced vasoconstrictions only modestly affect vascular resistance.[28] A study on patients with septic shock who were treated with norepinephrine showed an association between increased mean arterial pressure and increased urine output and a decreased RRI.[29]

In this prospective study, RRI assessed by ROC curves and the AUC to distinguish between non-AKI and AKI groups was 0.705 (95% CI: 0.588–0.826) for preoperative RRI. However, the most accurate cut-off value obtained in our study for preoperative RRI was 0.68, with a sensitivity of 70% and specificity of 67%. In combination with other markers, it could be helpful in predicting the risk.

On pump CABG surgery is a high-risk procedure. Therefore, routine intraoperative evaluation of RRI before surgery can prevent further injury to the kidney which is at a higher risk. By knowing elevated RRI before surgery, further renal insult can be prevented by avoiding nephrotoxic drugs and maintaining renal perfusion pressure at the optimal side during the perioperative period.

Limitations

This is a single-center study and small sample size. TEE examination was performed only once in intraoperative period before sternotomy. The sensitivity and specificity were low, which emphasized that there are factors other than RRI contributing to AKI in the postoperative period. Only single examiner performed the TEE measurement.

In summary, an increased intraoperative RRI is an independent predictor of AKI in the postoperative period in patients undergoing CABG surgery. Thus, in addition to other markers, the routine RRI assessment could be helpful to predict AKI in the postoperative period. The cut-off value of RRI should be >0.68 to predict AKI in the postoperative period. In future, more studies are required to confirm our observations and on large cohorts.

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Conflicts of interest
There are no conflicts of interest.

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