Tachycardia-Induced Change of Atrial Refractory Period in Humans

Rate Dependency and Effects of Antiarrhythmic Drugs

Wen-Chung Yu, MD; Shih-Ann Chen, MD; Shih-Huang Lee, MD; Ching-Tai Tai, MD; An-Ning Feng, MD; Benjamin Ing-Tiau Kuo, MD; Yu-An Ding, MD; Mau-Song Chang, MD

Background—Atrial fibrillation (AF) has been shown to shorten the atrial effective refractory period (ERP) and make the atrium more vulnerable to AF. This study investigated the effect of atrial rate and antiarrhythmic drugs on ERP shortening induced by tachycardia.

Methods and Results—Seventy adult patients without structural heart disease were included. For the first part of the study, right atrial ERP was measured with a drive cycle length of 500 ms before and after 10 minutes of rapid atrial pacing using five pacing cycle lengths (450, 400, 350, 300, and 250 ms) in 10 patients. For the second part of the study, the remaining 60 patients were included to study the effects of antiarrhythmic drugs on changes in atrial ERP induced by AF. Atrial ERP was measured with a drive cycle of 500 ms before and after an episode of pacing-induced AF. After the patients were randomized to receive one of six antiarrhythmic drugs (procainamide, propafenone, propranolol, d-l-sotalol, amiodarone, and verapamil), atrial ERP was measured before and after another episode of pacing-induced AF. In the first part of the study, atrial ERP shortened significantly after 10 minutes of rapid atrial pacing, and the degree of shortening was correlated with pacing cycle length. The second part of the study showed that atrial ERP shortened after conversion of AF (172±15 versus 202±14 ms, P<0.0001) and that ERP shortening was attenuated after verapamil infusion (−4.6±1.2% versus −15.1±3.4%, P<0.001) but was unchanged after infusion of the other antiarrhythmic drugs. Furthermore, all of these antiarrhythmic drugs could decrease the incidence and duration of secondary AF.

Conclusions—The atrial ERP shortening induced by tachycardia was a rate-dependent response. Verapamil, but not other antiarrhythmic drugs, could markedly attenuate this effect. However, verapamil and the other drugs could decrease the incidence and duration of secondary AF. (Circulation. 1998;97:2331-2337.)

Key Words: antiarrhythmia agents ■ atrium ■ fibrillation ■ electrophysiology

Atrial fibrillation (AF) is a common cardiac arrhythmia. It is frequently associated with disabling symptoms and has been shown to increase cardiovascular morbidity and mortality, even in patients without underlying heart disease.1-4 Epidemiological studies have shown that paroxysmal AF can progress to chronic AF in patients with or without underlying structural heart disease.5,6 In addition, the incidence of successful restoration and maintenance of sinus rhythm was higher in patients with recent-onset AF than in those with chronic AF.7,8 These findings suggested that AF was a progressive disease and that AF might be self-perpetuating. Wijffels et al9 demonstrated that maintenance of AF by pacing in the normal goat heart resulted in the development of sustained AF within 1 to 3 weeks; these findings suggested that shortening of the effective refractory period (ERP; the so-called “electrical remodeling”) was the main underlying electrophysiological change. In humans, AF of <10 minutes’ duration has also been shown to shorten the ERP of the atrium.10 Goette et al11 demonstrated that the atrial ERP shortening induced by rapid pacing could be blocked with verapamil infusion in an animal study. As shown in these studies, rapid atrial pacing as well as AF can cause significant shortening of atrial ERP.9,11 Whether atrial ERP shortening is a specific response to AF or a common response to a rapid atrial rate is not clear. On the other hand, antiarrhythmic drugs are still the mainstay therapy for patients with AF. In patients with paroxysmal AF, class IA, class IC, or class III antiarrhythmic drugs are frequently used to restore and maintain sinus rhythm.12-16 For patients with AF and rapid ventricular response, β-blockers and calcium channel blockers are commonly used to control the symptomatic rapid ventricular response.17,18 However, the effects of different classes of antiarrhythmic drugs on AF-induced ERP shortening have not been fully elucidated. The purposes of this study were to investigate the rate dependency of atrial ERP change and to evaluate the effects of different antiarrhythmic drugs on tachycardia-induced changes in atrial ERP.

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Atrial Fibrillation and Atrial Refractory Period

Characteristics of Atrial Fibrillation (AF) Before (B) and After (A) Antiarrhythmic Drugs

<table>
<thead>
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<td>31/26</td>
<td>125±12</td>
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<td>20 (35%)</td>
<td>17 (30%)</td>
<td>54 (26%)</td>
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MBP indicates mean blood pressure; MHR, mean heart rate; and Pt, patient.

*P<0.01, B vs A; †P<0.01 compared with procainamide.

Methods

Patient Population
This study included 70 patients referred to our laboratory for electrophysiological testing and radiofrequency catheter ablation of paroxysmal supraventricular tachycardia. There were 37 men and 33 women with a mean age of 48±18 years. They were all free from structural heart disease, as assessed by transthoracic echocardiography and coronary angiography. Ten patients (4 men and 6 women; mean age, 48±18 years) were included in the first part of the investigation to study the rate dependency of atrial ERP shortening; the other 60 patients (33 men and 27 women; mean age, 49±6 years) were excluded from further antiarrhythmic drug study. Then the remaining 10 patients (4 men and 6 women; mean age, 48±6 years) were included in the second part to study the effects of antiarrhythmic drugs on atrial ERP shortening induced by AF. These latter 60 patients were randomized into six groups, and the age and sex distributions among the groups were similar (Table).

Electrophysiological Testing
All patients were studied in the postabsorptive, nonsedated state after giving written, informed consent, and the antiarrhythmic drugs were discontinued for >5 half-lives. Three quadripolar electrode catheters, which had an interelectrode spacing of 2 to 5 to 2 mm (Mansfield EP), were positioned in the high right atrium, the His bundle position, and the right ventricular apex, respectively. One decapolar electrode catheter (Daig Corp) was inserted into the coronary sinus via the right internal jugular vein. ECG leads I, aVF, and V6, and the intracardiac electrograms were recorded (Cardiolab, Prucka Engineering, Inc, or PPG MIDAS 2500). Pacing was performed with a programmable stimulator (DTU-215, Bloom Associates, Ltd).

Study Protocol

Determination of Atrial ERP
The study protocol was approved by the Committee of Human Subject Research at this institute. After successful radiofrequency ablation of supraventricular tachycardia, one quadripolar electrode catheter was positioned in the right atrial appendage; electrodes 1 and 2 were used for pacing, and electrodes 3 and 4 were used to record the local right atrial electrogram. This electrode catheter was used for determination of ERP. Another electrode catheter was positioned at the high lateral wall of the right atrium; this electrode was used for rapid atrial pacing or induction of AF.

The mean atrial capture threshold was 0.58±0.20 and 0.56±0.22 mA for the right atrial appendage and high lateral free wall, respectively. Pacing was performed at twice the diastolic threshold. Atrial ERP was measured by an incremental technique, with 2-ms steps at basic drive cycle lengths of 500 ms for eight beats. Atrial ERP was defined as the longest S1-S2 coupling interval that failed to result in atrial capture. The baseline atrial ERP was measured three times and averaged. In the present study, atrial ERP refers to the effective refractory period of the right atrial appendage.

Rate Dependency Study
Ten patients were included in this part of the study. After baseline ERP determination, the right atrium was paced for 10 minutes with cycle lengths of 450, 400, 350, 300, and 250 ms. The sequences of pacing cycle length were randomized in this study. Atrial ERP was measured repeatedly at the termination of each pacing session until it returned to within 2 ms of the baseline value. Furthermore, we compared the effects of verapamil on pacing-induced and AF-induced ERP shortening in an attempt to evaluate whether the electrophysiological mechanism behind ERP shortening is similar. Eight of the 10 patients underwent atrial pacing with a 250-ms cycle length after infusion of verapamil (0.15 mg/kg of body weight for a loading dose for 10 minutes and 0.3 mg·kg⁻¹·h⁻¹ for maintenance). Ten minutes after the loading dose, atrial ERP was measured again and then measured repeatedly at the termination of another pacing episode until it returned to within 2 ms of the preloading value.

Antiarrhythmic Drug Study to Assess Changes in Atrial ERP After AF
Sixty patients were included in this part of study. After the baseline atrial ERP measurement, AF was induced by burst atrial pacing at cycle lengths of 160 to 190 ms (18 patients needed a 10-mA current for pacing to induce AF). After at least 7 minutes of AF (including the duration of rapid, atrial burst pacing for inducing AF and the duration of induced AF), the AF was allowed to spontaneously convert to sinus rhythm. Immediately on conversion to sinus rhythm, atrial ERP was measured repeatedly until it returned to within 2 ms of the baseline value. Three patients experienced sustained AF (>30 minutes) during the baseline study; they were cardioverted and excluded from further antiarrhythmic drug study. Then the remaining patients were randomly assigned to receive an infusion of 1 of 6 antiarrhythmic drugs: procainamide (15 mg/kg of body weight for...
of atrial ERP persisted for 6 minutes, 5 seconds after termination of pacing. Similarly, pacing of the right atrium with a cycle length of 300, 350, or 400 ms significantly shortened the first postpacing ERP; the values decreased from 197±11 to 176±9 ms (−10.9±2.4%, P<0.001), 196±12 to 180±12 ms (−8.0±3.7%, P=0.002), and 198±15 to 186±11 ms (−6.3±3.8%, P=0.02), respectively. However, pacing of the right atrium with a cycle length of 450 ms did not shorten the first postpacing ERP (198±11 versus 195±13 ms, P>0.05). The degree of ERP shortening was correlated with pacing cycle length (r=0.7, P<0.001).

**Changes in ERP After AF**

Data from the 57 patients in the second part of the study were pooled to construct the effect of AF on ERP before antiarrhythmic drugs. Before induction of AF, the right atrial ERP was 202±14 ms, which was not significantly different from those before each pacing session. The duration of induced AF, including the time required for atrial burst pacing, was 10.4±1.9 minutes (range, 7.5 to 15.1 minutes). The first atrial ERP measured immediately after conversion of AF was 172±15 ms (−15.1±3.2%, P<0.0001 versus pre-AF ERP). Comparison of the degree of ERP shortening induced by atrial pacing and AF showed that AF tended to cause more shortening of ERP than did atrial pacing with a cycle length of 250 ms (−15.1±3.2% versus −12.4±2.0%, P=0.04).

**Recovery of the Atrial ERP Change**

**Recovery of ERP Change After Atrial Pacing and AF**

The temporal recovery of atrial ERP after each pacing cycle length is shown in Figure 1. The postpacing atrial ERP remained significantly reduced for 6.1±0.2, 5.2±0.2,
4.6 ± 0.3, and 3.2 ± 0.1 minutes after termination of pacing with a pacing cycle length of 250, 300, 350, and 400 ms, respectively. Comparison of these data showed that the duration of postpacing ERP shortening lasted longer after pacing with a shorter cycle length. A significant shortening of the post-AF atrial ERP persisted for 6.1 ± 0.3 minutes after termination of AF. The temporal recovery of atrial ERP after AF was not different from that after atrial pacing with a cycle length of 250 ms (Figure 1).

To assess the effect of a secondary episode of AF on the course of recovery of atrial ERP, the temporal recovery curves of ERP were plotted for patients with and without a secondary episode of AF (Figure 2). There was no significant difference in the temporal recovery course between these two groups of patients.

Effects of Antiarrhythmic Drugs

Effects of Antiarrhythmic Drugs on Postpacing ERP Change

Before verapamil infusion, the prepacing and postpacing ERPs were 197 ± 11 and 172 ± 10 ms, respectively (−12.7%, P < 0.001). After verapamil infusion, the prepacing and postpacing ERPs were 203 ± 15 and 194 ± 13 ms, respectively (−4.4%, P < 0.01). Verapamil infusion markedly attenuated the effect of ERP shortening induced by rapid atrial pacing (−12.7% versus −4.4%, P < 0.001; Figure 3). In addition, the recovery of ERP shortening became more rapid after verapamil infusion (3.0 ± 0.3 versus 6.0 ± 0.1 minutes, P < 0.001).

Effects of Antiarrhythmic Drugs on Post-AF ERP Change

Baseline atrial ERPs were similar among the six groups; however, atrial ERP obtained after verapamil infusion was shorter than those after other antiarrhythmic drugs. However, the first post-AF measurement of atrial ERP after verapamil was similar to those of other groups. The effects of antiarrhythmic drugs on post-AF ERP change and its temporal recovery are shown in Figure 4. After antiarrhythmic drug infusion, pre-AF and post-AF ERPs were 227 ± 16 and 193 ± 18 ms, respectively, for the procarainamide group; 223 ± 14 and 191 ± 16 ms for the propafenone group; 209 ± 15 and 183 ± 15 ms for the propranolol group; 242 ± 29 and 205 ± 25 ms for the dl-sotalol group; 231 ± 15 and 196 ± 13 ms for the amiodarone group; and 198 ± 14 and 189 ± 14 ms for the verapamil group. The degree of atrial ERP shortening was similar before and after infusion of procarainamide (−14.6 ± 4.2% versus −15.0 ± 2.3%, P > 0.05), propafenone (−14.2 ± 3.3% versus −14.3 ± 3.5%, P > 0.05), propranolol (−14.2 ± 4.3% versus −14.3 ± 3.5%, P > 0.05), and dl-sotalol (−14.2 ± 4.3% versus −14.3 ± 3.5%, P > 0.05).
Inducibility of Secondary AF After Antiarrhythmic Drugs

The characteristics of secondary AF induced during determination of post-AF ERP are summarized in the Table. During the baseline study, 54 secondary episodes of AF were unintentionally induced in 20 patients while their post-AF atrial ERP was being measured (2.7 ± 1.3 episodes per patient). The first episode of secondary AF was induced at a mean interval of 56 ± 51 seconds after spontaneous conversion of AF. Secondary episodes of AF lasted 55 ± 73 seconds (ranging from 4 seconds to 4.4 minutes). The mean A1-A2 coupling interval that induced secondary episodes of AF was 169 ± 19 ms (P < 0.005 versus pre-AF atrial ERP). The atrial ERP measured immediately after spontaneous conversion of secondary episodes of AF was not significantly different from the A1-A2 that induced secondary episodes of AF (166 ± 30 versus 169 ± 19 ms, P > 0.05).

After infusion of antiarrhythmic drugs, 26 secondary episodes of AF were unintentionally induced in 17 patients while their post-AF atrial ERP was being measured (1.6 ± 1.1 episodes per patient). The onset of the first episode of secondary AF was 40 ± 34 ms after termination of AF. The duration of secondary AF was shorter than that before drug infusion (32 ± 26 versus 55 ± 73 seconds, P < 0.001). In addition, the A1-A2 coupling interval that induced secondary AF was longer than that before drug infusion (187 ± 26 versus 169 ± 19 ms, P = 0.005). Thus, antiarrhythmic drug infusion reduced the inducibility of secondary AF. The results also showed that the patients with secondary AF after antiarrhythmic drugs were the same patients who had experienced secondary AF before antiarrhythmic drug infusion.

Comparison among the different groups before administration of drugs showed that the number of patients with secondary episode of AF, the number of AF episodes per patient, the onset of the first episode of secondary AF, and the duration of secondary episodes of AF were similar. Furthermore, comparison among the different groups after administration of drugs showed that the aforementioned parameters were also similar.

Discussion

Main Findings

In this study, we demonstrated that both short-duration, rapid atrial pacing and AF shortened atrial ERP. The atrial ERP shortening induced by rapid atrial pacing was a rate-dependent response: the shorter the pacing cycle length, the greater the decrease in atrial ERP. Also, the time course of atrial ERP recovery was similar between rapid atrial pacing and AF. In addition, verapamil infusion attenuated the change in atrial ERP, and the commonly used class IA, IC, II, and III antiarrhythmic drugs had no effect on the change in atrial ERP. However, all antiarrhythmic drugs tested did decrease the incidence and duration of secondary AF.

Rate Dependency of ERP Shortening of the Atria

Mapping of the activation pattern of AF has confirmed the hypothesis that AF is a multiple-wavelet reentrant tachycardia.19–21 The wavelength of the wavelets, which is defined as the product of ERP and conduction velocity, plays a critical role in the induction and maintenance of AF.22,23 Previous studies have demonstrated that high-frequency atrial pacing and sustained AF lead to shortening of atrial ERP, without a significant change in conduction velocity.9–11,24–26 A shorter ERP can create a shorter wavelength, which makes AF easier to be induced and sustained. In other words, AF might beget AF. However, there were great variations in tachycardia cycle lengths used to induce ERP shortening in these published studies: two studies used pacing-induced AF, and the other four used rapid atrial pacing with cycle lengths ranging from 50 to 200 ms.9–11,24–26 In the present study, we demonstrated that atrial pacing with a cycle length ranging from 250 to 400 ms for 10 minutes could cause significant shortening of atrial ERP and that ERP shortening induced by tachycardia was a rate-dependent response. Rapid atrial pacing with a cycle length of 250 ms for 10 minutes had an effect on atrial ERP that was comparable to a 10-minute AF episode. The time course of ERP recovery after termination of pacing and the response to verapamil were also similar between rapid atrial pacing and AF. These data suggested that tachycardia-induced ERP shortening was not a specific response to AF. Achieving at a critical rate, atrial tachyarrhythmia could also shorten atrial ERP as did AF.

Effects of Antiarrhythmic Drugs on Tachycardia-Induced Change in Atrial ERP and Secondary AF

Effects on Atrial ERP

Antiarrhythmic drugs have been commonly used to convert AF or prevent its recurrence. However, long-term treatment has not been satisfactory: as much as a 50% recurrence has been reported.27 A breakthrough AF, if it persists long enough, may have a significant effect on atrial electrophysiology. In the present study, we demonstrated that the commonly used class IA (procainamide), class IC (propafenone), class II (propranolol), and class III (dl-sotalol and amiodarone) antiarrhythmic drugs could not prevent the shortening of ERP induced by short-duration AF. Only verapamil, a class IV antiarrhythmic drug, could attenuate the shortening of atrial ERP. Furthermore, lesser shortening of ERP after termination of AF would permit a more rapid recovery of ERP. This effect was also observed in the verapamil-treated group only. One study on ventricular fibrillation showed that increases in calcium transients and calcium overload were associated with postfibrillation ventricular dysfunction.28 Similarly, atrial dysfunction was noted after a short duration of AF, and this dysfunction was prevented by verapamil
infusion and exaggerated by a calcium channel agonist.\textsuperscript{20} Previous animal and human studies have shown that verapamil infusion can block ERP changes induced by high-frequency atrial pacing or AF.\textsuperscript{11,20,30} These data suggested that calcium overload was the underlying mechanism of the tachycardia-induced ERP change. However, other possible mechanisms about intracellular calcium handling merit further investigation.

On the other hand, potassium channels play a critical role in repolarization, and changes in potassium channel function can affect the measurement of ERP.\textsuperscript{31} In this study, we demonstrated that class III antiarrhythmic drugs (\textit{dl}-sotalol and amiodarone), despite their effects on prolongation of ERP, could not prevent the change in ERP induced by short-duration AF. These data suggested that potassium channels might not play a critical role in the change in ERP induced by AF of short duration.

\textbf{Effects on Secondary AF}

Inducibility and sustenance of AF depend on the presence of a critical number of reentrant wavelets in the atrium.\textsuperscript{22,23} The product of atrial ERP and conduction velocity (defined as wavelength) determines how many wavelets can exist in the atrium; therefore, a shorter atrial ERP may lead to a greater number of wavelets and thus, make AF easier to be sustained. In contrast, a greater prolongation of atrial ERP could result in a lower incidence of secondary AF because the wavelengths of reentry wavelets are increased by prolongation of ERP. In this study, the first episode of secondary AF usually occurred at the first several ERP determinations. This finding was compatible with the wavelength hypothesis, because the first several ERPs were the shortest post-AF ones in each patient. A shorter ERP would produce a shorter wavelength, which would increase inducibility of AF.

The results of the current study and of the one by Dao et al\textsuperscript{10} both showed that verapamil could significantly decrease the incidence of secondary AF. In contrast to the study of Dao et al, we found that procainamide also significantly prevented secondary AF. In the study by Dao et al, they set the prolongation of atrial ERP at $\approx \%10$ (14.1\% in this study), and the total dose of procainamide (344±155 mg) was lower than usual. In our current study, a larger dose of procainamide and a greater increase in atrial ERP than those in the study of Dao et al might account for the different results.

\textbf{Study Limitations}

First, this study population consisted of patients with structurally normal hearts and no clinically documented AF, and the response in patients with paroxysmal or chronic AF or in patients with structural heart disease may be different. Second, verapamil infusion attenuated the effect of ERP shortening induced by short-duration tachycardia. Whether this result could be extrapolated to tachycardia of longer duration or chronic AF needs further investigation. Third, that verapamil infusion slowed a ventricular response during AF may have been associated with a more favorable hemodynamic response and may have contributed to its effect in the prevention of ERP shortening. However, similar ventricular rate and blood pressure changes were observed after infusion of propafenone, propranolol, \textit{dl}-sotalol, and amiodarone; however, these drugs could not prevent ERP shortening. Thus, prevention of ERP shortening by verapamil may not be due to its slowing effect on ventricular rate during AF. Fourth, we did not use total autonomic blockade during this study; we think that this condition would be more like the clinical one, and propranolol, propafenone, \textit{dl}-sotalol, and amiodarone already have a $\beta$-adrenergic–blocking effect.

\textbf{Clinical Implications}

This study demonstrated that a brief episode of tachycardia or AF significantly shortened atrial ERP, which might make the atrium more vulnerable to future AF. Furthermore, previous studies have demonstrated that a short duration of AF can impair atrial contractile function.\textsuperscript{29} The tachycardia-induced electrical and mechanical dysfunction can be attenuated by verapamil infusion. Early intervention to terminate AF should be considered a therapeutic goal, because such intervention disrupted the process of tachycardia-induced atrial dysfunction.

\textbf{Conclusions}

The atrial ERP shortening induced by tachycardia is a rate-dependent response. The shorter the tachycardia cycle length, the greater the decrease in atrial ERP. Verapamil infusion can markedly blunt this effect, but class IA, IC, II, and III antiarrhythmic drugs have no effect. However, verapamil and the other drugs can decrease the incidence and duration of secondary AF.

\textbf{Acknowledgments}

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