*Original Article*

# Enhanced Left Atrial Reservoir, Increased Conduit, and Weakened Booster Pump Function in Hypertensive Patients with Paroxysmal Atrial Fibrillation

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**The aim of this study was to evaluate whether paroxysmal atrial fibrillation (PAF) has an impact on left atrial (LA) function in hypertensive patients and, if so, to select clinical factors influencing this relationship. Sixty-four essential hypertensive patients with PAF (group EHf) and fifty-five patients without PAF (group EH) were enrolled. Using acoustic quantification, the maximal and minimum LA volume ($LAV_{max}$, $LAV_{min}$), the LA volume at the end of rapid emptying (EREV), and the LA volume at the onset of atrial emptying (OAEV) were measured. The LA total emptying volume (TE; TE = $LAV_{max} - LAV_{min}$), LA rapid emptying volume (RE; RE = $LAV_{max}$ – EREV), and left atrial ejection fraction (LAEF) = (OAEV – $LAV_{min}$)/OAEV × 100% were calculated. $LAV_{max}$, $LAV_{max}$ indexed to body surface area ($LAV_{max}$I), TE and RE were significantly increased in group EHf. LAEF was clearly lower in group EHf than in group EH. The linear regression analysis showed that the frequency and total number of PAF episodes were the factors with the greatest influence on $LAV_{max}$I ($r$=0.787, $p$<0.05). TE and frequency of PAF episodes were the most influential factors on RE ($r$=0.902, $p$<0.01). These results suggest that the occurrence of PAF in hypertensive patients is associated with enhanced LA reservoir and conduit function and worse booster pump function. The enhancement of LA reservoir function may be related to the frequency and total number of PAF episodes, and the increased LA conduit function may be related to the LA total emptying volume and frequency of PAF episodes. (*Hypertens Res* 2008; 31: 395–400)**

***Key Words*: paroxysmal atrial fibrillation, hypertension, left atrial, atrial function**

## Introduction

Atrial fibrillation (AF) and hypertension are two prevalent and often coexistent conditions in clinical practice. Hypertension is associated with left ventricular hypertrophy, impaired ventricular filling and left atrial (LA) enlargement. These changes in cardiac structure and physiology favor the development of atrial fibrillation, and then increase the risk of thromboembolic complications (*1*).

The left atrium modulates left ventricular filling through three components: a phase of reservoir or expansion during systole, a conduit phase during diastole, and an active contractile component during late diastole (*2*). LA structural and

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functional changes occur in patients with hypertension, and previous reports have indicated a direct relationship between arterial hypertension and LA dysfunction (*3*, *4*). Loss of LA pumping and dilatation of the LA chamber are often the result of atrial fibrillation, but few studies have investigated the relationship between paroxysmal atrial fibrillation (PAF) and LA function in hypertensive patients.

Several modalities, such as nuclear scintigraphy and angiography, have been used to assess LA performance by measuring changes in LA volume over time (*5*). These techniques are somewhat limited by their expense and their requirement of radiopharmaceutical agents. M-mode LA dimension and LA volumes measured by the biplane area-length method have been shown to be increased in patients with PAF (*6*, *7*). However, the M-mode method is expected to become increasingly inaccurate as the LA enlarges.

The acoustic quantification (AQ) method allows instantaneous cavity measurements to provide on-line assessment of atrial volumes, and the usefulness of AQ to assess atrial volume and function has been validated in a previous study (*8*). The present study was designed to assess the impact of PAF on LA reservoir, conduit and booster pump function in hypertensive patients, and to identify the clinical factors influencing this relation.

## Methods

### Study Patients

Sixty-four hypertensive patients (39 men and 25 women; mean age 54.03±7.36 years; range 39–72 years; group EHf) who satisfied the following criteria were enrolled between January 2000 and February 2004: documentation of recurrent and self-terminating AF with episodes lasting no more than 7 days (*9*). Patients with persistent or permanent AF, valvular heart disease and hyperthyroidism were not included. Any past history of PAF, the total number of PAF episodes, and the mean frequency of PAF episodes were included as baseline data.

Fifty-five hypertensive patients without history of PAF (35 men and 20 women; mean age 54.18±10.63 years; range 28–70 years; group EH) were included. In the vast majority of cases, the hypertension was mild or well controlled with therapy. All patients had normal left ventricular systolic function and were in sinus rhythm at the time of examination.

The normal subjects group (group N) consisted of 49 patients (30 men and 19 women; mean age 52.73±10.67 years; range 37–76 years) with no history of PAF, hypertension or other cardiovascular disease. Groups were matched for age and gender.

### Conventional Echocardiography

All patients and normal subjects underwent two-dimensional, M-mode and Doppler echocardiography. All examinations were performed using a commercially available SONOS 5500 (Philips Corp., Andover, USA) ultrasound system. M-mode-derived LA anterior-posterior dimension was measured in the parasternal long axis view and LA anterior-posterior dimension indexed to body surface area was calculated.

We measured the left ventricular septal and posterior wall thickness, left ventricular end-systolic and end-diastolic dimensions, and left ventricular ejection fraction. According to the mitral and pulmonary vein flow, the left ventricular diastolic dysfunction was classified as an abnormal relaxation pattern (defined as an $E/A$ ratio $<1$ or an $E/A$ ratio $=1$ to 2 and a deceleration time [DT] $>240$ ms; Grade 1), pseudonormal relaxation pattern (normal $E/A$ ratio and DT but abnormal pulmonary venous inflow pattern of reversed systolic/diastolic forward flow ratio; Grade 2), or restrictive filling pattern (defined as an $E/A$ ratio $>2$ or an $E/A$ ratio $=1$ to 2 and a DT $\leq 140$ ms; Grade 3), as previously described (*10*, *11*).

### Acoustic Quantification

AQ is an automated online technique that analyzes the ultrasound backscatter to identify the blood–tissue interface of cardiac chambers and generate volume waveforms within a defined region of interest (*12*, *13*). The automated border detection system is activated and optimized by adjusting the total and lateral gain and temporal gain compensation. The AQ-derived instantaneous volume in volume over time waveforms is displayed together with the electrocardiography tracing.

Parameters measured included the largest LA volume at the end of ventricular systole ($LAV_{max}$), the smallest LA volume after atrial emptying at the end of ventricular diastole ($LAV_{min}$), the LA volume at the end of rapid emptying (EREV), and the LA volume at the onset of atrial emptying (OAEV). LA onset atrial emptying volume index (OAEVI) = OAEV/body surface area.

LA reservoir function was assessed using total emptying volume (TE) = $LAV_{max} - LAV_{min}$, LA end-systolic volume index ($LAV_{max}I$) = $LAV_{max}$/body surface area.

Parameters of LA conduit function included: rapid emptying volume (RE) = $LAV_{max}$ − EREV, and rapid emptying fraction of total emptying (REF) = ($LAV_{max}$ − EREV)/($LAV_{max} - LAV_{min}$) × 100%.

Parameters of atrial booster pump function included: atrial emptying volume (AE) = OAEV − $LAV_{min}$, LA ejection fraction (LAEF) =AE/OAEV × 100%, and active emptying fraction of total emptying (AEF) = (OAEV − $LAV_{min}$)/( $LAV_{max} - LAV_{min}$) × 100%.

### Statistical Analysis

All values were expressed as the means±SD. Values in different groups were compared using a one-way ANOVA test for continuous variables. Linear regression analysis was carried out to identify the factors influencing the values of LA

**Table 1. Baseline Characteristics and Echocardiographic Data of the Hypertensive Patients with (Group EHf) and without PAF (Group EH) and Comparison among Patients and Normal Subjects (Group N)**

| | Group N ($n$=49) | Group EH ($n$=55) | Group EHf ($n$=64) |
|---|---|---|---|
| Age, years | 52.73±10.67 | 54.18±10.63 | 54.03±7.36 |
| Male/female gender, No. | 30/19 | 35/20 | 39/25 |
| Heart rate, beats/min | 67.86±10.75 | 70.93±11.33 | 68.45±11.03 |
| History of hypertension, years | | 11.05±10.07 | 10.20±9.23 |
| Systolic BP, mmHg | 117.65±9.59 | 149.77±21.43*** | 146.45±21.03*** |
| Diastolic BP, mmHg | 79.10±8.75 | 94.20±12.83*** | 89.21±12.12** |
| Body mass index, kg/m$^2$ | 24.00±3.36 | 27.59±2.96*** | 26.72±3.39* |
| LA dimension, cm | 3.10±0.23 | 3.45±0.47*** | 3.77±0.28***$^{\#}$ |
| LA dimension index, cm/m$^2$ | 1.80±0.16 | 1.87±0.32 | 2.10±0.28**$^{\#}$ |
| LV septal wall thickness, cm | 0.95±0.16 | 1.32±0.25*** | 1.26±0.19*** |
| LV posterior wall thickness, cm | 0.96±0.13 | 1.16±0.16*** | 1.15±0.17*** |
| LVMI, g/m$^2$ | 79.95±19.16 | 121.64±40.25*** | 113.32±35.23** |
| LVEF (M-mode) | 0.65±0.05 | 0.66±0.10 | 0.65±0.05 |
| *E*/*A* ratio | 1.23±0.21 | 0.83±0.25*** | 1.13±0.37$^{\#\#\#}$ |
| Diastolic dysfunction grade | 0.56±1.04 | 1.33±0.75** | 1.00±0.92 |
| Mild to moderate mitral regurgitation, No. | | 3 | 5 |

PAF, paroxysmal atrial fibrillation; BP, blood pressure; LA, left atrial; LV, left ventricular; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; *E*/*A* ratio, *E*/*A* ratio of mitral flow. Compared with normal subjects, *$p$<0.05, **$p$<0.01, ***$p$<0.001; compared with hypertensive patients without paroxysmal atrial fibrillation, $^{\#}p$<0.05, $^{\#\#\#}p$<0.001.

function. All significance tests were 2-sided and $p$<0.05 was chosen as the cut-off for statistical significance. SPSS 11.0 was used to analyze all the data.

## Results

### Baseline Characteristics

A comparison of the baseline demographic and echocardiographic parameters among the three groups is displayed in Table 1. There were no significant difference in age, sex, heart rate and left ventricular ejection fraction among the three groups. No difference was found in history of hypertension, systolic and diastolic blood pressure, body mass index, left ventricular septal and posterior wall thickness and left ventricular mass index, diastolic dysfunction grade or the severity of mitral regurgitation between group EHf and group EH.

LA dimension and LA dimension indexed to body surface area were found to be significantly higher in group EHf than in group EH or group N. The *E*/*A* ratio of mitral flow was lower in group EH than in group EHf or group N.

### LA Reservoir Function and Size

$LAV_{max}$, $LAV_{min}$, EREV, OAEV, $LAV_{max}I$, OAEVI and TE were significantly increased in group EHf compared with group EH and group N (Table 2).

$LAV_{max}$ and $LAV_{max}I$ were correlated positively with the frequency and total number of PAF episodes ($r$=0.500–0.630, $p$<0.01–0.05) in group EHf. The linear regression analysis showed that the frequency and total number of PAF episodes were the most influential factors on $LAV_{max}I$ ($r$=0.787, $p$<0.05) (Table 3). The total number of PAF episodes was the most influential factor on $LAV_{max}$ ($r$=0.595, $p$<0.05).

### LA Conduit Function

The RE values (group N, 27.41±10.34; group EH, 30.82±16.15; group EHf, 41.52±12.77 mL; $p$<0.01 for group EHf *vs*. group EH, $p$<0.001 for group EHf *vs*. group N) were significantly higher in group EHf compared with group EH and group N. The REF in group EHf (0.73±0.14) was higher than that in group EH (0.64±0.18), although the difference was not significant. RE was correlated positively with $LAV_{max}$, $LAV_{max}I$ and TE ($r$=0.48–0.82, $p$<0.05–0.001) in group EHf. The linear regression analysis showed that the TE and frequency of PAF episodes were the most influential factors on RE ($r$=0.902, $p$<0.01).

### LA Booster Pump Function

Hypertensive patients with and without PAF had similar AE, and the AE values for both groups were greater than those in normal subjects. LAEF in group EHf was significantly lower than that in group EH (EHf: 0.43±0.15 *vs*. 0.53±0.15; $p$<0.01), although there was no significant difference in AEF

**Table 2. Comparison of Left Atrial Acoustic Quantification Parameters among Patients and Normal Subjects**

| | Group N ($n$=49) | Group EH ($n$=55) | Group EHf ($n$=64) |
|---|---|---|---|
| $LAV_{min}$ (mL) | 12.26±8.10 | 13.85±9.38 | 21.07±12.50***,## |
| $LAV_{max}$ (mL) | 45.25±17.34 | 61.22±23.17** | 81.64±20.25***,### |
| EREV (mL) | 19.79±10.96 | 30.39±16.49** | 39.07±18.09***,# |
| OAEV (mL) | 19.25±9.34 | 30.15±15.27** | 38.64±17.25***,# |
| RE (mL) | 27.41±10.34 | 30.82±16.15 | 41.52±12.77***,## |
| AE (mL) | 8.35±4.26 | 16.29±9.82*** | 16.51±9.99** |
| TE (mL) | 35.69±14.13 | 47.36±18.36** | 59.70±17.17***,## |
| REF | 0.75±0.09 | 0.64±0.18** | 0.73±0.14 |
| AEF | 0.24±0.09 | 0.34±0.16** | 0.27±0.16 |
| LAEF | 0.45±0.15 | 0.53±0.15* | 0.43±0.15## |
| $LAV_{max}I$ (mL/m$^2$) | 24.83±9.68 | 32.85±11.84* | 46.22±15.16***,### |
| OAEVI (mL/m$^2$) | 10.61±4.61 | 16.28±8.36** | 22.70±11.52***,## |

$LAV_{min}$, the smallest LA volume after atrial emptying at the end of ventricular diastole; $LAV_{max}$, the largest LA volume at the end of ventricular systole; EREV, LA volume at the end of rapid emptying; OAEV, LA volume at the onset of atrial emptying; RE, LA rapid emptying volume; AE, LA atrial emptying volume; TE, total emptying volume; REF, rapid emptying fraction of total emptying; AEF, active emptying fraction of total emptying; LAEF, LA ejection fraction; $LAV_{max}I$, LA end-systolic volume index; OAEVI, LA onset atrial emptying volume index; LA, left atrial. Compared with normal subjects, *$p$<0.05, **$p$<0.01, ***$p$<0.001; compared with hypertensive patients without paroxysmal atrial fibrillation, #$p$<0.05, ##$p$<0.01, ###$p$<0.001.

**Table 3. The Linear Regression Analysis of $LAV_{max}$, $LAV_{max}I$ and RE in Group EHf**

| Regression equation | Correlation coefficient | $r^2$ | $p$ value |
|---|---|---|---|
| $LAV_{max}I$=34.730+4.498×Freq+0.083×Number | 0.787 | 0.619 | 0.014 (Freq), 0.032 (Number) |
| $LAV_{max}$=73.723+0.181×Number | 0.595 | 0.354 | 0.019 |
| RE=0.039+0.686×TE−3.735×Freq | 0.902 | 0.814 | 0.000 (TE), 0.004 (Freq) |

$LAV_{max}$, the largest LA volume at the end of ventricular systole; $LAV_{max}I$, LA end-systolic volume index; RE, LA rapid emptying volume; Freq, frequency of paroxysmal atrial fibrillation (PAF) episodes; Number, total number of PAF episodes; TE, total emptying volume.

between group EHf and EH (EHf: 0.27±0.16 *vs*. 0.34±0.16).

## Discussion

### LA Reservoir Function and Influential Factors

The LA enlarges in association with many factors, including aging, atrial fibrillation, hypertension, diastolic dysfunction, and heart failure with low ejection fraction (*14*). Chronic hypertension is associated with an increase in LA volumes (*15*), and LA reservoir function is augmented in hypertensive patients (*16*). In our study, $LAV_{max}$, $LAV_{max}I$ and TE were clearly increased in both group EHf and EH. Furthermore, $LAV_{max}$, $LAV_{max}I$ and TE were significantly higher in group EHf than in group EH. There were no evident differences in age, systolic and diastolic blood pressure, diastolic dysfunction grade, left ventricular ejection fraction or the severity of mitral regurgitation between group EHf and EH, which implies that PAF itself may contribute to the increase in the largest LA volume and enhance the reservoir function in hypertensive patients. These results were consistent with previous studies (*7*, *17*).

Large prospective trials have established that LA enlargement is an independent risk factor for the development of AF (*18*). On the other hand, several studies have suggested that atrial enlargement is also a consequence of AF. Although none of these studies established a causal relationship between atrial dilatation and AF, it is suggested that atrial dilatation and AF are mutually dependent. The occurrence of AF has been associated with a loss of atrial contractility, and an increase in atrial compliance and atrial size (*19*), and this would partly support our data on the relationship between the frequency and total number of PAF episodes and the largest LA volume.

### LA Booster Pump Function

Chronic hypertension is associated with an increase in LA pump function (*4*, *15*). Augmented LA booster pump function is one of the mechanisms compensating for decreased early

filling in patients with reduced left ventricular compliance, whereas a loss of atrial contraction, as a result of atrial fibrillation, reduces cardiac output by approximately 15–20% (*20*).

An increase in LA contractility is considered to be caused by the increase of LA volume (Frank-Starling's law) (*21*). As a result of optimal use of the Frank-Starling mechanism of the atrial muscle, atrial shortening is remarkably augmented with chamber dilation. When the extent of the atrial shortening and expansion is diminished, despite the geometrical advantage of a further increase in atrial diameter, extreme dilation no longer provokes the Frank-Starling response and the atrial myocardium is made to operate on a "descending limb" of function (*2*).

In our study, the LA volumes preceding atrial emptying (OAEV) and OAEVI were significantly higher while LAEF was clearly lower in group EHf than in group EH, indicating that the increase in preload of LA no longer improved the performance of the LA booster function. Moreover, both OAEV and $LAV_{min}$ were increased in group EHf, and thus there was no difference in AE between group EHf and group EH. Extreme dilation and pathological abnormalities of LA muscle (*e.g.*, fibrosis) may account for the decreased LA booster function in hypertensive patients with PAF (*22*). It has been demonstrated that both the atrial fibrosis correlated with a decrease in LA fractional area shortening in a heart failure model (*23*) and the extensive atrial fibrosis in a hypertension model were similar to those found in congestive heart failure (CHF), which contributes to the genesis of AF (*22*). Regression of myocardial fibrosis has been shown to have beneficial effects in clinical studies (for review, see Takeuchi *et al*. (*24*)).

## LA Conduit Function

Chronic hypertension is associated with an increase in LA volumes and a decrease in LA rapid emptying function (*15*), and the occurrence of PAF in hypertension has been associated with enlargement of the left atrium and "normalization" of the pattern of left ventricular early filling (*17*).

Our study has shown that the *E*/*A* ratio of mitral flow was "normal" and the LA rapid emptying volume was higher in group EHf. Although the difference of REF was not significant, RE was clearly higher in group EHf compared with group EH and group N ($p<0.01$–$0.001$).

The early filling of left ventricle is affected by many other factors, such as LA pressure and left ventricular systolic and diastolic function. Since there were no differences in left ventricular ejection fraction, systolic and diastolic blood pressure, left ventricular mass index or diastolic dysfunction between group EHf and group EH, the increase of RE in group EHf is more likely due to enhancement of LA reservoir function and LA pressure than to the difference of left ventricular diastolic function.

A previous study has demonstrated the importance of LA reservoir function as a contributor to the early emptying of LA in hypertensive patients (*16*). Increased reservoir function may play an important role in accelerating left ventricular filling by helping to maintain an enhanced atrioventricular pressure gradient during diastole (*25*). Our present results clearly demonstrate a close relationship between the LA total emptying volume and rapid emptying volume in hypertensive patients with PAF.

To our knowledge, the present study is the first to demonstrate that the characteristics of PAF episodes have a close link with LA reservoir and conduit function in hypertensive patients with PAF, which implies that controlling the frequency and total number of PAF episodes in hypertensive patients may prevent the continuing enlargement of LA volume and improve LA reservoir and conduit function, thereby reducing the potential for AF recurrence (*9*).

In conclusion, these results suggest that the occurrence of PAF in hypertensive patients is associated with enhanced LA reservoir and conduit function and worse booster pump function and is independent of left ventricular hypertrophy and diastolic dysfunction. The enhancement of LA reservoir function may be related to the frequency and total number of PAF episodes and the increased LA conduit function may be related to the LA total emptying volume and frequency of PAF episodes.

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