The effect of coronary angiography timing and use of cardiopulmonary bypass on acute kidney injury after coronary artery bypass graft surgery

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ABSTRACT

Objective: Acute kidney injury is a common but serious complication of coronary artery bypass grafting. We investigated whether the effect of the timing of coronary angiography on acute kidney injury after coronary artery bypass grafting is influenced by the use of cardiopulmonary bypass.

Methods: We included, retrospectively, 2371 patients who underwent coronary artery bypass grafting whether cardiopulmonary bypass was used (on-pump coronary artery bypass) or not (off-pump coronary artery bypass). Postoperative acute kidney injury was defined by the consensus Kidney Disease: Improving Global Outcomes Definition and Staging criteria. Multivariate logistic regression and propensity score analysis were performed to evaluate the association of the time interval between coronary angiography and coronary artery bypass grafting with postoperative acute kidney injury.

Results: The incidence of acute kidney injury was higher in patients who underwent coronary angiography 7 days or less before coronary artery bypass grafting than in those who underwent it more than 7 days before coronary artery bypass grafting (42.7% vs 38.5%, $P = .037$). There was significant interaction between the timing of coronary angiography and the use of cardiopulmonary bypass for postoperative acute kidney injury ($P = .019$). The time interval between coronary angiography and surgery was independently associated with postoperative acute kidney injury in patients undergoing on-pump coronary artery bypass only. In an adjusted propensity score model, coronary angiography within 7 days of on-pump coronary artery bypass was a predictor of postoperative acute kidney injury (odds ratio, 1.742; 95% confidence interval, 1.144-2.653; $P = .010$).

Conclusions: A shorter interval between coronary angiography and surgery influenced the occurrence of acute kidney injury in patients undergoing on-pump coronary artery bypass. However, the interval is not an independent risk factor for the development of postoperative acute kidney injury in patients who undergo off-pump coronary artery bypass. (J Thorac Cardiovasc Surg 2016;152:254-61)

The incidence of AKI in each operation performed within 7 days after CABG or not.

Central Message

A shorter interval between coronary angiography and surgery affects the occurrence of AKI in patients undergoing CABG with CPB.

Perspective

A shorter interval between coronary angiography and surgery increased the risk of postoperative AKI in patients undergoing ONCAB but did not affect the development of postoperative AKI in patients undergoing OPCAB. Our current evidence should be considered when you need to increase the convenience of patients, reduce the economic burden of patients, and shorten the hospital stay.

See Editorial Commentary page 262.

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Received for publication May 15, 2015; revisions received Feb 4, 2016; accepted for publication Feb 19, 2016; available ahead of print April 5, 2016.

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0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2016.02.063>

Acute kidney injury (AKI) is a serious complication of coronary artery bypass grafting (CABG) that shows an incidence of 3% to 30%, depending on the definition

Scanning this QR code will take you to supplemental data and tables for this article.

Abbreviations and Acronyms

AKI	= acute kidney injury
CABG	= coronary artery bypass grafting
CI	= confidence interval
CPB	= cardiopulmonary bypass
ICU	= intensive care unit
KDIGO	= Kidney Disease: Improving Global Outcomes Definition and Staging
ONCAB	= on-pump coronary artery bypass
OPCAB	= off-pump coronary artery bypass
OR	= odds ratio
RRT	= renal replacement therapy
sCr	= serum creatinine

used, and is associated with increased short-term morbidity and mortality.¹⁻³ There is no single mechanism that explains cardiac surgery–associated renal injury. Instead, it is the result of a complex interplay between cardiopulmonary bypass (CPB) and a number of other factors.^{4,5} Although the identification of factors that increase the risk of AKI development is important to prevent postoperative AKI after CABG, most known risk factors are unmodifiable, such as advanced age, gender, diabetes, poor cardiac function, preoperative renal dysfunction, and emergency operation.^{6,7} Nonetheless, the control of modifiable risk factors can reduce the occurrence of AKI. Cardiac surgery 1 day or less after coronary angiography has been associated with an increased risk of postprocedural AKI in some studies but not in others.⁸ In our previous study, however, the risk of postoperative AKI was not related to the time between coronary angiography and off-pump coronary artery bypass (OPCAB).⁹ Moreover, some studies have reported that neither use nor duration of CPB is an independent risk factor for postoperative deterioration in the glomerular filtration rate or for the occurrence of AKI.^{10,11}

Although numerous studies have been performed in this research field, no report to date has compared the effect of the time from coronary angiography to CABG according to CPB use. Thus, we investigated whether the effect of the timing of coronary angiography on AKI after CABG is influenced by the use of CPB. We hypothesized that a short interval between coronary angiography and CABG would be associated with an increased risk of AKI development and that a shorter interval between coronary angiography and CABG would have a more serious impact on the occurrence of AKI in patients undergoing on-pump coronary artery bypass (ONCAB).

MATERIALS AND METHODS**Subjects**

This study retrospectively reviewed the electronic medical records and laboratory results of all patients who underwent CABG with or without CPB at Asan Medical Center between January 2006 and December 2012. The study protocol was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea (AMC IRB 2014-0623). During the study period, 2643 patients underwent ONCAB or OPCAB. However, 153 patients underwent emergency or urgent surgery, 97 patients were on hemodialysis, and 16 patients had undergone other valve surgery; in addition, there was no record of the interval between the coronary angiography and the operation for 6 patients. Thus, a total of 2371 patients were finally included (Figure 1).

Demographic variables examined included patient age, gender, and body mass index; history of hypertension, diabetes, smoking, or previous intervention or surgery of the coronary artery; cerebrovascular disease, hemorrhagic stroke, transient ischemic attack, or severe narrowing of the carotid arteries; peripheral artery disease, defined as stenosis of 1 or more peripheral arteries with more than 50% occlusion of the vessel lumen except the cerebral and carotid artery; and preoperative renal dysfunction, determined by an estimated glomerular filtration rate less than 60 mL/min/1.73 m² based on preoperative creatinine clearance, calculated using the Modification of Diet in Renal Disease equation II.¹² The baseline laboratory values were defined as measured values the day before surgery or immediately before surgery when coronary angiography was performed on the same day of operation. Clinical data for the 2371 patients who underwent isolated elective CABG were obtained from the CABG and anesthesia database of Asan Medical Center and from a retrospective review of the computerized patient record system. This study was performed in accordance with Strengthening the Reporting of Observational Studies in Epidemiology criteria.¹³

Perioperative Management

Preoperative management, anesthetic, and surgical techniques were standardized for all patients.¹⁴ Coronary angiography, CABG, and perioperative management were performed in the standard manner, and the day of the elective surgery was chosen by the cardiac surgeons. The routine protocol for patients scheduled for angiography at Asan Medical Center has been reported.⁹ In our institution, CABG

FIGURE 1. Enrollment of patients. *ONCAB*, On-pump coronary artery bypass; *OPCAB*, off-pump coronary artery bypass.

was performed by 4 experienced cardiac surgeons, who incidentally preferred OPCAB rather than ONCAB. The decision to use CPB was made at the discretion of the attending cardiac surgeon. Indicated criteria of ONCAB were as follows: moderate to severe cardiomegaly; anticipation of difficult surgical approaches due to anatomic variances of coronary artery; poor-quality target vessels, including intramyocardial vessels, diffusely diseased vessels, and calcified coronary vessels; hemodynamic instability; impaired left ventricular function; and severe pulmonary disease.

Definitions and End Point

The primary end point was the impact of the timing between coronary angiography and surgery on AKI development. Postoperative AKI was defined according to Kidney Disease: Improving Global Outcomes Definition and Staging (KDIGO) criteria using the maximal change in serum creatinine (sCr) during the first 7 postoperative days compared with the preoperative baseline values.¹⁵ AKI was defined by either of the following: an increase in sCr 0.3 mg/dL or greater within 48 hours or an increase in sCr 1.5 times baseline or greater, which was known or presumed to have occurred within the prior 7 days. AKI also was staged for severity according to the following criteria:

Stage 1, increase in sCr 0.3 mg/dL or greater or to 1.5 to 1.9 times the baseline.

Stage 2, increase in sCr to 2.0 to 2.9 times the baseline.

Stage 3, increase in sCr to 3.0 or more times the baseline; increase in sCr 4.0 mg/dL or greater or initiation of renal replacement therapy (RRT).

We assessed the association of postoperative AKI with postoperative outcomes, such as time to extubation, intensive care unit (ICU) and hospital stay, and mortality. One-year RRT or death collectively refers to cases of RRT and deaths that occurred during the first postoperative year. For the confirmation of 1-year RRT or death, our investigators examined the electronic medical records, national health insurance status, or registration of death and conducted a telephone interview with the family of the patients.

Statistical Analysis

All of the data in the study were summarized as mean $\pm$ standard deviation or medians with interquartile range (when the distribution of values is skewed) for continuous variables or numbers and percentages for categorical variables. In univariate analysis to compare the differences between groups, categorical data were analyzed using the chi-square or Fisher exact tests. The Student *t* test or Mann–Whitney rank-sum test was used for continuous variables.

Univariate logistic regression analysis was used to identify demographic, preoperative laboratory, and coronary angiographic factors significantly associated with AKI development (Table E1). Variables with a *P* value less than .1 in univariate logistic regression analysis were included in the multivariable logistic regression analysis to determine independent factors for AKI. First, the effect of time interval between coronary angiography and CABG on AKI development was analyzed as a continuous variable in univariate and multivariable logistic models. We performed log transformation on this variable to account for a possible nonlinear relationship between coronary angiography timing and AKI. To assess whether the effect of the time interval between coronary angiography and CABG on postoperative AKI was influenced by the use of CPB, we tested for the presence of any interaction between the timing of coronary angiography and the use of CPB. Subsequently, patients were divided into 2 groups on the basis of the use of CPB (ie, ONCAB and OPCAB). We also analyzed the days between coronary angiography and CABG as categorical variables using 7 days as the cutoff. This cutoff was based on our preliminary analysis including the receiver operating characteristic curve analysis (*P* = .020, data not shown) and regression analysis and a previous report suggesting that after being exposed

contrast, renal function usually returns to preexisting levels within 7 to 21 days.^{16,17} Also, to control for selection bias related to covariates, we performed a propensity score analysis. Without regard to outcome variables, the propensity scores for the likelihood of receiving coronary angiography 7 or less days before CABG were developed and a hierarchical logistic regression model to calculate the propensity score was applied (details are provided in Supplemental Methods). Then, an unadjusted logistic regression model was developed using a propensity score for independent predictors of the development of postoperative AKI after CABG; the obtained predictors were subsequently tested in an adjusted logistic regression model. The adjusted logistic regression model was built using variables that showed a *P* value less than .1 in the unadjusted logistic propensity score regression model. A stepwise approach was used and confirmed by backward and forward methods. The significance within the models was evaluated with the Wald test, whereas the strength of the association of variables with AKI was estimated by calculating the odds ratios (ORs) and 95% confidence intervals (CIs). The adjusted logistic model was calibrated by the Hosmer–Lemeshow goodness-of-fit test, as well as residual diagnostics (deviance and dfBetas); model discrimination was evaluated by using the area under the receiver operating characteristic curve. The process was repeated to confirm the impact of the timing between coronary angiography and surgery on AKI development in each operation group. All tests were 2-sided with the alpha level set at 0.05 for statistical significance. All statistical analyses were performed using SPSS 21.0 (SPSS Inc, Chicago, Ill) and SAS 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

The demographic characteristics, preoperative laboratory findings, and intraoperative variables of the 2371 included patients are shown in Table 1. In total, 964 patients (40.7%) had postoperative AKI. The incidence of AKI differed between the types of surgery: 49.8% in patients who underwent ONCAB and 36.8% in patients who underwent OPCAB (*P* < .001). Moreover, the incidence of AKI was significantly higher in patients who underwent coronary angiography ≤ 7 days before ONCAB than in those of > 7 days (55.7% vs 44.2%, *P* = .003; Figure 2). There were no significant differences in preoperative renal function, preoperative laboratory levels including sCr, and elapsed time interval from coronary angiography to operation between patients who underwent ONCAB and patients who underwent OPCAB (Table 1).

Postoperative morbidity and mortality are shown in Table 2. Patients affected by postoperative AKI experienced a longer time to extubation, ICU stay, and hospital stay. Moreover, the rates of in-hospital death and 1-year mortality were significantly higher in patients who experienced postoperative AKI than in those without this complication (*P* < .001 and *P* = .011, respectively). There were higher occurrences of RRT and more deaths during the first postoperative year in patients affected by postoperative AKI than in those without AKI (*P* < .001). The reoperation rate, the Cardiovascular Sequential Organ Failure Assessment score during the first 24 hours of ICU stay, and the weight change were higher in the patients affected by AKI than in those not

TABLE 1. Baseline and operative characteristics of study patients stratified by type of surgery

	ONCAB (n = 701)	OPCAB (n = 1670)	P value
Age (y)	63.5 ± 9.0	63.7 ± 9.3	.643
Male	514 (73.3%)	1286 (77.0%)	.056
Body mass index (kg/m ²)	24.7 ± 3.0	24.6 ± 2.9	.911
Hypertension	416 (59.3%)	1071 (64.1%)	.029
Diabetes mellitus	322 (45.9%)	776 (46.5%)	.822
Smoking			<.001
No	340 (48.5%)	750 (44.9%)	
Ex-smoker	231 (33.0%)	473 (28.3%)	
Current	130 (18.5%)	447 (26.8%)	
Congestive heart failure	33 (4.7%)	43 (2.6%)	.008
Cerebrovascular disease	236 (33.7%)	350 (21.0%)	<.001
Peripheral vascular disease	26 (3.7%)	98 (5.9%)	.033
eGFR <60 mL/min/1.73 m ²	125 (17.8%)	279 (16.7%)	.511
Liver disease	18 (2.6%)	46 (2.8%)	.890
Preoperative medication			
ACEi	315 (44.9%)	692 (41.4%)	.112
Beta-blocker	401 (57.2%)	1073 (64.3%)	.001
Calcium channel blocker	446 (63.6%)	1206 (72.2%)	<.001
Insulin	61 (8.7%)	459 (27.5%)	<.001
Oral hypoglycemic agents	271 (38.7%)	598 (35.8%)	.191
Statin	469 (66.9%)	1188 (71.1%)	.044
Aspirin	578 (82.5%)	1197 (71.7%)	<.001
Clopidogrel	452 (64.5%)	870 (52.1%)	<.001
Diuretics	161 (23.0%)	290 (17.4%)	.002
Logistic euroSCORE	6.0 ± 6.9	3.2 ± 3.5	<.001
Preoperative laboratory values			
Hematocrit (%)	38.2 ± 4.9	38.6 ± 4.9	.117
Creatinine (mg/dL)	1.0 ± 0.3	1.0 ± 0.5	.719
Total bilirubin (mg/dL)	0.7 ± 0.3	0.7 ± 0.3	.748
Albumin (g/dL)	3.7 ± 0.5	3.8 ± 0.4	<.001
Uric acid (mg/dL)	5.5 ± 1.5	5.6 ± 1.5	.461
Ejection fraction (%)	53.7 ± 13.0	56.7 ± 10.2	<.001
Days from CAG to CABG	8 (5-15)	7 (4-15)	.647
≤ 7 d	341 (48.6%)	857 (51.3%)	.242
Grafts per patients, n	3 (2-3)	3 (2-4)	.036
Anesthetic time (min)	312.0 ± 77.4	306.5 ± 67.0	.152
Crystalloid (mL)*	1093.5 ± 548.4	1622.9 ± 731.0	<.001
Colloid (mL)*	724.0 ± 347.2	1166.6 ± 388.4	<.001
Packed red blood cell*	460 (65.6%)	857 (51.3%)	<.001
Fresh frozen plasma*	91 (13.0%)	76 (4.6%)	<.001
Cell salvage blood*	0 (0-0)	0 (0-240)	<.001
AKI	349 (49.8%)	615 (36.8%)	<.001

Data are expressed as the mean ± standard deviation, median (25th, 75th percentiles), or number (percentage). *ONCAB*, On-pump coronary artery bypass; *OPCAB*, off-pump coronary artery bypass; *eGFR*, estimated glomerular filtration rate; *ACEi*, angiotensin-converting enzyme inhibitor; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *CAG*, coronary angiography; *CABG*, coronary artery bypass grafting; *AKI*, acute kidney injury. *Used during operation.

affected (Table E2). Most (75%) of the patients who were affected by AKI had mild AKI (KDIGO stage 1). Although mortality rates were similar, extubation time and duration of stay in the ICU and the hospital were

FIGURE 2. The incidence of AKI in each operation performed within 7 days after CABG or not. The incidence of AKI was significantly higher in patients who underwent coronary angiography ≤ 7 days before ONCAB than in those of > 7 days (55.7% vs 44.2%; *P* = .003). However, there was no significant difference in development of AKI between in patients who underwent OPCAB within 7 days after coronary angiography and in those > 7 days after coronary angiography (*P* = .543). *AKI*, Acute kidney injury; *CABG*, coronary artery bypass graft surgery; *CAG*, coronary angiography; *ONCAB*, on-pump coronary artery bypass graft surgery; *OPCAB*, off-pump coronary artery bypass graft surgery.

significantly longer in patients with mild AKI than without AKI (Table E3).

In unadjusted univariate analysis, a shorter time interval between coronary angiogram and CABG was significantly associated with an increased risk of postoperative AKI (OR, 0.921; 95% CI, 0.858-0.989; *P* = .023 in log-transformed continuous variables and OR, 1.191;

TABLE 2. Mortality and morbidity in the study cohort with reference to acute kidney injury development

	No AKI (n = 1407)	AKI (n = 964)	P value
Time to extubation (h)	8.1 (6.0-12.3)	10.5 (7.0-17.0)	<.001
ICU stay (h)	47.5 (43.0-50.5)	49.5 (44.5-86.4)	<.001
Hospital stay (d)	8.0 (7.0-9.0)	9.0 (7.0-12.0)	<.001
AKI stage by KDIGO			<.001
KDIGO 0	1407 (100%)		
KDIGO 1		723 (75.0%)	
KDIGO 2		127 (13.2%)	
KDIGO 3		114 (11.8%)	
In-hospital death	3 (0.2%)	23 (2.4%)	<.001
1-y mortality	11 (0.8%)	19 (2.0%)	.011
In-hospital RRT	0 (0%)	62 (6.4%)	<.001
1-y RRT or death	89 (6.3%)	204 (21.2%)	<.001

Data are expressed as the median (25th, 75th percentiles) or number (percentage). *AKI*, Acute kidney injury; *ICU*, intensive care unit; *KDIGO*, Kidney Disease: Improving Global Outcomes Definition and Staging; *RRT*, renal replacement therapy (1-year RRT or death, cases of RRT, or the number of deaths that occurred during the first postoperative year).

TABLE 3. Multivariable logistic analysis for acute kidney injury in study patients who underwent elective coronary artery bypass grafting after coronary angiography

	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
	CABG (n = 2371)		ONCAB (n = 701)		OPCAB (n = 1670)	
Age	1.013 (1.002-1.023)	.016			1.018 (1.005-1.031)	.007
Hypertension	1.335 (1.107-1.609)	.002	1.495 (1.060-2.180)	.022	1.285 (1.023-1.613)	.031
eGFR <60 mL/min/1.73 m ²	1.759 (1.358-2.280)	<.001	1.951 (1.144-3.328)	.014	1.668 (1.230-2.261)	.001
Insulin	1.367 (1.097-1.704)	.005			1.507 (1.190-1.909)	.001
Hematocrit	0.960 (0.939-0.981)	<.001			0.953 (0.928-0.978)	<.001
Albumin	0.374 (0.291-0.479)	<.001	0.271 (0.173-0.426)	<.001	0.443 (0.329-0.596)	<.001
Uric acid	1.149 (1.079-1.222)	<.001	1.173 (1.037-1.327)	.011	1.143 (1.062-1.230)	<.001
Use of CPB	3.099 (1.782-5.392)	<.001				
CAG interval* (CPB use)	0.775 (0.667-0.901)	.001	0.810 (0.688-0.954)	.012		
CAG interval* (CPB nonuse)	0.931 (0.851-1.019)	.121			0.929 (0.849-1.017)	.110
Interaction (CAG interval* use of CPB)		.040				
CPB time			1.007 (1.003-1.011)	<.001		
Transfused pRBC†			1.198 (1.087-1.320)	.001		

CI, Confidence interval; CABG, coronary artery bypass grafting; ONCAB, on-pump coronary artery bypass; OPCAB, off-pump coronary artery bypass; eGFR, estimated glomerular filtration rate; CPB, cardiopulmonary bypass; CAG, coronary angiography; pRBC, packed red blood cells. *Log-transformed. †During operation.

95% CI, 1.010-1.403, $P = .037$ in categorical variables) (Table E1). There was significant interaction between the timing of coronary angiography and the use of CPB for postoperative AKI ($P = .019$). After adjusting by the multivariable analysis, the result was not changed (Table 3). In multivariable logistic analysis, early surgery after coronary angiography was significantly associated with an increased risk of postoperative AKI in patients who underwent ONCAB (OR, 0.810; 95% CI, 0.688-0.954; $P = .012$). However, the interval between coronary angiography and operation was not significantly associated with an increased risk of AKI in patients who underwent OPCAB (OR, 0.929; 95% CI, 0.849-1.017; $P = .110$). Other risk factors for postoperative AKI in ONCAB and OPCAB cases are shown in Table 3. In secondary analyses performed using a 7-day interval cutoff, we found similar results (Table E4).

In regard to propensity score matching analysis, independent predictors of AKI development and their ORs in the adjusted logistic regression model are listed in Table 4. In the adjusted logistic regression propensity score model, coronary angiography within 7 days of ONCAB was a predictor of postoperative AKI (OR, 1.742; 95% CI, 1.144-2.653; $P = .010$). According to the logistic regression propensity score model, the interval between coronary angiography and OPCAB was not associated with an increased risk of postoperative AKI (unadjusted $P = .241$ and adjusted $P = .250$).

DISCUSSION

The results of our present investigation indicate that the risk of AKI after CABG was influenced by the time interval between the coronary angiography and the operation.

TABLE 4. Adjusted odds ratio and 95% confidence intervals using a propensity score for acute kidney injury in study patients after coronary artery bypass grafting

	Adjusted for propensity score†,‡		Adjusted for propensity score†,§		Adjusted for propensity score†,	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
	CABG		ONCAB		OPCAB	
Renal dysfunction	3.143 (2.014-4.905)	<.001	6.033 (2.338-15.572)	<.001	2.309 (1.464-3.642)	<.001
CAG interval ≤ 7 d	1.224 (0.999-1.499)	.051	1.742 (1.144-2.653)	.010	1.147 (0.910-1.450)	.250
Anesthetic time			1.010 (1.004-1.015)	<.001		
Infused crystalloid*	0.999 (0.999-1.000)	<.001			0.999 (0.999-1.000)	<.001
Infused colloid*			0.998 (0.997-0.999)	<.001		
Transfused pRBC*	1.294 (1.177-1.423)	<.001	1.275 (1.065-1.527)	.008	1.154 (1.028-1.296)	.015

CI, Confidence interval; CABG, coronary artery bypass grafting; ONCAB, on-pump coronary artery bypass; OPCAB, off-pump coronary artery bypass; CAG, coronary angiography; pRBC, packed red blood cells. *During operation. †Propensity score developed for the likelihood of receiving CAG interval ≤ 7 days. ‡Hosmer–Lemeshow goodness-of-fit test $P = .467$, C-stat = 0.635. §Hosmer–Lemeshow goodness-of-fit test $P = .096$, C-stat = 0.639. ||Hosmer–Lemeshow goodness-of-fit test $P = .390$, C-stat = 0.643.

However, the type of CABG—whether CPB was used or not—had different effects on the development of postoperative AKI. The occurrence of postoperative AKI in patients who underwent OPCAB was not affected by the time interval between the coronary angiography and the operation. To the best of our knowledge, our current report is the first to show that the effect of coronary angiography timing on AKI after CABG is influenced by the use of CPB.

Consistent with the findings of our present study, a number of previous studies reported that a short interval between coronary angiography and cardiac surgery could increase the risk of postoperative AKI.^{2,8,18-22} Although a short time between coronary angiography and cardiac surgery has been associated with increased risk of postprocedural AKI in some reports, most of these studies involved patients who underwent ONCAB or OPCAB concomitant with valve or aorta surgery using CPB.^{18,20-22} In contrast, we investigated how the relationship between the timing of the coronary angiography and the use of CPB affected renal function in a large group of patients who underwent elective CABG and adjusted the influence of potential confounding factors using multivariable logistic and propensity analyses.

Another important finding of our present study was that there was significant interaction between the timing of coronary angiography and the use of CPB in relation to postoperative AKI. The timing of coronary angiography did not affect the development of AKI in patients who underwent OPCAB. Our multivariable logistic and adjusted propensity score analyses showed that the interval between coronary angiography and subsequent OPCAB was not an independent predictor of the development of postoperative AKI, in contrast with ONCAB. Our previous study also found that the risk of postoperative AKI was not related to the time between coronary angiography and OPCAB.⁹ By avoiding the use of CPB, OPCAB is expected to have a more beneficial effect on renal function than ONCAB in terms of AKI risk reduction.⁹

In contrast to our current findings, some previous studies have reported that a short interval between diagnostic coronary angiography and OPCAB is associated with an increased risk of postoperative AKI.²³⁻²⁵ One of these studies included a relatively small number of patients,²⁴ and the report of Ji and colleagues²⁵ excluded a time interval from coronary angiography until subsequent surgery of less than 24 hours. Zhang and colleagues²⁶ also reported that one of the independent risk factors for postoperative AKI was OPCAB that was performed 24 hours or less after coronary angiography. However, they included patients who only underwent OPCAB after coronary angiography during the same hospitalization and

had an interval between OPCAB and coronary angiography of 30 days or less, and they created only 4 subgroups according to the interval between coronary angiography and OPCAB (≤ 24 , 24-48, 48-72, and >72 hours).²⁶ All of these differences in the study design might have influenced their results.

Our present study revealed that a shorter interval between coronary angiography and CABG influenced the occurrence of AKI in patients undergoing ONCAB. It is unclear why postoperative AKI is associated with a short interval between coronary angiography and ONCAB. However, some reports have hypothesized that AKI is related to a “double hit” on renal function.^{2,18,22} Contrast agents used for coronary angiography before cardiac surgery could induce renal damage, such as contraction of renal blood vessels and ischemia-mediated oxidative stress, and cytotoxic effects are independently associated with increased postoperative AKI.^{3,19} Several studies have reported that postoperative AKI is a consequence of interplay among different pathophysiologic mechanisms, with patient-related factors and CPB being major causes.^{4,27} These factors include concomitant valve surgery with CABG; the bypass procedure itself, such as the crossclamp time, duration of CPB, severe hemodilution (as reflected by nadir hematocrit), and low oxygen delivery during CPB; and low cardiac output syndrome in the postoperative course.^{3,7,28} In agreement with previous results showing that the use of CPB worsened renal function,^{3,4,6,7,27-29} our present findings have revealed a higher incidence of postoperative AKI in patients who underwent ONCAB than in those who underwent OPCAB.

Indications for OPCAB surgery vary widely. In general, patients who were elderly with 2 or more comorbidities, such as calcified aorta, recent stroke, severe carotid disease, and renal dysfunction, were preferentially approached by an off-pump technique, given that their anatomy allowed this approach to be effective and safe.^{30,31} In our study, the patients undergoing OPCAB were more current smokers and had a higher incidence of hypertension and peripheral vascular disease. Otherwise, the patients undergoing OPCAB had a lower logistic European System for Cardiac Operative Risk Evaluation than those undergoing ONCAB. The low-risk patients might be selected for OPCAB in some centers. It is clear that the greatest benefit of OPCAB surgery may be in patients with the highest risk and in elderly patients. In contrast to prospective randomized trials of nonselected patients, this study intentionally selected patients on the basis of anatomy and patient comorbid conditions for the off-pump group because we aimed at maximal incremental risk reduction for all patients and the greatest therapeutic margin.³¹ However, it would be another unexpected bias. Thus, we cannot completely

exclude the possibility that this unknown bias may have influenced our results.

The incidence of postoperative AKI in our patient cohort is higher than reported by previous studies on the incidence of AKI after OPCAB or on-pump cardiac surgery according to the Risk, Injury, Failure, Loss, and End-stage kidney disease criteria or AKI Network criteria.¹⁻³ A wide disparity between our cohort and other studies may be due to the use of the KDIGO definition of AKI and differences of management strategies in the pericatheterization period or perioperative care protocol, such as the use of inotropes, vasoactive agents, and fluid administration. In our institution, use of 6% hydroxyethyl starch 130/0.4 was generally available. Our strategy of fluid management restricted crystalloid use, and the crystalloid/colloid volume ratio was lower than reported in other studies,²⁴ especially in the AKI group. Several recent studies demonstrated that intraoperative hydroxyethyl starch administration was associated with the occurrence of postoperative AKI.^{32,33} The use of hydroxyethyl starch would have influenced the increasing incidence of postoperative AKI. We are continually working on reducing the occurrence of postoperative AKI, and further studies are needed.

On the basis of its results, our present study may have clinical significance. Our study revealed that a shorter interval between coronary angiography and CABG had a serious effect on the occurrence of AKI in patients undergoing ONCAB only. The timing of coronary angiography did not affect the development of postoperative AKI in patients who underwent OPCAB. Our current evidence should be considered when seeking greater convenience for patients, reducing the economic burden, and reducing the hospital stay.^{34,35} However, this hypothesis requires a further large prospective, randomized, controlled study to be confirmed.

Study Limitations

First, this was a retrospective single-center observational study with inherent limitations and possible selection biases. Because of the observational nature of this study, our findings should be regarded as hypothesis generating. Thus, we attempted to adjust for variables collected in our database by assessing the impact of the interval between coronary angiography and CABG on postoperative AKI while using stratification on the propensity score. Second, we did not verify if the contrast agents induced renal damage before surgery, although preexisting kidney injury was accepted as an important risk factor for AKI. However, in our previous study, we found that ionic contrast agents or a high dose of intravenous contrast agent was not a predictor of postoperative AKI.⁹ Finally, we were unable to identify the pathologic mechanisms accounting for the different effects of CPB and the interval between coronary

angiography and CABG on postoperative AKI. Thus, further analysis is needed to elucidate this unknown mechanism.

CONCLUSIONS

A shorter interval between coronary angiography and CABG influenced the occurrence of AKI in patients undergoing ONCAB. However, the interval is not an independent risk factor for the development of postoperative AKI in patients who undergo OPCAB.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: acute kidney injury, cardiopulmonary bypass, coronary angiography, coronary artery bypass grafting, off-pump coronary artery bypass grafting

SUPPLEMENTAL METHODS

To control the selection bias related to covariates, a propensity score for the likelihood of receiving coronary angiography 7 days or less before CABG was developed, and a hierarchic logistic regression model to calculate the propensity score was applied. In this case, the propensity score represented the estimated probability of receiving coronary angiography 7 days or less before CABG (vs >7 days) as a function of the patient's baseline and comorbidities, as well as preoperative cardiac medications, age, gender, body mass index, diabetes, hypertension, smoking, congestive heart failure, cerebrovascular disease, peripheral vascular disease, preoperative liver disease, preoperative angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, insulin, oral hypoglycemic agents, statins, aspirin, clopidogrel, diuretics, preoperative hematocrit, creatinine, total bilirubin, albumin, uric acid, and preoperative left ventricular ejection fraction (c statistic 0.635). The propensity score was based on the following variables: preoperative renal dysfunction, coronary angiography within 7 days before surgery, use of

CPB, anesthetic time, infused fluid in the operating room, and transfused blood components in the operating room. This process generated a propensity score between 0 and 1, and patients who received coronary angiography 7 days or less before the CABG were matched 1:1 to patients who received coronary angiography more than 7 days before the CABG. After the propensity score match was performed, we assessed the differences between the 2 groups. Absolute standardized differences were estimated to evaluate the prematch imbalance and postmatch balance. An absolute standardized difference of 0% indicated no residual bias, and differences less than 15% were considered inconsequential.

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TABLE E1. Univariate logistic analyses

	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
	CABG (n = 2371)		ONCAB (n = 701)		OPCAB (n = 1670)	
Age	1.029 (1.019-1.038)	<.001	1.014 (0.997-1.031)	.097	1.037 (1.025-1.049)	<.001
Gender	1.057 (0.873-1.280)	.568	0.914 (0.654-1.227)	.597	1.100 (0.870-1.391)	.427
Body mass index	0.995 (0.967-1.023)	.709	0.991 (0.943-1.043)	.736	0.996 (0.962-1.031)	.809
Hypertension	1.534 (1.291-1.823)	<.001	1.605 (1.184-2.174)	.002	1.573 (1.272-1.947)	<.001
Diabetes mellitus	1.448 (1.228-1.707)	<.001	1.166 (0.866-1.570)	.311	1.614 (1.321-1.972)	<.001
Smoking						
Nonsmoker	1		1		1	
Ex-smoker	1.074 (0.886-1.302)	.468	1.215 (0.870-1.698)	.253	0.997 (0.786-1.265)	.981
Smoker	0.948 (0.771-1.165)	.609	1.053 (0.703-1.578)	.802	0.965 (0.757-1.231)	.775
CHF	2.055 (1.293-3.265)	.002	2.814 (1.289-6.145)	.009	1.508 (0.821-2.769)	.185
CVD	1.542 (1.278-1.861)	<.001	1.451 (1.059-1.988)	.021	1.442 (1.135-1.833)	.003
PVD	1.257 (0.874-1.807)	.217	1.643 (0.735-3.673)	.226	1.251 (0.826-1.893)	.29
eGFR <60 mL/min/1.73 m ²	3.156 (2.526-3.944)	<.001	3.460 (2.250-5.321)	<.001	3.082 (2.367-4.014)	<.001
Liver disease	1.383 (0.841-2.275)	.201	1.268 (0.495-3.253)	.621	1.457 (0.808-2.625)	.211
ACEi	1.415 (1.199-1.670)	<.001	1.294 (0.961-1.744)	.09	1.449 (1.185-1.773)	<.001
Beta-blocker	1.028 (0.868-1.217)	.750	0.897 (0.665-1.211)	.479	1.156 (0.938-1.424)	.174
CCB	0.901 (0.754-1.076)	.249	0.689 (0.506-0.939)	.018	1.107 (0.885-1.384)	.373
Insulin	1.431 (1.176-1.741)	<.001	1.124 (0.665-1.902)	.662	1.787 (1.435-2.224)	<.001
OHA	1.259 (1.062-1.491)	.008	1.158 (0.854-1.569)	.346	1.288 (1.048-1.583)	.16
Statin	0.796 (0.666-0.950)	.012	0.619 (0.451-0.850)	.003	0.922 (0.741-1.147)	.467
Aspirin	1.112 (0.919-1.344)	.275	1.182 (0.800-1.746)	.4	1.002 (0.804-1.250)	.983
Clopidogrel	0.982 (0.833-1.159)	.833	1.050 (0.771-1.431)	.756	0.880 (0.721-1.074)	.208
Diuretics	1.206 (0.980-1.483)	.077	1.096 (0.771-1.559)	.61	1.198 (0.924-1.552)	.172
Logistic euroSCORE	1.091 (1.068-1.115)	<.001	1.058 (1.030-1.087)	<.001	1.110 (1.073-1.148)	<.001
Hematocrit	0.905 (0.889-0.921)	<.001	0.918 (0.889-0.948)	<.001	0.899 (0.880-0.919)	<.001
Creatinine	2.510 (1.975-3.191)	<.001	2.798 (1.720-4.552)	<.001	2.448 (1.860-3.222)	<.001
Total bilirubin	0.650 (0.480-0.881)	.005	1.021 (0.584-1.785)	.943	0.524 (0.359-0.763)	.001
Albumin	0.252 (0.203-0.313)	<.001	0.206 (0.138-0.307)	<.001	0.290 (0.224-0.377)	<.001
Uric acid	1.156 (1.095-1.220)	<.001	1.211 (1.096-1.338)	<.001	1.140 (1.068-1.217)	<.001
Ejection fraction	0.984 (0.977-0.992)	<.001	0.977 (0.996-0.989)	<.001	0.993 (0.984-1.003)	.168
CAG interval (log transformed)	0.921 (0.858-0.989)	.023	0.791 (0.688-0.910)	.001	0.961 (0.884-1.046)	.358
CPB use	1.701 (1.423-2.033)	<.001				
Interaction (CAG interval* CPB use)		.019				
Anesthetic time	1.001 (1.000-1.002)	.152	1.004 (1.002-1.006)	<.001	0.999 (0.997-1.000)	.163
CPB time			1.009 (1.005-1.013)	<.001		
Anastomosed vessels, n	0.952 (0.874-1.036)	.251	1.140 (0.972-1.338)	.108	0.897 (0.810-0.993)	.036
RBC*	1.877 (1.586-2.221)	<.001	2.342 (1.699-3.2229)	<.001	1.602 (1.310-1.958)	<.001
FFP*	1.733 (1.264-2.376)	.001	2.273 (1.428-3.620)	.001	1.001 (0.621-1.612)	.998
Cell salvage blood*	0.731 (0.612-0.873)	.001	0.787 (0.482-1.286)	.339	0.854 (0.697-1.046)	.127
Crystalloid*	1.000 (0.999-1.000)	<.001	1.000 (1.000-1.000)	.773	1.000 (0.999-1.000)	<.001
Colloid*	1.000 (0.999-1.000)	<.001	1.000 (0.999-1.000)	.488	1.000 (0.999-1.000)	.013

CI, Confidence interval; CABG, coronary artery bypass grafting; ONCAB, on-pump coronary artery bypass; OPCAB, off-pump coronary artery bypass; CHF, congestive heart failure; CVD, cerebrovascular disease; PVD, peripheral vascular disease; eGFR, estimated glomerular filtration rate; ACEi, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; OHA, oral hypoglycemic agent; euroSCORE, European System for Cardiac Operative Risk Evaluation; CAG, coronary angiography; CPB, cardiopulmonary bypass; pRBC, packed red blood cell; FFP, fresh-frozen plasma. *Admitted during operation.

TABLE E2. Morbidity in the study cohort with reference to acute kidney injury development

	No AKI (n = 1407)	AKI (n = 964)	P value
Reoperation	19 (1.4%)	29 (3.0%)	.007
CV-SOFA score	2.2 ± 1.2	2.5 ± 1.2	<.001
Weight change (kg)	1.0 ± 1.3	1.3 ± 1.4	<.001

Data are expressed as the mean ± standard deviation (median) or number (percentage). *AKI*, Acute kidney injury; *CV-SOFA*, Cardiovascular Sequential Organ Failure Assessment (score during the first 24 hours of ICU stay^{E1}).

TABLE E3. Mortality and morbidity in the study cohort with reference to mild acute kidney injury (Kidney Disease: Improving Global Outcomes Definition and Staging 1) development

	No AKI (n = 1407)	KDIGO 1 (n = 723)	P value
Time to extubation (h)	8.1 (6.0-12.3)	10.0 (7.0-16.0)	<.001
ICU stay (h)	47.5 (43.0-50.5)	49.0 (43.5-72.0)	<.001
Hospital stay (d)	8.0 (7.0-9.0)	8.0 (7.0-10.0)	<.001
In-hospital death	3 (0.2%)	5 (0.7%)	.130
1-y mortality	11 (0.8%)	12 (1.7%)	.076

Data are expressed as the median (25th, 75th percentiles) or number (percentage). *AKI*, Acute kidney injury; *KDIGO*, Kidney Disease: Improving Global Outcomes Definition and Staging; *ICU*, intensive care unit.

TABLE E4. Relationship between coronary artery bypass grafting performed 7 days or less after coronary angiography and acute kidney injury

	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
	CABG (n = 2371)		ONCAB (n = 701)		OPCAB (n = 1670)	
Age	1.013 (1.002-1.023)	.015			1.018 (1.005-1.031)	.007
Hypertension	1.341 (1.112-1.616)	.002	1.543 (1.096-2.172)	.013	1.285 (1.023-1.613)	.031
eGFR <60 mL/min/1.73 m ²	1.748 (1.349-2.266)	<.001	1.972 (1.164-3.341)	.012	1.668 (1.230-2.261)	.001
Insulin	1.364 (1.094-1.699)	.006			1.507 (1.190-1.909)	.001
Hematocrit	0.961 (0.940-0.981)	<.001			0.953 (0.928-0.978)	<.001
Albumin	0.372 (0.290-0.477)	<.001	0.246 (0.158-0.383)	<.001	0.443 (0.329-0.596)	<.001
Uric acid	1.149 (1.080-1.222)	<.001	1.173 (1.037-1.327)	.011	1.142 (1.061-1.230)	<.001
Use of CPB	1.517 (1.153-1.995)	.003				
CAG interval* (CPB use)	1.609 (1.170-2.211)	.003	1.503 (1.073-2.106)	.018		
CAG interval* (CPB nonuse)	1.154 (0.932-1.428)	.188			1.161 (0.938-1.437)	.171
Interaction (CAG ≤7 d* use of CPB)		.029				
CPB time			1.008 (1.004-1.012)	<.001		
Transfused pRBC†			1.664 (1.158-2.392)	.006		

CI, Confidence interval; CABG, coronary artery bypass grafting; ONCAB, on-pump coronary artery bypass; OPCAB, off-pump coronary artery bypass; eGFR, estimated glomerular filtration rate; CPB, cardiopulmonary bypass; CAG, coronary angiography; pRBC, packed red blood cell. *Log-transformed. †During operation.