Background: Renal dysfunction is associated with a higher rate of atrial fibrillation in clinical practice. This study investigated the associations between renal function, left ventricular (LV) diastolic dysfunction, and postoperative atrial fibrillation (POAF).

Methods and Results: A total of 265 consecutive patients who underwent cardiac surgery were prospectively enrolled in the study. Echocardiography was performed before cardiac surgery. The patients were divided into 3 groups based on estimated glomerular filtration rate (eGFR) (group 1, ≥90 ml·min⁻¹·1.73 m⁻²; group 2, 60–90 ml·min⁻¹·1.73 m⁻²; and group 3, <60 ml·min⁻¹·1.73 m⁻²). POAF occurred in 83 of 265 patients (31.3%). The rate of new-onset POAF increased from 15.2% (12/79) in group 1 to 27.8% (27/97) in group 2 and 49.4% (44/89) in group 3 (P<0.001). Further, with increasing renal dysfunction from groups 1 to 3, the rate of LV diastolic dysfunction – defined as E/e’ >15 – also increased (group 1, 19.0%; group 2, 38.1%; and group 3, 48.3%; P<0.001). Absolute eGFR was significantly correlated with E/e’ ratio (r=−0.39, P<0.001). Renal function remained as the independent predictor of POAF on multivariate analysis (odds ratio, 1.90; 95% confidence interval: 1.26–2.87; P=0.002).

Conclusions: In patients undergoing cardiac surgery, decreased eGFR was associated with an increased rate of LV diastolic dysfunction with a subsequent increase in the rate of POAF. (Circ J 2013; 77: 2303–2310)

Key Words: Atrial fibrillation; Coronary artery bypass graft; Renal function
Methods

Subjects
In this prospective study, we recruited 340 consecutive patients who underwent cardiac surgery at Shin Kong Wu Ho-Su Memorial Hospital between January 2008 and December 2010. The inclusion criteria were as follows: (1) presence of significant coronary artery disease with an indication for coronary artery bypass grafting; (2) presence of significant valvular heart disease (except mitral valve disease) requiring valve replacement or valvuloplasty; (3) absence of mitral valve disease; (4) absence of hemodialysis; (5) absence of AF, paced rhythm, or any rhythm other than normal sinus rhythm; (6) absence of history of AF; and (7) acceptable echocardiographic image quality. A total of 268 patients who met these criteria were included in the study. Following cardiac surgery, three patients who received early antiarrhythmic drugs for ventricular arrhythmia were excluded from the study. Thus, a total of 265 patients were enrolled in the study (mean age, 62.2±9.8 years; 203 male).

Clinical reports, echocardiographic reports, and complete medical records were prospectively collected to investigate the relationships between renal function, diastolic function, and the risk of developing new-onset POAF after cardiac surgery. In addition, clinical diagnosis of diabetes, hypertension, hyperlipidemia, and chronic obstructive pulmonary disease were recorded. Each participant’s medical records were reviewed to determine if any diagnosis of heart failure had been made. Each medical encounter was reviewed to determine whether the documented clinical information fulfilled Framingham criteria. This study was approved by the institutional review board for human subjects at Shin Kong Wu Ho-Su Memorial Hospital, and the patients provided written informed consent before participating in the study. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

Laboratory Examination
Blood samples were collected before cardiac surgery, and hemoglobin and serum creatinine levels were measured. Anemia was defined according to the National Kidney Foundation’s Kidney Dialysis Outcomes Quality initiative (K/DOQI) recommendation, that is, hemoglobin <11.0 g/dl (or hematocrit <33%) in premenopausal women and <12.0 g/dl (or hematocrit <37%) in adult men and postmenopausal women.

- eGFR was calculated using the Modification of Diet in Renal Disease Study (MDRD) formula: 186.3×serum creatinine (mg/dl)−1.154×age−0.203×(0.742 if female). The patients were divided into 3 groups according to eGFR, and the cut-offs for eGFR used for grouping were determined based on previous studies: group 1, ≥90 ml·min−1·1.73 m−2; group 2, 60–90 ml·min−1·1.73 m−2; and group 3, <60 ml·min−1·1.73 m−2. Groups 1, 2, and 3 included 79, 97, and 89 patients, respectively.

Echocardiography
Echocardiography was performed by an experienced sonographer (S.-K.C.) before cardiac surgery. The diastolic measurements of LV end diastolic diameter (LVEDD), interventricular septal wall thickness (SWTd), and posterior wall thickness (PWTd) (in millimeters) were used to calculate LV mass (LVM) using the formula recommended by the American Society of Echocardiography:

\[
LVM (g) = \left(0.8 \times \frac{1.04 \times (LVEDD + SWTd + PWTd)}{(LVEDD)^3} - (LVEDD)^3\right) + 0.6 g
\]

The LV mass index (LVMI, g/m²) was defined as LVM normalized by body surface area. According to this formula, LV hypertrophy (LVMH) is defined as LVMI >131 g/m² in men and as >100 g/m² in women.

Doppler echocardiography was performed to determine the early mitral inflow velocity (E), and tissue Doppler imaging evaluation was done to determine the medial mitral anulus velocity during passive filling (e’). Diastolic dysfunction was defined as an E/e’ ratio >15, as previously described.

Measurement of LV End-Diastolic Pressure (LVEDP)
All subjects received coronary angiography and LVEDP measurement with a standard protocol before cardiac surgery. A 6-F pigtail catheter was advanced across the aortic valve and into the LV for measuring the LVEDP. LVEDP was determined using a calibrated fluid-filled system before left ventriculography. LVEDP was measured at the Z-point, which is identified on the LV pressure trace as the point at which the slope of the ventricular pressure upside changes. It is approximately 50 ms after the electrocardiogram (ECG) Q wave and generally coincides with the ECG R wave.

POAF and Outcome Assessment
All patients were monitored with continuous ECG telemetry for the occurrence of POAF until the day of hospital discharge. A standard 12-lead ECG was recorded in every patient suspected of an arrhythmic event. POAF was defined as any documentation of sustained AF episodes lasting >30 s recorded on continuous telemetry throughout hospitalization or on ECG outside of the hospital setting within 30 days following cardiac surgery as previously described. Diagnosis of POAF was confirmed by an experienced cardiologist (H.-M.L.). In addition, the cardiologist who made the diagnosis of POAF had no information about the renal function, echocardiographic features, and other parameters.

Clinical morbidity was defined as thromboembolic event (ischemic stroke, transient ischemic accident, myocardial infarction, or peripheral embolism), surgical wound bleeding or infection requiring reconstruction, gastric intestinal bleeding requiring blood transfusion, and sepsis. All morbidity and mortality were prospectively recorded within the 30-day clinical follow-up period following cardiac surgery.

Statistical Analysis
Quantitative data are expressed as mean±SD. Data were compared using 2-sample t-tests for independent samples. Differences in proportion were compared using chi-square test or Fisher’s exact test, as appropriate. Analysis of variance was used to analyze the non-parametric data. P<0.05 was considered statistically significant. Multivariate analysis with a logistic regression model was conducted to identify the baseline variables independently associated with new-onset POAF. The variables that were independently associated with POAF are presented as odd ratios (ORs) along with the 95% confidence intervals (CI). A significant OR was obtained if 95% CI exceeded 1, with P<0.05.

Results

Clinical Characteristics
The mean subject age was 62 years (range, 38–84 years). There were 203 men (77%) and 62 women (23%). Of the total number of 265 patients, 77% had hypertension, 54% diabetes, and 34% heart failure. Among these, 248 patients (93.6%) received coronary artery bypass surgery; the remaining 15 (5.7%) and 2...
Renal Dysfunction, Diastolic Dysfunction, and POAF

Surgical procedures vs. renal function group are listed in Table 2. There were no significant differences in surgical procedure type, rate of on- or off-pump surgery, duration of bypass or operation, amount of blood transfusion, and perioperative catecholamine infusion among the 3 renal function groups. The postoperative medications were also not significantly different among the 3 renal function groups.

Renal Dysfunction, LV Hypertrophy, and Diastolic Dysfunction

The preoperative echocardiographic hemodynamic parameters in the renal function groups are summarized in Table 1. There were no differences in SWTd, PWTd, LVEDd, LVM, or LV ejection fraction among the renal function groups. With decreasing renal function, however, the LA diameter (group 1, 38.9±6.6 mm; group 2, 39.5±6.4 mm; group 3, 40.7±6.1 mm;
increased. Additionally, there was significant correlation between absolute eGFR and E/e’ ratio (r=−0.39, P<0.001).

Furthermore, as the renal function decreased from group 1 to 3, LVEDP increased (group 1, 20.8±8.5 mmHg; group 2, 22.9±6.2 mmHg; group 3, 24.1±7.2 mmHg; P=0.04).

Renal Function and Incidence of New-Onset POAF

The overall incidence of new-onset POAF was 31.3% (n=83), occurring at a median of 2 days (range, 0–28 days) after cardiac surgery. Rate of new-onset POAF differed among the 3 renal function groups. The rate of new-onset POAF increased from 15.2% (12/79) in group 1 to 27.8% (27/97) in group 2 and 49.4% (44/89) in group 3 (P<0.001; Figure 1), occurring at an average of 2.8±1.5 days, 4.6±6.6 days, and 3.27±3.0 days after cardiac surgery (P=0.35), respectively.

The incidence of POAF as a function of renal function and diastolic function is shown in Figure 2. Patients in renal function group 1 without diastolic dysfunction had a lower risk (9.8%) of developing POAF. Patients in renal function group 3 with diastolic dysfunction were at a higher risk of developing POAF (57.1%).

The Kaplan-Meier curve for freedom from POAF is shown in Figure 3. Poor renal function was associated with higher rates of POAF following cardiac surgery (log-rank test; P<0.001). Significant predictors of POAF based on univariate regression analysis are shown in Table 3. Age, anemia, LVH, LV diastolic dysfunction, and renal function were significantly associated with the risk of new-onset POAF. According to multivariate regression analysis, after adjusting for clinical and echocardiographic risk factors, the LV diastolic dysfunction (OR, 1.79; 95% CI: 1.01–3.17; P=0.046) and renal function group (OR, 1.90; 95% CI: 1.26–2.87; P=0.002) remained as independent predictors of POAF (Table 4).

LVMI (group 1, 107.9±40.8 g/m²; group 2, 115.1±37.6 g/m²; group 3, 129.5±47.1 g/m²; P=0.003), and mitral E/e’ ratio (group 1, 11.5±10.8; group 2, 15.0±8.7; group 3, 23.3±11.7; P<0.001) increased. Additionally, there was significant correlation between absolute eGFR and E/e’ ratio (r=−0.39, P<0.001).

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Renal Dysfunction, Diastolic Dysfunction, and POAF

Renal Function and Outcome After Cardiac Surgery

Post-surgical outcome vs. renal function group is summarized in Table 5. There were no significant differences in intensive care unit stay among the 3 renal function groups. The 30-day mortality rate following cardiac surgery were similar among the 3 renal function groups, but patients in the advanced renal dysfunction group tended to have a longer total hospital stay, higher 30-day morbidity rate, and higher morbidity or mortality rates.

Table 3. Predictors of Postoperative AF (Univariate Analysis)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.01–1.07</td>
<td>0.005</td>
</tr>
<tr>
<td>Men</td>
<td>1.04</td>
<td>0.56–1.93</td>
<td>0.90</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.97</td>
<td>0.91–1.04</td>
<td>0.44</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.59</td>
<td>0.94–2.70</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.72</td>
<td>0.88–3.33</td>
<td>0.11</td>
</tr>
<tr>
<td>Renal function group</td>
<td>2.37</td>
<td>1.65–3.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-blockers</td>
<td>0.76</td>
<td>0.43–1.35</td>
<td>0.35</td>
</tr>
<tr>
<td>ACEIs or ARBs</td>
<td>1.10</td>
<td>0.64–1.87</td>
<td>0.73</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.72</td>
<td>1.02–2.90</td>
<td>0.04</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.03</td>
<td>0.97–1.08</td>
<td>0.34</td>
</tr>
<tr>
<td>LVH</td>
<td>1.98</td>
<td>1.16–3.38</td>
<td>0.01</td>
</tr>
<tr>
<td>LV diastolic dysfunction†</td>
<td>2.31</td>
<td>1.36–3.95</td>
<td>0.002</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.99</td>
<td>0.98–1.01</td>
<td>0.47</td>
</tr>
<tr>
<td>On-pump procedure</td>
<td>1.09</td>
<td>0.62–1.90</td>
<td>0.77</td>
</tr>
<tr>
<td>Duration of cardiopulmonary bypass</td>
<td>1.00</td>
<td>0.99–1.01</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Anemia defined as hemoglobin <11.0 g/dl (or hematocrit <33%) in premenopausal women and hemoglobin <12.0 g/dl (or hematocrit <37%) in adult men and postmenopausal women; LVH defined as LVMi >100 g/m² in women or LVMi >131 g/m² in men; LV diastolic dysfunction defined as E/e’ >15. AF, atrial fibrillation; CI, confidence interval; LV, left ventricular; OR, odds ratio. Other abbreviations as in Table 1.
Major Findings
The present study included a cohort of patients who underwent cardiac surgery for coronary artery disease or valvular disease. We investigated the associations among renal function, LV diastolic dysfunction determined on preoperative echocardiography, and the occurrence of POAF following cardiac surgery. The main findings were as follows: (1) decreased eGFR was associated with increased LV diastolic dysfunction; (2) decreased eGFR was associated with an increased rate of new-onset POAF; and (3) decreased eGFR was associated with worse 30-day outcome.

Renal Function, Diastolic Dysfunction, and POAF
Among the patients with less severe chronic kidney disease not undergoing hemodialysis, the prevalence of AF was similar to that in patients with end-stage renal disease. A recent study has demonstrated that the prevalence of AF gradually increases with decreasing eGFR, which is unrelated to increasing age. These findings suggest that processes influencing the development of AF likely occur early in the course of the decline in eGFR.

In concordance with the previous studies, the present study has demonstrated that patients with worse renal function tend to have higher rate of anemia, LVH, diastolic dysfunction and LA enlargement. Potential mechanisms that may explain the relationship between anemia and the development of LVH and diastolic dysfunction have previously been reviewed, which include reduced oxygen delivery to the myocardium leading to myocyte necrosis, increased cardiac load due to anemia, and activation of the sympathetic nervous system.

Increased diastolic dysfunction in these patients suggests that impaired active myocardial relaxation can further stiffen the ventricle, causing reduced chamber compliance and increased LVEDP, which may cause a substantial increase in LA size. LA enlargement is a marker of both the severity and chronicity of diastolic dysfunction and the magnitude of LA pressure elevation. In addition, previous studies have demonstrated poor renal function to be associated with lower LA voltage and longer activation time, rather than structural changes in the LA. These findings suggest that decreased eGFR amplifies the risk of POAF following cardiac surgery, and that these changes are mediated by both the structural and electrical remodeling of the LA.

Anticoagulant and Antiplatelet Therapy in Patients With POAF
New-onset POAF is associated with a 2–3-fold increase in postoperative risk for stroke. Anticoagulation may reduce the neurological complications associated with this arrhythmia. The risks of pericardial bleeding, however, must be weighed against the need for anticoagulation. Current guidelines recommend that anticoagulation is probably indicated in patients with POAF. The addition of clopidogrel to aspirin, however, might be considered in patients with POAF in whom anticoagulant is considered unsuitable due to patient preference or the physician’s assessment of the patient’s ability to safely sustain anticoagulation.

Clinical Implications
To date, prophylactic therapies for new-onset POAF after cardiac surgery have been largely empirical. In addition to prophylactic antiarrhythmic therapy for POAF, identification and control of the risk factors is expected to play an important role in decreasing the rate of new-onset POAF in at-risk cardiac patients. The present results shows that decreased eGFR is significantly associated with a higher rate of new-onset POAF, longer hospital stay and worse 30-day morbidity or mortality. Therefore, in patients with renal insufficiency undergoing cardiac surgery, it is important to prevent and attenuate the deterioration in renal function by optimal medical therapy for the underlying comorbidity such as hypertension and diabetes, along with the avoidance of nephrotoxic agents.

<table>
<thead>
<tr>
<th>Table 4. Predictors of Postoperative AF (Multivariate Analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>LVH</td>
</tr>
<tr>
<td>LV diastolic dysfunction</td>
</tr>
<tr>
<td>Renal function group</td>
</tr>
</tbody>
</table>

Anemia defined as hemoglobin <11.0 g/dl (or hematocrit <33%) in premenopausal women and hemoglobin <12.0 g/dl (or hematocrit <37%) in adult men and postmenopausal women; LVH defined as LVMi >100 g/m² in women or LVMi >131 g/m² in men; LV diastolic dysfunction defined as E/e’ >15. Abbreviations as in Tables 1, 3.

<table>
<thead>
<tr>
<th>Table 5. Post-Surgical Outcome vs. Renal Function Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong> (n=79)</td>
</tr>
<tr>
<td>ICU stay (days)</td>
</tr>
<tr>
<td>Total hospital stay (days)</td>
</tr>
<tr>
<td>Morbidity</td>
</tr>
<tr>
<td>Thromboembolic event</td>
</tr>
<tr>
<td>Ischemic stroke or TIA</td>
</tr>
<tr>
<td>MI</td>
</tr>
<tr>
<td>Peripheral embolism</td>
</tr>
<tr>
<td>Surgical wound bleeding or infection requiring reconstruction</td>
</tr>
<tr>
<td>Gastric intestinal bleeding</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Morbidity or mortality</td>
</tr>
</tbody>
</table>

Data given as n (%) or mean±SD. ICU, intensive care unit; MI, myocardial infarction; TIA, transient ischemic accident.
Further prospective and large-scale trials are necessary to clarify this association.

**Study Limitations**

We investigated POAF occurring within 30 days after cardiac surgery. Participants with paroxysmal or asymptomatic AF would have been missed if these events occurred outside of the hospital. The incidence of POAF in the present study may therefore have been underestimated, which would have biased the results and worked against the significant association between chronic kidney disease and POAF in the present study. The median period of onset of POAF in the present study, however, is similar to that in previous studies, in which POAF onset was typically observed within 7 days following cardiac surgery.\(^1\)\(^2\) Second, with regard to the 30-day mortality, the differences among the 3 renal function groups did not reach statistical significance. This may be due to the low event rate in the present study. Further studies with a larger sample size with sufficient power may be able to demonstrate a significant statistical difference in the 30-day mortality in such patients. Another limitation of this study was the lack of specific data for systemic inflammation, such as C-reactive protein, an important consideration in the postoperative state. The incidence of POAF, however, peaked on the third postoperative day, which corresponds to time to peak inflammation after cardiac surgery.\(^4\)\(^9\) Fourth, using the MDRD formula, calculation of eGFR is greatly influenced by age, which is a risk factor for POAF. Therefore, it is possible that POAF occurred only because the patients were old. Finally, the ACC/AHA guidelines recommend the preoperative use of β-blocker or amiodarone to prevent POAF,\(^3\)\(^8\) but only around 70% of the present subjects received β-blocker before cardiac surgery. The prescription of β-blocker might be underused in reality. The present patients, however, had personalized treatment, and according to the experience and judgment of their physicians, so the treatment algorithms might be inconsistent.

**Conclusion**

Impaired eGFR was associated with diastolic dysfunction and increased risk for the development of POAF. The adverse effects of renal impairment on diastolic dysfunction appear to occur from the early stages of declining eGFR. In patients undergoing cardiac surgery, renal dysfunction and diastolic dysfunction are important issues requiring attention.

**Acknowledgments**

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