Effect of Phenylephrine on Focal Atrial Fibrillation Originating in the Pulmonary Veins and Superior Vena Cava

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OBJECTIVES
This study was aimed at evaluating the effects of phenylephrine infusion on the occurrence of focal atrial fibrillation (AF).

BACKGROUND
Paroxysmal AF can be initiated by ectopic atrial beats originating in the pulmonary vein (PV) or superior vena cava (SVC). The effect of change in autonomic tone on this focal AF is unknown.

METHODS
This study included 12 patients with frequent bursts of AF documented by 24-h Holter monitoring. The number and coupling interval of spontaneous ectopic activity and bursts of AF were evaluated for 1 min before and after phenylephrine (2 to 3 μg/kg) injection.

RESULTS
After detailed mapping, four patients had a focus located in the left superior PV, six in the right superior PV and two in the SVC. In 10 patients with AF foci originating in the PVs, the frequency of ectopic activity (19.5 ± 27.4 vs. 11.4 ± 22.9 beats/min, p = 0.059) was reduced as well as AF bursts (14 ± 3 vs. 1.8 ± 2.7 bursts/min, p = 0.005) before versus after phenylephrine injection; the minimal coupling interval of ectopic activity and AF bursts became longer compared with baseline. The maximal percent increase in sinus cycle length after phenylephrine injection was significantly greater in patients with complete suppression of AF compared with those with partial suppression (43 ± 19 vs. 14 ± 5%, p = 0.01). However, no significant effect of phenylephrine on AF originating in the SVC was found.

CONCLUSIONS
Change in autonomic tone induced by phenylephrine injection was effective in suppressing focal AF originating in the PVs but not in the SVC. (J Am Coll Cardiol 2000;36:788–93)

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It is now considered that paroxysmal atrial fibrillation (AF) may be initiated by a single or repetitive ectopic atrial beats originating from a firing focus (1,2). The sources of a firing focus have been located mostly in the pulmonary veins (PV), as well as in the superior vena cava (SVC), the coronary sinus ostium and the crista terminalis (1–4). Although clinical observation indicates that onset of paroxysmal AF is associated with change of vagal or sympathetic activity, the role of autonomic influences in the initiation of focal AF originating in the PVs or SVC is still unknown (5). In a previous report, we demonstrated that infusion of isoproterenol could provoke spontaneous occurrence of focal AF originating in the PVs, and beta-adrenergic blocking agents could suppress initiation of this focal AF (6). Abnormal automaticity enhanced by an increase in sympathetic tone may be the underlying mechanism of focal AF (7,8). Based on accentuated antagonism, we hypothesized that an increase in vagal tone can decrease automaticity and suppress initiation of focal AF (9).

The purpose of this study was to evaluate the effect of change in autonomic tone induced by phenylephrine infusion on the occurrence of focal AF originating in the PVs or SVC.

METHODS
Patients. The study population consisted of 12 patients (11 men and 1 woman, mean age 63 ± 19 years) with frequent bursts of paroxysmal AF documented by 24-h Holter monitoring. All of them were drug-refractory and referred to this institute for electrophysiologic study and radiofrequency ablation. Seven patients had structural heart diseases, and three patients had left atrial enlargement (Table 1).

Electrophysiologic study. Each patient gave informed consent. All antiarrhythmic drugs were discontinued for at least five half-lives before the study. Two quadripolar catheters (Mansfield Division, Boston Scientific Corp., Watertown, Massachusetts) with 2-mm interelectrode spacing and 5-mm spacing between bipoles were placed in the anterolateral right atrium and His bundle area via the right or left femoral vein. A deflectable, decapolar catheter (Daig Corp., Minnetonka, Minnesota) with 2-mm interelectrode spacing was placed in the SVC and posterior right atrium via the right femoral vein. A deflectable, decapolar catheter (Daig Corp., Minnetonka, Minnesota) with 2-mm
interelectrode spacing and 5-mm spacing between bipoles was positioned in the coronary sinus via the right internal jugular vein, with the proximal electrode pair at the ostium as confirmed by contrast injection during fluoroscopy. After an atrial transseptal procedure, two long sheaths (8-French, Daig Corp., Minnetonka, Minnesota), SL1 for the right PVs and SR0 for the left PVs, were put into the left atrium through the interatrial septum (3,6). Two deflectable, 20 pole catheters (Daig Corp., Minnetonka, Minnesota) with 2-mm interelectrode spacing were placed in the right superior pulmonary vein (RSPV) and left superior pulmonary vein (LSPV), or inferior PVs if necessary, guided by the selective pulmonary venography with the first proximal electrode straddling the ostium of the PV (3,6).

Intravenous heparin was administered in a dose of 2,000 to 3,000 U at half-hour intervals, if needed, to maintain the activated clotting time.

A programmed digital stimulator (DTU-215, Bloom Associate Ltd., Reading, Pennsylvania) was used to deliver electrical impulses of 2.0 ms in duration at twice the diastolic threshold. Intracardiac bipolar electrograms were displayed simultaneously with surface electrocardiogram on a multichannel recorder (Cardiolab System, Prucka Engineering, Houston, Texas) and stored on an optical disk. All measurements were made with digital calipers at a sweep speed of 100 to 200 mm/s. In the beginning, we waited to find the spontaneous onset of bursts of AF by repetitive ectopic atrial beats in the baseline or after infusion of isoproterenol (up to 4 μg/min for 5 min). If no AF was found, intermittent atrial pacing (8 to 12 beats) with cycle length 250 to 300 ms from the right atrium or coronary sinus was used to facilitate the occurrence of spontaneous AF. If spontaneous AF did not appear, induction of sustained AF followed by external cardioversion was performed to observe the spontaneous onset of bursts of AF. Details of the provocative maneuvers are described in a previous report (3).

Phenylephrine infusion. After bursts of paroxysmal AF occurred, endocardial tracing and blood pressure were recorded for a baseline period of 5 min. Phenylephrine injection with a bolus dose of 2 mg/kg was then performed to evaluate the magnitude of the resulting increase in systolic blood pressure (10). In the case of inadequate blood pressure response (>15 mm Hg increase), an additional dose of 1 mg/kg was given. The recording was continued until blood pressure returned to the baseline. The peak effect of phenylephrine was expressed in terms of the increase in systolic blood pressure (10).

From the baseline to the peak effect of phenylephrine, the increase in sinus cycle length (SCL) was calculated by subtracting the SCL in the post-PHE period from that in the baseline. The SCL increase was expressed as the percentage increase of the baseline SCL (%). The peak effect of phenylephrine was defined as the difference between the baseline SCL and the SCL at the time of peak response.

### Table 1. Clinical and Electrophysiologic Characteristics of the Studied Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>SHD</th>
<th>LSPV</th>
<th>PV Focus</th>
<th>Initiation Mode</th>
<th>Before PHE</th>
<th>After PHE</th>
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<tr>
<td>1</td>
<td>71</td>
<td>M</td>
<td>HCVD</td>
<td>–</td>
<td>RSPV</td>
<td>I</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>M</td>
<td>–</td>
<td>–</td>
<td>RSPV</td>
<td>I</td>
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<td>3</td>
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<tr>
<td>3</td>
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<td>M</td>
<td>IHD, HCVD</td>
<td>+</td>
<td>RSPV</td>
<td>C</td>
<td>15</td>
<td>2</td>
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<tr>
<td>4</td>
<td>54</td>
<td>F</td>
<td>HCVD</td>
<td>–</td>
<td>LSPV</td>
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<td>10</td>
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<td>5</td>
<td>50</td>
<td>M</td>
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<td>LSPV</td>
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<td>6</td>
<td>69</td>
<td>M</td>
<td>HCVD</td>
<td>–</td>
<td>LSPV</td>
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<tr>
<td>7</td>
<td>73</td>
<td>M</td>
<td>HCVD</td>
<td>–</td>
<td>LSPV</td>
<td>I + P</td>
<td>4</td>
<td>3</td>
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<tr>
<td>8</td>
<td>67</td>
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<td>HCVD</td>
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<td>8</td>
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<tr>
<td>9</td>
<td>31</td>
<td>M</td>
<td>–</td>
<td>–</td>
<td>RSPV</td>
<td>I + P</td>
<td>6</td>
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<tr>
<td>10</td>
<td>73</td>
<td>M</td>
<td>IHD</td>
<td>–</td>
<td>RSPV</td>
<td>I</td>
<td>25</td>
<td>15</td>
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<td>Mean ± SD</td>
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<td></td>
<td></td>
<td></td>
<td>19.5 ± 27.4</td>
<td>182 ± 42</td>
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<tr>
<td>11</td>
<td>53</td>
<td>M</td>
<td>–</td>
<td>–</td>
<td>SVC</td>
<td>I + P</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>69</td>
<td>M</td>
<td>–</td>
<td>–</td>
<td>SVC</td>
<td>S</td>
<td>0</td>
<td>16</td>
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</table>
ephrine injection was defined as the time when there was a maximal increase in sinus cycle length.

For each patient, the following variables were analyzed: 1) a maximal percentage of increase in sinus cycle length, 2) number and coupling interval of atrial premature beats originating from an AF focus for 1 min before phenylephrine injection, 3) number and coupling interval of bursts of AF for 1 min before phenylephrine injection, 4) number and coupling interval of atrial premature beats for 1 min after the peak effect of phenylephrine injection, 5) number and coupling interval of bursts of AF for 1 min after the peak effect of phenylephrine injection.

Radiofrequency catheter ablation. The earliest activation of the PV potential, or SVC potential, or right atrial potential preceding the onset of spontaneous AF was targeted for ablation. Radiofrequency energy was delivered to that site with an EPT-1000 generator (EP Technologies, Mountain View, California). Each application of radiofrequency energy was delivered for 20 to 40 s with a maximal temperature setting of 60°C. If patients had burning pain, cough or severe bradycardia, energy application was stopped immediately, and the maximal temperature was reset to 50 to 55°C. Procedural success was defined as: no appearance of spontaneous repetitive atrial premature beats or AF using the same provocative protocol as before ablation. Heparin (1,000 U/h) was continuously administered for 24 h, and oral coumadin was given for two months with maintenance of an international normalized ratio level between 2.0 and 3.0.

Statistical analysis. Quantitative values are expressed as mean ± SD. Statistical analysis was performed using Mann-Whitney rank sum test for comparison of data in different groups and Wilcoxon signed ranks test for paired comparison. A p value of < 0.05 was considered significant.

RESULTS

Electrophysiologic characteristics. In the electrophysiologic laboratory, one patient presented with bursts of AF, and the other 11 patients were in sinus rhythm. After the
performance of provocative maneuvers, atrial premature beats and bursts of AF occurred in the 11 patients (six by isoproterenol infusion, three by atrial pacing during isoproterenol infusion and two by cardioversion of induced AF followed by reinitiation). After detailed mapping of the earliest activation preceding the onset of AF, four patients had an initiating focus located in the LSPV, six in the RSPV and two in the SVC as demonstrated in Table 1.

**Effects of phenylephrine on frequency of atrial premature beats and bursts of AF.** In 10 patients with AF foci originating in the PVs, phenylephrine increased systolic blood pressure from 133 ± 22 to 184 ± 25 mm Hg, and sinus cycle length increased from 708 ± 91 to 927 ± 174 ms. During the reflex bradycardia, ectopic activity was completely suppressed in 3 of 10 patients. The mean number of atrial premature beats for 1 min after the peak

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**Figure 2.** (A) Before administration of phenylephrine, the minimal coupling interval of atrial fibrillation (AF) burst originating in the RSPV was 120 ms. (B) After administration of phenylephrine, the minimal coupling interval of AF burst was prolonged to 172 ms. CSD = distal coronary sinus; CSM = middle coronary sinus; CSO = ostial coronary sinus; HRA = high right atrium; RSPV = right superior pulmonary vein.
The effect of phenylephrine injection tended to be less than that before phenylephrine injection (11.4 ± 22.9 vs. 19.5 ± 27.4, p = 0.059). The minimal coupling interval of atrial premature beats after phenylephrine injection was significantly longer than that before phenylephrine injection in seven patients with partial suppression (205 ± 48 vs. 182 ± 42 ms, p = 0.018). During the reflex bradycardia, bursts of AF were completely suppressed in 6 of 10 patients; it was reduced by 76 ± 6% in the remaining 4 patients (Fig. 1). The mean number of AF bursts for 1 min after the peak effect of phenylephrine injection was significantly less than that before phenylephrine injection (1.8 ± 2.7 vs. 14 ± 3, p = 0.005). The mean minimal coupling interval of the first beat of bursts of AF after phenylephrine injection was significantly longer than that before phenylephrine injection in the four patients with partial suppression (189 ± 24 vs. 148 ± 25 ms, p = 0.048; Fig. 2). The maximal percentage of increase in sinus cycle length after phenylephrine injection was significantly greater in patients with complete suppression of AF compared with those with partial suppression (43 ± 19 vs. 14 ± 5%, p = 0.01).

In two patients with AF foci originating in the SVC, adequate increase of systolic blood pressure (51 and 36 mm Hg, respectively) and sinus cycle length (26% and 16%, respectively) after phenylephrine injection was noted, but the number and coupling interval of AF bursts did not change, suggesting no effects of phenylephrine injection on frequency of AF originating in the SVC (Table 1).

Radiofrequency ablation and follow-up. Radiofrequency catheter ablation was successfully performed in all 12 patients without any complications. During the follow-up period of 7.8 ± 1.3 months, no patient had recurrence of AF without antiarrhythmic drugs.

DISCUSSION

Major findings. In this study we first demonstrated that change in autonomic tone after phenylephrine infusion could completely or partially suppress ectopic activity and bursts of AF originating in the PVs, but not in the SVC. This finding suggested autonomic influence plays an important role in the initiation and termination of focal AF.

Mechanism of paroxysmal AF originating in the PVs and SVC. Although a focal source of AF has been demonstrated in humans, the real mechanism of this AF is still not clear. Cheung (8) demonstrated that the PV of the guinea-pig can develop spontaneous activity and act as an ectopic focus in atrial arrhythmia in the presence of ouabain. Furthermore, he also reported that pace-making activity was observed in cardiac cells at the distal end of the PVs; noradrenaline could increase and acetylcholine could decrease the spontaneous activity from the PV (7). In a previous study from this laboratory, the beta-blocker (propranolol) and calcium channel blocker (verapamil) were effective in suppressing ectopic activity originating in the PVs (6). Thus, the mechanism of focal AF originating in the human PVs or SVC may be due to abnormal automaticity.

Moreover, the results of this study suggest that the mechanism of focal AF originating in the PVs or SVC may be different from that of the so-called “vagal AF” in which vagal activation results in enhancement of AF occurrence (5). The promising results of linear lesions limited to the right atrium in patients with idiopathic vagal AF by Gaita et al. (11) further support the assumption that various clinical patterns of AF may be due to different substrate sensitivity to the autonomic nervous system (5).

Effects of phenylephrine infusion on ectopic activity and AF originating in the PVs or SVC. In this study, change in autonomic tone after phenylephrine infusion could completely or partially suppress ectopic activity and bursts of AF originating in the PVs. Furthermore, the coupling intervals of ectopic activity or AF increased after phenylephrine infusion. Previous studies have demonstrated that reflex vagal activation after phenylephrine infusion is effective in suppressing premature ventricular complexes in man; decreasing the rate of automatic firing by increased vagal tone may be the underlying mechanism (12,13). In addition, a withdrawal of sympathetic tone when carotid sinus nerves are stimulated after phenylephrine infusion may contribute to the suppressive effects on frequency of ectopic activity and bursts of AF; the prolongation of atrial refractory period caused by sympathetic withdrawal may also play a role in the lengthening of the coupling intervals of ectopic activity and bursts of AF (14,15).

On the other hand, phenylephrine infusion had no effect on suppressing ectopic activity and AF originating in the SVC in this study. Scherlag et al. (16) have demonstrated that high-frequency stimulation of cardiac autonomic nerve in the vicinity of the SVC in dogs induced atrial premature beats followed by atrial tachycardia and AF; these arrhythmias could be abolished by beta-receptor blockers and atropine. In the human heart, Gardner et al. (17) showed that the PVs have a richer supply of cardiac nerves arising from bilateral vagus nerves and cervical sympathetic ganglia and trunks compared with the SVC. Thus, the differential effects of phenylephrine infusion on frequency of ectopic activity and bursts of AF originating in either the PVs or SVC may be due to nonuniform vagal innervation in the human heart. However, the effect of phenylephrine infusion on focal activity in the SVC was evaluated in only two patients; therefore, further studies are needed to confirm these initial results.

Study limitation. A potential limitation of this study was the use of phenylephrine to induce reflex changes in autonomic tone. The antiarrhythmic effects might result from direct alpha receptor stimulation. However, the direct electrophysiologic effects of phenylephrine are relatively minor when compared with the indirect reflex changes (18,19). Furthermore, phenylephrine has no discernible effect on atrial refractoriness in dogs pretreated with nadolol and atropine (20). In addition, this study included only
patients with frequent bursts of paroxysmal AF. Whether other subgroups of paroxysmal AF are suppressed by phenylephrine infusion or not deserves further investigation.

Conclusions. Frequent bursts of focal AF originating in the PVs could be initiated by beta-adrenergic stimulation after isoproterenol infusion and suppressed by change in autonomic tone after phenylephrine infusion. This finding implied that autonomic influences may play an important role in the clinical occurrence of focal AF.

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REFERENCES