Impact of Renal Dysfunction on Left Atrial Low-Voltage Areas in Patients With Atrial Fibrillation

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Background: The presence of residual left atrial low-voltage areas (LVA) has been shown to be strongly associated with atrial fibrillation (AF) recurrence after pulmonary vein isolation. A preliminary study showed that concomitant chronic kidney disease (CKD) increased the rate of AF recurrence. The association between CKD and LVA, however, has not been elucidated. In the present study, we investigated the association between CKD severity and LVA prevalence.

Methods and Results: In total, 183 consecutive AF patients who underwent initial ablation for AF were enrolled in this retrospective observational study. Serum cystatin C before ablation was measured, and the estimated glomerular filtration rate (eGFR) was calculated. LVA were defined as sites of left atrial electrogram amplitude <0.5 mV. Of 183 patients, 76 (42%) had LVA. Patients with LVA had lower eGFR calculated using cystatin C (74±22 vs. 86±24 mL/min/1.73 m², P=0.001). The optimal cut-off of the calculated eGFR was 71.5 mL/min/1.73 m², corresponding to a 79.4% sensitivity, 50% specificity, and 67.2% predictive accuracy. LVA occurred more frequently in patients with more severe categories of CKD. On multivariate analysis, eGFR <71.5 mL/min/1.73 m² was an independent predictor of LVA (odds ratio, 3.3; 95% CI: 1.4–7.8; P=0.006).

Conclusions: CKD severity was correlated with left atrial LVA prevalence in patients with AF undergoing catheter ablation.

Key Words: Atrial fibrillation; Low-voltage area; Renal dysfunction; Substrate

Methods

From December 2014 to January 2016, we retrospectively enrolled 183 consecutive cases of initial ablation for AF. As part of our standard procedure, serum cystatin C was measured, and the estimated glomerular filtration rate (eGFR) was calculated prior to ablation. Patients who could not maintain sinus rhythm after electrical cardioversion followed by PVI were excluded. Other exclusion criteria were age <20 years, left atrial thrombus, severe coronary artery disease requiring revascularization, and prior catheter ablation of AF. The study complied with the Declaration of Helsinki. Written informed consent for the ablation and use of data in the study was obtained from all patients, and the protocol was approved by the Institutional Review Board of Kansai Rosai Hospital.

We classified cases into 6 groups according to GFR. GFR categories were defined according to Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines: G1 (n=60), >90 mL/min/1.73 m²; G2 (n=100), 60–89 mL/min/1.73 m²; G3a (n=10), 45–59 mL/min/1.73 m²; G3b (n=9), 30–44 mL/min/1.73 m²; G4 (n=2), 15–29 mL/min/1.73 m²; G5 (n=1), <15 mL/min/1.73 m².

Catheter ablation has been established as an effective therapy for atrial fibrillation (AF). Some patients, however, need repeat ablation due to the recurrence of atrial tachyarrhythmias. Electrograms with reduced amplitude on atrial endocardial voltage maps correlate with atrial scarring, as detected on delayed-enhancement magnetic resonance imaging.1 The presence of left atrial low-voltage areas (LVA) has been shown to be strongly associated with the recurrence of atrial tachyarrhythmias, and the addition of guided ablation of LVA improves procedural outcomes compared with pulmonary vein isolation (PVI) alone.2–4 A preliminary study showed that concomitant chronic kidney disease (CKD) increases the rate of recurrence of AF.5

Hemodynamic and metabolic abnormalities exist in CKD patients.6,7 These factors can induce atrial fibrosis,8 and are associated with the presence of LVA.1

To the best of our knowledge, the association between CKD and LVA prevalence has not been completely elucidated. The objective of the present study was to investigate the association between LVA prevalence and CKD severity.
Operators attempted to maintain contact force between 10 and 30 g to ensure that the degree of contact between the catheter and myocardium was appropriate. PVI was considered complete when the 20-pole circular catheter no longer recorded any PV potentials. If atrial flutter occurred spontaneously or was induced by atrial burst stimuli, additional ablation was performed. In addition, AF triggers originating from non-PV foci induced by isoproterenol infusion were also ablated.

Following PVI, detailed voltage mapping using a bipolar 3.5-mm tip catheter was performed during sinus rhythm using previously described methods.\(^3\)\(^10\) Mapping points were acquired to fill all color gaps on the voltage map using the electroanatomical mapping system, with an interpolation threshold of 15 mm for the fill threshold and 23 mm for the color threshold. In addition, high-density mapping was added at sites where LVA were recorded to exactly delineate their extent. Adequate endocardial contact was confirmed by stable electrograms, the distance to the geometry surface, and increased contact force ≥5 g. The bandpass filter was set at 30–500 Hz. Each acquired point was classified according to the peak-to-peak electrogram as follows: >0.5 mV, healthy; 0.2–0.5 mV, diseased; and <0.2 mV, scarred. LVA were defined as sites of ≥3 adjacent low-voltage points of <0.5 mV, as per our previous study.\(^3\) The target number of mapping points was >100 points throughout the left atrium. Similar to our previous study, the left atrium was divided into 6 segments: anterior, septal, posterior, roof, inferior, and posterolateral.\(^3\) Representative cases are shown in Figure 1.

Long-term rhythm outcomes were followed for 24 months in 181 patients, while 2 patients were lost to follow-up. Patient follow-up was performed as routine visits, usually every 3 months in the first year and every 6 months thereafter. Patients who could not visit hospital were contacted by a physician and asked about their symptoms. A 12-lead electrocardiogram was performed at each routine consultation, and Holter electrocardiography was performed 6 months after the procedure. AF recurrence was defined as atrial tachyarrhythmias >30 s and occurring ≥90 days after the procedure.

**Statistical Analysis**

Continuous data are expressed as mean ± SD. Categorical data are presented as absolute values and percentages. Tests for significance were conducted using the unpaired t-test for continuous variables and the chi-squared test for categorical variables. We also performed receiver operating characteristic (ROC) curve analysis between eGFR and LVA prevalence. Kaplan-Meier analysis and the log-rank test were performed to investigate the association between recurrence of atrial tachyarrhythmia and LVA prevalence. Univariate and multivariate logistic regression analyses were used to determine the clinical factors associated with LVA prevalence. Variables with P ≤ 0.05 in the univariate models, or factors that could influence both CKD and LVA, were included in the multivariate analysis. All analyses were performed using SPSS version 24.0.0.0\(^\text{TM}\) (SPSS, Chicago IL, USA).

**Results**

PVI was successfully completed in all cases. Patient characteristics are shown in Table 1. Of the 23 patients with CKD stage G3a–G5 (eGFR <60 mL/min/1.73 m\(^2\)), the presumed
Patients with LVA were significantly older, more frequently female, and had a lower body mass index (BMI), lower hemoglobin, higher CHA2DS2-VASc score, higher brain natriuretic peptide (BNP), larger left ventricular diastolic diameter, and more frequent mitral regurgitation.
### Table 2. Patient Characteristics vs. Presence of LVA

| Variable                        | All (n=183) | LVA | Univariate analysis | Multivariate analysis |
|---------------------------------|-------------|-----|---------------------|-----------------------|
|                                 | With (n=76) | Without (n=107) | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Age (years)                     | 67±9.4      | 70±7.4 | 64±9.9 | 1.1 | <0.001 | – | – |
| Age (years)/10-year increment   | 6.7±0.9     | 7.0±0.7 | 6.4±1.0 | 2.2 | <0.001 | 2.2 | (1.5–3.3) | 0.008 |
| Females                         | 49 (27)     | 27 (36) | 22 (21) | 2.1 | 0.02 | 2.1 | (1.1–4.1) | 0.12 |
| BMI (kg/m²)                     | 24.3±3.8    | 23±3.3 | 25±4.0 | 0.9 | 0.01 | 0.9 | (0.8–0.97) | 0.04 |
| CHA2DS2-VASc score              | 2.3±1.4     | 2.7±1.6 | 2.0±1.3 | 1.4 | 0.001 | – | – |
| Persistent AF                   | 82 (45)     | 40 (53) | 42 (39) | 1.7 | 0.07 | 1.8 | (0.95–3.1) | 0.24 |
| Congestive heart failure        | 23 (13)     | 11 (15) | 12 (11) | 1.3 | 0.51 | – | – |
| Hypertension                    | 110 (61)    | 44 (58) | 66 (62) | 0.9 | 0.61 | 0.5 | (0.5–1.6) | 0.12 |
| Diabetes mellitus               | 27 (15)     | 12 (16) | 15 (14) | 1.2 | 0.74 | – | – |
| Vascular disease                | 18 (10)     | 10 (13) | 8 (8) | 1.9 | 0.21 | 1.3 | (0.7–5.0) | 0.70 |
| Hemoglobin (g/dL)               | 14.0±1.4    | 13.7±1.5 | 14.1±1.3 | 0.78 | 0.03 | 0.9 | (0.63–0.97) | 0.64 |
| BNP (pg/mL)                     | 106±111     | 138±132 | 84±88 | 1.01 | 0.002 | – | – |
| Log BNP                         | 1.8±0.5     | 1.9±0.5 | 1.7±0.5 | 2.9 | 0.001 | 0.9 | (1.0–1.01) | 0.64 |
| eGFR (mL/min/1.73m²)            | 81±24       | 74±22 | 86±24 | 0.98 | 0.001 | – | – |
| eGFR <71.5mL/min/1.73m²         | 60 (33)     | 38 (50) | 22 (21) | 3.9 | 0.001 | 3.3 | (2.0–7.4) | 0.006 |
| LVDD (mm)                       | 47±5        | 46±6 | 48±5 | 0.9 | 0.03 | 0.9 | (0.88–0.99) | 0.72 |
| LVEF (%)                        | 64±9        | 65±9 | 64±8 | 1.01 | 0.61 | – | – |
| LVMi (g/m²)                     | 97±88       | 86±25 | 104±112 | 0.99 | 0.31 | 0.97 | (0.98–1.01) | 0.03 |
| LAD (mm)                        | 39±7        | 40±7 | 39±6 | 1.04 | 0.08 | 1.1 | (0.99–1.01) | 0.02 |
| MR ≥mild                        | 52 (28)     | 29 (38) | 23 (22) | 2.3 | 0.02 | 1.4 | (1.2–4.3) | 0.43 |

Data given as mean±SD or n (%). LVA, low-voltage area. Other abbreviations as in Table 1.

**Figure 3.** Presence of low-voltage areas (LVA) vs. chronic kidney disease (CKD) severity. eGFR, estimated glomerular filtration rate.
Low-Voltage Areas and Renal Dysfunction

Low-Voltage Areas and Renal Dysfunction

Abnormalities, such as oxidative stress, sympathetic hyperactivity, activation of the renin-angiotensin-aldosterone system, and left atrial enlargement, which reflect left atrial pressure, increase with CKD severity and might be involved in atrial fibrosis and the presence of LVA.

Patients with LVA were significantly older, more frequently female, and had lower BMI and hemoglobin, higher CHA2DS2-VASc scores, higher BNP, smaller left ventricular diastolic diameter, and more mitral regurgitation than those without LVA, which is in agreement with previous reports. Other factors, such as hypertension, vascular diseases, left ventricular hypertrophy, burden of AF, and left atrial diameter, could influence both CKD and LVA. Given that age, BMI, left ventricular mass index, and left atrial diameter were also predictors of LVA on multivariate analysis, the relationship between CKD and LVA is still controversial. Even after being adjusted by these factors, however, eGFR <71.5 mL/min/1.73 m² was a predictor of LVA prevalence.

In our study, the rate of freedom from atrial tachyarrhythmia recurrence was higher than in a previous study reported by Yamaguchi et al. The PV reconnection rate for the second ablation was similar between patients with and without LVA (72.2% vs. 84.6%, P=0.42).

**Discussion**

In this retrospective observational study, we analyzed 183 cases of AF ablation and investigated the association between the prevalence of LVA and CKD. The main findings were as follows: (1) LVA were present in 42% of the total study population; (2) LVA were more prevalent in patients with the more severe categories of CKD, G3a–G5 (P=0.005); and (3) freedom from AF recurrence was significantly lower in patients with CKD (Figure 4A).

We found that the eGFR calculated using cystatin C was a good predictor of LVA prevalence. Cystatin C is a non-glycosylated, low-molecular-weight protein produced by all nucleated cells at a constant rate. Cystatin C predicted LVA presence more accurately than serum creatinine, possibly because cystatin C has the advantage of being less influenced by dietary protein and muscle mass.

Decreased eGFR was closely associated with the presence of LVA. CKD patients have many hemodynamic, neuroendocrine, and metabolic abnormalities, such as left atrial pressure elevation, sympathetic hyperactivity, activation of the renin-angiotensin-aldosterone system, and oxidative stress. These factors can induce atrial fibrosis, which is associated with LVA.

LVA were significantly associated with the more severe categories of CKD, G3a–G5. Abnormalities, such as oxidative stress, sympathetic hyperactivity, activation of the renin-angiotensin-aldosterone system, and left atrial enlargement, which reflect left atrial pressure, increase with CKD severity and might be involved in atrial fibrosis and the presence of LVA.

In our study, the rate of freedom from atrial tachyarrhythmia recurrence was higher than in a previous study reported by Yamaguchi et al. The PV reconnection rate for the second ablation was similar between patients with or without LVA. The PVI outcome was the same in both groups in the present study. The reason might be the proportion of LVA. In the Yamaguchi et al study, the proportion of areas with low voltage was 18%. In the present study, however, the proportion of areas with low voltage was 7.7%. Yamaguchi et al also reported that the extent of LVA was an independent predictor of recurrence. In their study, if the proportion of areas with low voltage was <5%, the rate of freedom from atrial tachyarrhythmia recurrence was >70%. This result was similar to that of our study.
The present study has several clinical implications. First, eGFR measurement is a non-invasive method for predicting LVA prevalence. Second, the outcome was poorer in patients with LVA, similar to a previous study, suggesting that prediction of outcome is possible by assessing CKD severity.

Several limitations exist in this study. First, given that serum cystatin C is associated with many factors, measurements performed only before the procedure might not be reflective of long-term renal impairment. Second, we could not completely stratify severe CKD patients, such as those with CKD G4 or G5, because of the small sample size. Third, because we conducted voltage mapping after completion of PVI, LVA existence might not have been determined. Fourth, ablation lesions other than PVI were operator dependent, which could possibly affect the result. The influence of inconsistent ablation lesion set on the ablation outcome, however, would be small, because patients receiving extra-PV ablation were not very common. Finally, statistical analyses were limited by the relatively small size of the study population.

Conclusions

CKD severity was correlated with left atrial LVA prevalence in AF patients undergoing catheter ablation.

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Disclosures

The authors declare no conflicts of interest.

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