

## The Early Stage of the Atrial Electroanatomic Remodeling as Substrates for Atrial Fibrillation in Hypertensive Patients

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**Background**—Hypertension is one of the most important risk factors for atrial fibrillation (AF). Recent studies suggest right atrial remodeling in hypertensive patients may be associated with increased inducibility of AF. This study sought to characterize the electroanatomic features of left and right atria and pulmonary veins (PVs) in hypertensive patients.

**Methods and Results**—A prospective observational study was conducted on patients who underwent ablation for paroxysmal supraventricular tachycardia or paroxysmal AF. Electrophysiological features of the PVs and atria, including event-related potentials, conduction time, and inducibility and vulnerability of AF, were characterized during cardiac catheterization. Anatomic and hemodynamic features were assessed by using echocardiographic and computer tomography imaging. When 15 hypertensive patients with paroxysmal supraventricular tachycardia were compared with 17 normotensive patients with paroxysmal supraventricular tachycardia, the hypertensive patients had significantly shortened PV event-related potentials with increased dispersions ( $P<0.001$ ) but slightly prolonged atrial event-related potentials ( $P=NS$ ) and had prolonged interatrial and intra-atrial conduction times ( $P<0.001$ ). Additionally, the hypertensive patients had increased vulnerability and inducibility of AF and prolonged duration of induced AF ( $P<0.01$ ). All of these changes were more pronounced in hypertensive patients with paroxysmal AF. Anatomically, compared with the normotensive patients, the diameters of 4 PVs in the hypertensive patients with paroxysmal supraventricular tachycardia were significantly enlarged ( $P<0.01$ ) and became more remarkable in hypertensive patients with paroxysmal AF ( $P<0.0001$ ), although the diameter and volume index of the left atrium among 3 groups were similar.

**Conclusions**—The hypertensive patients showed electroanatomic changes associated with increased vulnerability to AF, including shortened event-related potentials with increased dispersion, prolonged conduction time, and increased PV diameter, but these changes were not appreciated in the atria. Additionally, these changes became more dramatic in hypertensive patients with paroxysmal AF. (*J Am Heart Assoc.* 2014;3:e001033 doi: 10.1161/JAHA.114.001033)

**Key Words:** atrial fibrillation • atrium • hypertension • pulmonary veins • remodeling

Hypertension is 1 of the most important risk factors of atrial fibrillation (AF).<sup>1</sup> In the Framingham Heart Study and the Manitoba Follow-up Study,<sup>2,3</sup> hypertensive patients have a 1.4- to 1.9-fold greater risk of AF than do normotensive subjects. Hypertension is also the number one independent risk factor for AF simply because of its worldwide

prevalence.<sup>4</sup> However, although the association of hypertension with AF has been well established, its underlying mechanism in the development of AF remains unknown.

Current experimental evidence suggests that hypertension associated with left ventricular (LV) hypertrophy and impaired LV diastolic function may increase left atrial (LA) pressure (and result in enlargement), thereby slowing atrial conduction velocity; this favors the development and maintenance of AF.<sup>5,6</sup> However, there is distinct lack of clinical data describing the electroanatomic properties in hypertensive patients with or without AF.

Recently, Medi et al<sup>7</sup> compared right atrial (RA) electrophysiological activity in hypertensive patients without AF with the activity in a normotensive group. They found a significantly slowed conduction with slightly shortened event-related potentials (ERPs) in hypertensive patients, which may be associated with an increased inducibility of AF. Nevertheless, studies have yet to be conducted detailing the role of the LA in the context of pulmonary vein (PV) electrophysiology,

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which acts as a critical substrate for AF initiation and maintenance<sup>8,9</sup> and therefore remains an important therapeutic target in AF management.<sup>10,11</sup>

In the current study, we aimed to prospectively evaluate electroanatomic properties in hypertensive patients with and without AF. We sought to identify whether hypertensive patients exhibited abnormal electrophysiology and any anatomic substrate for the development of AF. In addition, we aimed to determine whether such abnormalities varied in severity in comparing hypertensive patients with and without AF.

## Methods

The study protocol was preapproved by the Research Development and Human Ethics Committee at the First Affiliated Hospital of Dalian Medical University. All patients gave written informed consent before enrolling in the study.

## Study Population

Of 68 patients who were referred to the First Affiliated Hospital of Dalian Medical University for ablation procedures for paroxysmal supraventricular tachycardia (PSVT) or paroxysmal AF (PAF) between February 2011 and July 2012, 44 patients were included in the present study. Seventeen patients had PSVT due to concealed left atrioventricular accessory only. Fifteen patients of these had a history of longstanding systemic hypertension with PSVT ( $6.27 \pm 3.65$  years) with an average blood pressure  $\geq 140/90$  mm Hg in 24 hours. And, 12 of 44 patients were diagnosed with longstanding systemic hypertension ( $10.83 \pm 6.69$  years) and PAF ( $4.67 \pm 1.97$  years). Exclusion criteria included persistent AF (AF onset lasting  $>7$  days) or permanent AF; any current or previous amiodarone use; LV ejection fraction  $<50\%$ ; congenital, ischemic, or valvular heart disease; stroke; diabetes mellitus; body mass index  $>30$  kg/m<sup>2</sup>; and renal impairment.

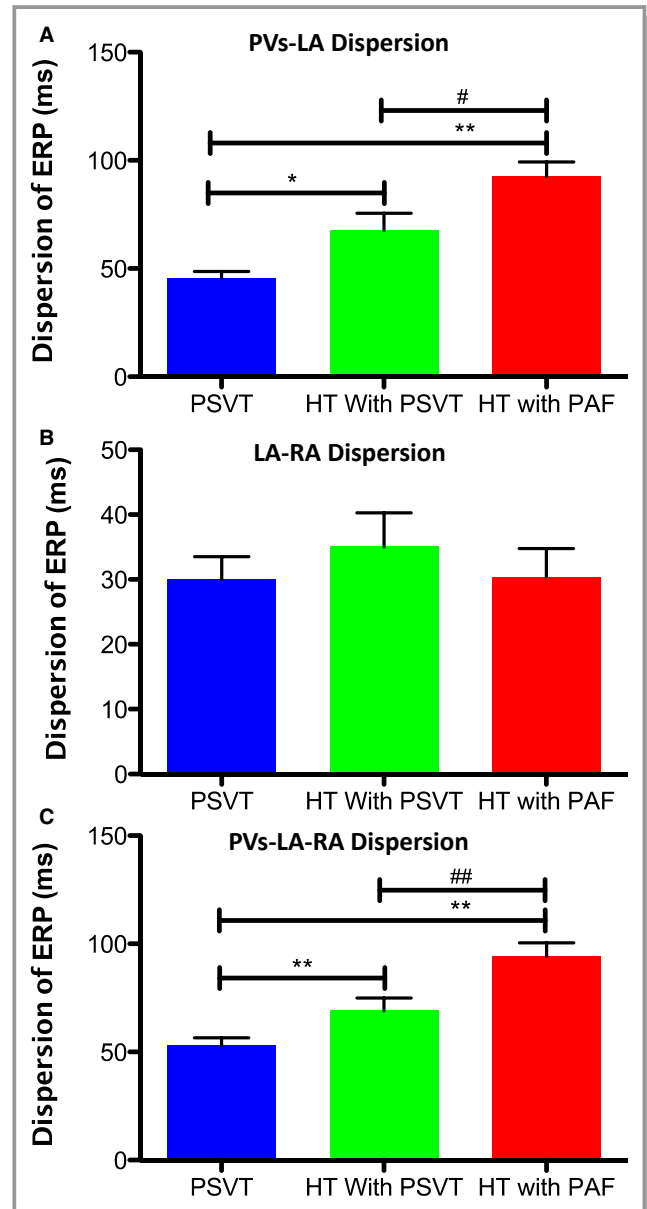
## Clinical Examination

The clinical examinations and questionnaires included 12-lead ECG, 24-hour Holter study, transthoracic echocardiography, computer tomography, and a detailed history of conditions and review of medications. All antiarrhythmic medications were discontinued for  $>5$  half-lives before any procedures were performed.

Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg. PSVT was diagnosed with ECG recorded at PSVT onset and confirmed on the basis of the following electrophysiology study. PAF was defined as episodes of AF that were detected with use of the Holter monitor and were spontaneously terminated within 7 days of onset.

## EP Studies

Electrophysiological studies were performed in sinus rhythm on fasting patients with conscious sedation. The following catheters were positioned via the femoral venous approach (Figure 1A): (1) 20-pole decapolar Lasso catheters (Biosense-Webster, Inc) at the antrum of the PVs; (2) 10-pole catheter (St Jude Medical Inc) within the coronary sinus (CS); (3) 3.5-mm-tip catheter (Biosense-Webster, Inc) at the high RA (HRA);



**Figure 1.** Dispersion of effective refractory periods (ERPs) in 3 groups. A, Dispersion of EPR among left atria (LA) and pulmonary veins (PVs). B, Dispersion of ERP between right atria (RA) and LA. C, Dispersion of ERP among RA, LA, and PVs. \* $P < 0.05$ , \*\* $P < 0.01$  vs PSVT; # $P < 0.05$ , ## $P < 0.01$  vs HT with PSVT. HT indicates hypertension; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal superior ventricular tachycardia.

and (4) 2-pole catheter (St Jude Medical Inc) at the inferior RA (IRA). Standard surface ECGs and bipolar endocardial electrograms with filter from 30 to 500 Hz were continuously monitored and stored. ERPs were measured at 8 different sites: left superior PV, left inferior PV, right superior PV, right inferior PV, HRA, IRA, and proximal and distal CSs (CSp and CSd, respectively). Each ERP was measured at twice diastolic threshold at cycle lengths of 500 ms. The average ERP tested twice at each site was used. The “ERP” was defined as the longest coupling interval failing to propagate to the atrium (Figure 1B). “Dispersion of ERP” was defined as the range between the longest and shortest ERP for each patient within any designated area.<sup>12</sup>

“AF” was defined as any rapid atrial activity (rate >350 beats/min) with irregular cycle length, polarity, configuration, and amplitude on atrial electrograms lasting >5 cycles.<sup>12</sup> “Vulnerability window” (VW) was defined as the range of coupling intervals of the extrastimulus at which AF was induced.<sup>12</sup>

Interatrial and intra-atrial activation times were measured at a cycle length of 500 ms. Activation time between PV and LA was calculated by subtracting the earliest PV signal from the last CSp activation signal. LA intra-atrial activation time was calculated by subtracting the earliest CSp signal from the last CSd signal recorded on the CS catheter. Interatrial activation time was calculated by subtracting the earliest HRA signal from the last CSd signal recorded.

### Measurement of the Hemodynamics With Echocardiography

Transthoracic echocardiography was performed using an ultrasound system (Vivid 7; GE), equipped with a 3.5-MHz transducer. Chamber dimensions were evaluated at standard

sections, including LA diameter, LV end-diastolic diameter, LV end-systolic diameter, LV wall thickness, LA volume index, and LV ejection fraction.

### Measurement of the PV Diameters With Computed Tomography Scanning

Multislice computed tomography was performed using a GE LightSpeed VCT 64 Slice CT (GE Medical Systems) at a thickness of 0.625 mm with a prospective ECG-triggered x-ray tube modulation in all patients. Nonionic contrast was used to image PVs. PV diameters were measured with the maximal anterior–posterior distance in the oblique-sagittal view by consensus of 2 observers unaware of the clinical data.

### Statistical Analysis

Continuous variables were expressed as mean±SD, and categorical variables were expressed as frequencies and percentages. ANOVA was used to compare 3 groups. Comparisons between 2 groups were made using the unpaired Student's *t* test for continuous variables and the  $\chi^2$  test for categorical variables. Values of  $P<0.05$  were considered significant. All analyses were performed by using SPSS version 16.0 for Windows (SPSS Inc).

## Results

### Baseline Demographics of the Study Population

As shown in Table 1, the average age of the 44 patients was 57.09±7.11 years, and 50% of patients were male. There was no significant difference in age ( $P=0.257$ ) or sex ( $P=0.939$ ) among the 3 groups. Hypertensive patients had significantly

**Table 1.** Patient Characteristics

	PSVT (n=17)	HT With PSVT (n=15)	HT With PAF (n=12)	<i>P</i> Value
Mean age, y	54.82±7.20	58.60±5.95	58.42±8.28	0.257
Males	9 (52.9%)	7 (46.7%)	6 (50%)	0.939
Systolic BP, mm Hg	119.12±9.06	155.33±8.96	152.50±7.83	<0.0001
Diastolic BP, mm Hg	75.29±7.39	93±3.02	93.5±3.78	<0.0001
HT history, y	—	6.27±3.65	10.83±6.69	0.006
PSVT history, y	13.82±6.00	15.33±4.80	—	0.379
PAF history, y	—	—	4.67±1.97	—
ACEI/A2RB use, %	0	5 (33)	9 (75)	<0.0001
Calcium channel blockers, %	6 (35)	9 (60)	5 (42)	0.357
β-Receptor blockers, %	4 (24)	8 (53)	4 (33)	0.210

PSVT indicates paroxysmal superior ventricular tachycardia; HT, hypertension; PAF, paroxysmal atrial fibrillation; BP, blood pressure; ACEI, angiotensin-converting enzyme inhibitor; vARB, angiotensin II receptor blocker.

increased systolic and diastolic blood pressures ( $P<0.0001$  versus the normotensive patient with PSVT). Duration of PSVT history had no significant difference in patients with or without hypertension ( $P=0.379$ ). Patients with PAF had a longer history of hypertension (~4 years) than did those with PSVT ( $P=0.006$ ), while the average blood pressure was comparable ( $P=0.406$  for systolic blood pressure,  $P=0.809$  for diastolic blood pressure). PAF patients had used more angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers than had the hypertensive patients with PSVT (75% versus 33%,  $P<0.01$ ). However, there was no significant difference in the use of calcium channel blockers ( $P=0.357$ ) or  $\beta$ -receptor blockers ( $P=0.21$ ).

### Changes of ERPs in the Hypertensive Patients

Eight ERP sites were tested and compared among the 3 groups (Table 2). Hypertensive patients had significantly shortened PV ERPs ( $P<0.05$ ) compared with normotensive patients. Furthermore, PV ERP shortening was particularly pronounced in hypertensive patients with PAF ( $P<0.01$ ). Atrial ERPs, tested at CSp, CSd, HRA, and IRA, were slightly prolonged in hypertensive patients with PSVT compared with normotensive patients with PSVT ( $P=NS$ ). Atrial ERPs were slightly shortened in hypertensive patients with PAF ( $P=NS$ ).

### Increased Heterogeneity of ERPs in the Hypertensive Patients

As shown in Figure 1, dispersion was defined as the difference in ERPs from site to site. Dispersion of ERPs was compared between the LA (CSp and CSd) and PVs (left inferior

PV, left superior PV, right inferior PV, right superior PV) (PV-LA, Figure 1A), between the LA and RA (HRA and IRA) (LA-RA, Figure 1B), and among the RA, LA, and PVs (LA-RA-PV, Figure 1C), respectively. Compared with normotensive patients with PSVT, hypertensive patients with PSVT showed significantly increased dispersion of ERPs either between PVs and LA ( $67.67\pm30.64$  versus  $45.09\pm12.98$ ,  $P<0.05$ ) or among the RA, LA, and PVs ( $86.0\pm22.85$  versus  $53.24\pm13.57$ ,  $P<0.05$ ). Furthermore, significant changes in ERP dispersion were detected in hypertensive patients with PAF, compared with hypertensive patients with PSVT ( $92.5\pm23.4$ ,  $P<0.01$  for PV-LA,  $94.17\pm21.51$ ,  $P<0.05$  for LA-RA-PV versus the hypertensive patients with PSVT) and the normotensive patients with PSVT ( $P<0.01$  for both PV-LA and LA-RA-PV). However, ERP dispersions between LA-RA were comparable among the 3 groups ( $P=0.67$ ).

### Increased Intra-atrial and Interatrial Activation Times in Hypertensive Patients

The interatrial (HRA-CSp) and intra-atrial (CSp-CSd) activation times during HRA pacing were slightly prolonged in hypertensive patients with PSVT compared with those in normotensive patients ( $P=0.08$  in HRA-CSp,  $P=0.09$  in CSp-CSd) (Table 3). However, prolongations became more remarkable and significant in hypertensive patients with PAF ( $P<0.01$  versus hypertensive patients with PSVT,  $P<0.001$  versus normotensive patients). More important was that activation times from PVs to CSp during PV pacing were prolonged significantly in hypertensive patients with PSVT compared with those in normotensive patients ( $P<0.05$ ) and in hypertensive patients with PAF ( $P<0.001$  versus normotensive patients,  $P<0.01$  versus hypertensive patients with PSVT).

**Table 2.** Effective Refractor Periods in 8 Sites

	PSVT (n=17)	HT With PSVT (n=15)	HT With PAF (n=12)	P Value
LSPV	218±26	201±25*	175±17 <sup>†§</sup>	<0.0001
LIPV	221±24	202±18*	184±22 <sup>†‡</sup>	<0.0001
RSPV	224±22	202±28*	173±24 <sup>†§</sup>	<0.0001
RIPV	225±17	206±31*	183±26 <sup>†#</sup>	<0.0001
CSp	230±25	242±12	228±9	0.092
CSd	226±19	240±26	224±17	0.117
HRA	217±17	229±25	221±17	0.204
IRA	223±14	232±21	220±14	0.151

PSVT indicates paroxysmal superior ventricular tachycardia; HT, hypertension; PAF, paroxysmal atrial fibrillation; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; CSp, paroxysmal of coronary sinus vein; CSd, distal of coronary sinus vein; HRA, high right atria; IRA, inferior right atria.

\* $P<0.05$ , <sup>†</sup> $P<0.01$  vs PSVT; <sup>‡</sup> $P<0.05$ , <sup>§</sup> $P<0.01$  vs HT with PSVT.

**Table 3.** Interatrial and Intra-atrial Conduction Times

	PSVT (n=17)	HT With PSVT (n=15)	HT With PAF (n=12)	P Value
LSPV-CSp	39±13	51±11*	67±15 <sup>†§</sup>	<0.0001
LIPV-CSp	32±12	40±10*	54±11 <sup>†§</sup>	<0.0001
RSPV-CSp	43±14	53±11*	70±14 <sup>†§</sup>	<0.0001
RIPV-CSp	35±12	42±10	56±11 <sup>†§</sup>	<0.0001
CSp-CSd	37±13	44±9	54±13 <sup>†‡</sup>	<0.01
HRA-CSp	69±16	79±15	99±10 <sup>†§</sup>	<0.0001

PSVT indicates paroxysmal superior ventricular tachycardia; HT, hypertension; PAF, paroxysmal atrial fibrillation; LSPV, left superior pulmonary vein; CSp, paroxysmal of coronary sinus vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; CSd, distal of coronary sinus vein; HRA, high right atria.

\* $P<0.05$ , <sup>†</sup> $P<0.01$  vs PSVT; <sup>‡</sup> $P<0.05$ , <sup>§</sup> $P<0.01$  vs HT with PSVT.

## Increased VWs, Inducibility, and Duration of AF in the Hypertensive Patients

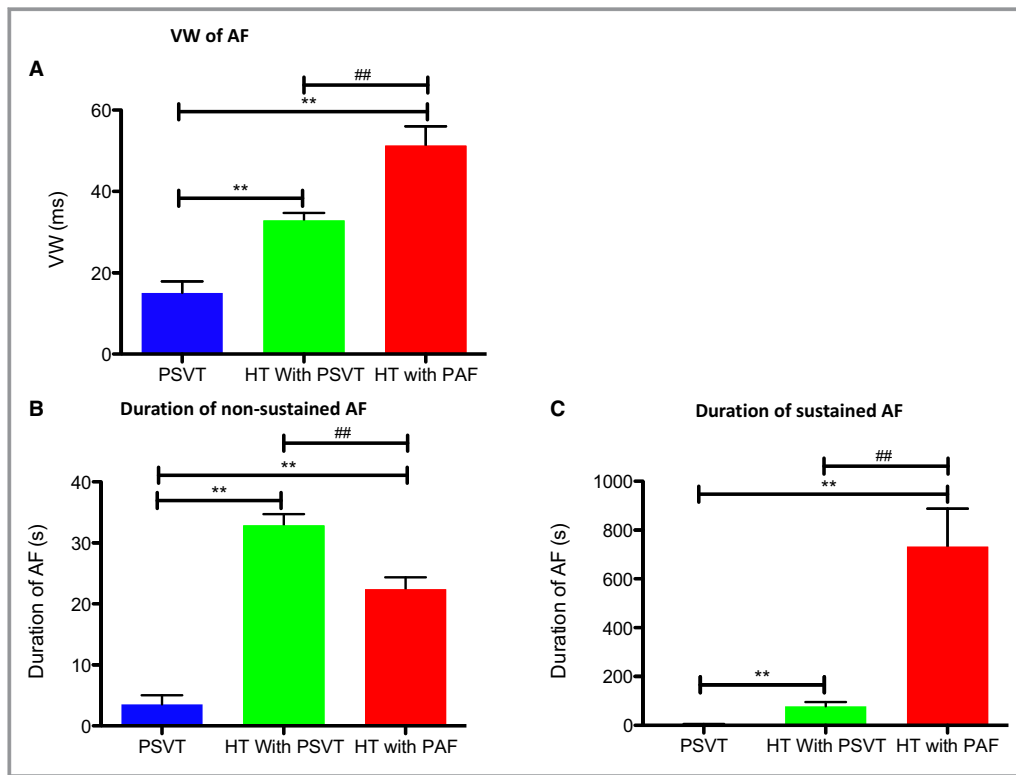
AF inducibility and VWs were examined in 3 groups at pacing sites of the left superior PV with programmed pacing (S1S2). The VWs of AF were significantly wider in hypertensive patients than in normotensive patients with PSVT ( $46 \pm 8.9$  ms versus  $16 \pm 4.8$  ms,  $P < 0.01$ ), and VWs were even wider in hypertensive patients with PAF ( $70 \pm 14.1$  ms versus normotensive patients,  $P < 0.01$ , versus hypertensive patients with PSVT,  $P < 0.01$ ), as shown in Figure 2A.

Nonsustained AF (<30 seconds) was induced in 3 (18%) of 17 normotensive patients with PSVT, in 7 (47%) of 15 hypertensive patients with PSVT ( $P < 0.05$  versus normotensive patients), and in 8 (67%) of 12 hypertensive patients with PAF ( $P < 0.05$  versus normotensive patients,  $P = 0.132$  versus hypertensive patients with PSVT). Compared with normotensive patients, longer durations of induced nonsustained AF were shown in hypertensive patients with PSVT ( $15.0 \pm 5.89$  versus  $3.6 \pm 2.08$  seconds in normotensive patients,  $P < 0.01$ ) and with PAF ( $22.4 \pm 5.63$  seconds,  $P < 0.01$  versus normotensive patients or versus hypertensive patients with PSVT) (Figure 2B).

Moreover, as shown in Figure 2C, sustained AF (lasting >30 seconds) was not induced in any of the normotensive patients with PSVT but was inducible in 3 (20%) of 15 hypertensive patients with PSVT ( $P < 0.01$  versus normotensive patients) and in 5 (41.67%) of 12 hypertensive patients with PAF ( $P < 0.01$  versus normotensive or versus hypertensive patients with PSVT). The average duration of sustained AF was longer in hypertensive patients with PAF ( $864 \pm 226$  seconds) than in those with PSVT ( $90 \pm 30$  seconds,  $P < 0.01$ ).

## Dilated PVs in the Hypertensive Patients

Anatomic features of the heart were evaluated on echocardiography and computed tomography scanning. As shown in Table 4, average LV ejection fraction was 64%, with no significant difference among the 3 groups ( $P = 0.196$ ) during sinus rhythm. Compared with normotensive patients, hypertensive patients had increased LV mass index ( $P < 0.0001$ ) and thickness ( $P < 0.05$ ). There were no differences in LV end-diastolic diameter ( $P = 0.79$ ), LV end-systolic diameter ( $P = 0.781$ ), and volume index ( $P = 0.152$ ) of the LA among the 3 groups. However, compared with normotensive patients with PSVT, the diameters of 4 PVs in hypertensive patients with



**Figure 2.** Increased vulnerability window, and duration of induced-AF in the 3 groups. A, Increased VW in the hypertensive with PSVT and with PAF. B, Duration of induced nonsustained AF. C, Duration of induced sustained AF. HT indicates hypertension; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal superior ventricular tachycardia; VW, vulnerable windows of atria. \*\* $P < 0.01$  vs PSVT; ## $P < 0.01$  vs HT with PSVT.



**Table 4.** Anatomic and Dynamic Features

	PSVT (n=17)	HT With PSVT (n=15)	HT With PAF (n=12)	P Value
<b>Echocardiography</b>				
LA diameter, mm	34.59±1.46	37.33±6.26	38.33±7.23	0.149
LAVI, mL/m <sup>2</sup>	36.00±12.03	41.96±10.20	42.40±5.64	0.152
LVEDd, mm	44.59±3.39	45.67±6.15	45.66±4.91	0.79
LVEDs, mm	27.24±2.11	26.6±3.79	27.33±3.08	0.781
LV septal thickness, mm	10.47±1.55	11.6±1.68*	11.83±1.4*	0.045
LV mass index, g/m <sup>2</sup>	98.69±14.01	112.45±16.84*	115.02±22.92*	<0.0001
LVEF, %	62±5.5	65.5±6.12	64.4±4.48	0.196
<b>Computed tomography imaging</b>				
LSPV diameter, mm	17.24±1.35	18.60±1.45*	20.00±1.75 <sup>†‡</sup>	<0.0001
LIPV diameter, mm	14.59±1.23	15.67±1.11*	16.75±1.06 <sup>†‡</sup>	<0.0001
RSPV diameter, mm	17.65±1.46	19.27±2.05*	20.83±2.04 <sup>†‡</sup>	<0.0001
RIPV diameter, mm	14.24±1.39	15.13±0.74*	16±0.74 <sup>†‡</sup>	<0.0001

PSVT indicates paroxysmal superior ventricular tachycardia; HT, hypertension; PAF, paroxysmal atrial fibrillation; LA, left atrium; LAVI, left atrial volume index; LVEDd, left ventricular diameter in diastole; LVEDs, left ventricular diameter in systole; LV, left ventricle (ventricular); LVEF, left ventricular ejection fraction; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein.

\* $P<0.05$ , <sup>†</sup> $P<0.01$  vs PSVT; <sup>‡</sup> $P<0.05$  vs HT with PSVT.

PSVT were enlarged significantly ( $P<0.01$ ) and became remarkably large in hypertensive patients with PAF ( $P<0.0001$ ).

## Discussion

### Main Findings

In the present study, compared with normotensive patients with PSVT, hypertensive patients with PSVT have evidence of (1) significantly shortened ERP in PVs but not in atria; (2) increased dispersion of ERPs; (3) slowing of interatrial and intra-atrial conduction velocities, especially conduction from PVs to the LA; (4) increased inducibility and VWs of AF; and (5) enlarged diameters of PVs but not of atria. In addition, these changes were more pronounced in hypertensive patients with PAF than in those with PSVT.

### Electroanatomic Remodeling of PVs in Hypertensive Patients Predisposes to AF

A series of studies have shown the established role of shortened ERP and its increased spatial dispersion heterogeneity in the promotion of AF.<sup>12–14</sup> However, regarding ERPs in hypertensive patients, previous experimental studies indicated inconsistent results. Some studies showed shortened ERPs,<sup>15–17</sup> but others showed prolonged ERPs or no changes in ERPs.<sup>7,18,19</sup> Our findings not only concur with the recently reported findings of Medi et al<sup>7</sup> (demonstrating prolonged

atrial ERP and globally slowed conduction in the RA of hypertensive patients) but also are the first to report that hypertension shortened PV ERPs and slowed conduction from PVs to atria to a greater extent than in atrial ERPs and intra-atrial conduction. The shortening of PV ERPs was independent of PAF, in which AF may shorten PV ERPs as a mechanism of “AF begets AF.”<sup>9,16,20</sup> In addition, anatomic remodeling of PVs was detected in hypertensive patients with PSVT, when the function and volume of LV and LA were in normal ranges. This suggests PV remodeling may be the earliest sign of hypertension-related structural remodeling long before atria are affected, and this is consistent with electrical remodeling in PVs. Therefore, electroanatomic remodeling of PVs could be 1 mechanism by which hypertension predisposes individuals to AF.<sup>15,21</sup>

### Potential Mechanisms of Hypertension in AF

#### Trigger activity

Previous studies demonstrated the role of PVs in the initiation and maintenance of AF by multiple wavelet reentry and focal (trigger) activities.<sup>20,22,23</sup> In hypertension, persistent elevations of ventricular pressure result in impaired dysfunction of LV diastole, as well as increased intra-atrial pressure. As a stretch stimulus, increased intra-atrial pressure can acutely produce afterdepolarizations through stretch-activated channels.<sup>24</sup> Kalifa et al<sup>25</sup> demonstrated that increased intra-atrial pressure promoted trigger activity within PVs on a

stretch-related AF mode but not within the LA. Antihypertensive therapy also resulted in a decreased frequency of AF episodes or premature atrial contractions.<sup>26,27</sup> Additionally, in hypertension, the activated sympathetic nervous system and the renin-angiotensin system shortened action potential duration and delayed conduction, promoting AF.<sup>28,29</sup> Also, any burst of sympathovagal activities could facilitate AF induction by causing phase 3 early afterdepolarizations, resulting in triggered activity.<sup>30</sup>

### **Multiwave reentry**

In the present study, diverse or opposite ERPs between atria and PVs in response to hypertension will further increase heterogeneities within the adjoining areas between the LA and PVs (also called the PV antrum). Therefore, these distinct differences in ERPs formed functional conduction delays within the PV antrum, which is also reflected by prolonged conduction times through the PV antrum. Combination of the shortening of refractoriness and slowing of conduction resulted in a shorter atrial wavelength, which increased the maximum number of wavelets with small sizes, established in the multiple wavelet theory of AF.<sup>21,31,32</sup>

### **Arrhythmogenic substrate**

LA dilation is associated with an increased risk of AF. Increased LA size changes its electrophysiological properties and may result in ERP shortening and conduction slowing.<sup>7,18,19</sup> In the Framingham study, the adjusted risk of AF increased by 39% for every 5-mm increment in LA size.<sup>4</sup> And, reduced LA diameter with antihypertension therapy was associated with reduced incidence of new-onset AF.<sup>26</sup> It also reported that 21% of hypertensive patients were found with an enlarged LA without evidence of ventricular hypertrophy.<sup>33</sup> The present study indicated that significantly enlarged PVs developed in hypertensive patients with increased inducibility of AF without significant LA changes, which might be an earlier detectable change than the atrial changes. Additionally, PV enlargement became more significant in hypertensive patients with PAF, as indicated by arrhythmogenic PVs.<sup>34,35</sup>

### **Study Limitations**

This was an observational study to investigate the mechanism of increased AF in hypertensive patients who underwent catheter ablation for PSVT or PAF. The patient population may not be comprehensively representative of a hypertensive population. Only consenting patients, who met strict inclusion and exclusion criteria, were enrolled; therefore, patient selection bias may limit clinical adaptation of the results. Therefore, a larger study is warranted as the conclusions of this study are limited to poorly controlled hypertensive

patients, especially with the relatively small size of the patient population in this study. It would be beneficial to evaluate whether patients with well-controlled hypertension have PV changes or that, as blood pressure control worsened, PV changes became more pronounced. The sample size may not be sufficient to reach the conclusion that hypertension is the only reason for increased risk of AF to hypertensive patients. However, PV changes in such poorly controlled hypertensive patients may indicate some electroanatomic remodeling earlier than in atrial dimension. There are 2 possible explanations: one is that the electric remodeling reflects the heart's functional reservoir, which provides early and fast adaptation to stretch stress, and the other is that the parameters of ERP, VW, and duration of AF are more sensitive to electroanatomic remodeling in PVs than those of atrial dimension.

Another limitation of the study was that antihypertensive regimens were not controlled in the 3 groups. In particular, angiotensin-converting enzyme inhibitors were used more often in hypertensive patients with PAF than in the other 2 groups, which may inhibit the electroanatomic remodeling as previously reported.<sup>36</sup> However, changes in hypertensive patients with PAF were more remarkable than in the hypertensive patients with PSVT, which provided important information of early remodeling of PVs in hypertension as a potential therapeutic target in the prevention of AF development.

### **Perspectives**

Clinically, both the success rate and long-term recurrence rate of PV isolation were lower in AF patients with hypertension than those without.<sup>10</sup> It has been speculated that there might be other mechanisms behind this association other than the role of PVs.<sup>37</sup> However, the present study indicated a measurable phenomenon of electroanatomic remodeling in PVs, detectable earlier than atrial dimensional changes, which may provide a substrate of AF pathogenesis in hypertensive patients. The changes in PVs appear to increase heterogeneity between PVs and atria, thereby promoting AF development. These changes suggest that PV electroanatomic remodeling is one of the (if not the main) mechanism of AF in hypertensive patients in this study. In the development of AF in hypertensive patients, there exists an early quantifiable stage of electroanatomic remodeling not in atria but in PVs. Although the heterogeneous sample study was small, our data suggest such patients sustain a higher risk of AF. Aggressive intervention should be considered, from adequately controlling blood pressure to PV isolation. However, a large, well-designed study on a cohort of hypertensive patients with long-term follow-up would help to solidify the mechanism between early remodeling and AF.

## Conclusion

The present study suggested for the first time, to our knowledge, that hypertensive patients possess shortened ERPs with increased dispersion in PVs, dilated PV diameters, and increased vulnerability and inducibility of AF with prolonged duration compared with normotensive patients with PSVT. The changes became remarkable and dramatic when AF episodes manifest in the hypertensive patient.

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## Disclosures

None.

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