

The effect of cardiopulmonary bypass time on renal function after coronary artery bypass grafting

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ABSTRACT

Objectives: In this study, we aimed to evaluate the effect of duration of cardiopulmonary bypass (CPB) on postoperative acute kidney injury (AKI) in patients who underwent coronary artery bypass grafting (CABG).

Patients and methods: A total of 251 patients (222 males, 29 females; mean age: 61±9.4 years; range, 37 to 88 years) who underwent elective CABG operation between January 2014 and January 2018 were retrospectively analyzed. The patients were divided into three groups by considering the duration of CPB as 0 to 60 min (Group 1), 60 to 120 min (Group 2), and ≥120 min (Group 3). Preoperative, operative, and postoperative data and renal functions of the patients were evaluated using the Acute Kidney Injury Network (AKIN) criteria.

Results: In all three groups, a statistically significant decrease in hemoglobin and estimated glomerular filtration rate (eGFR) values and a statistically significant increase in blood urea nitrogen (BUN) and creatinine values were found (p<0.05). In Group 2 and Group 3, postoperative BUN and creatinine value were significantly higher and eGFR value was significantly lower than Group 1 (p<0.05). In terms of postoperative data, the rate of acute renal failure (ARF) requiring dialysis was significantly higher in Group 2 and Group 3 than Group 1 (p<0.05). The postoperative mortality rate was significantly higher in Group 3 than Group 1 (p<0.05).

Conclusion: In terms of postoperative mortality and morbidity, it is important to identify the risk factors for AKI and to take appropriate precautions for the risk factors. Minimizing perfusion time in patients undergoing CPB may help to decrease the incidence of CPB-induced AKI.

Keywords: Acute kidney injury, cardiopulmonary bypass time, coronary artery bypass grafting.

Heart diseases are still the leading causes of death worldwide. The main reason is the mortality related to course of the diseases and surgical practice of these diseases. Cardiovascular surgery has the risk of lung damage, infection, neurological problems, and renal disease. These complications may cause high mortality and morbidity.^[1]

The kidneys are the most vulnerable organs for cardiopulmonary bypass (CPB). Renal failure, which is a common disease for elderly, is associated with a high mortality rate. Nephrotoxic drugs, cardiogenic shock, major surgical procedures, and intensive care unit (ICU) stay are the main causes of renal failure.^[2-4] The most common and important form of renal failure after cardiac surgery is acute kidney injury (AKI). Cardiopulmonary bypass-related non-pulsatile and hypothermic perfusion, and low blood pressure cause hemodilution, decreased renal perfusion, decreased

estimated glomerular filtration rate (eGFR), and increased renal vascular resistance. The increase of renal vascular resistance causes the increase of angiotensin II secretion and, consequently, renal blood perfusion decreases. Decreased renal perfusion also increases the release of oxygen radicals. Embolic materials related to aggregated platelets and damaged erythrocyte cells cause the occlusion of renal tubules. All these problems increase the risk of postoperative

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AKI.^[5] It is important to investigate the negative effects of CPB, which is essential for cardiac surgery practice, for renal functions.

In the present study, we aimed to investigate the effect of duration of CPB on postoperative AKI in patients who underwent coronary artery bypass grafting (CABG).

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Izmir Katip Celebi University, Faculty of Medicine, Department of Cardiovascular Surgery between January 2014 and January 2018. A total of 251 patients (222 males, 29 females; mean age: 61±9.4 years; range, 37 to 88 years) who underwent elective CABG operation were included. The patients who had preoperative renal diseases and patients who were scheduled for cardiac surgery combined with CABG were excluded. The patients were divided into three groups according to CPB times as follows: 0 to 60 min (Group 1), 60 to 120 min (Group 2), and >120 min (Group 3). Patient's pre-, intra-, and postoperative data were recorded. Renal status of the patients was evaluated according to creatinine and eGFR levels. Acute kidney injury was defined according to the Acute Kidney Injury Network (AKIN) criteria^[6] as follows: Stage 1, an increased postoperative creatinine level of ≥1.5, but <2 times, compared to baseline; Stage 2, an increased postoperative creatinine level of ≥2, but <3 times, compared to baseline; and Stage 3, an increased postoperative creatinine level of ≥3 times, compared to baseline. All groups were compared according to creatinine levels. A written informed consent was obtained from each patient. The study protocol was approved by the Izmir Katip Celebi University, Faculty of Medicine Ethics Committee (date/no: 25.04.2019/188). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Baseline demographic and clinical characteristics including age, sex, body surface area, redo surgery, diabetes mellitus, hypertension, chronic obstructive lung disease, smoking, neurological dysfunction, ejection fraction, pre- and postoperative hemoglobin, white blood cell (WBC), blood urea nitrogen (BUN), creatinine, and eGFR levels were recorded. Intraoperative data including coronary bypass graft counts, CPB time, aortic cross-clamp time, transfusion rate, and postoperative data including mechanical

ventilation time, revision, neurological complication, hemodialysis, ICU stay, in-hospital stay, and mortality rate were noted. Patient's preoperative creatinine levels were the baseline values for the calculation of eGFR. The Cockcroft-Gault formula was used to calculate eGFR (Figure 1).

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD), while categorical variables were expressed in number and frequency. The Kolmogorov-Smirnov test was used to analyze the distribution of the variables. Due to the unbalanced distribution, the non-parametric tests were used. The Kruskal-Wallis and Mann-Whitney U test were used to analyze quantitative independent data. The Wilcoxon test was used to analyze dependent quantitative data. The chi-square test or Fisher's exact test were used to analyze qualitative independent data. A *p* value of <0.05 was considered statistically significant.

RESULTS

Baseline demographic and clinical characteristics of the patients are shown in Table 1. There was no statistically significant difference among the groups in terms of age, sex, diabetes mellitus, chronic obstructive lung disease, smoking status, renal failure, hypertension, and redo surgery (*p*>0.05). However, preoperative ejection fraction was significantly lower in Group 3 compared to Groups 1 and 2 (*p*<0.05).

There was no statistically significant difference among the groups in terms of WBC and hemoglobin levels in the pre- and postoperative period. However, the WBC value increased in the postoperative period compared to the preoperative period and hemoglobin levels decreased in the postoperative period compared to baseline (*p*<0.05) (Table 2).

There was no significant difference among the groups in terms of preoperative BUN values (*p*>0.05). However, the postoperative BUN values increased in

$$eGFR = \frac{(140 - \text{Age [year]} \times \text{weight [kg]})}{(72)^* \times (\text{serumcreatinine [mg/dL]})}$$

Figure 1. Cockcroft-Gault formula for eGFR calculation.
eGFR: Estimated glomerular filtration rate.

Table 1 Preoperative data													
	Group 1 (n=100)			Group 2 (n=100)			Group 3 (n=51)			p			
	n	%	Mean±SD	Median	n	%	Mean±SD	Median	n		%	Mean±SD	Median
Age (year)			60.2±9.7	61.5			61.9±8.5	63.0			60.7±10.7	60.0	0.382*
Sex													0.015†
Male	92	92.0			89	89.0			41	76.5			
Female	8	8.0			11	11.0			10	23.5			
Diabetes mellitus													0.198†
(-)	65	65.0			53	53.0			28	54.9			
(+)	35	35.0			47	47.0			23	45.1			
Hypertension													0.488†
(-)	42	42.0			50	50.0			25	49.0			
(+)	58	58.0			50	50.0			23	45.1			
Smoking													0.147†
(-)	46	46.0			57	57.0			31	60.8			
(+)	54	54.0			43	43.0			20	39.2			
COPD													0.999†
(-)	88	88.0			88	88.0			45	88.2			
(+)	12	12.0			12	12.0			6	11.8			
Chronic renal failure													1.000†
(-)	100	100.0			100	100.0			51	100.0			
(+)	0	0.0			0	0.0			0	0.0			
Redo surgery													1.000†
(-)	98	98.0			100	100.0			51	100			
(+)	1	1.0			0	0.0			0	0.0			
Preoperative EF (%)			55.3±7.3	60.0			53.2±7.8	55.0			49.6±9.4	50.0	0.000*
Body surface area			1.9±0.1	1.9			1.9±0.2	1.9			1.9±0.3	1.9	0.585*
EuroSCORE			3.1±2.3	3.0			2.6±1.9	2.0			3.5±1.8	3.0	0.014*

SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; EF: Ejection fraction; * Kruskal-Wallis test; † Chi-square test.

Table 2
Laboratory data

	Group 1 (n=100)		Group 2 (n=100)		Group 3 (n=51)		<i>p</i> *
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	
Preoperative WBC ($\times 10^3$)	8.2±2.2	8.0	7.9±2.0	7.8	8.2±2.0	7.7	0.506
Postoperative WBC ($\times 10^3$)	13.1±3.6	12.8	13.5±4.2	12.8	14.4±4.0	13.6	0.149
<i>p</i> †	0.000		0.000		0.000		
Preoperative hemoglobin ($\times 10^3$)	13.2±1.4	13.1	13.1±1.5	13.2	12.7±1.6	12.9	0.172
Postoperative hemoglobin ($\times 10^3$)	9.6±1.3	9.4	9.5±1.3	9.5	9.2±1.2	9.1	0.118
<i>p</i> †	0.000		0.000		0.000		
Preoperative BUN	16.3±5.3	15.0	17.6±4.5	17.0	17.0±6.1	16.0	0.052
Postoperative BUN	18.0±5.3	17.5	19.9±6.7	18.5	20.1±5.8	20.0	0.015
<i>p</i> †	0.000		0.000		0.000		
Preoperative creatinine (mg/dL)	0.9±0.1	0.82	0.9±0.2	0.89	0.9±0.2	0.84	0.057
Postoperative creatinine (mg/dL)	1.0±1.0	0.86	1.1±0.3	0.97	1.11±0.36	1.04	0.001
<i>p</i> †	0.003		0.000		0.000		
Preoperative eGFR	114.8±19.8	118.9	108.2±21.1	107.7	111.1±22.2	115.5	0.057
Postoperative eGFR	109±25.9	113.1	96.4±33.1	97.1	92.6±30.8	89.2	0.001
<i>p</i> †	0.000		0.000		0.000		

SD: Standard deviation; WBC: White Blood cells; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; * Kruskal-Wallis test (Mann-Whitney U Test); † Wilcoxon Signed Rank test.

all groups compared to baseline ($p < 0.05$). Postoperative BUN levels in Groups 2 and 3 were higher compared to Group 1 ($p < 0.05$). There was no significant difference in postoperative BUN levels between Groups 2 and 3 ($p > 0.05$).

Preoperative creatinine levels did not significantly differ among the groups ($p > 0.05$). However, postoperative creatinine levels increased in all

groups compared to baseline ($p < 0.05$). Postoperative creatinine levels were significantly higher in Groups 2 and 3, compared to Group 1 ($p < 0.05$). There was no significant difference in postoperative creatinine levels between Groups 2 and 3 ($p > 0.05$).

Preoperative eGFR levels did not significantly differ among the groups ($p > 0.05$). However, postoperative eGFR levels decreased in all groups compared to

Table 3
Postoperative AKI rate

	Group 1 (n=100)				Group 2 (n=100)				Group 3 (n=51)				<i>p</i>
	n	%	Mean±SD	Median	n	%	Mean±SD	Median	n	%	Mean±SD	Median	
AKI													0.021†
(+)	4	4.0			10	10.0			9	17.6			
(-)	96	96.0			90	90.0			42	82.4			
AKI Stage													
I	3	3.0			8	8.0			5	9.8			
II	0	0.0			2	2.0			4	7.8			
III	1	1.0			0	0.0			0	0.0			
AKI rate			1.2±1.3	1.06			1.2±0.3	1.09			1.2±0.3	1.15	0.006*

AKI: Acute kidney injury; SD: Standard deviation; * Kruskal-Wallis test (Mann-Whitney U Test); † Chi-square test.

	Table 4 Postoperative data												p
	Group 1 (n=100)				Group 2 (n=100)				Group 3 (n=51)				
	n	%	Mean±SD	Median	n	%	Mean±SD	Median	n	%	Mean±SD	Median	
CPB time (min)			52.5±7.3	54.5			90.2±15.9	89.5			136.0±17.0	130.0	0.000*
Cross-clamp time (min)			27.0±5.3	26.0			49.1±12.4	47.5			67.7±17.7	66.0	0.000*
Postoperative hemodialysis													0.001
(-)	100	100.0			92	92.0			43	84.3			
(+)	0	0.0			8	8.0			8	15.7			
IABP													0.022†
(-)	97	97.0			91	91.0			43	43.0			
(+)	3	3.0			9	9.0			8	15.7			
Extubation time (h)			8.5±3.9	7.0			12.7±12.1	8.5			33.4±91.8	15.0	0.000*
ICU stay (day)			2.7±1.2	2.0			3.1±2.8	2.0			4.8±4.0	4.0	0.000*
Drainage (mL)			825±345	750			980±583	800			1163±927	950	0.018*
Used blood products			3.1±2.5	2.0			3.7±2.7	3.0			5.2±2.6	5.0	0.00*
Revision													0.869†
(-)	96	96			96	96			47	92.2			
(+)	4	4.0			5	5.0			3	5.9			
Neurologic problem													0.668†
(-)	98	98.0			94	94.0			48	94.1			
(+)	2	2.0			4	4.0			2	3.9			
Hospital stay (day)			7.7±3.3	7.0			8.0±4.3	7.0			11.5±8.0	8.0	0.000*
Mortality													0.005†
(-)	100	100.0			100	100.0			49	96.1			
(+)	0	0.0			3	3.0			5	9.8			

SD: Standard deviation; CPB: Cardiopulmonary bypass; IABP: Intra-aortic balloon pump; ICU: Intensive care unit; * Kruskal-Wallis test (Mann-Whitney U Test); † Chi-square test.

preoperative levels ($p < 0.05$). Postoperative eGFR levels were significantly lower in Groups 2 and 3, compared to Group 1 ($p < 0.05$). There was no significant difference in postoperative eGFR levels between Groups 2 and 3 ($p > 0.05$). Laboratory data are shown in Table 2.

The AKIN scores were significantly higher in Groups 2 and 3, compared to Group 1 ($p < 0.05$). However, there was no significant difference between Groups 2 and 3 in terms of the AKIN scores ($p > 0.05$) (Table 3).

The cross-clamp time and CPB time were significantly longer in Group 3 compared to Groups 1 and 2, and they were also significantly higher in Group 2 compared to Group 1 ($p < 0.05$) (Table 4).

The number of patients requiring dialysis was higher in Groups 2 and 3, compared to Group 1 ($p < 0.05$). There was no significant difference between Groups 2 and 3 ($p > 0.05$). Intra-aortic balloon pump (IABP) use and mechanical ventilation time were statistically higher in Group 3, compared to Groups 1 and 2 ($p < 0.05$). Transfusion rate, ICU stay, and in-hospital stay were also higher in Group 3, compared to Group 1 ($p < 0.05$). There was no statistically significant difference between Groups 1 and 2 in terms of these parameters.

The need for drainage and revision was statistically significantly higher in Group 3, compared to Group 1; however, there was no significant difference between Groups 1 and 2. There was no significant difference among the groups in terms of neurological complications ($p > 0.05$). However, the mortality rate was higher in Group 3, compared to Group 1 ($p < 0.05$), although there was no significant difference between Groups 1 and 2 (Table 4).

DISCUSSION

With the aging population, the prevalence of coronary artery disease has been increasing all around the world recently. As the aging population increases, the number of CABG operations also increases.^[7] The CABG is still the gold-standard technique for the treatment of coronary artery disease. Mortality rate varies between 2.5 and 26%.^[7] Renal damage is a frequent complication after CABG and is usually seen as a mild creatinine increase. However, in some cases, creatinine increase may be high or AKI may complicate

prognosis in patients with high comorbidities, leading to the increased mortality.^[8]

Hemodialysis need after cardiac surgery ranges between 1 and 7%. Mortality rate in patients with renal failure is 60%.^[9,10] There is also the increased rate of infection and prolonged hospital stay in patients who have CPB-related AKI.^[11] Therefore, postoperative renal dysfunction is an important complication due to its relation with postoperative mortality and morbidity.^[12,13] The main causes of CPB-related AKI are decreased perfusion pressure, nephrotoxic agents, and CPB-related inflammatory response.^[14-16] The main goal of CPB is to maintain tissue perfusion. Perfusionist regulates this process by coordinating the mean arterial pressure and CPB flow rate.

Extracorporeal circulation with CPB produces systemic inflammatory response. As the CPB time increases, the risk of systemic inflammatory response syndrome (SIRS) also increases.^[17] There are many studies showing that a CPB time longer than 80 min poses a significant risk for SIRS.^[18] Review of the literature also reveals that there is a relation between AKI and CPB, as described previously before a relation between CPB and SIRS. Zhiwei et al.^[19] concluded that prolonged perfusion time was related to AKIN Stage ≥ 2 renal damage and it was a major risk factor for postoperative AKI. In our study, we analyzed patients according to CPB time. We showed that the increased CPB time was strongly related to AKI as follows: Group 1, 4% ($n=4$); Group 2, 10% ($n=10$), and Group 3, 17.6% ($n=9$). The AKIN scores were higher in Groups 2 and 3, compared to Group 1 ($p < 0.05$). We found that one (1%) patient in Group 1, two (2%) patients in Group 2, and four (7.8%) patients in Group 3 had AKIN \geq Stage 2, respectively.

In another study including acute renal failure patients after cardiac surgery, Bove et al.^[12] included 5,068 patients and they found that 171 patients had AKI after cardiac surgery. In addition, 94 patients needed renal replacement therapy and patients who needed renal replacement therapy had a longer mean CPB time (116 ± 51.2 min) compared to those who did not (82 ± 31.7). They concluded that decreased CPB time also decreased the CPB-related AKI. In our study, 16 patients needed postoperative hemodialysis (Group 2, $n=8$, 8%; Group 3, $n=8$, 15.7%). The need for hemodialysis was significantly higher in Groups 2 and 3, compared to Group 1; however, there was no statistically significant difference between

Groups 2 and 3. The main goal of the intraoperative patient management in terms of CPB is to manage optimal perfusion pressure, flow rate, hemodilution, and CPB time. Therefore, managing CPB time in an appropriate level would reduce the AKI risk, postoperative morbidity, and mortality.^[20]

In a study by Elmanday et al.,^[21] CPB time had a statistically significant importance for the development of postoperative AKI. They found that postoperative creatinine and BUN levels were significantly higher and eGFR levels were significantly lower in the AKI group, compared to non-AKI group. In our study, there was no significant difference in the preoperative creatinine, BUN, and eGFR values. However, postoperative creatinine and BUN levels were higher in Groups 2 and 3, compared to Group 1. Also, the eGFR levels were significantly lower in Groups 2 and 3, compared to Group 1. Perioperative anemia is another important indicator of postoperative AKI.^[22,23] In our study, we showed that there was no statistically significant difference in the hemoglobin levels among the groups.

Patients with left ventricular dysfunction have an increased AKI risk.^[22] Low cardiac output and the need for inotropic or mechanical support after cardiac surgery are also major risk factors for AKI.^[22] In our study, three (3%) patients in Group 1, nine (9%) patients in Group 2, and eight (15.7%) patients in Group 3 needed IABP. The need for IABP in Group 3 was significantly higher, compared to Group 1. Ortega-Loubon et al.^[24] performed a study about AKI-related ICU stay and mortality after CABG in 435 patients. The mean ICU stay for their patients with and without AKI was 7.4 ± 9.3 days and 2.7 ± 2.2 days, respectively. The 30-day mortality rate was 18.5% and 3.1% in patients with and without AKI, respectively. In our study, we found that the ICU stay and in-hospital stay were higher in Group 3, compared to the other groups. There was no significant difference between Groups 1 and 2. The mortality rate in Group 3 was significantly higher compared to Group 1. In the literature, there is a limited number of studies regarding AKI and neurological complications after cardiac surgery. A study by Ryden et al.^[25] showed that postoperative neurological complication in patients with AKI were higher compared to those without postoperative AKI. In our study, there was no significant difference among the groups ($p > 0.05$).

The main limitations of this study include its single-center, retrospective design with a relatively small sample size. In addition, only creatinine and eGFR values were used for the AKIN classification; however, there are many other sensitive parameters such as renal-specific proteins to calculate renal function and eGFR. Screening of the risk factors along with the measurement of novel biomarkers may enable early diagnosis of patients who are susceptible to AKI and may be helpful to tailor the appropriate treatment protocol.

In conclusion, the incidence of CPB-related AKI is still high in our surgical practice. The most important way to reduce the risk of CPB-related AKI is to manage the modifiable risk factors for patients and extracorporeal circulation technique. It is a good option to prefer off-pump techniques for patients who have a high postoperative AKI risk. Furthermore, decreasing the inflammatory response and CPB time for on-pump procedures may also contribute to prevent AKI.

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