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Preoperative Urinary pH is Associated with Acute Kidney Injury After Cardiac Surgery in Non-Diabetic Patients

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ABSTRACT

Background: Acute kidney injury is a common complication of cardiac surgery that increases morbidity and mortality. The present study aims to analyze the association of preoperative urinary pH with acute kidney injury after isolated coronary artery bypass graft surgery (CABG).

Methods: We retrospectively reviewed the data of 270 adult non-diabetic patients who underwent isolated CABG surgery with normal renal function. The perioperative data of the patients included demographic data, laboratory findings, morbidity, and mortality. The patient population was divided into four groups: Group I, patients with preoperative urinary pH=5; Group II, patients with preoperative urinary pH=5.5; Group III, patients with preoperative urinary pH=6-6.5; and Group IV, patients with preoperative urinary pH ≥ 7.0. Kidney injury was interpreted according to the Kidney Disease: Improving Global Outcomes (KDIGO).

Results: There were 108 patients (40%) in Group I, 44 patients (16.3%) in Group II, 78 patients (28.9%) in Group III, and 40 patients (14.8%) in Group IV. Postoperative acute kidney injury (AKI) occurred in 39 patients (36.1%) in Group I, 4 patients (9.1%) in Group II, and 2 patients (2,5%) in Group III. None of the patients developed AKI in Group IV. Renal replacement therapy was required in 8 patients (2.3%) (6 patients from Group I; 2 patients from Group II; P = .016). Thirty-day mortality occurred in 5 patients (1.9%) (5 patients from Group I; none from other groups; P = .017). All of the patients required renal replacement therapy. Logistic regression analysis revealing the presence of lower pH levels preoperatively was shown to be associated with increased incidence of postoperative AKI (OR: 0.193; 95% CI: 0.103-0.361; P < .001).

Conclusion: Low preoperative urinary pH (≤5.5) results in severe acute kidney injury and increases the rate of morbidity and mortality after isolated CABG.

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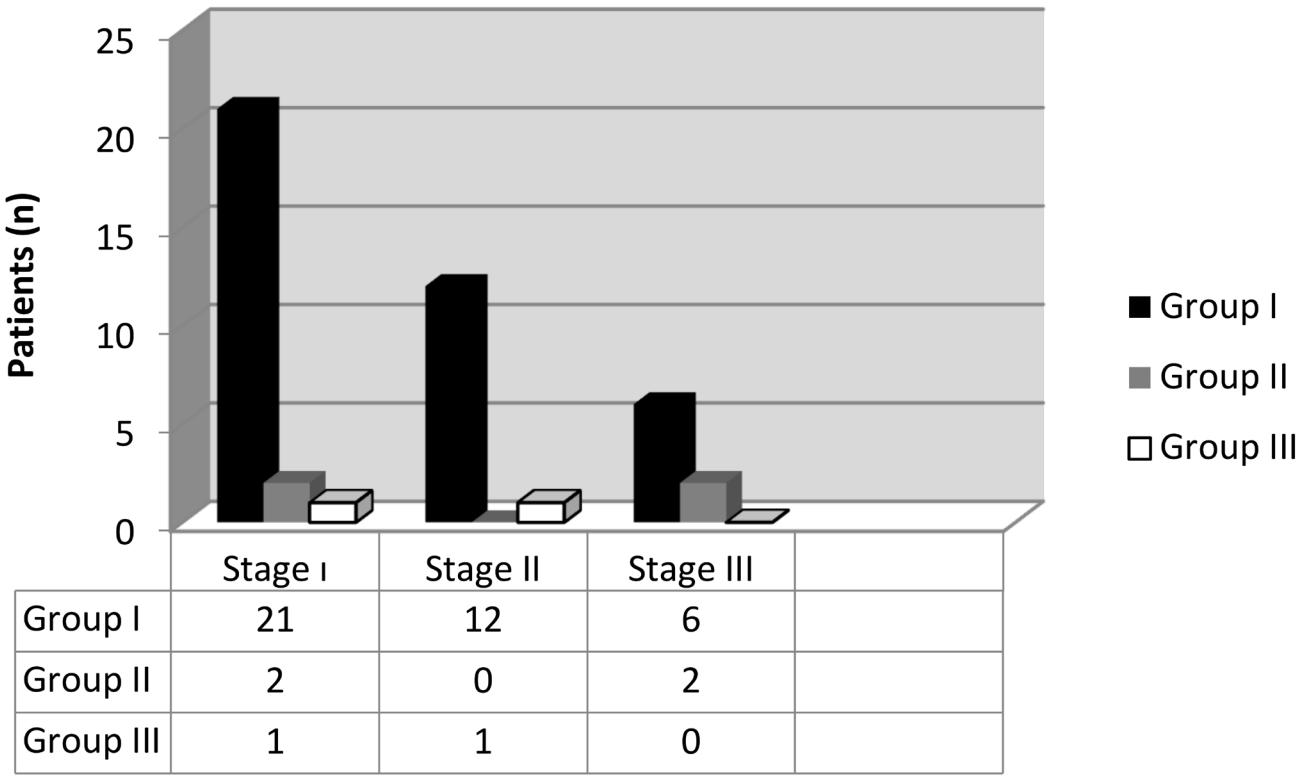
INTRODUCTION

Acute kidney injury (AKI) is a devastating and even lethal complication after cardiac surgery. It is associated with a significant increase in costs, due to increased length of hospital stay [Lassnigg 2004; Mao 2013]. The development of AKI after cardiac surgery is common, and it occurs in up to 30% of patients [Schopka 2014]. It significantly increases mortality and morbidity [Lassnigg 2004], and to decrease these adverse events, many studies have focused on identifying preventative strategies as well as biomarkers for AKI after cardiac surgery [Mao 2013]. A thorough understanding of the mechanisms and risk factors underlying the development of AKI may aid in identifying useful biomarkers and designing preventive methods. Major risk factors of AKI development are advanced age, diabetes mellitus, hypertension, hyperlipidemia, impaired left ventricular function, severe arteriosclerosis of the aorta, and preexisting renal dysfunction [Doddakula 2007; Weerasinghe 2001; Tekeli 2016]. Other crucial causes of AKI are suggested to be inflammatory response syndrome (SIRS) due to cardiopulmonary bypass (CPB), organ hypoperfusion, and mainly renal and nonpulsatile flow [Träger 2016; O'Neal 2016]. Cardiopulmonary bypass results in the destruction of cells, primarily red blood cells and hemolysis occurs. Due to this destruction, there is free hemoglobin and iron in the plasma. Free iron is nephrotoxic; it results in the generation of reactive oxygen species (ROS) and acute tubular necrosis, due to occlusion of renal tubules by methemoglobin casts [Haase 2007]. This situation is aggravated when the urine pH is acidic [Zager 1989]. In this study, we aimed to analyze the association of preoperative urinary pH with acute kidney injury after isolated coronary artery bypass graft surgery (CABG).

MATERIALS AND METHODS

Patients: After we received institutional review board approval, we retrospectively reviewed the data of 270 adult patients who underwent isolated CABG surgery with normal renal function (baseline serum creatinine value <1.4 mg/dL) from January 2017 to January 2019. All patients previously had granted permission for the use of their medical records for research purposes. The clinical data of the patients included demographic data, laboratory data, length of stay, in-hospital complications, and mortality. The patient population



	Stage I	Stage II	Stage III	
Group I	21	12	6	
Group II	2	0	2	
Group III	1	1	0	

Comparison of groups and KDIGO stages.

was divided into four groups: Group I, patients with preoperative urinary pH = 5; Group II, patients with preoperative urinary pH = 5.5; Group III, patients with preoperative urinary pH = 6-6.5; and Group IV, patients with preoperative urinary pH ≥ 7.0.

The primary outcome was the development of AKI. Kidney injury was interpreted according to the Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine criteria that are explained as Stage I, Stage II, and Stage III, according to the changes in serum creatinine levels within 48 hours of surgery (Table 1) [KDIGO 2012]. Excluded from the study were patients either on hemodialysis or peritoneal dialysis; those with emergent surgery, recent myocardial infarction, or peripheral vascular disease; and patients undergoing operations other than or in conjunction with CABG.

Preoperative urine pH was measured using Cobas 6500 urine analyzer (F. Hoffmann-La Roche AG, Basel, Switzerland). The reference range of urine pH at our institution is 5-8.

CABG Procedure: All operations were performed in a standardized approach by a Terumo roller pump (Terumo Advanced Perfusion System 1, USA), membrane oxygenators (Inspire 8, LivaNova Sorin Group, Italy). Mild to moderate (28-32°C) hypothermia and pulsatile flow of 2.2-2.4 L/m^2 were used. Myocardial protection was achieved with tepid antegrade blood cardioplegia, and a "hot shot" (250mL-500 mL) was delivered just before the removal of the aortic cross-clamp. The perfusion pressure was kept over 70mmHg at all times. Induction and maintenance of general anesthesia with endotracheal intubation were standardized in all the patients (fentanyl, midazolam, and isoflurane in oxygen with air). The same surgical team performed all of the operations.

Postoperative management: Postoperatively, patients were followed in the intensive care unit (ICU), according to protocols of our institution. Electrocardiography, systemic mean arterial pressure, central venous pressure, pulmonary artery and wedge pressures, cardiac output and index, arterial blood gases, chest tube output, and hourly urine output were monitored. Serum electrolytes were measured in conjunction with arterial blood gas measurement. Fluid and electrolyte imbalances immediately were corrected with appropriate management. Hematocrit values <25% were corrected with erythrocyte suspension administration. Daily blood urea nitrogen (BUN), serum and urea creatinine, and serum electrolytes uniformly were measured in all patients until discharge from the hospital. Preoperative and postoperative creatinine clearances and peak creatinine clearance were calculated, according to the formulations reported in the literature [Lassnigg 2000; Cockcroft 1976]. The indication criteria for renal replacement therapy (RRT), hyperkalemia (>6 mmol/L), oliguria <0.5mL/kg/h for 12 hours or anuria, and metabolic acidosis were determined by our staff nephrologists. Vascular access for RRT was with a dual lumen catheter via a central venous vein. Patients were heparinized to achieve activated clotting time of 200 seconds. Fresenius polysulfone filter (Fresenius Medical care AG, Bad Homburg, Germany) was used for filtration.

Table 1. Acute Kidney Injury Network (KDIGO) criteria

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline or ≥0.3 mg/dl (≥26.5 μmol/L) increase	<0.5 ml/kg/h for 6-12h
2	2.0-2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3 times baseline or ≥4.0 mg/dL (≥353.6 μmol/L) increase or initiation of RRT or in patients <18 years a decrease in eGFR <35 mL/min/1.73 m^2	<0.3 ml/kg/h for ≥24 h or anuria ≥ 12 h

Statistical analysis: All statistics were performed using SPSS version 17.0 for Windows (IBM Corporation, New York, USA). Continuous variables were expressed as mean ± SD and were compared by unpaired Student's t-test or chi-squared test. The effect of preoperative urinary pH on AKI after CABG was determined using logistic regression analysis, and the results were expressed as odds ratio (OR) with a 95% confidence interval (CI). A *P*-value <0.05 was considered statistically significant.

RESULTS

Patient demographics and perioperative data are shown in Table 2. Preoperative patient characteristics and intraoperative data did not assure statistical significance between the groups, except metabolic syndrome and body mass index (BMI). There were 108 patients (40%) in Group I, 44 patients (16.3%) in Group II, 78 patients (28.9%) in Group III, and 40 patients (14.8%) in Group IV. Postoperative AKI occurred in 39 patients (36.1%) in Group I, 4 patients (9.1%) in Group II, and 2 patients (2.5%) in Group III. None of the patients developed AKI in Group IV. There were 41 patients (15.2%) in the study population with metabolic syndrome, of which 25 patients were in Group I, 9 patients in Group II, 5 patients in Group III, and 2 patients in Group IV (*P* = .001). There were 74 patients (27.4%) in the study population with body mass index (BMI) >30kg/m^2, of which 38 patients were in Group I, 17 patients in Group II, 11 patients in Group III, and 8 patients in Group IV (*P* = .003).

The preoperative mean serum creatinine was 0.90 ± 0.21mg/dL in Group I, 0.85 ± 0.22 mg/dl in Group II, 0.89 ± 0.20mg/dL in Group III, and 0.96 ± 0.21mg/dL in Group IV (*P* = .103). Postoperative peak serum creatinine levels were higher in Group I patients than other three groups (1.26 ± 0.61 mg/dL, 1.02±0.33 mg/dL, 1.02 ± 0.29 mg/dL and 0.99 ± 0.24 mg/dL, respectively, *P* < .001).

When results were compared regarding KDIGO stage, the 39 patients in Group I included 21 patients (53.8%) in KDIGO stage I, 12 patients (30.8%) in KDIGO stage II, and 6 patients (15.4%) in KDIGO stage III. Four patients in Group II included 2 patients (50%) in the KDIGO stage I and 2 patients in KDIGO stage III. Two patients in Group III included 1 patient (50%) in KDIGO stage I and 1 patient (50%) in KDIGO stage II (Figure). Logistic regression analysis revealing the presence of lower pH levels preoperatively was shown to be associated with increased incidence of postoperative AKI (OR: 0.193; 95% CI: 0.103-0.361; *P* < .001).

The mean ICU time was 62.4 ± 35.1 hours in Group I, 50.7 ± 20.4 hours in Group II, 53.2 ± 26.6 hours in Group III, and 46.9 ± 24.5 hours in Group IV (*P* = .012); in-hospital stay time was 7.4 ± 3.1 days in Group I, 6.5 ± 2.0 days in Group II, 6.3 ± 2.2 days in Group III, and 6.4 ± 1.6 days in Group IV (*P* = .024). The intra-aortic balloon pump (IABP) support was required in 3.3% of patients (7 patients in Group I, 1 patient in Group II, and 1 patient in Group III; *P* = .020). The mean ventilatory support time was 13.2 ± 20.2 in Group I, 8.7 ± 3.6 in Group II, 7.8 ± 3.4 in Group III, and 7.2 ± 2.5 in Group IV, *P* = .013) and one of these patients required tra¬cheotomy.

Renal replacement therapy was required in 2.3% (N = 8) of patients (6 patients were in Group I, and 2 patients were in Group II, *P* = 0.016). The creatinine value before the commencement of RRT was 3.25 ± 0.563 mg/dL. RRT was started 28 hours-50 hours after surgery and used for 7 days. The mean creatinine level was 1.32 ± 0.81 mg/dL prior to discharge, and none of the patients became hemodialysis dependent. The 30-day mortality occurred in 5 patients (1.9%) (all patients from Group I; none from other groups; *P* = .017). All of these patients required RRT, and they died due to low cardiac output and multiorgan failure.

DISCUSSION

In our study, we analyzed the effect of preoperative urine pH as a biomarker of AKI after CABG. Acute kidney injury was observed in 16.7% of the patients in our study. Postoperative AKI occurred in 39 patients in Group I, 4 patients in Group II, and 2 patients in Group III. None of the patients developed AKI in Group IV. Logistic regression analysis revealing the presence of lower pH levels preoperatively was shown to be associated with increased incidence of postoperative AKI (OR: 0.193; 95% CI: 0.103-0.361; *P* < .001). Renal dysfunction after cardiac surgery is a frequent and devastating complication; however, the exact mechanism still is unclear. The main problem with AKI management is the lack of its early diagnostic measures. Many strategies are reported to prevent this dreadful complication, and many preoperative biomarkers were studied to predict which patients will have postoperative AKI and/or RRT [Mirmuhammad-Sadeghi 2013; Findik 2016; Kocogulları 2017; Prowle 2015; Albert 2018].

The intraoperative causative mechanisms of AKI during cardiac surgery are CPB induced SIRS that results in

Table 2. Baseline and perioperative characteristics of patients

Clinical characteristics	Group I* (N = 108)	Group II† (N = 44)	Group III‡ (N = 78)	Group IV§ (N = 40)	*P*||
Age, years	60.7 ± 11.1	62.1 ± 10.3	60.2 ± 10.6	62.7 ± 8.7	.555
Female, %	22.2	22.7	28.2	25	.810
Body mass index, >30 kg/m^2, %	35.2	38.6	14.1	20	.003
Hypertension, %	54.6	61.3	55.1	75	.129
Metabolic syndrome, %	23.1	20.4	6.4	5	.001
LV function, %	55.7 ± 8.8	52.2 ± 10.1	54.7 ± 8.7	55.1 ± 7.1	.177
CPB time, min	105.0 ± 32.4	117.7 ± 35.0	117.9 ± 37.6	115.8 ± 45.6	.061
Cross-clamp time, min	60.1 ± 20.9	67.0 ± 27.2	67.4 ± 21.4	65.9 ± 24.9	.116
Serum creatinine, mg/dL	0.90 ± 0.21	0.85 ± 0.22	0.89 ± 0.20	0.96 ± 0.21	.103
Creatinine clearance, mL/min	93.9 ± 37.8	87.0 ± 39.2	85.8 ± 37.3	86.6 ± 36.9	.569

Data are presented as mean ± SD where indicated. CPB indicates cardiopulmonary bypass; LV left ventricle. *Group I: patients with preoperative urinary pH=5, †Group II: pH=5.5, ‡Group III: pH=6-6.5, and §Group IV: pH ≥ 7.0. ||Chi-square and unpaired Student t tests.

production of excessive ROS, ischemia-reperfusion and also leads to generation of free oxygen radicals, hypoperfusion of the organs, mainly the kidneys, and hemolysis due to mechanical destruction of the cellular elements of the blood, mainly erythrocytes, as a result of contact with foreign surfaces of the extracorporeal circulation lines and also cardiotomy suction [Haase 2007; Bailey 2015; Loef 2002]. Hemolysis results in the release of free hemoglobin that forms casts with methemoglobin and causes tubular obstruction and ultimately renal cellular necrosis. In animal models, renal tubular necrosis is shown to be aggravated when the urine pH is acidic [Zager 1989]. Lower urinary pH mostly is seen in patients with diabetes, metabolic syndrome, obesity, and chronic kidney disease [Chung 2018; Nakanishi 2012]. It is suggested that low urinary pH is a consequence of acidification of body fluids, and metabolic changes result in acidification of body fluids [Chung 2018].

Although we excluded diabetic and chronic kidney disease patients from our study, we did not exclude patients with obesity and metabolic syndrome. There were 41 patients (15.2%) in the study population with metabolic syndrome, of which 25 patients were in Group I (P = .001), meaning that patients with metabolic syndrome in our study had lower urinary pH preoperatively that was statistically significant. It also is reported in our study that metabolic syndrome is an independent risk factor for AKI development after cardiac surgery (OR: 22.607; 95% CI: 10.106-50.574; P < .001).

Similarly, there were 74 patients (27.4%) in the study population with body mass index (BMI) >30kg/m^2, of which 38 patients were in Group I (P = .003), meaning that obese patients in our study have lower urinary pH preoperatively that is statistically significant. As obesity significantly was observed in Group I, we divided Group I into two subgroups as BMI >30kg/m^2 and BMI <30kg/m^2 to analyze the increase in AKI risk due to urinary pH or high BMI. Statistical results revealed that both high BMI and low urinary pH independently increased the risk of AKI (OR: 7.692; 95% CI: 3.159-18.732; P < .001). Obesity also is reported as an independent risk factor for AKI development after cardiac surgery in the present study (OR: 9.372; 95% CI: 4.593-19.125; P < .001). Worcester et al published a paper analyzing the mechanisms for higher urine pH in normal women, and they speculated this could be related to differential absorption of food anions between women and men. They stated this situation might be needed to preserve bone mineral in women, which may be depleted during pregnancy. However, our results in the present study revealed no statistically significant difference between men and women regarding urinary pH (P = .465).

Alkalization of the urine with sodium bicarbonate is thought to prevent the tubular necrosis as at higher urinary pH, conversion of hemoglobin to met-hemoglobin is reduced and tubular obstruction by casts is prevented. Additionally, it also is suggested that higher urinary pH may be protective against oxidant injury, which is the result of free iron resulting in the generation of ROS [Haase 2007]. There is no consensus about the administration of sodium bicarbonate perioperatively for the alkalization of the urine, however. In a multicenter double-blinded randomized trial by Haase et al, it is revealed that bicarbonate infusion did not reduce kidney injury after cardiac surgery, and they reported harmful effects of it, even association with increased mortality [Haase 2013]. Similarly, Heringlake et al reported that a perioperative infusion of sodium bicarbonate did not improve renal function in cardiac surgery patients in a prospective observational cohort study [Heringlake 2012]. In a recent meta-analysis regarding the effect of urine alkalization with sodium bicarbonate for patients undergoing PCI, it is suggested that there was a significant reduction in the incidence of contrast-induced AKI, serum creatinine, and estimated glomerular filtration rate but no significant differences were observed in the reduction of length of hospital stay, requirement for dialysis and mortality [Dong 2016]. Wetz et al analyzed the effect of perioperative

infusion of sodium bicarbonate in patients undergoing CABG with CPB and reported that the incidence of postoperative AKI significantly was reduced in the sodium bicarbonate received patients than controls primarily in the patients with a lower preoperative risk of AKI [Wetz 2015]. We did not try to perioperatively alkalize the urine. We corrected the arterial blood pH, according to the measurement results of arterial blood gas.

The mean ICU time, the length of hospital stay, and mean ventilatory support times statistically were longer in Group I. This could be due to the increased use of RRT in patients with lower urinary pH.

Postoperative renal dysfunction affects not only mortality, but also quality of life. AKI plays a vital role in postoperative mortality and morbidity in cardiac surgery patients. The rate of RRT is suggested to be 6% in patients with a high prevalence of AKI [Uchino 2005]. Among the patients who developed AKI, RRT was applied to 18.6 % of the patients in our study group with lower urinary pH (Groups I and II) and none in Groups III and IV, where the difference statistically was significant. The 30-day mortality was 1.9 % (N = 5) in the lower urinary pH group (Group I) and none in the other groups. We tried to emphasize in our study that the need for RRT and mortality significantly is increased in patients with lower urinary pH. We think further studies with higher populations are required in this field.

The major limitation of the study is its retrospective data; thus randomized prospective studies are necessary to confirm these results.

CONCLUSIONS

Low preoperative urinary pH levels increase the incidence of AKI following cardiac surgery. Low preoperative urinary pH results in a more severe AKI increases the frequency of RRT and mortality rate.

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