Blood Pressure Control and the Reduction of Left Atrial Overload is Essential for Controlling Atrial Fibrillation

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Summary

The purpose of this study was to investigate whether the ideal control of atrial fibrillation (AF) associated with hypertensive patients depends on the usage of renin-angiotensin system (RAS) inhibitors or whether it occurs regardless of the kind of antihypertensive agents used. The control of AF was compared in 112 outpatients between 1) those with or without the administration of RAS inhibitors, and 2) those with an ideal or poor control of the blood pressure (BP) regardless of the kind of antihypertensive therapy used.

The therapies with or without RAS inhibitors did not yield any significant difference in the AF control states, even though RAS inhibitors had been administered to the patient group with a high proportion of organic heart disease. The ideal BP control group exhibited a significantly better AF control in comparison to the poor BP control group. The former group had a significantly smaller left atrial diameter determined by ultrasonic echocardiography. BP control itself may essentially be important for preventing AF in the general patient population. Poor BP control seemed to have an affect on worsening AF possibly via left ventricular diastolic dysfunction, followed by left atrial overload. (Int Heart J 2009; 50: 445-456)

Key words: Atrial fibrillation, Hypertension, Renin-angiotensin system, Left atrial overload

Atrial fibrillation (AF) is a common and clinically important complication in patients with hypertension.1-6) With the recent increase in elderly people, the prevalence of AF patients associated with hypertension is increasing.1) The risk of AF in hypertensive subjects was shown to have increased by 1.4 times in the Manitoba follow-up study4) and 1.9 times in the Framingham Heart Study7) in comparison to normotensive subjects. Although the clinical significance of hypertension as a risk factor for AF has been established, no prophylactic method

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Paroxysmal AF (PAF) is treated mainly by the administration of antiarrhythmic agents to both prevent the occurrence of AF and to restore sinus rhythm. In PAF patients associated with hypertension, however, a backbone antihypertensive therapy is considered important for preventing PAF (so called “upstream therapy”). Several investigators have documented that the inhibition of the renin-angiotensin system (RAS) using angiotensin converting enzyme inhibitors (ACEIs) or type 1 angiotensin receptor blockers (ARBs) is an idealistic strategy for protection against any atrial remodeling in patients with AF, especially that associated with cardiovascular disorders including hypertension.\(^8\)\(^-\)\(^10\)

However, other reports have documented that no difference in the occurrence of PAF was observed between the use of RAS inhibitors and other conventional antihypertensive agents.\(^11\),\(^12\) It is possible that the level of the control of the blood pressure (BP) itself is essentially important for controlling PAF in hypertensive patients.\(^13\) Thus, there is controversy over whether an ideal PAF control would be obtained depending on whether or not RAS inhibitors are used.

Certain anatomical and physiological changes, for example, the enlargement of the left atrial diameter (LAD) caused by a left atrial pressure overload associated with left ventricular hypertrophy,\(^8\) may be associated with the occurrence of PAF. The question as to whether an effective antihypertensive therapy can reduce the incidence of AF with a reduction in the left atrial overload remains unsolved.

To answer these questions, we retrospectively analyzed the relationship between the control of AF and BP in outpatients, targeting in particular the kind of antihypertensive agents used to control BP. We also analyzed the left atrial diameter (LAD) using ultrasonic echocardiography (UCG) in those patients in order to determine the effects of the atrial overload on the AF occurrence.

**Methods**

**Patient population and PAF event study:** One hundred and twelve outpatients who regularly (once or twice a month) visited the Cardiovascular Division of Asahikawa Medical College Hospital from 2000 to 2007 and who were diagnosed with PAF based on the evidence obtained from ECG recordings were enrolled in this study. PAF was defined as AF that had continued for no longer than 7 days prior to the start of the study. On the other hand, persistent AF was defined as AF that continued for more than 7 days, and permanent AF was defined as that for which no restoration of sinus rhythm was expected. Patients with persistent and permanent AF at the start of the study were excluded. There was no intention to select patients based on their age, sex, background disease,
or medications, including antiarrhythmic and antihypertensive agents. Associated heart diseases were diagnosed by conventional examinations performed in the outpatient clinic such as the ECG, chest X-rays, echocardiography (UCG) and, in selected patients, cardiac scintigraphy and cardiac magnetic resonance imaging. The patients treated by nonpharmacological therapies were excluded from the investigation.

All patients were divided into clusters based on the following 2 classification criteria.

**Study 1. The classification was according to the antihypertensive agents administered:** The patients were divided into the following 3 groups; 1) 38 patients without hypertension, whose definition was a systolic BP of < 140 mmHg and diastolic BP of < 90 mmHg who did not receive any antihypertensive therapy (group NT), 2) 40 patients treated with antihypertensive agents other than ACEIs/ARBs (group HT), and 3) 34 patients treated with ACEIs/ARBs (group A-HT).

**Study 2. Classification according to the state of the BP control:** Regardless of the antihypertensive therapy, the patients in groups HT and A-HT were divided into 2 categories; 1) 39 patients whose outpatient clinic BP was controlled with a systolic BP of < 130 mmHg and diastolic BP < 85 mmHg (Ideal-BPC), and 2) 35 patients whose outpatient clinic BP was a systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg (Poor-BPC).

In both studies, the age, gender, heart rate, background cardiac and non-cardiac disorders, and antiarrhythmic agents used were compared among the groups and between categories. The antihypertensive agents administered were also compared between the categories in study 2. The BP was compared before and after the start of the antihypertensive agents.

In all patients, the state of the PAF control was assessed by the occurrence of events presumed to be PAF. An “event” was defined as follows; 1) the occurrence of palpitations continuing for more than 30 minutes, 2) visits to the outpatient clinic or hospitalizations for AF events confirmed by an ECG, and 3) capturing AF by chance on an ECG during an ordinary outpatient visit. ECG evidence of AF in definition 1 and palpitations in definition 3 were not necessary. In every group and category, the occurrence of events was followed for at least 2 years in the patients within group 1 with classification 1 (no hypertension), or after the start of the antihypertensive agents in the other patients, and the percent ratio of the number of event-free patients to the total patients included (Event-FR) were periodically (basically one or two visits a month) checked.

**LAD determined from the UCG:** In all patients, the LAD determined by the UCG recording were analyzed, and compared between the Ideal-BPC and Poor-BPC patient categories. The timing of the sampling was arbitrary during the
study, but was limited to 1) after the antihypertensive therapy had been started, and 2) before the occurrence of any AF events as defined in the above-mentioned criteria.

Statistics: The differences in patient characteristics among groups in study 1 and between categories in study 2 were tested by Fisher’s exact probability test. The difference between the BP before and after the antihypertensive therapy was compared using Student’s paired t test. Kaplan-Meier analysis was employed to compare the decline in the Event-FR among the groups and between categories. The differences in the BPs and LAD between the Ideal-BPC and Poor-BPC categories were compared using Student’s non-paired t test. A P value of < 0.05 was considered significant.

Results

The mean duration of the antihypertensive therapy in the hypertensive patients was 2.5 ± 1.6 years. The type of antihypertensive agent used was arbitrarily selected by the outpatient doctors. The type and timing of the start of the antiarrhythmic therapy also varied. In the patients without hypertension, the mean duration of the follow-up was 2.9 ± 0.8 years.

Study 1. Control of AF and antihypertensive agents: Table I lists the patient characteristics. The age, gender, incidence of DM, dyslipidemia, and the administration of antiarrhythmic agents did not differ among the groups. However, the incidence of organic heart disease was significantly (P < 0.01) higher in group A-HT (71%) than in groups NT (0%; P < 0.01) and HT (33%; P < 0.05).

Figure 1 presents a comparison of systolic and diastolic BPs before and after the antihypertensive therapy. In group HT, the antihypertensive drugs used are as follows; calcium channel blockers: 88%, diuretics: 25%, beta blockers: 20%, others: 15%.

Table I. Comparison of the Patient Characteristics Among the Groups in Study 1

<table>
<thead>
<tr>
<th></th>
<th>NT (n = 38)</th>
<th>HT (n = 40)</th>
<th>A-HT (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62 ± 14</td>
<td>64 ± 7</td>
<td>64 ± 9</td>
</tr>
<tr>
<td>Male (%)</td>
<td>68</td>
<td>63</td>
<td>47</td>
</tr>
<tr>
<td>Heart rate (/min)</td>
<td>74 ± 5</td>
<td>76 ± 12</td>
<td>72 ± 10</td>
</tr>
<tr>
<td>Incidence of organic heart disease (%)</td>
<td>0*</td>
<td>33*</td>
<td>71</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>69</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy (%)</td>
<td>23</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Others (%)</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Incidence of diabetes (%)</td>
<td>29</td>
<td>40</td>
<td>32</td>
</tr>
<tr>
<td>Incidence of dyslipidemia (%)</td>
<td>18</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Percentage of patients receiving antiarrhythmic therapy (%)</td>
<td>92</td>
<td>75</td>
<td>88</td>
</tr>
</tbody>
</table>

In group HT, the antihypertensive drugs used are as follows; calcium channel blockers: 88%, diuretics: 25%, beta blockers: 20%, others: 15%.

*: P < 0.05, **: P < 0.01 versus A-HT. +: Percentage of patients to whom class I or III antiarrhythmic agents were administered.
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After antihypertensive therapy. In both the HT and A-HT groups, the BP significantly decreased after the medication, and the values after the therapy did not differ between the 2 groups.

Figure 1. Comparison of the systolic (■) and diastolic (●) blood pressures before and after the antihypertensive therapy. NT: no hypertension, HT: hypertension treated by agents other than angiotensin converting enzyme inhibitors (ACEIs) or type 1 angiotensin receptor blockers (ACEIs/ARBs), A-HT: hypertension treated by ACEIs/ARBs. The values (mmHg) are presented as the mean ± SE. Each value is described below the graph. The BPs after the therapy (*) did not differ between the HT and A-HT groups.

Figure 2. Comparison of the 2-year time course of the event free ratio (Event-FR). The declivity of the curve was weakest in group NT, which resulted in a best Event-FR at the 2-year follow-up (88%, $P < 0.05$) among the 3 groups. The declivity of the Event-FR curve did not differ between groups HT and A-HT, with an Event-FR at the 2-year follow-up of 61% and 56% (ns), respectively.
Figure 2 compares the 2-year time course of the Event-FR. The declivity of the Event-FR curve was weakest in group NT, which resulted in a best Event-FR at the 2-year follow-up (88%, $P < 0.05$) among the 3 groups. Of note, the declivity of the Event-FR curve did not differ between groups HT and A-HT, with an Event-FR at the 2-year follow-up of 61% and 56% (NS), respectively.

**Study 2. Difference in the control of AF according to the BP control:** Table II lists the comparative patient characteristics between the categories of study 2. Age,
gender, incidence of DM, dyslipidemia, and the administration of antiarrhythmic drugs did not differ among the groups. In this classification, the incidence

![Figure 4](image1.png)

**Figure 4.** Comparison of the 2-year time courses of the Event-FR. The declivity of the Event-FR curve was weakest in category Ideal-BPC, with an Event-FR at the 2-year follow-up of 83%. On the other hand, the Event-FR curve was steepest in category Poor-BPC, with an Event-FR at the 2-year follow-up of 23% ($P < 0.05$ versus category Ideal-BPC).

![Figure 5](image2.png)

**Figure 5.** Comparison of the mean left atrial diameter (LAD) on echocardiography between both categories. The values are presented as the mean ± SE. The LAD was $39 \pm 4$ mm in category Ideal-BPC whereas it was $43 \pm 7$ mm in category Poor-BPC ($P < 0.05$).
of background organic heart disease and the patients treated by RAS inhibitors also did not differ.

Figure 3 compares the mean BP between the Ideal-BPC and Poor-BPC categories. Before the antihypertensive therapy, no significant difference was observed between the 2 categories. After the antihypertensive therapy, the systolic and diastolic BPs were 119 ± 10 mmHg and 68 ± 7 mmHg in category Ideal-BPC, whereas they were 138 ± 7 mmHg and 83 ± 7 mmHg in category Poor-BPC ($P < 0.05$ in both systolic and diastolic BPs), respectively.

Figure 4 compares the 2-year time course of Event-FR. The declivity of the Event-FR curve was weaker in Ideal-BPC, with an Event-FR at the 2-year follow-up of 83%. On the other hand, the Event-FR curve was steeper in Poor-BPC, with an Event-FR at the 2-year follow-up of 23% ($P < 0.05$ versus Ideal-BPC).

**Study 3. LAD determined by UCG:** Figure 5 demonstrates the comparison of the mean LAD between both categories. The LAD was 39 ± 4 mm in Ideal-BPC, whereas it was 43 ± 7 mm in category Poor-BPC ($P < 0.05$).

**Discussion**

In several cardiovascular disorders including hypertension, a mechanical stretch of the myocardial cell promotes a Ca inflow and increase in angiotensin II. Angiotensin II activates extracellular signal–regulated kinase (ERK) which causes intercellular fibrosis of the atria, resulting in a conduction delay that facilitates reentry. Thus, angiotensin II may deeply affect the occurrence and perpetuation of AF. On the basis of this concept, many experimental and clinical investigations have targeted the efficacy of RAS inhibition for the prevention of AF.\(^{8-10,15-18}\) Okazaki, et al reported in an experimental study in rats that candesartan inhibited atrial fibrosis caused by treatment with L-NAME, an NOS inhibitor.\(^{9}\) Kumagai, et al observed that RAS inhibitors blocked both the shortening of the atrial effective refractory period (electrical remodeling) and atrial fibrosis (anatomical remodeling) in a high-frequency pacing canine AF model.\(^{10}\) Clinically, in the results of a subanalysis of the Losartan Intervention For Endpoint (LIFE) study, losartan significantly inhibited new onset AF in comparison with atenolol.\(^{8}\) Therefore, it seemed that RAS inhibitors may be an ideal therapy for an upstream therapy for AF.

On the other hand, it was suggested that other antihypertensive agents, such as calcium channel blockers, may also prevent AF.\(^{19}\) The results of a meta-analysis by Healey, et al suggested that the AF protection effect of RAS inhibitors in the hypertension patient group was controversial.\(^{13}\) Hansson, et al suggested that AF prevention did not differ between the use of RAS inhibitors and
other antihypertensive drugs. Therefore, it is possible that the BP lowering itself may have an inhibitory effect on AF.

This study aimed to elucidate the relationship between the kind of antihypertensive agents and AF occurrence, and the importance of the BP control itself. The first main finding in this study was that the PAF event-free maintenance did not differ between the groups with (group A-HT) or without (group HT) treatment with RAS inhibitors. Surprisingly, the best event-free maintenance was obtained in group NT, representing no hypertension, and in both the HT and A-HT groups the event-FR did not differ. Next, focusing on the importance of the BP control, the hypertensive patients were shuffled and reclassified into 2 categories (Ideal-BPC and Poor-BPC) in this study. As a result, Ideal-BPC exhibited a much higher Event-FR at the 2-year follow-up in comparison with Poor-BPC. The Event-FR of Ideal-BPC (83%) was relatively close to that of group NT (no hypertension) in classification 1 (88%) rather than those of groups HT and A-HT (61% and 56%, respectively). These results suggest that the BP control itself was superior to the type of antihypertensive agents for controlling PAF.

When discussing the mechanism of the effectiveness of antihypertensive therapy for AF, the structural changes in the heart caused by the hypertension should be seriously considered. In general, patients with AF have a larger LAD than those with sinus rhythm. In hypertensive patients, a progression of the left ventricular hypertrophy and resultant cardiac remodeling may cause diastolic dysfunction, which causes a left ventricular inflow disturbance followed by a modification of the atrial hemodynamics yielding an elevation in the atrial pressure and atrial dilatation. Theoretically, it may cause atrial remodeling which may have a deep connection with the occurrence of AF. The Framingham study revealed that a 5 mm increase in the LAD produced a 39% increase in the incidence of AF. Thus, a left atrial overload and the resultant LAD increase would be a favorable predictor of cardiac remodeling and a parameter of the efficacy of antihypertensive and antiarrhythmic therapies. On the basis of this concept, the mean LAD observed on the echocardiography was compared between the Ideal-BPC and Poor-BPC categories in this study. The LAD was significantly smaller in the Ideal-BPC category, indicating that good BP control caused a lesser left atrial overload. Thus, it is postulated that a strict BP control leads to a left atrial overload reduction and resultant ideal PAF control.

Cardiac remodeling and a left atrial overload are not expressed only in patients with hypertension. Several organic heart diseases such as ischemic heart disease, cardiomyopathy, and valvular heart disease can develop into chronic heart failure associated with a left atrial overload. Recent mega-trials have revealed the efficacy of RAS inhibitors on the incidence of AF in several patient
populations with heart disease. In the present study, it is worth noting that the incidence of organic heart disease was significantly higher (71%) in group A-HT. As this study was performed retrospectively, it is natural that our group A-HT predominantly included patients associated with organic heart disease. Thus, our results can be interpreted as follows; even for patient populations that have organic heart disease in the majority of the subjects, the AF-suppression effect of RAS inhibitors was comparable to that of the other antihypertensive therapy patient group (group HT) that had a lower incidence (33%) of organic heart diseases. This interpretation may support the viewpoint that RAS inhibition is a potent upstream therapy for AF in hypertensive patients.

However, in our results from study 2, the proportion of patients with organic heart disease and those treated by ACEIs/ARBs did not differ between the Ideal-BPC and Poor-BPC categories. Accordingly, it should be emphasized that the BP control itself was essentially important for controlling the AF associated with hypertension. Our results also suggest that good BP control was significantly associated with the left atrial overload reduction, which is an indispensable factor for controlling AF.

Thus, in the present study we proposed 2 important factors affecting the occurrence and worsening of AF; poor BP control and the consequent left atrial overload. However, the factors concerning the AF occurrence are more complicated. Some investigators provided evidence that inflammatory reactions are closely related to the occurrence and persistence of AF. Statin therapy or fish intake were also reported to reduce the risks of AF. To give a definitive resolution to the question what are the exact factors affecting the AF occurrence, we must wait for the results of several ongoing world-wide prospective studies, including those in our country.

Conclusion: To investigate whether an ideal PAF control is obtained depending on the usage of RAS inhibitors or regardless of the type of antihypertensive agents used, we retrospectively compared the control of AF in 112 outpatients between 1) those with or without the administration of RAS inhibitors, and 2) those with an ideal or poor BP control regardless of the type of antihypertensive therapy used. Therapies with or without RAS inhibitors did not yield any significant difference in the control of AF, even though RAS inhibitors had been administered to the patient group with a high proportion of organic heart disease. The ideal BP control group exhibited a significantly better AF control in comparison to the poor BP control group. The former group had a significantly smaller LAD observed in the UCG recording. Thus, it seemed that RAS inhibitors were comparatively effective for preventing AF in patients with hypertension and structural heart disease. However, the BP control itself may essentially be important for preventing AF in the general patient population. It is speculated
that a poor BP control may have the affect of worsening the AF possibly via the left ventricular diastolic dysfunction and left atrial overload that follow.

REFERENCES


