

# Clinical and serological predictors for the recurrence of atrial fibrillation after electrical cardioversion

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## Aims

Although electrical cardioversion (CV) is effective in restoring sinus rhythm in patients with atrial fibrillation (AF), AF frequently recurs in spite of antiarrhythmic medications. We investigated the predictors of failed CV and AF recurrence after successful CV.

## Methods and results

In 81 patients (M:F = 63:18, 59.1 ± 10.5 years old) with AF who underwent CV, clinical, image, and CV findings (energy requirement, immediate recurrence of AF < 15 min), and pre-CV serological markers were evaluated. Results: (i) During 13.1 ± 10.6 months of follow-up, 8.6% (7/81) showed failed CV, 59.26% (48/81) showed AF recurrence, and 32.1% (26/81) remained in sinus rhythm (no recurrence). (ii) Failed CV showed higher plasma levels of transforming growth factor (TGF)-β ( $P = 0.0260$ ) than those with successful CV. (iii) Patients with AF recurrence were older (60.4 ± 9.0 years old vs. 55.3 ± 12.5 years old,  $P = 0.0220$ ), had a higher incidence of spontaneous echo contrast (SEC; 68.1 vs. 40.0%,  $P = 0.0106$ ), a lower prescription rate of angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB; 27.0 vs. 50.0%,  $P = 0.0248$ ) or spironolactone (0.0 vs. 19.2%,  $P = 0.0007$ ), and lower plasma levels of stromal cell-derived factor (SDF)-1α ( $P = 0.0105$ ).

## Conclusion

Post-CV recurrence commonly occurs in patients with age > 60 years, SEC, under-utilization of ACE-I/ARB or spironolactone, and low plasma levels of SDF-1α. High plasma level of TGF-β predicts failed CV.

## Keywords

Atrial fibrillation • Electrical cardioversion • Recurrence • Predictor

## Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, leading to significant morbidity and disability and resulting in limited quality of life.<sup>1</sup> It has been reported that appropriate rhythm control may have a mortality benefit in patients with AF.<sup>2,3</sup> Although electrical cardioversion (CV) is known to be effective in restoring sinus rhythm in patients with persistent AF (PeAF), AF frequently recurred in spite of concomitant medication with antiarrhythmic drugs (AAD).<sup>4,5</sup> Approximately 50% of patients who successfully cardiovert initially experience AF recurrence within the first month after CV.<sup>6,7</sup> This is due to significant electrical remodelling,<sup>8</sup> structural changes of the atrial myocardium in patients with AF,<sup>9,10</sup> and the

limitations of AAD.<sup>2,4,5</sup> Although there have been several reports,<sup>11,12</sup> the predictors of successful CV or long-term maintenance of sinus rhythm in patients with PeAF are not yet clear. The development of appropriate clinical and serological predictors for recurrence after CV may reduce the number of unnecessary procedures, the risk of complications, and medical costs and may improve the clinical outcome of highly selected patients. Discovering predictors for post-CV recurrence also would contribute to the understanding of AF pathophysiology. Therefore, we investigated whether certain pre-CV factors, such as clinical parameters, imaging analyses, CV findings, and serological parameters related to matrix remodelling, fibrosis, atrial stretching, and chemotaxis, can predict failure or recurrence of AF after electrical CV.

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## Methods

### Study population

This study was approved by the Institutional Review Board of Anam Hospital of Korea University. All patients provided written informed consent. Eighty-one patients with PeAF (male: female = 63:18, mean age  $59.1 \pm 10.5$  years old) who underwent external electrical CV were included in the study. Patients with history of any previous CV, significant mitral valvular heart disease, huge left atrium (LA)  $> 55$  mm, a recent infection, surgery or acute coronary syndrome in the 2 months prior to the collection of blood samples were excluded. All patient maintained optimal anticoagulation, had been taking AAD for at least 1 month, and maintained them after CV. *Trans*-esophageal echocardiography was done to exclude intra-cardiac thrombus and to determine the existence of spontaneous echo contrast (SEC) on the same day of CV in every patient. The blood samples for the serological assays were drawn before sedation for external CV.

### Electrical cardioversion protocol

After obtaining written informed consent, electrical CV was performed under sedation with intravenous midazolam (0.05 mg/kg) and thio-pental sodium (60 mg/kg). A biphasic R-wave synchronized shock (Lifepak12, Physiocontrol Ltd, Redmond, WA, USA) was applied to the patients via self-adhesive skin electrodes (TZ Medical Inc., Portland, OR, USA) in an anterior–posterior position. We delivered an initial CV with 70 J. If the initial shock failed to terminate AF, the biphasic shock energy was gradually increased to 100, 150, and then 200 J serially (5 min intervals). If CV terminated AF successfully, the patient's cardiac rhythm was monitored for 15 min to detect an atrial premature complex (APC) or recurrence of AF. If AF returned within 15 min of termination by CV, we defined it as immediate recurrence of AF (IRAF). In patients with IRAF or frequent APCs, amiodarone 150 mg was administered intravenously and the same energy shock was repeated. Patients in whom AF remained even after 200 J CV or who exhibited repeated IRAF in spite of amiodarone were defined as failed CV.

### Biochemical analyses

We took 5 mL of peripheral blood immediately before CV to measure the plasma levels of several protein markers or chemokines by enzyme linked immuno-sorbent assay (ELISA): pro-atrial natriuretic peptide (ANP; Biomedica, Antony, France), matrix metalloproteinase (MMP)-9, transforming growth factor (TGF)- $\beta$ , and stromal cell-derived factor (SDF)-1 $\alpha$  (R&D Systems, Minneapolis, MN, USA). High sensitivity (hs) C-reactive protein was measured on a Hitachi 912 assay system (Roche Diagnostics, Indianapolis, IN, USA) using the Kamiya K-assay (Kamiya Biomedical Corp., Seattle, WA, USA), which quantitatively determines C-reactive protein by latex particle-enhanced immunoturbidimetric assay. We use the average values of chemokine assays with duplicated plasma samples with difference  $< 10\%$  of lower value to secure the reproducibility.

### Follow-up of patients

After CV, all patients were prospectively followed-up at outpatient clinic at 1, 2, 4, 8 weeks, and then every 3 months thereafter. Electrocardiography (ECG) was performed at every visit or anytime the patient reported palpitations. A Holter ECG (24 or 48 h) and/or event recorder was evaluated at 2 months in patients who did not recur. We classified the patients into three different groups according to clinical outcome as follows: (i) failed CV, (ii) AF recurrence after successful CV, and (iii) no recurrence.

### Statistical analysis

We evaluated the clinical factors [e.g. age, sex, LA size, ejection fraction (EF), SEC, and medication, such as angiotensin-converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), spironolactone, statin, and  $\beta$ -adrenoceptor blocker], CV findings (IRAF, post-CV APCs, final CV shock energy, intravenous amiodarone after failed AF termination), and serological factors (MMP-9, SDF-1 $\alpha$ , TGF- $\beta$ , pro-ANP, and hs-C-reactive protein) in terms of success or failure and the timing of recurrence. Comparisons between groups were analysed by the Mann–Whitney test or a *t*-test. In order to identify the predictors of failed CV or AF recurrence, univariate and multivariate logistic regression analyses and Cox regression analysis were performed. Atrial fibrillation free rates were compared in terms of clinical and serological parameters by utilizing Kaplan–Meier curves. All values were expressed as mean  $\pm$  SD. All statistical analyses were performed using SPSS version 12.0 and a *P*-value of less than 0.05 was considered statistically significant.

## Results

### Patient characteristics and clinical outcomes

We performed external electrical CV in 81 patients ( $59.1 \pm 10.5$  years old, 63 males) with PeAF. The mean LA size was  $45.5 \pm 6.0$  mm, the mean EF of the LV was  $48.7 \pm 15.1\%$ , and 57.7% of patients had SEC in LA. Angiotensin-converting enzyme inhibitor or ARB was prescribed in 30.9% of patients. The prescription rates of spironolactone,  $\beta$ -blocker, and statin were 7.4, 28.4, and 9.9%, respectively. All patients had been taking AAD for at least 1 month before and after CV (amiodarone 60.5%, other class IC AAD 39.5%). The mean number of electrical shock performed was  $1.9 \pm 1.4$ , the final successful CV energy was  $96.7 \pm 32.3$  J, and the cumulative CV energy was  $170.4 \pm 178.5$  J. Then 53.8% showed frequent APC after CV, and 9.9% showed IRAF; and 22.2% received intravenous amiodarone due to repeated IRAF or frequent APCs. Among the 81 patients, 8.6% (7/81) showed failed CV and 91.4% (74/81) underwent successful CV. We followed-up those 74 patients after successful CV for  $13.2 \pm 11.0$  months; and 64.9% (48/74) recurred AF and 35.1% (26/74) remained in sinus rhythm during the follow-up period. Among the patients with AF recurrence, a median time to recurrence was median time  $21.0 \pm 106.6$  days after CV, and 45.8% (22/48) recurred within 2 weeks after CV.

### Predictors for failed electrical cardioversion

Between the patients with failed CV and successful CV, there were no significant differences in age ( $63.7 \pm 8.5$  vs.  $58.62 \pm 10.6$  years old,  $P = 0.1104$ ), sex (male 85.7 vs. 77.0%,  $P = 0.3013$ ), LA size ( $42.5 \pm 6.9$  vs.  $45.8 \pm 5.9$  mm,  $P = 0.1037$ ), EF ( $44.7 \pm 24.4$  vs.  $49.1 \pm 14.1\%$ ,  $P = 0.2326$ ), the existence of SEC (50.0 vs. 58.3%,  $P = 0.3480$ ), or medications. However, the prescription rate of amiodarone was lower in patients with failed CV compared with those with successful CV (28.6 vs. 64.9%,  $P = 0.0301$ ). Immediate recurrence of AF was more common in the failed CV compared with the successful CV group (71.4 vs. 4.1%,  $P < 0.0001$ ). The pre-CV plasma level of TGF- $\beta$ , which reflects the degree of

fibrosis, was significantly higher in patients with failed CV ( $22.7 \pm 22.9$  ng/mL) than in those with successful CV ( $13.5 \pm 9.8$  ng/mL,  $P = 0.0260$ ). In the univariate logistic regression analysis, the existence of IRAF (OR 0.017, 95% CI 0.002–0.126,  $P < 0.001$ ), and a high final CV energy (OR 0.979, 95% CI 0.959–1.000,  $P = 0.046$ ) were closely related to failed CV.

### Predictors for recurrence after successful electrical cardioversion

The recurrence rate of AF after successful CV was 64.9% (48/74) during the  $13.2 \pm 11.0$  months follow-up. Table 1 summarizes comparisons of the clinical and serological parameters in the patients. The patients who showed AF recurrence were older than those without recurrence ( $60.4 \pm 9.0$  vs.  $55.3 \pm 12.5$  years old,  $P = 0.0220$ ). Although there was no significant difference in either body mass index, LA size or EF, SEC more commonly occurred in patients with AF recurrence (68.1%) than in those without recurrence (40.0%,  $P = 0.0106$ ). The prescription rates of ACE-I/ARB (27.1 vs. 50.0%,  $P = 0.0248$ ) and spironolactone (0.0 vs. 19.2%,  $P = 0.0007$ ) were significantly lower in AF recurrence group. However,  $\beta$ -blockers or statin did not affect clinical outcomes. The recurrence rates were 66.7% (32/48) in patients with amiodarone and 61.5% (16/26) in those with class IC AAD ( $P = 0.3780$ ). Pre-CV plasma levels of SDF-1 $\alpha$  ( $3.2 \pm 1.2$  vs.  $3.9 \pm 0.8$  ng/mL,  $P = 0.0105$ ) and pro-ANP ( $4.9 \pm 4.3$  vs.  $6.7 \pm 4.1$  nmol/L,  $P = 0.0477$ ) were lower in patients with AF recurrence

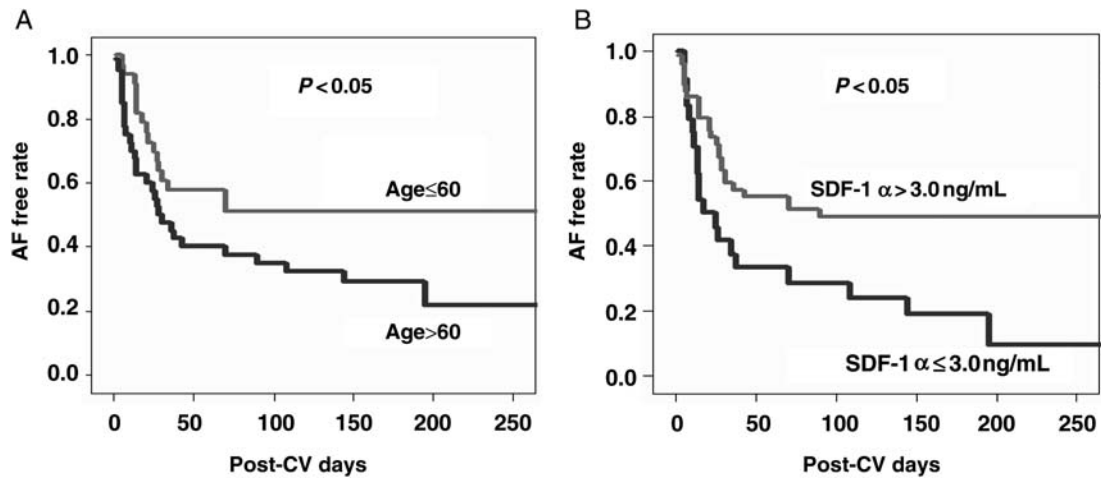
than in those without recurrence. In the univariate logistic regression analyses, it is shown that old age (OR 1.053, 95% CI 1.004–1.053,  $P = 0.035$ ), the existence of SEC (OR 2.833, 95% CI 1.060–7.573,  $P = 0.038$ ), under-utilization of spironolactone (OR 0.079, 95% CI 0.009–0.719,  $P = 0.024$ ), and lower SDF-1 $\alpha$  (OR 0.603, 95% CI 0.379–0.960,  $P = 0.033$ ) may predict AF recurrence. In the multivariate logistic regression analysis, the existence of SEC (OR 3.960, 95% CI 1.263–12.423,  $P = 0.018$ ) and low SDF-1 $\alpha$  (OR 0.537, 95% CI 0.302–0.954,  $P = 0.034$ ) were independent risk factors for AF recurrence. In the multivariate Cox regression analysis, age (HR 1.603, 95% CI 1.008–1.075,  $P = 0.015$ ) was an independent risk factor for AF recurrence. In Kaplan–Meier analyses, the AF recurrence rate was higher in patients who were older than 60 ( $P = 0.0295$ ), did not take spironolactone ( $P = 0.0263$ ), and had plasma SDF-1 $\alpha < 3.0$  ng/mL ( $P = 0.0114$ , Figure 1). There was no specific serological predictor that can predict early vs. late recurrence of AF after CV.

### Spontaneous echo contrast or left atrium size-dependent parameters

In patients with SEC, the LA size was larger ( $47.1 \pm 6.1$  vs.  $43.3 \pm 5.4$  mm,  $P = 0.0031$ ), the incidence of heart failure was higher (28.9 vs. 6.1%,  $P = 0.0055$ ), and pre-CV plasma levels of pro-ANP were higher ( $6.42 \pm 4.29$  vs.  $4.46 \pm 4.00$  nmol/L,  $P = 0.0221$ ) when compared with those without SEC (Table 2). The rate of AF recurrence was also higher (77.3 vs. 54.5%,  $P =$

**Table 1** Comparison of patients with atrial fibrillation recurrence and without recurrence after successful cardioversion

	Recurrence (n = 48)	No recurrence (n = 26)	P-value
Male (%)	81.25	69.23	0.1233
Age (years)	$60.44 \pm 8.99$	$55.27 \pm 12.52$	0.0220
Hypertension (%)	25.0	34.6	0.1940
Heart failure (%)	18.8	15.4	0.3605
Body mass index (kg/m <sup>2</sup> )	$24.2 \pm 2.9$	$25.5 \pm 3.5$	0.0731
LA size (mm)	$46.15 \pm 5.08$	$45.05 \pm 6.63$	0.2286
EF (%)	$48.93 \pm 14.51$	$49.50 \pm 13.67$	0.4346
SEC (%)	68.1	40.0	0.0106
ACE-I/ARB (%)	27.01	50.0	0.0248
$\beta$ -Blocker (%)	18.75	34.62	0.1125
Spironolactone (%)	0.00	19.23	0.0007
Statin (%)	8.33	15.38	0.1789
Amiodarone (%)	66.7	61.5	0.3321
J final (J)	$91.95 \pm 30.10$	$97.78 \pm 36.06$	0.2617
IRAF (%)	6.25	0.00	0.0991
IV AAD (%)	12.50	19.23	0.2220
APC (%)	59.57	50.0	0.2184
Bradycardia (%)	6.67	0.00	0.0961
MMP-9 (ng/mL)	$124.28 \pm 75.80$	$121.58 \pm 40.60$	0.4348
SDF-1 $\alpha$ (ng/mL)	$3.242 \pm 1.24$	$3.88 \pm 0.80$	0.0105
TGF- $\beta$ (ng/mL)	$13.38 \pm 8.15$	$13.61 \pm 11.93$	0.4652
Pro-ANP (nmol/L)	$4.92 \pm 4.36$	$6.68 \pm 4.09$	0.0477
Hs-C-reactive protein (ng/mL)	$4.29 \pm 11.20$	$4.01 \pm 12.68$	0.4616
Time to recurrence (days)	$51.17 \pm 106.58$	$0.00 \pm 0.00$	0.0086



**Figure 1** Kaplan–Meier curves suggest higher recurrence rate of AF after successful CV in patients with age >60 years old (A), and SDF-1 $\alpha$   $\leq$ 3.0 ng/mL (B).

**Table 2** Comparison of patients with spontaneous echo contrast and without spontaneous echo contrast

	SEC+ (n = 45)	SEC– (n = 36)	P-value
Male (%)	73.00	85.00	0.1100
Age (years)	59.22 $\pm$ 9.67	59.70 $\pm$ 10.12	0.4171
Hypertension (%)	35.6	21.2	0.0871
Heart failure (%)	28.9	6.1	0.0055
LA size (mm)	47.06 $\pm$ 6.05	43.26 $\pm$ 5.35	0.0031
EF (%)	49.17 $\pm$ 11.87	51.08 $\pm$ 14.92	0.2664
ACE-I/ARB (%)	37.78	33.33	0.3453
$\beta$ -Blocker (%)	24.44	30.30	0.2851
Spirinolactone (%)	6.67	9.09	0.3480
Statin (%)	11.11	12.12	0.4460
J success (J)	81.63 $\pm$ 25.81	85.00 $\pm$ 39.02	0.3270
J final (J)	94.72 $\pm$ 24.32	101.11 $\pm$ 41.63	0.2238
IRAF (%)	6.67	12.12	0.2058
IV AAD (%)	22.22	21.21	0.4582
APC (%)	52.27	54.55	0.4229
Brady (%)	2.33	6.45	0.1908
MMP-9 (ng/mL)	124.91 $\pm$ 59.46	112.60 $\pm$ 66.18	0.2145
SDF-1 $\alpha$ (ng/mL)	3.56 $\pm$ 1.17	3.38 $\pm$ 1.02	0.2441
TGF- $\beta$ (ng/mL)	15.14 $\pm$ 10.14	12.00 $\pm$ 9.71	0.1031
Pro-ANP (nmol/L)	6.42 $\pm$ 4.29	4.46 $\pm$ 4.00	0.0221
hs-C-reactive protein (ng/mL)	3.02 $\pm$ 9.00	5.45 $\pm$ 14.05	0.1892
Failure of CV (%)	6.67	9.09	0.3896
Recurrence (%)	77.27	54.54	0.0177
Time to recurrence (days)	34.61 $\pm$ 66.31	11.7 $\pm$ 21.43	0.0365

0.0177) and the time to recurrence was later (34.6  $\pm$  66.3 vs. 11.7  $\pm$  21.4 days,  $P = 0.0365$ ) in patients with SEC. However, the existent of SEC did not affect the rate of failed CV or other CV findings (Table 2). In patients with IRAF, the LA size was

smaller than in those without IRAF (40.7  $\pm$  4.6 vs. 46.0  $\pm$  5.9 mm,  $P = 0.0123$ ).

We also compared patients with LA  $\geq$ 45 mm to those with LA <45 mm (Table 3). In patients with LA  $\geq$ 45 mm, the incidence of

**Table 3** Comparison of patients with left atrium size  $\geq 45$  and  $< 45$  mm

	LA $\geq 45$ mm (n = 46)	LA $< 45$ mm (n = 35)	P-value
LA size (mm)	49.60 $\pm$ 3.54	40.06 $\pm$ 3.87	<0.0001
Male (%)	72.7	87.9	0.0540
Age (years)	58.86 $\pm$ 9.68	59.55 $\pm$ 10.05	0.3821
Hypertension (%)	32.6	21.2	0.1354
Heart failure (%)	18.2	21.2	0.3719
EF (%)	51.27 $\pm$ 8.899	49.81 $\pm$ 14.99	0.2969
SEC (%)	69.77	45.45	0.0164
ACE-I/ARB (%)	38.64	30.3	0.2274
$\beta$ -Blocker (%)	29.55	21.21	0.2079
Spirololactone (%)	11.36	3.03	0.0908
Statin (%)	13.64	6.06	0.1435
J success (J)	83.81 $\pm$ 30.92	79.06 $\pm$ 26.07	0.2433
J final (J)	92.97 $\pm$ 29.33	98.85 $\pm$ 31.54	0.2255
IRAF (%)	2.27	18.18	0.0080
IV AAD (%)	15.91	27.27	0.1146
APC (%)	53.49	54.55	0.4641
Bradycardia (%)	7.14	0.00	0.0661
MMP-9 (ng/mL)	124.72 $\pm$ 51.56	110.74 $\pm$ 71.48	0.1867
SDF-1 $\alpha$ (ng/mL)	3.41 $\pm$ 1.23	3.40 $\pm$ 0.92	0.4809
TGF- $\beta$ (ng/mL)	14.67 $\pm$ 11.05	12.88 $\pm$ 9.22	0.2429
Pro-ANP (nmol/L)	5.54 $\pm$ 4.18	5.11 $\pm$ 4.13	0.3254
hs-C-reactive protein (ng/mL)	3.47 $\pm$ 10.71	4.54 $\pm$ 12.44	0.3507
Failure of CV (%)	4.55	12.12	0.1125
Recurrence (%)	70.45	62.50	0.2364
Time to recurrence (days)	41.29 $\pm$ 104.08	23.83 $\pm$ 67.01	0.2150

SEC (69.8 vs. 45.5%,  $P = 0.0164$ ) was higher, but that of IRAF (2.3 vs. 18.2%,  $P = 0.0080$ ) was lower. However, the rates of failed CV and AF recurrence were not affected by LA size. Although the serological parameters were not different between the two groups, MMP-9 (139.6  $\pm$  49.97 vs. 107.78  $\pm$  65.15 ng/mL,  $P = 0.0285$ ) and SDF-1 $\alpha$  (3.76  $\pm$  1.26 vs. 3.24  $\pm$  0.99 ng/mL,  $P = 0.0261$ ) were significantly higher in patients with LA  $\geq 48$  mm than in those with LA  $< 48$  mm.

## Discussion

In the present study, we prospectively explored the predictors for failed CV and AF recurrence after electrical CV systemically. We found that AF recurrence commonly occurred in patients with age  $> 60$  years, SEC, under-utilization of ACE-I/ARB or spironolactone, and low SDF-1 $\alpha$ . High plasma level of TGF- $\beta$  predicts failed CV. Pre-determination of predictors for failed CV or AF recurrence might be useful for clinical decisions on rhythm control strategies and the understanding of pathophysiology in patients with AF.

### The roles of upstream therapy after electrical cardioversion of atrial fibrillation

Although  $\sim 50\%$  of patients who are successfully cardioverted initially experience AF recurrence within the first month after

CV,<sup>6,7</sup> AAD and upstream medical therapy are effective in preventing this. Nakashima et al.<sup>13</sup> first suggested the potential role of angiotensin II inhibitors for preventing atrial electrical and structural remodelling, and Madrid et al.<sup>14</sup> proved its effect in a prospective randomized clinical study in patients with AF after electrical CV. Angiotensin-converting enzyme inhibitor<sup>15,16</sup> and statin<sup>17</sup> also play roles in the inhibition of AF recurrence after CV. However, two recent randomized trials failed to reproduce the benefits of ARB.<sup>18,19</sup> Although these upstream therapies may reduce the recurrence rate of AF after electrical CV by preventing atrial structural remodelling, more clinical data support will be required.

### Immediate recurrence of atrial fibrillation and left atrium size in the recurrence of atrial fibrillation after cardioversion

The pathophysiology of AF is heterogeneous, and, like heart failure, includes various kinds of heart disease.<sup>20</sup> Like the diversity of AF pathophysiology, the factors related to failed CV or AF recurrence might be widespread. In our data, IRAF was more common in failed CV group and in patients with smaller LA ( $< 45$  mm) than in those with LA  $\geq 45$  mm. This finding suggests that an appreciable proportion of AF recurrence after CV in patients with PeAF was trigger-type AF without significant substrate remodelling or LA

enlargement. In those patients with IRAF without significant enlargement of the LA, radiofrequency catheter ablation (RFCA) might be a better strategy for rhythm control than repeated electrical CV. An enlarged LA may reflect the degree of structural remodeling and LA pressure and is one of predictors for recurrence after RFCA of AF.<sup>21,22</sup> However, LA diameter was not related to the failed CV or AF recurrence in this study or other previous studies.<sup>23,24</sup> With this in mind, one may ask why the meaning of LA diameter is different after electrical CV and RFCA. First, AAD were maintained after CV, but stopped within third month after RFCA in most institutes.<sup>21</sup> Second, CV does not change atrial critical mass, but RFCA reduces it which contains multiple reentries.<sup>20</sup> Third, the risk of recurrence after AF ablation is high in patients with an enlarged LA, because of the potential conduction gap on the long distance of linear ablation or non-pulmonary vein foci.<sup>25</sup> Forth, patient selection bias also contributes. In contrast, the mean LA diameter was 45.5 mm in this study, LA dimensions >65 mm have been reported to be associated with AF recurrence after CV.<sup>24</sup> We previously reported that poor mechanical reserve of the LA appendage predicts AF recurrence,<sup>11</sup> and prolonged atrial stunning after electrical CV is also related to poor clinical outcomes.<sup>26</sup> Therefore, atrial mechanical function may be more important in clinical outcomes after CV than atrial morphological changes.

## Spontaneous echo contrast and serological factors after cardioversion

In this study, the existence of SEC and low SDF-1 $\alpha$  were independent risk factors for AF recurrence. In patients with SEC, the LA diameter was long and pre-CV plasma levels of pro-ANP were elevated, but neither LA diameter nor pro-ANP level predicted AF recurrence. Rather, plasma levels of pro-ANP were slightly low in patients with recurrence in this study and others.<sup>27</sup> This finding suggests that AF recurrence is affected by LA function,<sup>11</sup> and LA diameter or the atrial capability to produce pro-ANP might be related with the chronicity of AF.

The chemokine SDF-1 $\alpha$  has been shown to play a key role in haematopoietic or endothelial progenitor cell trafficking in the myocardial ischaemia model.<sup>28–30</sup> However, the role of SDF-1 $\alpha$  has been poorly explored in the pathophysiology of AF. Goette *et al.*<sup>31</sup> report that SDF-1 $\alpha$  levels are higher in PeAF than paroxysmal AF or controls, and SDF-1 $\alpha$  plays some role in the restitution of haematopoietic progenitor cells after failed CV. The reason for the high recurrence of AF in patients with low plasma levels of SDF-1 $\alpha$  remains to be studied. Although it has been reported that high levels of hs-C-reactive protein are associated with an increased risk of recurrence of AF,<sup>12,32</sup> our data and Conway *et al.*<sup>33</sup> failed to prove its clinical predictive value. The plasma level of hs-C-reactive protein may be associated with the permanence of AF related to systemic inflammation or prothrombotic status.<sup>34</sup>

## Study limitations

The patients included in this study were a highly selected group referred for rhythm control, and the number of patients was also limited. The exclusion of patients with large atria bigger

than 55 mm may influence the outcomes related to LA size. We used multivariate logistic regression analysis, because the purpose of our study was to analyse the relationship between the recurrence and multiple variables rather than time-dependent recurrence predictors. Although we found that AF recurrence was more common in patients who were not taking spironolacton, this study was not designed to assess the efficacies of ACE-I/ARB or spironolacton, and the lower recurrence rate may barely reflect better treated heart failure or hypertension in selected patients. The peripheral blood samples may only partially reflect the remote process in the atria. Although we used AAD in all patients before and after CV, the proportion of amiodarone was 60.5% (49/81). We performed CV from 70 J biphasic shock which is lower than ACC/AHA/ESC 2006 guideline,<sup>35</sup> but the initial success rate with 70 J was 59.3% (48/81) being consistent to previous study.<sup>36</sup> Although it has been reported that obesity with sleep apnoea is a strong predictor for the recurrence of AF after SCV,<sup>37</sup> body mass index was not a predictor for recurrence in this study. It may be due to the patient group was relatively homogeneous Asian. We did not include AF duration as a variable due to ambiguity of AF symptom in some patients with PeAF.

## Conclusion

High level of TGF- $\beta$  was related with failed CV. Post-CV recurrence was more common in patients with age >60, SEC, and low SDF-1 $\alpha$  levels. Under-utilization of ACE-I/ARB or spironolactone was related to AF recurrence. However, LA size did not predict AF recurrence. These predictors for AF recurrence after CV might provide additional information in clinical decisions for rhythm vs. rate control and RFCA vs. repeated CV, in addition to helping with understanding of the pathophysiology.

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