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Coronary artery bypass surgery and acute kidney injury—impact of the off-pump technique

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Abstract

Background. Acute kidney injury (AKI) is a serious and frequent complication after coronary artery bypass grafting (CABG). Cardiopulmonary bypass (CPB) was identified as a major AKI risk factor after CABG. Our aim was to assess the impact of the off-pump coronary artery bypass (OPCAB) compared to the on-pump coronary artery bypass (ONCAB) technique on the rate and severity of AKI, while taking other risk factors for AKI into account.

Methods. An observational study of 201 consecutive adult patients was conducted; 100 were operated by the OPCAB and 101 by the ONCAB technique. All patients in each group were operated by a single, experienced surgeon. Fifteen pre-, intra- and postoperative variables that were repeatedly identified in previous studies as independent AKI risk factors were included in this analysis. AKI was defined as an increase of serum creatinine $\geq$50% or $\geq$0.3 mg/dL within 48 h and AKI severity was classified, according to current AKIN definitions.

Results. Significantly fewer OPCAB patients developed AKI compared to ONCAB (14.0 versus 27.7%; $P = 0.03$). OPCAB was associated with milder stages of AKI, whereas ONCAB patients had more severe AKI. Congestive heart failure and chronic kidney disease were independent risk factors for AKI. The OPCAB technique for CABG was identified as the only independent factor associated with lower incidence of AKI.

Conclusions. Using current AKI definitions and classifications, the OPCAB technique for CABG, which avoids CPB; was associated with a significantly lower rate and less severe AKI compared to ONCAB. The OPCAB technique was identified as the only modifiable and potentially protective factor against postoperative AKI.

Keywords: acute kidney injury; acute renal failure; cardiopulmonary bypass; coronary artery bypass grafting; off-pump coronary artery bypass

Introduction

Postoperative acute kidney injury (AKI), previously termed acute renal failure, is one of the most serious and frequent complications after coronary artery bypass grafting (CABG) [1–6]. Recent studies demonstrated that even small increases of serum creatinine following CABG are independently associated with increased mortality [2–4,7,8]. As no causal therapy for AKI is available at present, every effort has to be made to prevent AKI. Off-pump coronary artery bypass (OPCAB) grafting, which eliminates the need for cardiopulmonary bypass (CPB), has been reported to be associated with a lower incidence of AKI [9–14]. This issue is still controversial, as other studies did not confirm this finding [15–18]. All studies are limited as they lack a uniform definition of AKI. The definitions of AKI varied widely and were predominately based on large increments of serum creatinine, thus ignoring milder stages of AKI. Furthermore, previous studies analysing the impact of OPCAB on AKI considered only a limited number of variables and especially major postoperative risk factors for AKI were not regarded [3–5,9–13,16,17]. However, this issue is critical, as the CABG technique may be one of the few modifiable risk factors of AKI and the use of OPCAB may in turn aid in reducing postoperative AKI associated with CABG. Recently, a definition and classification of AKI was established by a consensus of all key critical care and nephrology societies worldwide [19]. This first globally developed AKI definition and classification incorporates the important finding that small increases of serum creatinine in AKI already negatively impact outcome.

The purpose of the present study was to assess the impact of the OPCAB technique on the incidence and severity of AKI, firstly applying the current AKI definition and

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classification and secondly taking into account in our analysis pre-, intra- and postoperative variables that were repeatedly identified as major independent risk factors for AKI.

Methods

Patients

In this cohort study, we included 201 of 210 consecutive adult Caucasian patients who underwent isolated CABG of multiple coronary arteries between February and November 2005 by two of eight cardiosurgical consultants in our institution, which is a tertiary referral centre. One hundred patients were operated by the OPCAB and 101 patients by the ONCAB technique. All 201 patients would have been eligible for CABG by either the OPCAB or ONCAB technique. One surgeon performed all OPCAB cases while the other surgeon performed all ONCAB cases. Both surgeons were equally experienced in coronary bypass surgery by the ONCAB technique with only one being proficient in OPCAB surgery. Both surgeons performed all their CABG during the study period exclusively by either the OPCAB or ONCAB technique. The daily operation schedule, which established the order of all surgical procedures and scheduled the surgeons to these procedures, assigned patients to one of the two surgeons and by this means to either the OPCAB or ONCAB technique. Neither of the two surgeons was involved in the planning or fixing of the daily operation schedule. Patient characteristics did not deliberately influence the assignment of patients to the respective surgeon or the CABG technique. Thus, the assignment of study patients to either OPCAB or ONCAB was unregulated and by chance. We excluded patients with end-stage renal disease receiving renal replacement therapy (RRT) ($n = 5$) and those who were started by OPCAB but were then converted to the ONCAB technique ($n = 4$).

Anaesthesia, surgery and intensive care treatment

In all patients, anaesthesia was induced with intravenous sufentanil (1 μg/kg), etomidate (50 μg/kg) and pancuronium (100 μg/kg). Anaesthesia was maintained with isoflurane (0.6–1.0%), discontinuously given sufentanil (0.3–0.5 μg/kg) and pancuronium (30 μg/kg). Intraoperatively, all patients received aprotinin (Bayer, Leverkusen, Germany) at a dose of 2.5 million KIU, and intravenous heparin targeted to achieve an activated clotting time of 400 s. At wound closure in OPCAB and after completion of extracorporal circulation in ONCAB, heparin was completely neutralized using protamine (Valeant, Eschborn, Germany) at a dose of 1 mg/100 IU of heparin. In OPCAB patients, distal anastomoses were performed using standard purchasable stabilizers (Ethicon-Cardiovations®, Johnson&Johnson, MO, USA). Nonpulsatile CPB with roller pumps was performed at mild hypothermia (32°C). The CPB circuit was primed with a 1600 mL solution containing lactate Ringer's solution, hydroxyethylstarch, mannitol, sodium bicarbonate and packed red blood cells, if required, to achieve a haemoglobin of at least 8 g/dL during CPB. A minimal flow rate of 2.4 L/m^2/min was maintained throughout CPB and the flow rate was adjusted based on haemodynamic parameters and central venous oxygen saturation. During CPB the mean arterial pressure was maintained between 60 and 80 mmHg. A 1000-mL cold cardioplegic solution (Custodiol®, Köhler Chemie, Alsbach-Hähnlein, Germany) was infused through the aortic root to achieve cardioplegia during aortic cross clamping in ONCAB patients. OPCAB surgery was performed at a mean arterial pressure between 70 and 100 mmHg. Deviations beyond this range were corrected with phenylephrine or nitroglyceride.

Postoperatively, all patients were admitted to the intensive care unit (ICU). All were later transferred to the intermediate care unit (IMC) and received standardized treatment, including serum creatinine measurements standardized at least twice daily on ICU and IMC from blood drawn between 7:00 and 8:00 a.m. and p.m., and once between 7:00 and 8:00 a.m., thereafter on regular wards until discharge. Anaesthesia was maintained in all patients with propofol (100 mg/h) for no longer than 24 h postoperatively. When longer anaesthesia was required, propofol was switched to sufentanyl (0.02 mg/h) and midazolam (5 mg/h). Fluid substitution was adjusted to a central venous pressure of 12 mmHg. The target level for the mean arterial pressure was ≥70 mmHg. Crystalloid fluids and inotrops were administered in the case of lower mean arterial pressure according to the specific clinical situation. In the absence of haemorrhage, intravenous heparin was applied for 2 h and 500 mg of intravenous acetylsalicylic acid 4 h after arrival on the ICU. Clinical data were extracted from the patients' records; laboratory data were retrieved from the hospital electronic laboratory report system. These data were complete for all patients until discharge from hospital or death with the exception of data on interleukin-6 that were available in 34 patients operated by the OPCAB technique and 27 by the ONCAB technique.

AKI definition and classification, and indication for renal replacement therapy

Postoperative AKI and its stages were diagnosed according to the GFR criteria of the current Acute Kidney Injury Network definitions. Information in regard to urine output exactly as required by these definitions was not documented [19]. AKI was diagnosed by an increase of serum creatinine ≥50% or ≥0.3 mg/dL, both from stabile preoperative baseline values and within 48 h. Severity of AKI was classified as stage 1 (serum creatinine increase by 50–100% or ≥0.3 mg/dL), stage 2 (serum creatinine increase by 101–200%) and stage 3 (serum creatinine increase by >200% of the need for RRT). Alternatively, stage 3 was defined by an increase of serum creatinine ≥0.5 mg/dL from baseline serum creatinine values ≥4.0 mg/dL [19]. We performed an analysis of the maximum AKI severity stage reached. RRT in the course of AKI was always initiated when needed, independent of the investigators by a team of eight nephrologists of our institution for the following indications: pulmonary oedema, oliguria defined as urine output <0.5 mL/kg body weight per hour for >6 h,

Table 1. Definitions of potential risk factors for acute kidney injury

Risk factor	Definition
Congestive heart failure	Ejection fraction <35% and/or NYHA stage III or IV
Chronic kidney disease	eGFR <60 mL/min/1.73 m^2 [11]
Diabetes	Fasting or casual blood glucose ≥126 or ≥200 mg/dL with polyuria or polydipsia, requiring antidiabetic medication
Peripheral vascular disease	Claudication, absent pedal pulses, previous lower extremity bypass and lower limb amputation for ischaemia
Chronic obstructive pulmonary disease	Daily cough with sputum for 3 months a year for at least 2 years and/or dyspnoea with forced expiratory volume in 1 s <75% of the inspiratory vital capacity, requiring bronchodilatory therapy
Emergency surgery	CABG required within hours to prevent morbidity or death based on medical factors relating to the patient's cardiac disease
Perioperative acute myocardial infarction	Increase of serum troponin I >9.0 ng/mL in the first 12 h postoperatively and >10.5 ng/mL thereafter [20]
Cardiogenic shock	Combination of systolic blood pressure <90 mm Hg, cardiac index <2.2 mm Hg and pulmonary capillary wedge pressure >18 mm Hg or the use of an intra-aortic balloon pump for >24 h postoperatively
Haemorrhagic shock	Systolic blood pressure <90 mm Hg with either re-exploration of the surgical situs for secondary haemorrhage or haemorrhagic drainage with a volume >1500 mL/day
Severe sepsis/septic shock	Combination of temperature >38°C, pulse rate >90/min and leukocytosis >12 000/μL, with all of the following criteria: (i) systolic blood pressure <90 mm Hg, (ii) dopamine >5 μg/kg/min, epinephrine or norepinephrine at any dose and (iii) lactate >2 mmol/L [21,22]
Rhabdomyolysis	Serum myoglobin >20 000 μg/L
Nephrotoxic medication	Administration of aminoglycosides (i.v.), amphotericin B (i.v.), vancomycin (i.v.) and non-steroidal anti-inflammatory drugs

eGFR, estimate glomerular filtration rate; i.v., intravenous.

metabolic acidosis or hyperkalaemia not responding to conventional treatment and uraemia defined as urea nitrogen of >100 mg/dL. RRT was available 24 h a day and no patient requiring RRT was denied RRT for futility.

Risk factors of AKI

After a systematic and comprehensive search in MEDLINE, we included all biologically plausible variables that were repeatedly identified in previous studies as major independent risk factors for AKI after CABG [1,3–6,9,13,15–17]. Definitions of variables are presented in Table 1. Definitions for intraoperative acute myocardial infarction, severe sepsis and septic shock are based on previous publications [20–22]. Serum creatinine was measured with an enzymatic colorimetric assay (Crea Plus, Roche Diagnostics, Mannheim, Germany), which is traceable to an isotope dilution mass spectrometry assay [23]. Therefore, the glomerular filtration rate could be estimated according to the simplified, recalculated equation derived from the Modification of Diet in Renal Disease study that is eGFR [mL/min/1.73 m^2] = 175 × (serum creatinine [mg/dL])$^{-1.154}$ × (age [years])$^{-0.203}$ × (0.742 if female) × (1.212 if African American) [23]. Hospital mortality after CABG was predicted by the EuroSCORE as previously published [24]. The maximum C-reactive protein value within the first 3 days and, when available, the interleukin-6 value within the first 24 h postoperatively were analysed to estimate postoperative systemic inflammatory response.

Statistics

Data are reported as mean ± SD unless otherwise indicated. After testing for normal distribution, continuous data were compared by Student's *t*-test, the Mann–Whitney rank-sum test or the one-way ANOVA on ranks with Dunn's multiple comparison procedure, and categorical data were compared by the Chi square, Fisher's exact test or the Cochran Armitage test of trend. Potential risk factors associated with AKI after CABG were coded as present or absent and assessed by bivariate analysis. Variables with a $P < 0.05$ in bivariate analysis were entered in the multivariate, proportional hazards regression analysis with censoring at the day of discharge from ICU or IMC. Proportional hazards regression analysis was applied to simultaneously adjust for multiple potential risk factors of AKI that were present for differing time periods during admission to ICU and IMC. A two-sided P value <0.05 was considered to be statistically significant. The risk ratio and 95% confidence intervals (95% CI) were calculated based on the model parameter coefficients. Model adequacy was assessed using the goodness-of-fit test by the −2 log likelihood ration. Standardized differences were applied to identify potential imbalances in confounders, and a value >0.10 was considered to indicate imbalances. The local institutional review board approved this study and waved the need for informed consent. The study is in accordance with the declaration of Helsinki.

Results

Pre- and intraoperative characteristics of the 100 patients operated by the OPCAB and the 101 patients operated by the ONCAB technique are shown in Table 2. There were no substantial differences with regard to gender, age, prevalence of diabetes, congestive heart failure and chronic kidney disease, body mass index and preoperative renal function as measured by serum creatinine and estimated glomerular filtration rate. The severity of coronary heart disease did not differ between both cohorts as indicated by similar rates of left main, two- and three-vessel diseases (Table 2). In addition, the predicted postoperative hospital mortality according to the EUROscore was almost identical. Furthermore, small values for standardized differences for most variables emphasize a good balance between both cohorts.

Table 2. Pre- and intraoperative patient data

	OPCAB	ONCAB	*P*	Standardized difference
Patients (*n*)	100	101	–	–
Female, *n* (%)	20 (20.0)	14 (13.9)	0.33	–
Age (years)	66.5 ± 10.7	66.6 ± 8.9	0.71	0.01
Coronary arteries with stenosis >70%				
Two-vessel disease, *n* (%)	71 (71.0)	74 (73.3)		–
Three-vessel disease, *n* (%)	29 (29.0)	27 (26.7)	0.84	–
Left main coronary artery with stenosis >50%, *n* (%)	22 (22.0)	21 (20.7)	0.97	
Diabetes mellitus, *n* (%)	34 (34.0)	29 (28.7)	0.51	–
Body mass index (kg/m^2)	27.5 ± 4.5	27.5 ± 3.7	0.49	0.00
Serum creatinine preoperatively (mg/dL)	1.16 ± 0.32	1.17 ± 0.24	0.23	0.04
Estimated glomerular filtration rate preoperatively (mL/h/1.73 m^2)	67.5 ± 16.8	66.6 ± 13.7	0.66	0.06
Chronic kidney disease, *n* (%)	29 (29.0)	25 (24.8)	0.60	–
Congestive heart failure, *n* (%)	13 (13.0)	14 (13.9)	0.96	–
EuroSCORE add	5.0 ± 2.6	5.0 ± 3.1	0.42	0.00
EuroSCORE log	5.5 ± 5.0	5.8 ± 6.7	0.35	0.05
Aortic cross clamp time (min)	n.a.	68 ± 30	–	–
Operating time (min)	247 ± 59	222 ± 54	0.01	0.44
Distal anastomoses (*n*)	2.8 ± 0.9	3.7 ± 1.1	<0.001	0.90
Proximal anastomoses (*n*)	1.7 ± 0.8	1.4 ± 0.8	0.03	0.38

Values are presented as mean ± SD.
OPCAB, off-pump coronary artery bypass; ONCAB, on-pump coronary artery bypass; n.a., not applicable.

Operating times were significantly different as a result of the different surgical techniques.

AKI developed in the early postoperative course. Significantly fewer OPCAB patients developed AKI, and OPCAB patients demonstrated a lower maximum serum creatinine postoperatively (Table 3). Whereas patients operated by the OPCAB technique presented predominately with the mildest stage AKI, the majority of those operated by ONCAB had severe forms of AKI. There was also a trend towards less requirement for RRT in OPCAB compared to ONCAB patients. Continuous RRT was the predominant modality in OPCAB (75%) and ONCAB patients (83%) ($P = 1.00$). RRT was initiated early postoperatively in both OPCAB and ONCAB patients (2.5 ± 1.8 versus 2.0 ± 1.1 days; $P = 0.95$). Indications for RRT were the following in OPCAB and ONCAB patients, respectively: pulmonary oedema ($n = 1$ versus 2), oliguria ($n = 2$ versus 7), hyperkalaemia ($n = 1$ each) and uraemia ($n = 1$ each). OPCAB patients demonstrated a substantially lower postoperative systemic inflammatory response indicated by lower C-reactive protein and interleukin-6 levels (Table 3). Combined length of stay in the ICU and IMC, renal function at hospital discharge as indicated by serum creatinine and mortality rate did not differ between patients operated by the OPCAB and ONCAB techniques (Table 3).

Patients with AKI demonstrated a markedly enhanced postoperative systemic inflammatory response indicated by higher C-reactive protein and interleukin-6 levels (Table 4). When comparing the four subgroups of OPCAB patients with and without AKI and ONCAB patients with and without AKI, both OPCAB and ONCAB patients with AKI showed higher C-reactive protein (25.9 ± 6.2 versus 17.7 ± 4.8 mg/dL and 30.1 ± 7.9 versus 22.6 ± 6.8 mg/dL; both $P < 0.05$) and interleukin-6 levels (443 ± 221 versus 304 ± 161 pg/mL and 689 ± 412 versus 540 ± 272 pg/mL; both n.s.).

In bivariate analysis, patients with AKI were older, had a higher rate of congestive heart failure and chronic kidney disease, and a higher incidence of postoperative cardiogenic and haemorrhagic shock compared to patients without AKI (Table 4). AKI patients were more often operated by the ONCAB than by the OPCAB technique, stayed in ICU and IMC longer and their renal function at hospital discharge was worse. Two patients operated by the OPCAB technique died having developed AKI from pulmonary failure and haemorrhagic shock, while one patient operated by the ONCAB technique died without AKI from multiorgan failure. A worst-case analysis with the hypothesis of the latter patient having developed AKI would support the findings presented. As demonstrated in Table 5, multiple proportional hazards regression identified preoperative congestive heart failure (HR 3.59, 95% CI 1.86–6.92; $P < 0.001$) and chronic kidney disease (HR 2.14, 95% CI 1.15–4.00; $P = 0.02$) as independent risk factors and OPCAB (HR 0.47, 95% CI 0.24–0.92; $P = 0.02$) as an independent protective factor for AKI. The goodness-of-fit test indicated a good model adequacy with $\chi^2 = 27.0$ and $P < 0.001$. Analysing the subgroups of patients with chronic kidney disease and congestive heart failure, OPCAB was also associated with lower incidences of developing AKI compared to the ONCAB technique. Risk ratios were 0.36 (95% CI 0.15–0.88; $P = 0.03$) for AKI in chronic kidney disease patients with OPCAB and 0.39 (95% CI 0.17–0.93; $P = 0.04$) for AKI in congestive heart failure patients with OPCAB. Of the four patients who were started by the OPCAB but were then converted to the ONCAB technique, one developed AKI stage 3, requiring RRT.

Discussion

Our data suggest that the OPCAB technique is an independent, protective factor for AKI in patients undergoing CABG. Considering 15 major pre-, intra- and postoperative risk factors that were repeatedly identified in previous

Table 3. Postoperative renal and general outcome data

	OPCAB	ONCAB	*P*
Acute kidney injury, *n* (%)	14 (14.0)	28 (27.7)	0.03
• Stage 1, *n* (%)	9 (9.0)	9 (8.9)	0.04
• Stage 2, *n* (%)	1 (1.0)	6 (5.9)	
• Stage 3, *n* (%)	4 (4.0)	13 (12.9)	
Maximum serum creatinine postoperatively (mg/dL)	1.42 ± 0.73	1.49 ± 0.60	0.03
Serum creatinine at hospital discharge (mg/dL)	1.22 ± 0.44	1.28 ± 0.42	0.24
Renal replacement therapy, *n* (%)	4 (4.0)	12 (11.9)	0.07
C-reactive protein (mg/dL)	19.1 ± 6.1	24.5 ± 7.5	<0.001
Interleukin-6 (pg/dL)	352 ± 213 ($n = 34$)	601 ± 358 ($n = 27$)	0.008
Length of stay on intensive and intermediate care unit (days)	3.1 ± 3.8	3.4 ± 3.0	0.17
Mortality, *n* (%)	2 (2.0)	1 (1.0)	0.99

OPCAB, off-pump coronary artery bypass; ONCAB, on-pump coronary artery bypass.

Table 4. Characteristics of CABG patients with and without acute kidney injury (AKI)

	AKI	No AKI	*P*
N	42	159	
Female gender, *n* (%)	7 (16.7)	27 (17.0)	0.86
Age (years)	69.7 ± 9.2	65.3 ± 9.8	0.02
Diabetes, *n* (%)	17 (40.5)	46 (28.9)	0.21
Congestive heart failure, *n* (%)	15 (35.7)	12 (7.5)	<0.001
Peripheral vascular disease, *n* (%)	6 (14.3)	24 (15.1)	0.91
Chronic obstructive pulmonary disease, *n* (%)	7 (16.7)	16 (10.1)	0.36
Serum creatinine preoperatively (mg/dL)	1.25 ± 0.46	1.14 ± 0.21	0.71
eGFR preoperatively (mL/min/1.73 m^2)	63.9 ± 17.6	67.9 ± 13.6	0.14
Chronic kidney disease, *n* (%)	17 (40.5)	37 (23.3)	0.04
Previous CABG, *n* (%)	3 (7.1)	5 (3.1)	0.46
Emergency surgery, *n* (%)	5 (11.9)	11 (6.9)	0.46
OPCAB, *n* (%)	14 (33.3)	86 (54.1)	0.03
C-reactive protein (mg/dL)	28.4 ± 7.5	20.1 ± 6.5	<0.001
Interleukin-6 (pg/dL)	576 ± 394 ($n = 15$)	413 ± 248 ($n = 46$)	0.04
AMI postoperatively, *n* (%)	6 (14.3)	11 (6.9)	0.23
Cardiogenic shock, *n* (%)	10 (23.8)	9 (5.7)	0.001
Haemorrhagic shock, *n* (%)	6 (14.3)	5 (3.1)	0.02
Severe sepsis or septic shock, *n* (%)	2 (4.8)	1 (0.6)	0.21
Rhabdomyolysis, *n* (%)	2 (4.8)	1 (0.6)	0.21
Intravascular contrast agent, *n* (%)	6 (14.3)	8 (5.0)	0.08
Nephrotoxic medication, *n* (%)	7 (16.7)	12 (7.5)	0.13
Length of stay on intensive and intermediate care unit (days)	7.2 ± 6.8	2.2 ± 1.4	<0.001
Serum creatinine maximum (mg/dL)	2.51 ± 1.02	1.19 ± 0.22	<0.001
Serum creatinine at discharge (mg/dL)	1.69 ± 0.76	1.14 ± 0.25	<0.001
Mortality, *n* (%)	2 (4.8)	1 (0.6)	0.21

AKI, acute kidney injury; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; OPCAB, off-pump coronary artery bypass.

studies, we identified the CABG technique as the only independent modifiable risk factor for AKI in our cohort [1,3–6,9,13,15–17]. This is critical as AKI is a serious and frequent complication after CABG, even minimal acute deteriorations of renal function substantially increase in-hospital and long-term mortality in patients after CABG and no causal therapy for AKI after CABG is presently available [2,3,7,8]. It is thus important to apply strategies that approach modifiable risk factors as the CABG technique to prevent AKI. To reduce the incidence of AKI, CABG using the OPCAB technique may be especially indicated in high-risk subgroups of patients with chronic kidney disease and congestive heart failure, as these were identified as independent, preoperative, non-modifiable risk factors of AKI in the previous and in this study [1,3–6,9,13,15,17], and, according to our results, the AKI rates were lower in these subgroups when they were operated by the OPCAB technique.

The aetiology of AKI after CABG is multifactorial and complex [1]. Besides risk factors for AKI that also apply to other patient populations, AKI can be attributed to the use of CPB. Factors intrinsic to CPB that have been demonstrated to contribute to AKI are aortic cross clamping, low perfusion pressure, non-pulsatile blood flow, the use of centrifugal pumps, haemodilution, use of protamine, generation of emboli, formation of free oxygen radicals and especially the induction of a massive systemic proinflammatory response [1]. These factors result in renal vasoconstriction and microthrombosis, and ischaemic and direct toxic renal injury. Our data confirm that postoperative systemic proinflammatory response is more pronounced in ONCAB than OPCAB and again more in AKI than in patients with

Table 5. Potential risk factors associated with acute kidney injury after coronary artery bypass grafting

	Bivariate analysis			Multivariate proportional hazards regression analysis		
	Risk ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Diabetes	1.40	0.90–2.17	0.21	–	–	–
Congestive heart failure	4.73	2.40–9.33	<0.001	3.59	1.86–6.92	<0.001
Peripheral vascular disease	0.94	0.41–2.17	0.91	–	–	–
COPD	1.66	0.73–3.76	0.36	–	–	–
Chronic kidney disease	1.74	1.10–2.76	0.04	2.14	1.15–4.00	0.02
Previous CABG	2.27	0.57–9.12	0.46	–	–	–
Emergency surgery	1.72	0.63–4.68	0.46	–	–	–
OPCAB	0.61	0.39–0.97	0.03	0.47	0.24–0.92	0.02
AMI postoperatively	2.06	0.81–5.26	0.23	–	–	–
Cardiogenic shock	4.21	1.96–13.86	0.001	1.50	0.71–3.18	0.29
Haemorrhagic shock	4.54	1.46–14.16	0.01	1.89	0.75–4.76	0.18
Severe sepsis/septic shock	7.57	0.70–81.51	0.21	–	–	–
Rhabdomyolysis	7.57	0.70–81.51	0.21	–	–	–
Intravascular contrast agent	2.84	1.04–7.74	0.08	–	–	–
Nephrotoxic medication	2.21	0.93–5.26	0.13	–	–	–

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; OPCAB, off-pump coronary artery bypass.

preserved renal function. However, our data do not permit us to differentiate the effect of these various factors. Other factors that potentially attenuate the proinflammatory response such as the use of heparin, aprotinine and propofol are unlikely to be effective as they were equally present in both OPCAB and ONCAB patients.

This knowledge about the serious adverse effects of CPB provides the pathophysiological basis for the finding that the avoidance of CPB by the OPCAB technique is associated with an overall lower AKI rate as well as with less severe stages of AKI. However, the protective effect of OPCAB on the incidence of AKI is still controversial. In several recent predominately large studies, OPCAB was associated with a lower risk of developing AKI, whereas some smaller studies did not confirm a beneficial effect of OPCAB on AKI [9–13,16,17]. A recent meta-analysis was also not able to resolve this issue as it demonstrated a reduction of AKI by the OPCAB technique in several, risk-adjusted observational studies with large patient cohorts but not in a smaller number of randomized-controlled studies with a limited number of patients [14]. There are two important causes for these conflicting results. First, previous studies applied widely varying, non-standardized definitions of AKI ranging from small increases of serum creatinine to the requirement of RRT [9–14,16,17]. Secondly, previous studies analysed a limited number of risk factors for AKI and potent postoperative risk factors were not considered [3–5,9–13,16,17].

This study adds to the growing body of evidence of a beneficial effect of OPCAB on AKI as it is, to our knowledge, the first study that applies the current definition and classification of AKI established by a consensus of all key critical care and nephrology societies worldwide, and it incorporates all widely established risk factors for AKI after CABG in its analysis [1,19]. This definition and classification comprises the important finding from recent cardiothoracic surgical studies that small increases of serum creatinine in AKI already have a major impact on outcome, it refines the RIFLE criteria of AKI by including a time limit and an absolute serum creatinine increase in the AKI definition, and it permits comparison of our data with future studies applying this internationally developed and accepted AKI definition [2,3,7,8,19,25]. Thus, the current AKI definition seems optimal to study the effect of OPCAB on AKI. The small increments of serum creatinine that define AKI by this definition fully explain the increased incidence of AKI compared to previous reports with less stringent definitions [4,5]. However, when comparably sensitive definitions are applied similar rates of AKI are observed [2,3,6,9,10,15]. The incidence of AKI in this report is at the head of studies applying RIFLE criteria to define AKI in CABG patients that may be caused by a higher co-morbid disease burden [26–28]. The latter may cause our findings not to be representative for the entire population of patients undergoing CABG. What still makes our findings noteworthy is that high-risk CABG patients are more likely to develop AKI and its associated complications. In addition, there have been two important trends in coronary artery bypass surgery towards older patients with more severe comorbidity and a higher incidence of postoperative AKI [29–31]. Consequently, this study focused on exactly the subpopulation of CABG patients that requires most attention to prevent AKI. The higher rate of RRT for AKI in the present study may arise from more severe AKI and the rather permissive indication for RRT at our institution [4–6,9,10]. Patients with AKI demonstrated a markedly prolonged ICU and IMC stay, which is associated with poorer patient outcome and increased costs [1,26]. This finding suggests an indirect impact of OPCAB on this important postoperative outcome variable and is consistent with a recent report [32]. At the same time, mortality was low with no difference between patients with and without AKI. However, the study was not powered to detect differences in mortality considering OPCAB as a co-factor and this issue must be a subject of future investigation.

This study is limited by its observational, non-randomized design with potential confounding, information and selection bias. However, demographic and clinical

characteristics of patients operated by the OPCAB and the ONCAB techniques, especially comorbidity and potential risk factors for AKI, were well balanced. Thus, bias in the assignment of patients to a surgical technique and a confounding effect of these factors on the outcome of the study are hardly likely. Restriction was applied as a strategy to reduce confounding and improve variability. The participation of only two surgeons, with equal experience in CABG, served to reduce surgical variability, which could have biased our results. This is a previously established method in studies comparing OPCAB and ONCAP but may limit generalizability of our results beyond the high-risk cohort that we studied [18]. This implies that our data do not permit us to separately distinguish between the impact of the surgical technique and the impact of the surgeon. The latter may have played a role despite equal experience of both surgeons. Other approaches to reducing confounding were the comprehensive search and inclusion of potential confounders as factors in the statistical analyses. Furthermore, it seems unlikely that confounding by indication, selection or information bias would have had substantial effects on outcome as (i) both cohorts did not differ with respect to disease severity, (ii) patients were assigned to OPCAB or ONCAB by chance, (iii) follow-up data were complete for all patients and worst-case analysis did not alter the results, (iv) potential confounding factors were determined according to definitions and (v) measurement of renal function was identical in all patients, thus inhibiting underestimation of the incidence of AKI. Finally, we performed a single-centre study with a low patient number and our results definitely require validation in a large multicentre study.

In conclusion, our data suggest that the OPCAB technique is an independent, modifiable and protective factor for AKI in patients undergoing CABG when all major pre-, intra- and postoperative risk factors are considered, and AKI is defined by small increases of serum creatinine as currently recommended. Additionally, the OPCAB technique is associated with less severe AKI. Chronic kidney disease and congestive heart failure shock were identified as other independent risk factors of AKI but they are non-modifiable as they are preoperative characteristics. As shown by the present investigation, patients with chronic kidney disease and with chronic heart failure or both may be a particular target population to prevent AKI by performing CABG using the OPCAB technique.

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