Predoperativna ledvična disfunkcija je napovedni dejavnik pooperativne atrijske fibrilacije pri bolnikih po kirurški revaskularizaciji srca

Preoperative renal dysfunction is a predictor of postoperative atrial fibrillation in coronary artery bypass patients

Avtor / Author
Miha Antonič[1,2]

Ustanova / Institute
[1]Univerzitetni klinični center Maribor, Klinika za kirurgijo, Oddelek za kardiokirurgijo, Maribor, Slovenija; [2]Univerza v Mariboru, Medicinska fakulteta, Katedra za kirurgijo, Maribor, Slovenija;
[1]University Medical Centre Maribor, Clinic for Surgery, Department for Cardiac Surgery, Maribor, Slovenia; [2]University of Maribor, Faculty of Medicine, Department for Surgery, Maribor, Slovenia;

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Naslov za dopisovanje / Correspondence
doc. dr. Miha Antonič, dr. med., Univerzitetni klinični center Maribor, Oddelek za kardiokirurgijo, Ljubljanska 5, 2000 Maribor, Slovenija
Telefon: +386 23211787
E-pošta: miha.antonic@guest.arnes.si

Izvleček

Namen: *Atrijska fibrilacija je najpogostejša motnja ritma po operacijah na srcu. Namen raziskave je bil preučiti vpliv predoperativne in intraoperativne ledvične funkcije med zunajtelesnim obtokom na pojavnost omenjene motnje ritma pri bolnikih po kirurški revaskularizaciji srca.*

Metode: *V retrospektivno opazovalno raziskavo je bilo vključenih 409 bolnikov po elektivni kirurški revaskularizaciji srca. Glede na pooperativni potek so bili bolniki razdeljeni na tiste, pri katerih je pooperativno prišlo do novonastale atrijske fibrilacije, in na tiste, pri katerih do atrijske fibrilacije ni prišlo. S pomočjo univariatnih in multivariatnih statističnih modelov smo preučili vpliv predoperativne ledvične funkcije (serumski kreatinin in ocenjena glomerulna filtracija) in intraoperativne ledvične funkcije (diureza med zunajtelesnim obtokom) na pojavnost novonastale pooperativne atrijske fibrilacije.*

Rezultati: *Pri 69 od 409 bolnikov*

Abstract

Purpose: *Atrial fibrillation is the most common arrhythmia following cardiac surgery. An association between preoperative kidney dysfunction and postoperative atrial fibrillation has been previously reported; however, no study has so far investigated the impact of kidney function during cardiopulmonary bypass on the incidence of atrial fibrillation. The aim of this study was to investigate the value of preoperative renal function and urine output during cardiopulmonary bypass as predictors of postoperative atrial fibrillation in patients undergoing elective coronary artery bypass.*

Methods: *This observational retrospective study included 409 patients who underwent elective coronary artery bypass surgery. According to whether or not atrial fibrillation developed postoperatively, the patients were divided into a sinus rhythm group (n = 340) and a new-onset atrial fibrillation group (n = 69). The impact of preoperative (serum* *je pooperativno prišlo do novonastale atrijske fibrilacije, kar predstavlja incidenco 16,9 %. Bolniki s pooperativno atrijsko fibrilacijo so bili starejši, imeli so višji EuroSCORE II in višje predoperativne koncentracije natriuretičnega peptida tipa b. Bolniki z atrijsko fibrilacijo so imeli slabšo predoperativno ledvično funkcijo (višjo predoperativno koncentracijo serumskega kreatinina in nižjo ocenjeno glomerulno filtracijo) kot tisti v sinusnem ritmu. Razlike med skupinama pri diurezi med zunajtelesnim obtokom ni bilo. Multivariatna analiza je kot neodvisne dejavnike tveganja za nastanek novonastale pooperativne atrijske fibrilacije potrdila višjo starost, iztisni delež levega prekata pod 30 % in nižjo predoperativno glomerulno filtracijo.*

Zaključek: *Raziskava je kot neodvisni dejavnik tveganja za nastanek pooperativne atrijske fibrilacije potrdila nižjo predoperativno glomerulno filtracijo, medtem ko vpliva diureze med zunajtelesnim obtokom na incidenco atrijske fibrilacije nismo dokazali.*

creatinine and estimated glomerular filtration rate) and intraoperative (urine output during cardiopulmonary bypass) kidney function on the incidence of new-onset postoperative atrial fibrillation was assessed using univariable and multivariable analyses.

Results: *Patients with atrial fibrillation were older, and had higher EuroSCORE II and higher preoperative B-type natriuretic peptide levels than patients with sinus rhythm. Preoperative renal function was worse (higher serum creatinine level and lower estimated glomerular filtration rate) in the atrial fibrillation group than in the sinus rhythm group. However, there were no differences between the groups in urine output during cardiopulmonary bypass. Multivariable analysis identified older age, left ventricular ejection fraction ≤30%, and lower preoperative estimated glomerular filtration rate as independent risk factors for new-onset postoperative atrial fibrillation.*

Conclusion: *Preoperative renal function—but not urine output during cardiopulmonary bypass—is a predictor of new-onset postoperative atrial fibrillation in patients undergoing elective coronary artery bypass surgery.*

INTRODUCTION

Postoperative atrial fibrillation (POAF) remains the most common rhythm disturbance in patients undergoing coronary artery bypass graft (CABG) surgery. The incidence ranges from 10% to 40%, depending on the population studied (1, 2). Most commonly, it occurs between the 2nd and 5th day after surgery. It is often a benign self-limiting disorder, converting to sinus rhythm after 1–3 days spontaneously or after introduction of antiarrhythmic therapy (2). However, it may sometimes lead to hemodynamic instability, systemic embolization, or complications related to anticoagulation and antiarrhythmic therapy, and is therefore a cause of morbidity and mortality and increased treatment costs (3).

Ageing of the population and the increase in the number of older patients undergoing cardiac surgery has resulted in increase in POAF incidence. Identification of risk factors that can help recognize patients at high risk for POAF would allow early institution of preventive measures (4). Advanced age, increased left atrial size, valvular disease, history of preoperative atrial fibrillation, aortic cross-clamp duration, chronic obstructive pulmonary disease (COPD), and low left ventricular ejection fraction (LVEF) have all been identified as risk factors for POAF after cardiac surgery (5–9). Some recent studies have also indicated an association between preoperative kidney dysfunction and the incidence of POAF after cardiac surgery (10, 11). However, most of these studies included a heterogeneous population of cardiac surgery patients (i.e., mitral and aortic valvular surgery patients as well as CABG patients). The exact mechanism by which renal dysfunction influences the development of POAF remains poorly understood. Stretching of the atria and pulmonary veins due to increased left atrial pressure and systemic inflammation have been suggested to be possible arrhythmogenic factors (11–13).

To the best of our knowledge, no study has so far investigated the impact of kidney function during cardiopulmonary bypass (CPB) on the incidence of POAF. The only available bedside, real-time, diagnostic parameter of kidney function is the urine output. It has been shown to have major clinical significance in the diagnosis of acute renal injury (AKI) in critically ill patients (14, 15) and may be superior to serum creatinine for early diagnosis of AKI (16, 17).

The aim of this study was to investigate the value of preoperative renal function and urine output during CPB as predictors of POAF in patients undergoing elective coronary artery bypass.

MATERIAL AND METHODS

The data of all adult patients who underwent elective on-pump coronary artery bypass surgery between January 2016 and January 2017 at the University Medical Centre, Maribor, Slovenia, were obtained from the electronic medical records. Patients were excluded if they had 1) preoperative acute or chronic renal failure requiring renal replacement therapy; 2) undergone concomitant valve surgery, 3) prior history of atrial fibrillation, 4) permanent pacemaker implanted, or 5) been exposed to contrast medium within 1 week before surgery. A total of 409 patients met these criteria and were included in this retrospective analysis.

This study was approved by the institutional medical ethics committee, and was performed in full accordance with the tenets of the Declaration of Helsinki. The need for written informed consent was waived because of the retrospective nature of the study.

Preoperative data analyzed included patient age, sex, New York Heart Association (NYHA) functional class, history of diabetes, peripheral artery disease, presence of chronic obstructive pulmonary disease (COPD), LVEF, EuroSCORE II, and serum B-type natriuretic peptide (BNP) level. Preoperative kidney function was assessed using the preoperative serum creatinine level and the estimated glomerular filtration rate (eGFR). The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (18). The intraoperative data analyzed included the number of bypass grafts, CPB time, aortic cross-clamp time, and urine output during CPB.

All patients received the same preoperative medication and the usual anesthesia protocol. A standard CABG, with full sternotomy, and CPB with mild hypothermia and antegrade and retrograde cold blood cardioplegia for cardiac protection was performed in all cases. CPB was primed with 1300 mL of Ringer solution, 250 mL of 20% mannitol, 3 mg/kg of methylprednisolone sodium succinate, 7500 units of unfractionated heparin, and an antibiotic (in most cases, 1 g of cefazoline). A nonpulsatile flow of 2.2–2.4 liters per square meter of body surface was maintained by a heart–lung machine using a roller pump. The target mean arterial pressure was 60 mmHg, and the lowest acceptable hematocrit level during CPB was 0.23.

All patients received the same standard postoperative intensive care unit (ICU) and ward care. This included continuous heart rhythm monitoring for 5 postoperative days, and vasopressor, inotropic, volume substitution, and diuretic therapy as determined by the anesthesiologist and intensive care physician. Generally, a mean arterial pressure of 65 mmHg and a central venous pressure of 10–15 mmHg was targeted.

The primary endpoints were 1) an episode of atrial fibrillation or flutter lasting >10 minutes or 2) the need for urgent intervention (e.g., electroconversion) due to atrial fibrillation of flutter with associated profound symptoms or hemodynamic instability during the first 5 postoperative days. The secondary endpoints were peak troponin I level during the first 72 hours after surgery, maximal serum C-reactive protein (CRP) level in the first 5 postoperative days, ICU stay, total hospital stay, incidence of sternal wound infection, stroke, and in-hospital mortality.

STATISTICAL ANALYSIS

The Kolmogorov–Smirnov test was used to test the numerical data for normal distribution. Normally distributed numerical data were expressed as the means ± standard deviation and analyzed using the Student's t-test. Non-normally distributed data were expressed as medians (interquartile range, IQR) and analyzed using the Mann–Whitney U test. Categorical variables were summarized as frequencies (percentages) and analyzed using the chi-square test or Fisher exact test (when the expected value in the contingency table was <5).

After a careful preselection of the variables based on previous research and literature overview (5–11), a binary logistic regression model using backward elimination method with a p-value criterion of 0.157 was constructed to assess the independent correlates to new-onset POAF (19–21). In this multivariate model, eGFR was chosen as the marker of preoperative renal function. In addition to eGFR, variables that were entered in the initial step of the regression model were patient age, presence of COPD, aortic cross-clamp time, preoperative BNP level, LVEF, and urine output during CPB. Receiver operating characteristic (ROC) analysis was used to evaluate the predictive accuracy of the chosen model. All statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

This retrospective study included a total of 409 patients. New-onset POAF during the first 5

Table 1: *basic demographics, comorbidities and preoperative medications*

	POAF group (n=69)	No POAF group (n=340)	p value
Mean age [y]	69.6 ± 7.8	64.5 ± 8.6	<0.001
Female sex	13 (18.8%)	62 (18.2%)	0.906
EuroSCORE II [%]	1.84 (IQR 3.00)	1.48 (IQR 1.71)	0.013
New York Heart Association class			0.485
I	0 (0%)	6 (1.8%)	
II	38 (55.1%)	188 (55.3%)	
III	26 (37.7%)	132 (38.8%)	
IV	5 (7,2%)	14 (3.4%)	
Left ventricular ejection fraction ≤30%	8 (11.6 %)	19 (5.6%)	0.065
Diabetes mellitus	22 (31.9%)	135 (39.7%)	0.223
Chronic obstructive pulmonary disease	6 (8.7%)	19 (5.6%)	0.405
Peripheral artery disease	24 (34.8%)	116 (34.1%)	0.915
B-type natriuretic peptide [pmol/L]	77 (IQR 125)	34 (IQR 70)	0.008
Beta-blockers	57 (82.6%)	275 (80.9%)	0.738
Amiodarone	6 (8.7%)	14 (4.1%)	0.124
Statins	59 (85.5%)	298 (87.6%)	0.627
ACEI or ARB	50 (72.5%)	261 (76.8%)	0.445

IQR – interquartile range; POAF – new-onset postoperative atrial fibrillation; ACEI - angiotensin converting enzyme inhibitor; ARB - angiotensin receptor blocker postoperative days occurred in 69/409 patients—an incidence rate of 16.9%. Table 1 shows the demographic and preoperative patient characteristics in POAF and non-POAF patients.

The two groups were comparable with regard to sex ratio; NYHA class; prevalence of LVEF ≤30%, COPD, peripheral artery disease, and diabetes; and the use of preoperative medications.

In the POAF group, the mean time from surgery to POAF onset was 2.77 ± 1.27 days, and the median POAF duration was 7 hours (IQR, 14 hours). All patients returned to normal sinus rhythm before discharge. Patients who developed POAF were significantly older (69.6 ± 7.8 years vs. 64.5 ± 8.6 years; p < 0.001); had a significantly higher EuroSCORE II risk profile (1.84% [IQR, 3.00%] vs. 1.48% [IQR, 1.71%]; p = 0.013); significantly higher preoperative BNP level (77 pmol/L [IQR, 125 pmol/L] vs. 34 pmol/L [IQR, 70 pmol/L]; p = 0.008); significantly higher preoperative serum creatinine level (87 mmol/L [IQR, 26 mmol/L] vs. 81 mmol/L [IQR, 26 mmol/L]; p = 0.046); and significantly lower preoperative eGFR (73.0 ± 19.9 mL/min/1.73 m2 vs. 86.3 ± 23.1 mL/min/1.73 m2; p < 0.001; Figure 1).

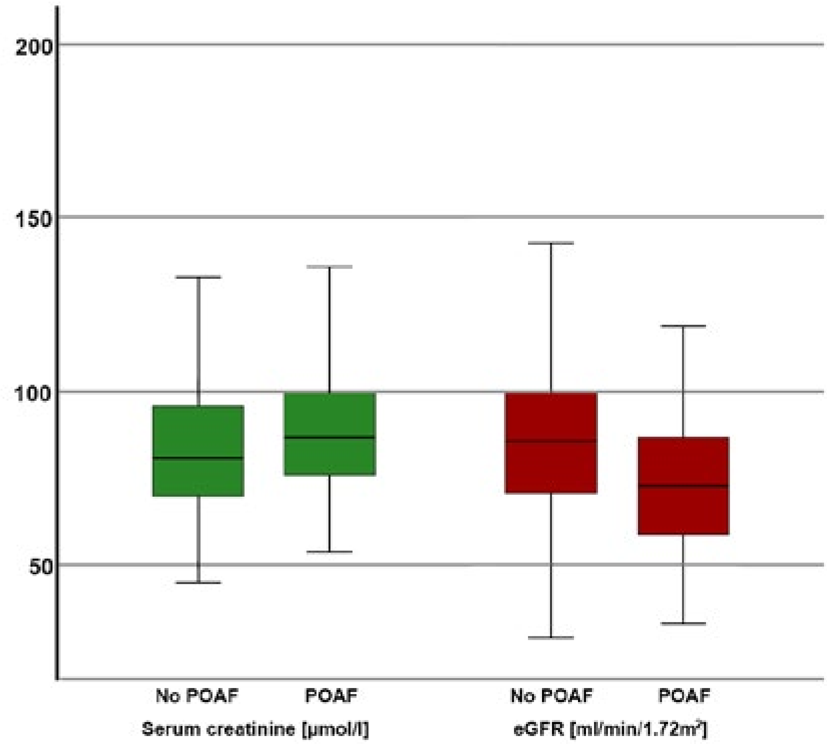

Figure 1. *Preoperative renal function assessment*
POAF – new-onset postoperative atrial fibrillation; eGFR – estimated glomerular filtration rate

The two groups were comparable with regard to the number of bypass grafts, CPB time, and aortic cross-clamp time. Urine output during CPB was also comparable between the two groups (2.96 ± 1.78 mL/kg/h vs. 3.11 ± 2.04 mL/kg/h; p = 0.598; Table 2).

Table 2: *Intraoperative data*

	POAF group (n=69)	No POAF group (n=340)	p value
Number of bypass grafts	4 (IQR 1)	4 (IQR 1)	0.673
CPB time [min]	107.7 ± 27.3	107.8 ± 28.6	0.972
Aortic cross-clamp time [min]	85.0 ± 22.2	83.9 ± 22.6	0.715
CPB urine output [ml/kg/h]	2.96 ± 1.78	3.11 ± 2.04	0.598

IQR – interquartile range; POAF – new-onset postoperative atrial fibrillation; CPB - cardiopulmonary bypass

Table 3 presents a comparison of the postoperative variables in the two groups. ICU stay and the total hospital stay were significantly longer in POAF patients. However, no significant differences were detected between the groups in the peak troponin level during the first 72 hours after surgery, postoperative CRP level, incidence of stroke, sternal wound infection, and in-hospital mortality.

The logistic regression model showed three variables to be independently associated with high risk of new-onset POAF; these were advanced patient age, LVEF ≤30%, and low preoperative eGFR (Table 4). The ROC curve showed a fair discriminative power of this model (area under curve [AUC] = 0.719; 95% CI: 0.650–0.788; p < 0.001; Figure 2).

Table 3: *Postoperative course and complications*

	POAF group (n=69)	No POAF group (n=340)	p value
Number of bypass grafts	4 (IQR 1)	4 (IQR 1)	0.673
CPB time [min]	107.7 ± 27.3	107.8 ± 28.6	0.972
Aortic cross-clamp time [min]	85.0 ± 22.2	83.9 ± 22.6	0.715
CPB urine output [ml/kg/h]	2.96 ± 1.78	3.11 ± 2.04	0.598

IQR – interquartile range; POAF – new-onset postoperative atrial fibrillation; CPB - cardiopulmonary bypass

Table 4: *Analysis of risk factors for perioperative atrial fibrillation – final step of the logistic regression analysis*

Variable	Odds ratio	95% CI	p value
Age [years]	1.059	1.014 – 1.106	0.009
LVEF ≤30%	2.574	0.794 – 8.343	0.115
Preoperative eGFR [mL/min/1.73 m2]	0.984	0.969 – 0.999	0.040

CI - confidence interval; LVEF – left ventricular ejection fraction; BNP - B-type natriuretic peptide; eGFR - estimated glomerular filtration rate

DISCUSSION

The pathogenesis of POAF after cardiac surgery is complex and multifactorial. Probable etiologic factors include intraoperative manipulation of the heart, surgical trauma to the atria, and local ischemia. Systemic factors such as sympathetic activation, systemic inflammation, and electrolyte disturbance have also been implicated in the genesis of POAF (22, 23). The exact mechanism by which renal dysfunction influences the development of POAF remains poorly understood, but fluid overload, electrolyte imbalance, hypertension, stretching of the pulmonary veins, and pathological activation of the renin–angiotensin–aldosterone axis (and consequent myocardial fibrosis) may all contribute (22, 24). However, regardless of the cause of POAF, the initiation and maintenance of re-entrant circuits of atrial fibrillation requires a combination of atrial conduction delay, prolonged circuit length, and shortened atrial refractory period (25). Stretching of the pulmonary veins and the left atrium increases atrial arrhythmogenic activity

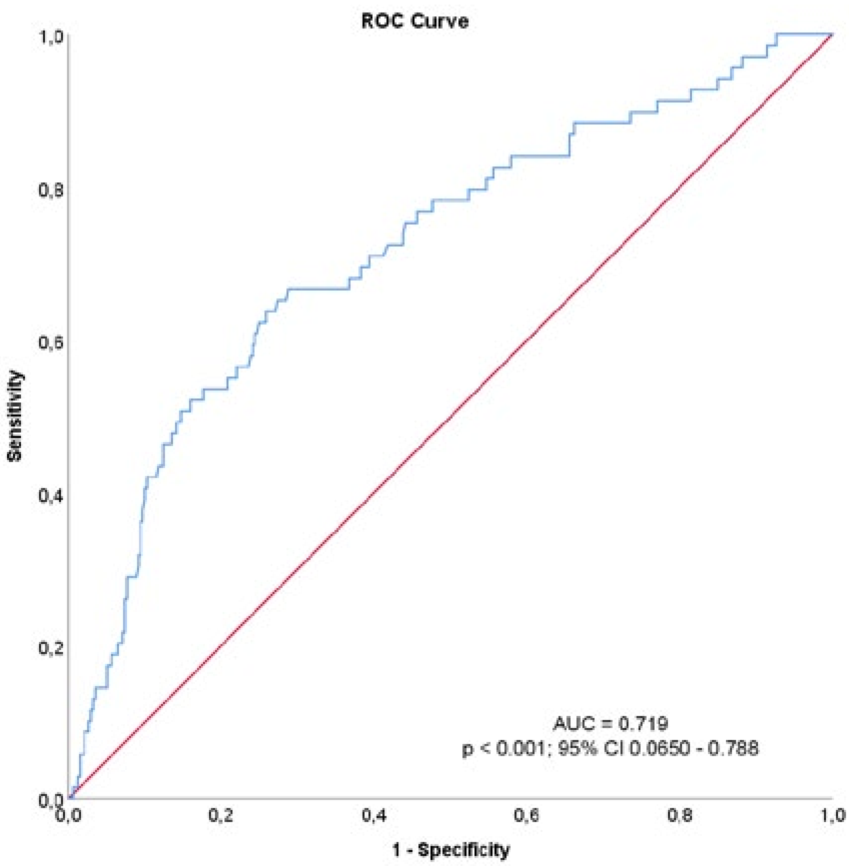

Figure 2. *Assessment of the discriminative power of the regression model using a receiver operator characteristic (ROC) curve . AUC – area under curve; CI – confidence interval*

(26, 27). Impaired kidney function has also been reported to be associated with decreased myocardial conduction velocity (27). Thus, impaired kidney function may be associated with both electrical and structural remodeling of the atrial myocardium (24, 27).

A previous study with a sample size of 3267 showed that the prevalence of atrial fibrillation in patients with mild and moderate decline of GFR was 2- to 3-fold higher than in the general population and was similar to the prevalence among patients with end-stage renal disease receiving chronic dialysis (28). These findings suggest that the processes involved in the development of atrial fibrillation occur early in the course of GFR decline (28). Some recent studies have also demonstrated an association between preoperative kidney dysfunction and increased incidence of POAF after cardiac surgery (10, 11, 24). Our finding of significant association between preoperative decline of eGFR and the development of POAF are consistent with these earlier studies.

Renal hypoperfusion, systemic embolization, and nephrotoxic medications are the main factors influencing renal function during CPB (29, 30). Urine output is an important early indicator of acute renal injury and is therefore widely used for monitoring renal function during CPB (14, 15, 31). In the present study, however, urine output during CPB was not an independent predictor of POAF.
This result may be partly explained by the fact that the mean urine output during the CPB was relatively high in both groups of patients (2.96 ± 1.78 mL/kg/h and 3.11 ± 2.04 mL/kg/h). Furthermore, only 8/409 (1.96%) patients had oliguria during CPB; i.e., urine output <0.5 mL/kg/h, as per the Acute Kidney Injury Network (AKIN) consensus definitions (32). Although these definitions only consider oliguria periods of 6, 12, and 24 hours, oliguria for shorter period, such as 2 hours, have also been suggested as triggers for therapeutic intervention in critically ill patients (15, 33). However, the mean CPB duration in our study was much shorter (107.7 ± 27.3 minutes and 107.8 ± 28.6 minutes, in the POAF and non-POAF groups, respectively). This may be an additional reason why urine output during CPB was not a significant predictor of POAF in the present study.

We recognize certain limitations in this study. First, the follow-up period was short (5 postoperative days); the effects of impaired perioperative kidney function may extend well beyond this period. Second, the analysis did not take into consideration the perioperative volume infused and the use of diuretic and vasopressor therapy.

Third, we only included patients who underwent standard on-pump, cardioplegia-arrested heart surgery. A less invasive, off-pump, beating-heart approach for myocardial revascularization has been increasingly adopted worldwide over the last two decades. There are reports showing that, in patients with preoperative renal dysfunction, mortality is lower with the off-pump technique than with the standard on-pump surgery (34); it is therefore possible that our findings may not apply to patients receiving the former technique.

In conclusion, urine output during CPB does not seem to be of value for predicting the incidence of POAF in low-risk CABG patients undergoing elective, on-pump surgery. However, preoperative renal function was confirmed to be an independent predictor of POAF. To the best of our knowledge this is the first study to investigate the effect of kidney function during CPB on the incidence of new-onset atrial fibrillation after surgery. Further research is necessary to clarify this topic.

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