Renal function is associated with risk of atrial fibrillation after cardiac surgery

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BACKGROUND: Atrial fibrillation (AF) frequently occurs after cardiac surgery and is responsible for increased morbidity and resource use. The aim of the present study was to evaluate the association of impaired renal function and the development of postoperative AF.

METHODS AND RESULTS: Patients undergoing elective cardiac surgery in the absence of significant left ventricular dysfunction (n=253; average age 65±11 years) were recruited to the present prospective study. Ninety-nine patients (39.1%) developed AF during the postoperative period. Creatinine clearance, estimated by the calculated glomerular filtration rate (GFR), was prospectively assessed to determine the association of baseline renal function and the development of postoperative AF. Baseline calculated GFR was assessed as a continuous and a categorical variable (normal: greater than 90 mL/min/1.73 m²; mildly decreased: 60 mL/min/1.73 m² to 89 mL/min/1.73 m²; and moderately to severely decreased: less than 60 mL/min/1.73 m²). Baseline creatinine clearance was 72±22.2 mL/min/1.73 m² and 78.8±23.5 mL/min/1.73 m² in patients with and without postoperative AF, respectively (P=0.02). There was an independent association between decreasing calculated GFR and the development of postoperative AF (OR for 10 mL decrease in calculated GFR: 1.21, 95% CI 1.02 to 1.39). In addition to calculated GFR, surgery for valvular heart disease (versus coronary artery bypass grafting [OR 2.23, 95% CI 1.09 to 3.14; P<0.01]), age (OR per 10-year increase in age 1.92, 1.18 to 2.59) and perioperative nonuse of beta-adrenergic blockers (OR 1.62, 95% CI 1.12 to 3.55; P<0.01) were identified as independent predictors of postoperative AF.

CONCLUSIONS: In the setting of cardiac surgery, impaired calculated GFR is associated with an increased risk for the development of postoperative AF. These data provide additional evidence supporting the association between renal dysfunction and adverse cardiovascular outcomes.

Key Words: Atrial fibrillation; Calculated glomerular filtration rate; Cardiac surgery; Creatinine clearance; Renal function

Atrial fibrillation (AF) is a common complication following cardiac surgery. The incidence of arrhythmia has not changed despite improvements in anesthetic and surgical techniques, and evidence suggests that it may be increasing (1). AF tends to occur within three to four days postoperatively, and in the minority of cases, it may result in inappropriate tachycardia, hypotension, heart failure, increase in the risk of cerebrovascular accidents and prolonged hospital stay (2-4). Most of the hospital stay prolongation seems to be attributed to the rhythm disturbance itself (5). Reducing the rate of postoperative AF is associated with a reduction in the

La fonction rénale s'associe au risque de fibrillation auriculaire après une chirurgie cardiaque

HISTORIQUE : La fibrillation auriculaire (FA) est fréquente après une chirurgie cardiaque et est responsable d'une augmentation de la morbidité et de l'utilisation des ressources. La présente étude vise à évaluer l'association entre la détérioration de la fonction rénale et l'apparition d'une FA postopératoire.

MÉTHODOLOGIE ET RÉSULTATS : Des patients qui subissent une chirurgie cardiaque non urgente en l'absence de dysfonctionnement ventriculaire gauche important (n=253; âge moyen de 65±11 ans) ont été recrutés pour la présente étude prospective. Quarante-vingt-dix-neuf patients (39,1 %) ont développé une FA pendant la période postopératoire. La clairance de la créatinine, estimée d'après le débit de filtration glomérulaire (DFG) calculé, a été évaluée de manière prospective pour déterminer l'association de la fonction rénale de départ et l'apparition d'une FA postopératoire. On a évalué le DFG calculé au départ comme une variable continue et catégorique (normal : supérieur à 90 mL/min/1,73 m², légèrement réduit : de 60 mL/min/1,73 m² à 89 mL/min/1,73 m², et modérément à fortement réduit : moins de 60 mL/min/1,73 m²). La clairance de la créatinine au départ était de 72±22,2 mL/min/1,73 m² et de 78,8±23,5 mL/min/1,73 m² chez des patients avec et sans FA postopératoire, respectivement (P=0,02). On remarquait une association indépendante entre la diminution du DFG calculé et l'apparition de FA postopératoire (RC pour une diminution de 10 mL du calcul de DFG : 1,21, 95 % IC 1,02 à 1,39). Outre le DFG calculé, on a établi que l'opération de la maladie cardiaque valvulaire (par rapport au pontage aortocoronarien [RC 2,23, 95 % IC 1,09 à 3,14; P<0,01]), l'âge (RC par décennie 1,92, 1,18 à 2,59) et la non-utilisation périopératoire de bloqueurs adrénergiques (RC 1,62, 95 % IC 1,12 à 3,55; P<0,01) étaient des prédicteurs indépendants de FA postopératoire.

CONCLUSIONS : En présence d'une chirurgie cardiaque, une détérioration du DGF calculé s'associe à une augmentation du risque d'apparition de FA postopératoire. Ces données s'ajoutent à la documentation probante pour étayer l'association entre le dysfonctionnement rénal et les issues cardiovasculaires négatives.

length of hospital stay and possible cost savings. Identifying patients who are vulnerable to postoperative AF allows targeting of those most likely to benefit from aggressive prophylactic intervention.

Similar to diabetes, heart failure and coronary artery disease, renal dysfunction continues to emerge as a major risk factor for adverse cardiovascular outcomes (6,7). The impact of renal dysfunction on the risk of postoperative AF has not previously been studied. The aim of the present study was to evaluate the association of impaired renal function and the development of postoperative AF following cardiac surgery.

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METHODS

Patient population

Patients included in the present analysis participated in the Study of Prevention of Postoperative Atrial Fibrillation (SPPAF) (4), which was a prospective trial conducted January 2001 to May 2002 at the General Hospital Wels, Austria (a 1050-bed tertiary care centre); the study was approved by the Ethical Committee (Human Subjects Institutional Review Board). The Department of Cardiac Surgery of the hospital performs more than 800 procedures using cardiopulmonary bypass annually and is considered one of the high-volume centres in Austria. All patients gave written, informed consent. Patients scheduled for standard open heart surgery with no evidence of any form of preoperative AF were screened for participation in the present study. Inclusion and exclusion criteria, as well as patient management (including surgical management), have been described in detail elsewhere (4). In brief, to be included, patients had to be hemodynamically stable and in normal sinus rhythm (SR). Exclusion criteria included myocardial infarction less than two weeks before surgery, unstable angina, ejection fraction less than 35%, heart rate of lower than 55 beats/min, advanced heart block or severe conduction disturbance, an implantable defibrillator, impaired renal function (with serum creatinine of more than 177 $\mu\text{mol/L}$ [2.0 mg/dL]).

AF prophylaxis was used in patients, according to the study protocol (4).

Outcome variables

A physician prospectively obtained demographic and outcome data from medical records.

The development of postoperative AF was the major outcome measure. AF was detected by electrocardiogram monitoring and defined as any documented AF of longer than 5 min, or for any length of time requiring intervention for angina or hemodynamic compromise.

The glomerular filtration rate (GFR), as an estimate for creatinine clearance (CrCl), was calculated by the Cockcroft-Gault formula: $(140 - \text{age [years]}) \times \text{weight [kg]} / (72 \times \text{serum creatinine concentration [mg/dL]}) \times 0.85$, if female (8). The formula was expressed per 1.73 m² of body surface area. The calculated GFR was defined as normal if it was 90 mL/min/1.73 m² or higher, mildly decreased if it was 60 mL/min/1.73 m² to 89 mL/min/1.73 m², and moderately to severely decreased if it was lower than 60 mL/min/1.73 m².

Patient follow-up was continued for the entire hospital stay. The relationship of postoperative AF to baseline and postoperative renal function was assessed.

Statistical analysis

All continuous variables are reported as the mean $\pm$ SD. Calculated GFR was assessed as a continuous and a categorical variable. The χ^2 and *t* tests were used for the analysis of categorical and continuous variables, respectively. The *t* test for trends across ordered groups was performed for the three calculated GFR groups. All tests were two-sided and were considered significant if $P \leq 0.05$. Multivariable logistic regression was used for the analysis of the primary outcome variable (AF), adjusting for clinical differences in baseline characteristics: age, weight, sex, calculated GFR (per 10 mL/min/1.73 m² decrease), surgery for valvular heart disease, number of bypass grafts, use of arterial conduit(s), beta-blocker use, preoperative heart rate, smoking status and baseline serum potassium levels. In addition, age, weight and sex were adjusted for in the multivariable analysis, because these parameters are only marginally taken into account in the GFR formula. Statistical analyses

were performed with a commercially available statistical software package (Statistica 6.0; StatSoft Inc, USA).

RESULTS

Baseline characteristics

Normal renal function was present in 64 patients (25.3%), mildly impaired calculated GFR was present in 119 patients (47%) and moderately to severely decreased renal function was present in 70 patients (27.7%). Lower calculated GFRs were associated with older age, male sex, nonsmoking status, lower body weight and lower frequency of diabetes. Patients with impaired renal function, compared with patients who had normal renal function, did not differ regarding blood pressure, heart rate, history of hypertension, duration of surgery and pump time (Table 1).

A total of 253 patients underwent cardiac surgery during the study period and were included in the analysis. Surgery included valve surgery in 44.7% (aortic valve surgery in 36%, mitral valve surgery in 8.3% and tricuspid valve surgery in 0.4%). Combined coronary artery bypass grafting and valve surgery was performed in 5.1%, and 0.4% had aortic and mitral valve surgery simultaneously. Patient age ranged from 26 to 85 years, with a median age of 68 years (108 [42.3%] were 70 years of age or older); 101 (39.9%) were women, 63 (24.9%) were diabetic and 45 (17.8%) had had a previous myocardial infarction. Baseline characteristics of the study population are listed in Table 2. This patient population was characterized by 95 of patients (37.5%) being older than 70 years of age, and 43 (17%) being older than 75 years.

Overall, 99 patients (39.1% of the total study population) developed AF during the postoperative period. The distribution of the onset of AF during the postoperative period showed a peak on day 2, with more than 95% of AF episodes occurring before day 5. Surgery for valvular heart disease was associated with a twofold increase in the rate of postoperative AF. Significantly fewer patients who subsequently developed AF were on preoperative long-term beta blockade than patients without AF (22.2% versus 48.7%; $P < 0.001$). Cerebrovascular accidents (SR group: 0%; AF group: 2%), postoperative ventricular tachycardia (SR group: 1.3%; AF group: 3%), and in-hospital mortality (SR group: 0%; AF group: 2%) rates did not differ significantly between the two groups (9).

Renal function and postoperative AF

Baseline CrCl was 72 ± 22.2 mL/min/1.73 m² and 78.8 ± 23.5 mL/min/1.73 m² in patients with and without postoperative AF, respectively ($P = 0.02$). Postoperative CrCl was 65.2 ± 23.4 mL/min/1.73 m² and 72.5 ± 24 mL/min/1.73 m² in patients with and without postoperative AF, respectively ($P = 0.02$). Decreasing calculated GFR was associated with higher rates of postoperative AF (OR 1.3 [95% CI 1.05 to 1.48] for patients with mildly impaired renal function and OR 1.64 [95% CI 1.19 to 1.88] for patients with moderately to severely decreased renal function).

There was a stepwise increase in the rate of postoperative AF among patients with normal, and mildly and severely impaired renal function. The absolute difference in the development of postoperative AF among patients in the highest calculated GFR group and patients in the lowest calculated GFR group was 18.9% (Figure 1). AF rates were 29.7%, 38.7% and 48.6% in patients with normal, mildly impaired and severely impaired renal function, respectively ($P < 0.05$ for trend).

Predictors of postoperative AF by multivariate analysis

There was an independent association between decreasing calculated GFR and development of postoperative AF (OR for 10 mL decrease

TABLE 1
Baseline characteristics by preoperative calculated glomerular filtration rate (GFR) groups

Characteristic	GFR ≥ 90 mL/min/1.73 m ² (n=64)	GFR 60 mL/min/1.73 m ² to 89 mL/min/1.73 m ² (n=119)	GFR <60 mL/min/1.73 m ² (n=70)	P*
Male sex, %	40	61.3	79.7	<0.05
Age, years (mean $\pm$ SD)	54.6 $\pm$ 10.9	65.8 $\pm$ 7.7	73.9 $\pm$ 5.2	<0.05
Weight, kg (mean $\pm$ SD)	87.4 $\pm$ 12	77.8 $\pm$ 9.8	66.3 $\pm$ 11.5	<0.05
Cigarette smoking, %	48.4	31.9	25.7	<0.05
Previous myocardial infarction, %	17.2	20.2	14.3	0.43
History of diabetes, %	29.7	28.6	14.3	0.06
Hypercholesterolemia, %	56.3	58.8	42.9	0.23
History of hypertension, %	53.1	67.2	64.3	0.39
Previous percutaneous coronary intervention, %	6.3	6.7	0	0.11
Admission systolic blood pressure, mmHg (mean $\pm$ SD)	137.6 $\pm$ 18	137.1 $\pm$ 18.9	139.9 $\pm$ 15.5	0.58
Admission diastolic blood pressure, mmHg (mean $\pm$ SD)	78.4 $\pm$ 10.1	78.5 $\pm$ 10.1	76.7 $\pm$ 10.8	0.64
Admission heart rate, beats/min (mean $\pm$ SD)	71.2 $\pm$ 10.4	70.4 $\pm$ 9.5	73.3 $\pm$ 12.2	0.69
Heart valve surgery, %	40.6	39.5	57.1	0.08
Left internal mammary artery bypass conduit, % of CABG	85.4	88.2	66.7	0.28
Coronary grafts, n (mean $\pm$ SD [median])	1.9 $\pm$ 1.7 (2)	2.2 $\pm$ 1.6 (3)	1.6 $\pm$ 1.7 (1)	0.39
Antiarrhythmic drug use, %	69.2	74.8	78.9	0.21
Beta-blocker use, %	42.2	39.5	32.9	0.35
Pump time, min (mean $\pm$ SD)	87.5 $\pm$ 42.7	85.3 $\pm$ 40.2	87 $\pm$ 37.3	0.88
Duration of surgery, min (mean $\pm$ SD)	161.8 $\pm$ 51.5	155.9 $\pm$ 52.1	156.4 $\pm$ 47.7	0.72

*P values are P for trend. CABG Coronary artery bypass grafting

in calculated GFR 1.21, 95% CI 1.02 to 1.39). In addition to calculated GFR, surgery for valvular heart disease (versus coronary artery bypass grafting), age and perioperative nonuse of beta-adrenergic blockers were identified as independent predictors of postoperative AF by multivariate logistic regression analysis (Table 3).

DISCUSSION

Among patients undergoing cardiac surgery, impaired renal function was associated with an increased risk of postoperative AF. Previous studies have found an association between renal complications and postoperative AF (10). The present study was the first to investigate patients undergoing heart surgery and describe the association of baseline GFR with the development of postoperative AF. The present study highlights the role of minor renal dysfunction as an emerging independent cardiovascular risk factor.

The evidence is overwhelming that in patients with even slightly reduced renal function, the risk of a cardiovascular event is dramatically increased, comparable in magnitude with that conferred by diabetes (11,12). Moreover, slight renal dysfunction exposes patients with a cardiac event to an excessive risk for adverse outcomes (13).

Through which mechanisms may impaired renal function have an impact on the risk for developing postoperative AF? One important factor is the early activation of the sympathetic nervous system as a result of excitation of intrarenal chemoreceptors and mechanoreceptors that send activating signals into the hypothalamus, where catecholamine turnover is increased, leading to increased efferent sympathetic nerve traffic, as shown in experimental (14) and clinical (15) studies. Increased sympathetic activity may be associated with adverse effects and a higher risk of postoperative AF, particularly in patients with cardiovascular comorbidities. A significant increase in sympathetic tone in the postoperative period has been demonstrated in patients who subsequently develop AF (16).

TABLE 2
Baseline characteristics of study patients

Characteristic	Total
Patients at risk, n	253
Age, years (mean $\pm$ SD)	65 $\pm$ 11
Body mass index, kg/m ² (mean $\pm$ SD)	27.5 $\pm$ 4
Sex, men/women (% male)	152/101 (60.1)
Ejection fraction, % (mean $\pm$ SD)	69 $\pm$ 8
Concomitant beta-blocker therapy, %	38.3
Hypertension*, %	62.8
Diabetes mellitus*, %	24.9
Symptoms of heart failure, %	38.3
Previous myocardial infarction, %	17.8
Pump time, min (mean $\pm$ SD)	86 $\pm$ 40
Valvular surgery, n (%)	113 (44.7)
Number of coronary grafts†, mean $\pm$ SD (median)	2 $\pm$ 2 (2)
Coronary artery bypass graft, n (%)	162 (64)
LIMA/RIMA‡, n (%)	134 (82.7)
Right coronary artery bypass graft†, n (%)	117 (72.2)
Beta-blockers‡, n (%)	97 (38.3)
Intensive care unit days, mean $\pm$ SD (median)	2 $\pm$ 5 (1)
Hospital days, mean $\pm$ SD (median)	12 $\pm$ 8 (11)

*Physician's diagnosis or appropriate medications for the disorder; †Percentage of patients with coronary artery bypass graft; ‡As preoperative therapy. LIMA Left internal mammary artery bypass conduit; RIMA Right internal mammary artery bypass conduit

In addition, there are several other pathogenetic pathways that may contribute to the increased risk of postoperative AF in patients with impaired renal function. Reduced calculated GFR is associated with increased oxidative stress and a state of microinflammation (17,18). Concentrations of the nitric oxide synthase

Figure 1 Calculated glomerular filtration rate and postoperative atrial fibrillation (AF)

inhibitor asymmetrical dimethylarginine are increased in renal patients (19). Recent studies have shown increased concentrations of biomarkers of inflammation (high sensitivity C-reactive protein, interleukin-6, etc) and a prothrombotic state (von Willebrand factor, dimers) in patients with relatively early renal failure (20,21). What is the trigger that causes the inflammatory response? Because intercellular adhesion molecule-1 expression is regulated by nuclear factor-kappa B (22), known signal substances activating nuclear factor-kappa B such as proinflammatory cytokines, angiotensin II and endothelin-1, oxidized lipids or advanced glycation end products may be involved, but a particularly hot candidate is oxidative stress.

Inflammation and pericardial lesions (pericarditis) are thought to play a role in the pathogenesis of postoperative AF (23,24). In addition, recent studies have confirmed that the nonpostoperative forms of AF are also related to inflammation (25). The fact that C-reactive protein measurement was not performed may be considered a shortcoming of the present study. However, previous analyses have revealed that postoperative white blood cell counts are associated with the risk of postoperative AF. After inclusion of postoperative white blood cell counts to the multivariate model (data not shown), the association of calculated GFR and postoperative AF remained unchanged.

Finally, increased blood pressure and (subclinical) left ventricular dysfunction were documented in patients with renal disease (26). These hemodynamic changes may contribute to a higher rate of postoperative AF (23). However, in the present study, we did not find meaningful differences in either the systolic or diastolic blood pressures of patients with impaired renal function compared with patients who had normal renal function. This can be at least partly explained by a 'diluting effect' of the high number of patients with pharmacologically treated hypertension in all groups of renal function.

Can renal function reliably be assessed by serum creatinine measurements only? The committee of the Kidney Disease Outcomes Quality Initiative guidelines recommended not to rely on serum creatinine measurements only, which are easily confounded by muscle mass, dietary intake and alterations of tubular creatinine transport, but to estimate GFR with an appropriate formula (27). None of the current formulas are completely satisfactory, but nevertheless, GFR can be accurately assessed by commonly used equations, such as the Modification of Diet in Renal Disease (MDRD) study group equation or the Cockcroft-Gault formula (13,28).

TABLE 3
Multivariate analysis of predictors for developing postoperative atrial fibrillation

Variable	OR (95% CI)	P
Baseline calculated GFR (per 10 mL decrease in GFR)	1.21 (1.02–1.39)	<0.05
Age (per 10-year increase in age)	1.92 (1.18–2.59)	<0.01
Surgery for valvular heart disease (versus coronary artery bypass grafting)	2.23 (1.09–3.14)	<0.01
No preoperative beta-adrenergic blockers	1.62 (1.12–3.55)	<0.01

GFR Glomerular filtration rate

The risk attributed to impaired renal function cannot be fully explained by the high prevalence of classic cardiovascular risk factors (29), as shown in the present study. After adjustment for clinical differences in baseline characteristics, calculated GFR remained associated with the risk of developing postoperative AF. Thus, pathogenetic factors specific for renal dysfunction may contribute to this elevated risk, even in states of minor renal dysfunction (13,30).

Patients with a serum creatinine of more than 177 µmol/L (2 mg/dL) were excluded from the SPPAF 'parent' study for safety reasons (4). This has to be considered a shortcoming of the present analysis.

Another important point is that the present study included a high number of patients undergoing surgery for valvular heart disease. These patients frequently did not have a clear indication for beta blockade, which may explain the relatively low rate of beta-blocker use in the present study. This particular characteristic of the present study needs to be considered, especially when data are compared with findings from other studies investigating the risk of postoperative AF after cardiac surgery.

CONCLUSIONS

In the setting of cardiac surgery, impaired calculated GFR is associated with increased risk for development of postoperative AF. These data provide additional evidence supporting the association between renal dysfunction and adverse cardiovascular outcomes.

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