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Correlation between inflammation state and successful medical cardioversion using bepridil for refractory atrial fibrillation

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ABSTRACT

Background: It has been reported that inflammation is associated with long-term maintenance of sinus rhythm after electrical cardioversion for non-valvular atrial fibrillation (AF). However, the relation between high-sensitive C-reactive protein (hs-CRP) and the recurrence of AF after medical cardioversion is unknown. On the other hand, bepridil is very effective in restoring sinus rhythm for patients with refractory AF.

Methods and results: In 119 patients with non-valvular AF lasting >6 months who failed to maintain sinus rhythm after medical cardioversion without bepridil or electrical cardioversion, we prescribed bepridil. We divided our patients into success group who maintained sinus rhythm for at least 6 months using bepridil and failure group, and compared the following parameters, which were measured just before prescription of bepridil, between the two groups: hs-CRP as a marker of inflammation, left ventricular end-diastolic dimension, ejection fraction, and left atrial dimension as echocardiographic markers, and the incidence of dyslipidemia, hypertension, and diabetes mellitus. After the treatment with bepridil, 57 patients converted to sinus rhythm; however, 12 patients among these 57 patients could not maintain sinus rhythm. Therefore, the success group consisted of 45 patients (38%). Univariate analysis revealed that left atrial dimension and the value of hs-CRP were significantly lower and ejection fraction was significantly higher in the success group than the failure group. Multivariate analysis showed that hs-CRP and left atrial dimension were independent factors for AF recurrence.

Conclusions: Bepridil is effective in restoring sinus rhythm for refractory AF patients. Inflammation, in addition to left atrial dimension, may be associated with successful cardioversion using bepridil.

Introduction

Some evidence has shown that inflammation, especially high-sensitive C-reactive protein (hs-CRP), is correlated with the presence of non-valvular atrial fibrillation (AF) [1,2]. Moreover, it has been reported that hs-CRP levels may identify the patients with a higher risk of unsuccessful cardioversion [3], as well as patients with AF recurrence [4,5]. Bepridil is one of the most powerful agents that can reverse AF and restore sinus rhythm [6–9]. Our previous report has shown that bepridil can maintain sinus rhythm in approximately 60% of patients with persistent AF after failed electrical cardioversion [9]. Therefore, in this study, we investigated whether inflammation, especially the hs-CRP levels, can be correlated with the efficacy of bepridil in patients with refractory persistent AF.

Methods

Study patients

Between June 2006 and January 2010, we prescribed bepridil for the purpose of cardioversion in patients with non-valvular AF lasting >6 months who failed to maintain sinus rhythm after medical cardioversion without bepridil or electrical cardioversion and who refused ablation therapy for AF. In this study, we defined refractory AF as patients who could not maintain sinus rhythm after medical cardioversion using at least two antiarrhythmic agents excluding bepridil. The duration of AF was determined by

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electrocardiogram and from the patients' declarations. We excluded patients with inflammatory or neoplastic diseases, coronary artery disease, valvular AF, congestive heart failure, or left ventricular dysfunction (ejection fraction <45%), and patients treated long term with corticosteroids or who had an implanted pacing device. All patients underwent echocardiography, 24-h Holter electrocardiography, and blood examination just before the prescription of bepridil. Anticoagulation therapy using warfarin was performed according to the current guidelines [10]. Before the prescription of bepridil, we tried to prescribe at least two antiarrhythmic agents including pilsicainide, propafenone, cibenzoline, or disopyramide. If the patients failed to recover to sinus rhythm through medical cardioversion without bepridil, we recommended electrical cardioversion. If they agreed to receive the electrical cardioversion, they underwent transesophageal echocardiography to check for a thrombus in the left atrium after admission [11]. The protocol of electrical cardioversion was as follows: a shock was delivered with external paddles positioned in the anterior-apex position connected to an external electrical cardioverter for biphasic external cardioversion. The first shock energy was delivered at 200 J. If the first shock attempt failed to convert to sinus rhythm, the second shock was delivered at 300 J. The next shock was delivered at 360 J. If cardioversion was unsuccessful at 360 J, intravenous antiarrhythmic agents, either pilsicainide or disopyramide, were added and a final cardioversion was attempted at 360 J. If the patients failed to recover to sinus rhythm after electrical cardioversion, we prescribed bepridil to be administered after discharge in the out-patient clinic. If the patients refused to receive electrical cardioversion, we prescribed bepridil without electrical cardioversion.

Administration of bepridil

In the study patients, bepridil was prescribed according to the following protocol [9]. Bepridil was given at an initial dose of 100 mg/day for 3 months, with titration to 150–200 mg/day if the low dose failed to restore sinus rhythm. Bepridil was continued for at least 12 months even if sinus rhythm was not recovered. Bepridil was discontinued if severe side effects including torsades de pointes occurred.

Parameters correlated with successful medical cardioversion using bepridil

Just before the administration of bepridil, a blood sample was drawn, and echocardiography was performed. Citrated plasma was stored at −70 °C until analysis. An immunonephelometry assay (Sekisui Medical Co. Ltd., Tokyo, Japan) was used to measure hs-CRP. Other serum markers including serum low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, fasting glucose, hemoglobin A1c, and creatinine were also measured.

On echocardiography before the administration of bepridil, we evaluated the left ventricular end-diastolic dimension, left ventricular ejection fraction, and left atrial dimension. We also evaluated the traditional coronary risk factors including dyslipidemia, hypertension, and diabetes mellitus. Dyslipidemia was identified in patients treated with medication or whose serum LDL cholesterol level was ≥140 mg/dl; hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg and/or the use of anti-hypertensive drugs; diabetes mellitus was identified as a glucose blood level >126 mg/dl and/or the use of anti-diabetic drugs. Medication including antiplatelet agents, calcium channel blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, β blockers and statins were also evaluated.

In this study, we defined the success group as the patients who could maintain sinus rhythm after the administration of bepridil for more than 6 months and the failure group as those who could not recover to sinus rhythm after bepridil or could not maintain sinus rhythm for over 6 months. We compared the above-mentioned factors between the two groups.

The ethics committee at Osaka Rosai Hospital approved this study, and written informed consent was obtained from all patients before the administration of bepridil.

Statistical analysis

All statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago, IL, USA). All results were expressed as means ± SD or number (%). The chi-square test or Fisher exact test was used to compare frequencies. Quantitative data were analyzed with the Mann–Whitney *U*-test. To find independent parameters for successful cardioversion of AF, univariate and multivariate analyses were performed. Variables in the univariate analysis that were significant ($p < 0.05$) were considered in multivariate models. To achieve discrimination ability of the independent parameters using multivariate analysis, a receiving operating characteristics (ROC) curve was plotted, and the optimal cut-off value for each parameter in minimizing the total number of false results and the area under the curve (AUC) were calculated. Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics

The study population consisted of 119 patients with nonvalvular AF (82 men and 37 women). The mean age of the patients studied was 62.7 ± 10.1 years. Among the 119 patients with refractory AF, 68 patients received electrical cardioversion but could not maintain sinus rhythm. The remaining 51 patients refused electrical cardioversion. Before the prescription of bepridil, pilsicainide was administered to 91 patients, propafenone to 43 patients, cibenzoline to 55 patients, and disopyramide to 65 patients. In addition, all 119 patients refused ablation therapy for AF. After treatment with bepridil, 57 patients converted to sinus rhythm; however, 12 patients among these 57 patients could not maintain sinus rhythm for more than 6 months. In these 12 patients, 7 patients received electrical cardioversion. Therefore, the success group consisted of 45 patients (38%), and the failure group consisted of the remaining 74 patients. Baseline clinical characteristics are summarized in Table 1.

Parameters for successful cardioversion using bepridil

As shown in Table 1, the values of hs-CRP and left atrial dimension were significantly lower and ejection fraction was significantly higher in the success group than in the failure group, while there were no significant differences in the other serum and echocardiographic parameters, coronary risk factors, or medications between the two groups. Therefore, the three significant markers—hs-CRP, ejection fraction, and left atrial dimension—were entered into a multivariate logistic model to identify independent parameters for successful cardioversion using bepridil. According to this analysis, hs-CRP and left atrial dimension were the independent parameters for successful cardioversion using bepridil (Table 2).

By constructing a ROC curve for hs-CRP and left atrial dimension, we identified an optimal cut-off value of 0.25 mg/dl as the hs-CRP that minimized false positive and negative results (AUC: 0.64), obtaining a sensitivity and specificity of 86% and 60%, respectively, and we identified an optimal cut-off value of 46 mm as the

Table 1
Baseline characteristics.

	Success group ($n=45$)	Failure group ($n=74$)	p-Value
Age (years)	62.1 ± 10.3	63.7 ± 9.9	0.403
Male (%)	62.2	73.0	0.229
LDL cholesterol (mg/dl)	102.8 ± 18.6	112.0 ± 95.3	0.422
HDL cholesterol (mg/dl)	52.4 ± 18.4	49.3 ± 10.6	0.377
Triglyceride (mg/dl)	198.6 ± 141.6	154.1 ± 92.9	0.060
Glucose (mg/dl)	106.9 ± 28.2	106.3 ± 21.4	0.908
Hemoglobin A1c (%)	5.9 ± 1.1	5.7 ± 0.9	0.138
hs-CRP (mg/dl)	0.22 ± 0.27	0.36 ± 0.42	0.027
Creatinine (mg/dl)	0.96 ± 0.19	0.90 ± 0.24	0.115
Echocardiographic parameters			
Dd	53.2 ± 10.0	52.5 ± 6.7	0.753
EF	64.8 ± 13.9	63.0 ± 8.3	0.043
Left atrial dimension	45.9 ± 5.3	48.2 ± 5.6	0.027
Coronary risk factors			
Dyslipidemia (%)	28.9	32.4	0.686
Hypertension (%)	53.3	44.6	0.576
Diabetes mellitus (%)	20.0	16.2	0.626
Medications			
Antiplatelet agents (%)	8.9	14.9	0.405
Calcium antagonists (%)	26.7	40.5	0.166
ACEI/ARB (%)	53.3	45.9	0.850
β blockers (%)	33.3	21.6	0.197
Statins (%)	26.7	21.6	0.656

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; hs-CRP, high-sensitive C-reactive protein; Dd, left ventricular end-diastolic dimension; EF, left ventricular ejection fraction; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2
Independent parameters for successful cardioversion using bepridil.

	Odds ratio (95% CI)	p-Value
Left atrial dimension (mm)	1.25 (1.05–1.48)	0.029
EF	1.42 (0.84–2.41)	0.090
hs-CRP	1.01 (1.00–1.02)	0.044

EF, ejection fraction; hs-CRP, high-sensitive C-reactive protein.

left atrial dimension that minimized false positive and negative results (AUC: 0.70), obtaining a sensitivity and specificity of 75% and 67%, respectively (Fig. 1).

Ninety-two patients (77%) received 100 mg/day of bepridil, 20 patients received 150 mg/day, and the other 7 received 200 mg/day. During the follow-up period, torsades de pointes or sudden cardiac death did not occur. Sinus bradycardia occurred in 5 patients, and prolonged QTc (>500 ms) occurred in 7 patients. Discontinuation of bepridil prevented these patients from suffering subsequent arrhythmic events.

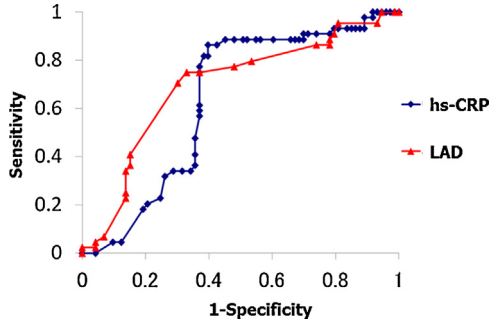

Fig. 1. Receiving operating characteristics (ROC) curve for high-sensitive C-reactive protein (hs-CRP), left atrial dimension (LAD), and successful cardioversion using bepridil.

Discussion

In the present study, we found that both left atrial dimension and hs-CRP levels were associated with successful cardioversion of refractory AF using bepridil.

Although control of the ventricular response is an acceptable treatment in certain subgroups of patients with AF, the restoration and maintenance of sinus rhythm remains the preferred strategy in many patients [12–15]. Although electrical cardioversion is the most commonly used method for sinus rhythm restoration in patients with persistent AF, 20% of patients undergoing electrical cardioversion do not convert [16], and 50% of patients who do successfully cardiovert initially experience AF recurrence within the first month after electrical cardioversion [12,13,17]. Thus, pharmacological cardioversion and maintenance of sinus rhythm are needed in many patients. It has been reported that bepridil (a multichannel blocker) is effective for maintaining sinus rhythm after cardioversion, even in patients with failed electrical cardioversion [9].

Inflammation has been implicated in the pathogenesis of several cardiovascular diseases, most notably atherosclerosis. There is now also substantial evidence linking inflammation to the initiation and perpetuation of AF [18]. Cardiac surgery and cardiopulmonary bypass induce a systemic inflammatory response that is manifested as higher levels of hs-CRP that may contribute to the high recurrence of postoperative AF [19]. Chung et al. first reported an association between AF and elevated hs-CRP in non-postoperative AF [20]. Thereafter, the association between hs-CRP and the presence of AF was supported by many studies [1,21].

In addition to providing insight into the relationship between inflammation and AF, the measurement of hs-CRP might be useful clinically to manage patients with AF. Relapse into AF after cardioversion is common and represents a challenging therapeutic problem. The measurement of hs-CRP prior to cardioversion may help in the risk stratification of patients at increased risk of recurrence. Some evidence has suggested that the measurement of baseline hs-CRP might provide prognostic information regarding the immediate and long-term success of electrical cardioversion [1,21–23]. The present study also showed that, in selected patients with refractory AF, hs-CRP in addition to left atrial dimension can be a good marker for predicting the effects of bepridil on the maintenance of sinus rhythm. With regard to left atrial dimension, Makita et al. also reported that left atrium size was one of the independent predictors for AF recurrence [24].

Our previous data showed that bepridil, especially low-dose bepridil (100 mg/day), could maintain sinus rhythm in refractory AF patients without fatal side effects. Although bepridil is an effective tool for AF conversion in some refractory cases, the substantial drug-related adverse effects, including sudden death, raised questions about using bepridil to treat AF. Because the mortality of AF patients is low even under a standard rate control strategy, the balance between the benefits and risks of bepridil should be determined on an individual basis [25]. This study demonstrated that hs-CRP in addition to left atrial dimension is useful for identifying individuals with refractory AF who are more likely to maintain sinus rhythm using bepridil.

Limitations

Except for hs-CRP levels, we did not assess the other inflammation markers including the tumor necrosis factor-alpha, interleukin-6, P-selectin, E-selectin, CD-40 ligand, and vascular cell adhesion molecule-1. However, although these inflammation markers were useful, they are expensive and less evident as compared to hs-CRP. Thus, we adopted hs-CRP as the screening marker

to predict the effects of bepridil in the patients with refractory AF in this study.

Conclusions

This study showed that when patients show preserved left atrial dimension and a low grade of inflammation, bepridil is effective in restoring sinus rhythm even for refractory AF, including AF cases in which electrical cardioversion has failed.

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