Short-Term Effect of Atrial Fibrillation on Atrial Contractile Function in Humans

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Background—Conversion of chronic atrial fibrillation (AF) is associated with atrial stunning, but the short-term effect of a brief episode of AF on left atrial appendage (LAA) emptying velocity is unknown. The purpose of this study was to determine whether a short episode of AF affects left atrial function and whether verapamil modifies this effect.

Methods and Results—The subjects of this study were 19 patients without structural heart disease undergoing an electrophysiology procedure. In 13 patients, LAA emptying velocity was measured by transesophageal echocardiography in the setting of pharmacological autonomic blockade before, during, and after a short episode of AF. During sinus rhythm, the baseline LAA emptying velocity was measured 5 times and averaged. AF was then induced by rapid right atrial pacing. After either spontaneous or electrical conversion, LAA emptying velocity was measured immediately on resumption of sinus rhythm and every minute thereafter. The mean duration of AF was 15.3±3.8 minutes. The mean baseline emptying velocity was 70±20 cm/s. The first post-AF emptying velocity was 63±20 cm/s (P<0.02 versus baseline emptying velocity). The post-AF emptying velocity returned to the baseline emptying velocity value after 3.0 minutes. The mean percent reduction in post-AF emptying velocity was 9.7±21% (range, 15% increase to 56% decrease). A second group of 6 patients were pretreated with verapamil (0.1-mg/kg IV bolus followed by an infusion of 0.005 mg·kg⁻¹·min⁻¹). In these patients, the first post-AF emptying velocity, 58±14 cm/s, was not significantly different from the pre-AF emptying velocity, 60±13 cm/s (P=0.08).

Conclusions—In humans, several minutes of AF may be sufficient to induce atrial contractile dysfunction after cardioversion. When atrial contractile dysfunction occurs, there is recovery of AF within several minutes. AF-induced contractile dysfunction is attenuated by verapamil and may be at least partially mediated by cellular calcium overload. (Circulation. 1999;99:3024-3027.)

Key Words: contractility ■ calcium ■ verapamil ■ echocardiography

Previous clinical studies have demonstrated left atrial appendage (LAA) contractile dysfunction after cardioversion of AF and have identified clinical and echocardiographic features associated with contractile dysfunction, including the duration of atrial fibrillation (AF). A study of pacing-induced AF in pigs demonstrated that a brief episode of AF induces acute atrial contractile dysfunction and that this can be blunted by verapamil. However, no prior studies have assessed the short-term effect of a brief episode of AF on left atrial contractility in humans or the effect of pretreatment with verapamil. Therefore, the purpose of this study was to measure the effect of pacing-induced AF on the LAA emptying velocity in patients and to determine whether verapamil modifies this effect.

Methods

Characteristics of the Study Population
The subjects of this study were 19 patients referred to the University of Michigan Hospital for radiofrequency catheter ablation of paroxysmal supraventricular tachycardia. Exclusion criteria consisted of an unwillingness to provide informed consent; a baseline rhythm of AF, atrial flutter, or atrial tachycardia; a contraindication to the use of propranolol or atropine; the presence of structural heart disease as determined by a transthoracic echocardiogram; the inability to induce AF by pacing; concurrent treatment with a calcium channel antagonist; or the inability to perform a transesophageal echocardiogram or to visualize the LAA. Among the 202 patients screened, 19 patients (9%) satisfied all criteria. There were 7 men and 12 women; their age was 43±13 years (mean±SD); and their mean left ventricular ejection fraction was 0.62±0.05.

Electrophysiological Testing
All antiarrhythmic drug therapy was discontinued ≥5 half-lives before the procedure. After informed consent was obtained, three 7-F sheaths were placed in a femoral vein, and 3 quadripolar electrode catheters were positioned in the high right atrium, His bundle position, and right ventricular apex. Patients were sedated with intravenous midazolam and fentanyl and received 3000 U heparin IV. Leads V₅, I, II, and III and intracardiac electrograms were recorded (Mingograph 7, Siemens-Elema AB). Pacing was performed with a programmable stimulator (Bloom Associates, LTD).

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**Study Protocol**

The study protocol, approved by the Human Research Committee, was performed after completion of the clinically indicated portion of the electrophysiology procedure. A quadrupolar electrode catheter was positioned in the right atrial appendage. The mean atrial capture threshold was 0.8±0.2 mA. Autonomic blockade was achieved by infusion of atropine (0.04 mg/kg) and propranolol (0.2 mg/kg) over ~5 minutes. The mean patient weight was 82±18 kg, and the mean atrope and propranolol dosages were 3.5±0.7 and 15.3±3.5 mg, respectively.

Transeosophageal echocardiography was performed in the electrophysiology laboratory by use of a 5.0-MHz phased-array biplane or multiplane transducer and a commercially available system (model 2500, Hewlett-Packard Co, or model UM9-OPT2, Advanced Technology Laboratories). In addition to the intravenous sedatives administered during the electrophysiology procedure, benzocaine 20% and lidocaine 10% topical spray were used to anesthetize the oropharynx. The transeosophageal echocardiography probe was inserted into the esophagus, and the LAA was visualized. LAA peak flow emptying velocity was measured with pulsed Doppler by placing the sample volume ~1 cm into the mouth of the atrial appendage. The emptying velocity was determined by averaging 5 consecutive cardiac cycles during sinus rhythm and 10 cycles during AF. The emptying velocity was measured in sinus rhythm before induction of AF. AF was then induced by bursts of right atrial pacing. The mean emptying velocity during AF was 52±21 cm/s. In 3 patients, the transeosophageal probe was removed for the first 10 minutes of AF because of persistent coughing. In these 3 patients, the probe was reinserted, and each patient tolerated the second intubation without discomfort or coughing. In every patient, the transesophageal probe was in proper imaging position at the time of conversion of AF to sinus rhythm.

In 13 patients, the study protocol was performed without pretreatment with verapamil. In this group of patients, there were no significant differences between the baseline and post-AF sinus cycle length (602±50 versus 593±75 ms, P=0.4), or atrial-His interval (75±13 versus 78±14 ms, P=0.7). Intravenous verapamil was administered after autonomic blockade and before induction of AF in a second group of 6 consecutive patients. Verapamil was administered at a dosage of 0.1 mg/kg over ~2 minutes. An infusion of 0.005 mg·kg⁻¹·min⁻¹ verapamil was started 3 minutes later and continued until the protocol was completed. The mean total verapamil dosage was 16.4±2.8 mg administered over 27.4±3.5 minutes. In these 6 patients, the post-AF sinus cycle length (785±109 ms) and atrial-His interval (96±27 ms) were the same as or longer than before verapamil (sinus cycle length, 735±79 ms, P=0.10; atrial-His interval, 87±15 ms, P=0.02).

After spontaneous cardioversion in 8 patients or electrical cardioversion in 11 patients in whom AF persisted >15 minutes, the post-AF emptying velocity was measured on resumption of sinus rhythm and at subsequent 1-minute intervals until the emptying velocity returned to the baseline emptying velocity value.

**Statistical Analysis**

Continuous variables are expressed as mean±SD. Continuous variables were compared with a t test, and categorical variables were compared by χ² analysis. Linear interpolation of the plotted serial measurement data was used to generate data for analysis of temporal changes of the emptying velocity. A value of P<0.05 was considered significant.

**Results**

**Pre-AF and Post-AF Emptying Velocity in the Absence of Verapamil**

Among the 13 patients who did not receive verapamil, LAA emptying velocity before induction of AF was 70±20 cm/s. The duration of induced AF, inclusive of the time required for atrial pacing, was 15.3±3.8 minutes (range, 14.75 to 19.5 minutes). Post-AF emptying velocity was measured an average of 9 times per patient (Table 1). The emptying velocity immediately after conversion of AF was 63±20 cm/s (P=0.02 versus baseline emptying velocity). The mean percent reduction in the first post-AF emptying velocity was 9.7±21% (range, 15% increase to 56% decrease). Post-AF emptying velocity was significantly less than the baseline emptying velocity for 3.0 minutes after conversion of AF (the Figure).

A ≥15% reduction in the post-AF emptying velocity occurred in 5 of 13 patients (38%). In these patients, the baseline emptying velocity was 64±21 cm/s, and the first post-AF emptying velocity was 42±18 cm/s (P<0.01). The mean percent decrease in emptying velocity was 32±13%, and post-AF emptying velocity remained significantly less than the baseline emptying velocity for 4.0±0.6 minutes. Spontaneous echocardiographic contrast was not observed in any patient.

The percent change in the first post-AF emptying velocity compared with baseline atrial emptying velocity did not

**TABLE 1. Change in LAA Emptying Velocity After Pacing-Induced AF**

<table>
<thead>
<tr>
<th>Pre-AF Emptying Velocity, cm/s</th>
<th>Post-AF Measurements</th>
<th>Time After AF Conversion, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>70±20</td>
<td>63±23</td>
<td>24±10</td>
</tr>
<tr>
<td>61±20</td>
<td>63±20</td>
<td>126±20</td>
</tr>
<tr>
<td>66±19</td>
<td>68±20</td>
<td>244±33</td>
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<tr>
<td>67±24</td>
<td>70±20</td>
<td>354±33</td>
</tr>
<tr>
<td>71±19</td>
<td>70±19</td>
<td>417±25</td>
</tr>
<tr>
<td>516±44</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P vs pre-AF emptying velocity. n=13 patients for all measurements.
Main Findings
The main findings of this study are that pacing-induced AF significantly reduces the LAA emptying velocity on resumption of sinus rhythm, that this reduction occurs after only \( \approx 15 \) minutes of AF, that temporal recovery of the contractile dysfunction occurs within a few minutes, and that pretreatment with verapamil prevents this AF-induced contractile dysfunction.

Possible Mechanisms
The rapid onset of reduced atrial contractility and the rapid recovery of LAA mechanical function found in this study after only a brief episode of AF imply that metabolic changes were responsible. Frequent\(^{17–19}\) and irregular\(^{20}\) depolarization of atrial myocytes during AF results in elevation of cytosolic calcium.\(^9\) The absence of AF-induced contractile dysfunction in patients pretreated with verapamil suggests that AF-induced cytosolic calcium overload may mediate this acute dysfunction.

Two experimental studies support the hypothesis that acute contractile dysfunction may be related to cellular calcium overload. The first study demonstrated in a Langendorff-perfused ferret heart that transient exposure to high intracellular calcium concentration results in decreased contractile responsiveness to calcium.\(^{21}\) A possible mechanism by which calcium overload may diminish the sensitivity of myofilaments to calcium is through activation of protein kinase C, which may interfere with myofilament responsiveness.\(^{21}\)

In a second study, in an open-chest pig model of pacing-induced AF, Leistad et al\(^9\) assessed the short-term effect of a 5-minute episode of AF on left atrial systolic shortening. Similar to the findings of the present study, there was a 29% reduction in atrial contractile function after AF, and this peak reduction occurred by 15 seconds after restoration of sinus rhythm and returned to baseline after \( \approx 5 \) minutes. Furthermore, left atrial systolic shortening was exacerbated by the calcium agonist BAY K8644 and attenuated by the calcium antagonist verapamil. The findings of the present study extend the results of experimental studies to humans and suggest that acute atrial contractile dysfunction is mediated by AF-induced changes in intracellular calcium concentration.

Of note is that the pre-AF emptying velocity was significantly less in patients who received verapamil compared with the patients in this study who did not receive verapamil. This finding may reflect the negative inotropic effect of calcium channel blockade but does not negate the main finding that pretreatment with verapamil prevented AF-induced contractile dysfunction.

Previous Clinical Studies
Several clinical studies have assessed LAA mechanics after cardioversion of AF.\(^1–6\) The major limitations of these studies were that there was no assessment of LAA function before the onset of AF and that the duration of AF was poorly defined. The present study is unique in that the duration of AF was timed and the LAA emptying velocity could be measured immediately before, during, and for several minutes after AF conversion.

A second feature of this study is that LAA dysfunction was defined as a reduction relative to the baseline emptying velocity. This definition has not been the conventional criterion for “atrial stunning.” Conventionally, atrial stunning refers to a reduction in atrial appendage contractile function after conversion of AF compared with the contractile function during AF before cardioversion.\(^1–6\) If this definition of stunning had been used in the present study, no contractile dysfunction would have been recognized, because the mean emptying velocity during AF (52\( \pm \)21 cm/s) was less than the emptying velocity after conversion. Therefore, future studies assessing atrial contractile dysfunction and its recovery should compare contractile function immediately after AF conversion to contractile function measured in sinus rhythm at a later time, after maximum recovery.

### Table 2. Change in LAA Emptying Velocity After Pretreatment With Intravenous Verapamil and Pacing-Induced AF

<table>
<thead>
<tr>
<th>Pre-AF Emptying Velocity, cm/s</th>
<th>Time After AF Conversion, s</th>
<th><em>P</em> vs baseline emptying velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>60(\pm)13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-AF measurement</td>
<td></td>
<td></td>
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<tr>
<td>58(\pm)14</td>
<td>53(\pm)27</td>
<td>0.08</td>
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<tr>
<td>59(\pm)11</td>
<td>85(\pm)31,</td>
<td>0.1</td>
</tr>
<tr>
<td>60(\pm)13</td>
<td>146(\pm)26,</td>
<td>0.2</td>
</tr>
<tr>
<td>59(\pm)13</td>
<td>222(\pm)22,</td>
<td>0.1</td>
</tr>
<tr>
<td>59(\pm)13</td>
<td>295(\pm)24,</td>
<td>0.1</td>
</tr>
<tr>
<td>59(\pm)12</td>
<td>491(\pm)62,</td>
<td>0.3</td>
</tr>
<tr>
<td>60(\pm)14</td>
<td>515(\pm)48,</td>
<td>0.6</td>
</tr>
<tr>
<td>61(\pm)14</td>
<td>593(\pm)43,</td>
<td>0.4</td>
</tr>
<tr>
<td>60(\pm)13</td>
<td>628(\pm)35,</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*P* vs pre-AF emptying velocity. n=6 patients for all measurements.
Autonomic Tone

Induction and conversion of AF are likely to heighten sympathetic tone, and this may mask or minimize AF-induced acute atrial dysfunction. To minimize the influence of autonomic tone and to assess the independent effect of AF on emptying velocity, atropine and propranolol were administered before induction of AF. A constant degree of autonomic blockade was confirmed by the absence of any significant differences in sinus cycle length or atrial-His interval before and after completion of the study protocol in those patients who did not receive verapamil.

Study Limitations

A limitation of this study is that the findings may be specific only to pacing-induced AF in subjects with structurally normal atria and may not apply to spontaneous episodes of AF or in patients with structurally abnormal atria. A second limitation is the small sample size. Although 202 patients were screened, the protocol was performed in only 9%. This low percentage largely reflects the reluctance of patients to consent to a transesophageal echocardiogram that was not clinically indicated. A third limitation is that the absence of change in post-AF emptying velocity in the verapamil group may have resulted because verapamil masked rather than prevented such a change. However, the different response to AF in the control versus verapamil group is strong evidence that calcium channel blockade is at least partly responsible for prevention of AF-induced contractile dysfunction.

Conclusions

Experimental and clinical investigations suggest that intracellular calcium overload contributes to AF-induced electrical remodeling and promotes recurrence of AF. Rapid17–19 and irregular20 depolarization of atrial myocytes as a result of AF results in elevation of cytosolic calcium. This increase in cellular calcium concentration may then serve as the common mediator of AF-induced electrical remodeling (by shortening the atrial refractory period) and AF-induced contractile dysfunction. Administration of intravenous verapamil before induction of AF has been reported to prevent electrical remodeling,22 and the findings of this study imply that pretreatment with verapamil may also prevent AF-induced reduction in LAA emptying velocity. Whether the use of verapamil before cardioversion of spontaneous episodes of persistent AF will blunt postcardioversion contractile dysfunction remains to be determined.

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