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BJAN-D-21-00080 - Original Investigation

Short running title: Sevoflurane anesthesia and AKI in CPB

Minimal fresh gas flow sevoflurane anesthesia and postoperative acute kidney injury in on-pump cardiac surgery: a randomized comparative trial

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Abstract

Background: Compound A is generated by sevoflurane when it reacts with carbon dioxide absorbers with strong bases at minimal fresh gas flow (FGF) and is nephrotoxic in animals. No conclusive data has shown increased risk in humans. The aim of this study was to investigate if minimal FGF promotes an increase in the incidence of acute kidney injury (AKI) when compared to high FGF in patients undergoing on-pump cardiac surgery under sevoflurane anesthesia.

Methods: Two hundred and four adult patients scheduled for on-pump cardiac surgery under sevoflurane anesthesia were randomly allocated to two groups differentiated by FGF: minimal FGF (0.5 L.min⁻¹) or high FGF (2.0 L.min⁻¹). Baseline creatinine measured before surgery was compared daily to values assayed on the first five postoperative days, and 24-hour urinary output was monitored, according to the KDIGO (Kidney Disease Improving Global Outcomes) guideline to define postoperative cardiac surgery-associated acute kidney injury (CSA-AKI). Creatinine measurements were also obtained 20 and 120 days after hospital discharge.

Results: Postoperative AKI occurred in 55 patients, 26 patients (29.5%) in the minimal FGF group and 29 patients (31.5%) in the high FGF group ($p = 0.774$). Twenty days after discharge, 11 patients (6.1%) still had CSA-AKI and 120 days after discharge only 2 patients (1.6%) still had CSA-AKI.

Conclusions: When compared to high FGF, minimal FGF sevoflurane anesthesia during on-pump cardiac surgery is not associated with increased risk of postoperative AKI in this population at high risk for renal injury.

KEYWORDS:

Acute kidney injury; Sevoflurane; Anesthesia; Occupational health

Introduction

Sustainable anesthesia involves the use of low fresh gas flow (FGF), avoiding waste anesthetic gases, reducing environmental pollution and promoting cost savings.[1] Low FGF also keeps inhaled gases moist and warm, limiting heat loss from the respiratory system. The use of carbon dioxide (CO₂) absorbers with strong bases (sodium hydroxide, potassium hydroxide), when combined with low FGF, increases canister temperature and reduces the amount of water in the absorber.[2] Under these conditions, sevoflurane is degraded into a vinyl ether metabolism product, Compound A, which causes dose-dependent nephrotoxicity in rats.[3] Newer CO₂ absorbers employ calcium hydroxide rather than strong bases and only produce Compound A when desiccated, while, to date, no conclusive data has shown increased risk associated with low FGF sevoflurane anesthesia in humans.[4] Despite this, the American Food and Drug Administration (FDA) determines that sevoflurane should not exceed 2 minimum alveolar concentration-hours (2 MAC-hours) at flow rates of 1 to < 2 L.min⁻¹ and to avoid FGF < 1 L.min⁻¹. [5] The authorities in Brazil have made no such formal recommendation.

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a major complication that leads to poor outcomes and has an incidence up to 40%.[6] The pathophysiology of CSA-AKI is a matter of intense debate and includes multiple etiologic factors such as inflammation, hypotension during cardiopulmonary bypass (CPB), blood transfusions, and contrast-induced nephropathy prior to surgery. There are several risk factors for CSA-AKI including age, hypertension, preoperative serum creatinine, peripheral vascular disease, respiratory system disease, diabetes, cerebral vascular disease, CPB duration, aortic clamping duration, use of an intra-aortic balloon pump, infection, reoperation, emergency surgery, low cardiac output and type of surgical procedure.[7]

In view of the FDA recommendation on the use of fresh gas flow in anesthesia with sevoflurane but the lack of solid evidence regarding postoperative renal function in anesthesia with this anesthetic agent in minimal fresh gas flow, especially in patients with higher risk, we decided to investigate if there is a difference in the postoperative renal function of patients submitted to cardiac surgery with extracorporeal circulation anesthetized with sevoflurane when comparing a fresh gas flow of $0.5 \text{ L}\cdot\text{min}^{-1}$ versus $2 \text{ L}\cdot\text{min}^{-1}$.

Methods

Study design and participants

This manuscript followed applicable CONSORT guidelines. After approval by the local ethics committee (São José Hospital, Criciúma, Santa Catarina, Brazil, protocol number 1.540.412), the trial was registered prior to patient enrollment on May 11th, 2016 (CAAE, number 55620516.3.0000.5364; Brazilian Clinical Trials Registry, number RBR-28br3m) and with written informed consent obtained from all subjects participating in the trial, from June 2016 to September 2018 we prospectively screened adult ASA (American Society of Anesthesiologists) physical status II and III patients of both sexes who were scheduled for on-pump cardiac surgery. Patients with baseline serum creatinine greater than $1.3 \text{ mg}\cdot\text{dL}^{-1}$, undergoing emergency surgery, with an intra-aortic balloon pump, with restrictive diastolic dysfunction (type III), or with left ventricular ejection fraction (LVEF) of less than 40% were excluded.

Anesthesia

A standard anesthesia technique was employed with all patients. After 8 hours of fasting for solid food and 4 hours for liquids, patients had a 14G peripheral intravenous (IV) catheter placed in the cephalic vein and infusion of 6 mL.kg⁻¹ lactated Ringer's solution was initiated. Patients were initially monitored with an indwelling arterial catheter, pulse oximetry, electrocardiography (DII, V4 and V5 leads) and bispectral index (BIS, Model A 2000[®], software Version 2.21, Aspect Medical Systems, Boston, MA, USA). Patients were given active conductive warming using an adult circulating water mattress fed from a warming device (Medi-Therm III, Model MTA 6900, Gaymar Industries Inc., Orchard Park, NY, USA) with temperature initially set at 38°C.

Following a 3-minute period of preoxygenation (FiO₂ of 1), induction of anesthesia was performed with sufentanil, 0.3 to 0.5 µg.kg⁻¹ IV (intravenous), propofol, 1.5 to 2.0 mg.kg⁻¹ IV, and rocuronium, 0.6 mg.kg⁻¹ IV, administered to facilitate tracheal intubation with a cuffed tube. Maintenance of anesthesia was achieved with age-adjusted minimum alveolar concentration sevoflurane values of 0.3–0.7, end-tidal sevoflurane concentration values of 0.3–1.6 vol% and BIS-guided anesthesia targeting values of 40–60. Continuous IV infusion of remifentanil in the range of 0.2 to 0.5 µg.kg⁻¹.min⁻¹, using a computer-controlled infusion pump (Perfusor[®] compact, BBraun, Melsungen, Germany) was titrated throughout the procedure to maintain mean arterial pressure (MAP) and heart rate (HR) at baseline values ± 20%. Values of MAP exceeding preoperative baseline values by more than 20% and/or HR exceeding preoperative baseline values by more than 20% were treated by increasing the rate of continuous infusion of remifentanil. When necessary, an infusion of nitroglycerine (0.8–1.5 µg.kg⁻¹.min⁻¹ IV) was initiated. Mean arterial pressure values lower than 20% below baseline values and unresponsive to remifentanil infusion reduction were evaluated with transesophageal echocardiography (TEE) and treated with boluses of fluids or with ephedrine, 5–10 mg IV. Inotropes and vasodilators were carefully titrated in case of ventricular dysfunction.

Lungs were ventilated mechanically with a volume-controlled mode using a Dräger Primus anesthesia workstation (Dräger Medical, Lübeck, Germany) or Aisys[®] Cs2 carestation (GE Datex-Ohmeda, München, Germany). Inspiratory pressure was set to maintain tidal volume between 6–8 mL.kg⁻¹. The respiratory rate was adjusted to maintain an end-tidal pressure of carbon dioxide close to 35 mmHg. The end-tidal

sevoflurane concentration, end-tidal pressure of oxygen, end-tidal pressure of carbon dioxide, nasopharyngeal and rectal temperatures, BIS and ventilation parameters were monitored with the built-in monitors on the Primus or GE workstations.

Blood glycemia control was evaluated with a glucose monitoring device (Optium Xceed, Abbott Diabetes Care Inc. Alameda, CA, USA). Glucose values were obtained every 20 minutes and treated if ≥ 150 mg.dL⁻¹. The CPB circuit was primed with 1200 mL of lactated Ringer's solution with the addition of heparin (300 U.kg⁻¹) to achieve an activated clotting time greater than 450 seconds. Cardiac arrest was achieved with cold crystalloid cardioplegia. The central temperature during CPB was maintained at a minimum of 34°C, MAP controlled at 60–80 mmHg and lowest permissible hemoglobin level set at 8 g.dL⁻¹ during maximal hemodilution. Total CPB and aorta clamping times were recorded. In both groups, during CPB, inhalational anesthesia was maintained with sevoflurane.

Postoperative analgesia was provided 15 minutes before the end of surgery with metamizole, 2 g IV, and patient-controlled analgesia was delivered through an infusion pump (Infusomat[®] Space, B. Braun, Melsungen, Germany, 2010) with morphine (2 mg bolus IV) and S (+) ketamine (0.2 mg.kg⁻¹ bolus IV), programmed with a 10-minute lockout interval. Dexamethasone, 8 mg IV, and ondansetron, 8 mg IV, were administered to prevent nausea and vomiting. Patients were transferred to the ICU on mechanical ventilation and with IV propofol (25 to 50 μ g.kg⁻¹.min⁻¹).

Groups and protocol

The groups were differentiated by FGF, with the minimal FGF group on 0.5 L.min⁻¹ in FiO₂ of 1 and the high FGF group on 2.0 L.min⁻¹ in FiO₂ of 1 according to the Baker[8] classification of FGF. In the minimal FGF group, for the first 15 minutes of anesthesia, FGF of 5 L.min⁻¹ with an FiO₂ of 1 was used to promote denitrogenation of the patient's circuit and tissues. After this period, the FGF was reduced to 0.5 L.min⁻¹ with an FiO₂ of 1. Every 20 minutes, an FGF of 2 L.min⁻¹, was administered for one minute, to remove possible accumulation of other gases from patient metabolism to the respiratory system.[9,10] In the high FGF group, FGF was maintained throughout the procedure at 2 L.min⁻¹ with an FiO₂ of 1. The CO₂ absorber (Atrasorb[®], São Paulo, SP, Brazil) in the anesthesia workstation canister was calcium hydroxide and sodium hydroxide for both groups. Randomization was performed electronically using a mobile device program

(Randomizer for Clinical Trial version 2.3, Medsharing SARL, Copyright 2012, France) with block size of 8 and 2 arms, just before anesthesia induction.

Outcomes

The primary outcome was the incidence of acute kidney injury according to the KDIGO guideline,[11] as measured by serum creatinine during the first five days after the surgery and compared to preoperative values, and 24-hour postoperative urinary output. Secondary outcomes were renal function 20 and 120 days after discharge, according to preoperative creatinine values and values 20 and 120 days after discharge.

Statistical analysis

Quantitative variables were described using mean and standard deviation. Categorical variables were presented as counts and percentages. Means were compared using *t* tests and counts using likelihood ratio chi-square tests. Urinary volume data were analyzed by generalized estimation equation (GEE) model using a matrix of exchangeable type including group factors (with and without CSA-AKI), time and interaction.

We used a logistic regression model to evaluate the association between FGF and the occurrence of CSA-AKI, adjusting for the effects of CPB time, diabetes, age, baseline creatinine, sex, and blood transfusion. Results were expressed as odds ratios and 95% confidence intervals (CI). *P*-values below 0.05 were deemed statistically significant. Data were analyzed using SPSS version 22.0.

Sample size calculations

We calculated that the enrollment of 154 patients in 1:1 rate of distribution (77 patients each group) would provide the trial with a power of 85% to detect a two-fold increase in the occurrence of AKI among patients using minimal FGF when compared to those under high FGF, considering a pooled AKI baseline rate of 22.6%⁶ and a two-sided significance level of 0.05.

Results

A total of 277 patients were initially eligible to participate in the study. After exclusions, 204 patients were included in the final randomization. Patient recruitment and flow are summarized in Figure 1. After losses to follow-up from the randomized groups, the final sample for analysis was 180 patients (92 in the high FGF group and 88

in the minimal FGF group). As shown in Table 1, there were no statistically significant differences between the groups in relation to demographic data, preoperative clinical data or intraoperative parameters. Most operations were coronary artery bypass grafts (CABG) (80.5%). Estimated glomerular filtration rate was calculated according to the CKD-EPI creatinine equation.[12]

Primary outcome: postoperative CSA-AKI in the first 5 postoperative days

The type of FGF used was not related to a statistically significant difference in the occurrence of CSA-AKI (odds ratio, 0.91; 95% CI, 0.48 to 1.71; $p = 0.774$) as demonstrated by the univariate analysis shown in Table 2. Baseline preoperative creatinine of patients with CSA-AKI was 0.93 ± 0.18 ($p = 0.049$) and prevalence of diabetes mellitus was 41.8% ($p = 0.017$) as demonstrated by the univariate statistical analysis of occurrence of CSA-AKI in the postoperative period (up to five days after the operation) according to the KDIGO criteria (Table 3). Out of the 180 patients analyzed, 55 (30.5%) had CSA-AKI in this period. Of these 55 patients, 39 patients (70.9%) were diagnosed with CSA-AKI exclusively on the basis of diuresis below $0.5 \text{ mL.kg}^{-1}.\text{h}^{-1}$ in less than 6–12-hours. Data obtained from the generalized estimation equation (GEE) showed a statistically significant difference between the groups in cumulative urine outputs at 6, 12 and 24 hours ($p = 0.044$). Eight patients (14.5%) were diagnosed with CSA-AKI only because of increases over baseline creatinine, with diuresis within the minimum limits of normality. Likewise, eight patients (14.5%) were diagnosed with CSA-AKI on the basis of both increase over baseline creatinine and low diuresis according to the KDIGO criteria. There were no statistical differences in patient demographics, type of operation, CPB time or use of vancomycin as a prophylactic antibiotic. The analysis of the primary outcome by intention-to-treat, considering all the 204 randomized patients, was similar to the per protocol analysis reported above (odds ratio, 1.14; 95% CI, 0.63 to 2.07; $p = 0.672$).

Secondary outcome: CSA-AKI 20 days and 120 days after Hospital Discharge

A total of 180 patients returned within 20 days after hospital discharge to measure serum creatinine. Of these, 11 had CSA-AKI (6.1%) and all of them were patients who had had CSA-AKI during the first 5 postoperative days, showing that these patients had not recovered from kidney injury, according to the KDIGO guideline. A large proportion of these patients were from the high FGF group, with a total of 9 patients.

Once more, fresh gas flow type had no influence on this outcome in the univariate analysis (odds ratio, 0.21; 95% CI, 0.05 to 1.02; $p = 0.053$). Creatinine measurements were only obtained for 121 patients (67.2%) at 120 days after hospital discharge, because of a high incidence of losses to follow up. Of these patients, only 2 (1.6%) still had CSA-AKI according to the KDIGO guideline.

Data from logistic regression for primary and secondary outcomes, 5 and 20 days after surgery, calculated by multivariate analysis and adjusted for CPB time, diabetes mellitus, age, baseline preoperative creatinine, sex and transfusion of packed red blood cells are shown in Table 2. We did not include data from patients seen 120 days after discharge in the logistic regression model because of the low rate of occurrence of CSA-AKI at this point.

Discussion

Reducing FGF in modern anesthesia practice is a goal to be achieved on a large scale. Unfortunately, issues related to the safety of this practice, especially when associated with the inhalational anesthetic sevoflurane and the risk of AKI related to the accumulation of Compound A, limit full use of the technique.[13] The safety of minimal and low FGF with sevoflurane in relation to renal function has already been tested in non-cardiac surgeries.[14] Our study shows the safety of administration of minimal FGF in a population at high risk of perioperative AKI using sevoflurane associated with the common and longstanding CO₂ absorber sodium hydroxide, which is a strong base known to produce Compound A, mainly when lower long-term FGF is used.[15] Short time regular intervals with high FGF were used as part of the classic minimal FGF technique and rarely cause significant impact on the accumulation of Compound A in the circuit.[9,10,16] In a recent meta-analysis, sevoflurane was shown not to increase creatinine and blood urea nitrogen (BUN) in healthy patients after elective surgeries with low FGF.[4] We therefore provide indirect (we did not measure Compound A) but reinforcing evidence that AKI associated with Compound A in humans is not clinically evident in clinical practice, even in the case of minimal FGF anesthesia.

We used simple measures for identification of AKI, i.e., creatinine and urinary output. From a clinical perioperative point of view, indications for renal replacement therapy and postoperative renal care are mainly based on these parameters. We found an incidence of CSA-AKI in the first five postoperative days of 30.5%, which is consistent

with previous studies.[6] This percentage decreased significantly after twenty days, falling to just 6.1%. Although a large number of patients were lost to follow-up, we obtained serum creatinine measurements at 3 months after hospital discharge for 121 patients, only 1.6% of whom had values exceeding 1.5x the preoperative values. These data are consistent with AKI related to cardiac surgery as described.[6]

A number of risk factors for CSA-AKI demonstrated in previous studies, such as the nature of the surgical procedure, duration of surgery, duration of CPB, duration of aortic cross-clamping and blood transfusion were not statistically significant in our study, which favored the analysis of the type of flow used. On the other hand, modest differences with respect to preoperative creatinine (0.93 ± 0.18 for CSA-AKI vs. 0.86 ± 0.20 for no CSA-AKI patients, $p = 0.049$) were related to the primary outcome. Although hypertension was not directly shown to be a predictor of CSA-AKI in our study, higher preoperative creatinine values could be a consequence of hypertensive nephrosclerosis and thus indirectly be related to postoperative kidney injury, just as it was demonstrated with diabetes mellitus. Including known risk factors for CSA-AKI such as CPB duration, diabetes mellitus, age, baseline creatinine, sex and blood transfusion in a logistic regression did not reveal evidence of differences in the primary outcome between the groups over the first five postoperative days (odds ratio, 0.88, 95% CI, 0.45 to 1.72, $p = 0.699$). However, in the same analytical model, 20 days after hospital discharge there was statistical significance for CSA-AKI in the high FGF group (odds ratio, 0.18, 95% CI, 0.03 to 0.97, $p = 0.046$), which can be explained by the low number of patients (only 11 patients had AKI 20 days after discharge).

The fact that there are currently CO₂ absorbers that do not produce compound A does not detract from the importance of this study for two reasons:[17] Firstly, the new CO₂ absorbers are more expensive and have a lower absorption capacity than sodium hydroxide, which results in anesthesia of questionable cost-effectiveness:[18,19] and secondly, the FDA recommends using higher FGF even with these expensive and modern absorbers, which could lead to increased costs and additional environmental pollution.

Waste anesthetic gases are responsible for occupational exposure of health personnel and are also a source of atmospheric pollution. Chronic exposure to isoflurane, sevoflurane, desflurane and nitrous oxide can lead to cytotoxicity and genome instability, according to evaluation of cells from buccal mucosa.[20] Other genetic alterations have also been demonstrated in anesthesiologists, surgeons, nurses

and technicians chronically exposed to inhaled anesthetics.[21,22] While some countries have established limits for operating room waste anesthetic gases,[23] several underdeveloped countries still lack regulation of occupational exposure to inhalational anesthetics. Low FGF anesthesia is clearly consistent with reducing occupational exposure to waste anesthetic gases.

Some authors consider that one risk factor for AKI is hypotension. For this reason, one possible limitation of our study is that we did not analyze MAP intraoperatively or compare it between groups, even though we strictly followed methodology for maintenance of normotension.[24] Another potential limitation of the study was that we did not analyze patients with serum creatinine values higher than 1.3 mg.dL⁻¹, but other studies with non-cardiac surgeries show that sevoflurane is safe at low FGF in patients with creatinine values higher than 1.5 mg.dL⁻¹. [25]

We conclude that, when compared to a high FGF (2.0 L.min⁻¹), the use of minimal (0.5 L.min⁻¹) FGF anesthesia with sevoflurane is not associated with increased incidence of postoperative AKI in on-pump cardiac surgery. Therefore, this practice should be routinely implemented and encouraged, not least considering the reduction in occupational exposure.[26,27] The present study reinforces the evidence showing that we can provide sustainable and cost-effective anesthesia in a population at high risk for AKI using sevoflurane at minimal FGF.

Prior presentations

Preliminary results at Anesthesiology 2018, San Francisco. Control/Tracking Number: 18-SA-5085-ASAHQ. Activity: Scientific Abstract. Title: Minimal Fresh Gas Flow Sevoflurane Anesthesia Is Not Associated with Postoperative Acute Kidney Injury In On-pump Cardiac Surgery Patients: A Randomized Controlled Trial. A2205, October 14, 2018, 1:00 PM - 3:00 PM. Room North, Hall D, Area B.

Clinical trial number

Local ethics committee (São José Hospital, Criciúma, Santa Catarina, Brazil, on 11 May 2016, protocol number 1.540.412, CAAE 55620516.3.0000.5364; Brazilian Registry of Clinical Trials [www.ensaiosclinicos.gov.br] number RBR-28br3m).

Authors' contributions

EBL: elaboration of the scientific project, randomization and anesthesia, data collection, preparation of the manuscript and statistical analysis; NSPM: preparation of the manuscript; LGB: preparation of the manuscript; PNJ: elaboration of the scientific project, preparation of the manuscript and statistical analysis.

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Conflicts of interests

The authors declare no conflicts of interest.

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Table 1 Patient Demographics, Preoperative Clinical Data and Intraoperative Parameters. Data are mean \pm SD or number of patients (%).

Characteristic	Groups	
	Minimal Fresh Gas Flow (0.5 L.min ⁻¹) n = 88	High Fresh Gas Flow (2 L.min ⁻¹) n = 92
Age (years)	61.2 \pm 9.0	60.0 \pm 8.4
Female sex	35 (39.8%)	31 (33.7%)
Body mass index (kg.m ⁻²)	27.6 \pm 4.2	27.7 \pm 3.8
Hypertension	75 (85.2%)	79 (85.9%)
Diabetes mellitus	27 (30.7%)	26 (28.3%)
Chronic obstructive pulmonary disease	22 (25.0%)	24 (26.1%)
Preoperative hemoglobin (g.dL ⁻¹)	12.8 \pm 1.6	13.3 \pm 1.3
Preoperative creatinine (mg.dL ⁻¹)	0.9 \pm 0.2	0.9 \pm 0.2
Estimated GFR (mL.min ⁻¹ /1.73 m ²)	83.9 \pm 16.9	85.4 \pm 17.3
Preoperative BUN (mg.dL ⁻¹)	39.5 \pm 11.5	37.3 \pm 10.3
Prophylactic Antibiotic		
Cephazolin	66 (76.7%)	67 (72.8%)
Vancomycin	20 (23.3%)	25 (27.2%)
Operation		
CABG	70 (79.5%)	75 (81.5%)
AVR	8 (9.1%)	6 (6.5%)
MVR	3 (3.4%)	7 (7.6%)
AVR + CABG	3 (3.4%)	2 (2.2%)
MVR + CABG	0 (0.0%)	2 (2.2%)
Adult Congenital	3 (3.4%)	0 (0.0%)
Bentall	1 (1.1%)	0 (0.0%)
Anesthesia time (min)	293.4 \pm 53.8	285.5 \pm 58.3
Cardiopulmonary bypass time (min)	61.9 \pm 19.3	59.8 \pm 20.6
Aortic cross clamp time (min)	39.2 \pm 16.1	39.3 \pm 16.0
Packed red blood cells transfusion	20 (22.7%)	14 (15.2%)

GFR, glomerular filtration rate; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; AVR, aortic valve replacement or repair; MVR, mitral valve replacement or repair; AVR + CABG, aortic valve replacement or repair with coronary artery bypass graft; MVR + CABG, mitral valve replacement or repair with coronary artery bypass graft.

Table 2 Univariate and Logistic Regression Analysis for Cardiac Surgery Associated Acute Kidney Injury (CSA-AKI).

	Minimal Fresh Gas Flow (0.5 L.min ⁻¹) n = 88	High Fresh Gas Flow (2 L.min ⁻¹) n = 92	Unadjusted		Adjusted	
			OR (95% CI)	<i>p</i>	OR (95% CI)*	<i>p</i>
Outcome						
CSA-AKI first 5 days	26 (29.5)	29 (31.5)	0.91 (0.48 – 1.71)	0.774	0.88 (0.45 – 1.72)	0.699
CSA-AKI after 20 days	2 (2.3)	9 (9.8)	0.21 (0.05 – 1.02)	0.053	0.18 (0.03 – 0.97)	0.046

*odds ratio (OR) and 95% confidence interval (CI) obtained in logistic regression model adjusting for cardiopulmonary bypass time, diabetes, age, baseline creatinine, sex, and blood transfusion.

Table 3 Univariate analysis for the occurrence of cardiac surgery associated acute kidney injury (CSA-AKI) in the first 5 postoperative days.

Characteristic	CSA-AKI (n = 55)	no CSA-AKI (n = 125)	<i>P</i>
Age (years)	62.1 ± 8.2	59.9 ± 8.9	0.112
Female sex	18 (32.7%)	48 (38.4%)	0.465
Body mass index (kg.m ⁻²)	27.4 ± 4.2	27.7 ± 3.9	0.662
Hypertension	48 (87.3%)	106 (84.8%)	0.661
Diabetes mellitus	23 (41.8%)	30 (24.0%)	0.017
Chronic obstructive pulmonary disease	16 (29.1%)	30 (24.0%)	0.474
Preoperative hemoglobin (g.dL ⁻¹)	13.1 ± 1.6	13.1 ± 1.5	0.929
Preoperative creatinine (mg.dL ⁻¹)	0.93 ± 0.18	0.86 ± 0.20	0.049
Preoperative blood urea nitrogen (mg.dL ⁻¹)	39.4 ± 10.6	38.0 ± 11.1	0.419
Vancomycin use	14 (25.9%)	31 (25.0)	0.896
Coronary artery bypass graft	46 (83.6%)	99 (79.2%)	0.483
Anesthesia time (min)	290.2 ± 55.8	289.0 ± 56.5	0.896
Cardiopulmonary bypass time (min)	57.5 ± 21.6	62.3 ± 19.0	0.132
Aortic cross clamp time (min)	38.2 ± 18.0	39.8 ± 15.2	0.539
Packed red blood cells transfusion	13 (23.6%)	21 (16.8%)	0.288
6-hour Urinary output (mL)	869.8.7 ± 437.1	1009.2 ± 412.9	0.042
12-hour Urinary output (mL)	1224.5 ± 565.3	1348.9 ± 501.8	0.142
24-hour Urinary output (mL)	1683.6 ± 718.6	1939.5 ± 694.7	0.025

Data are mean ± SD or number of patients (%).

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram.