

Mechanism of Immediate Recurrences of Atrial Fibrillation After Restoration of Sinus Rhythm

AMAN CHUGH, MEHMET OZAYDIN, CHRISTOPH SCHARF, STEVE W.K. LAI, BURR HALL, PETER CHEUNG, FRANK PELOSI, JR, BRADLEY P. KNIGHT, FRED MORADY, and HAKAN ORAL

From the Division of Cardiology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan

CHUGH, A., ET AL.: Mechanism of Immediate Recurrences of Atrial Fibrillation After Restoration of Sinus Rhythm. *An immediate recurrence of AF may occur after restoration of sinus rhythm. Although pulmonary vein (PV) isolation has been shown to prevent immediate recurrence of AF, the specific trigger for immediate recurrence of AF has not been described. In 89 consecutive patients (mean age 53 ± 11 years) who had sinus rhythm restored by spontaneous or transthoracic cardioversion in the course of a PV isolation procedure, electrograms recorded within a PV and in the adjacent left atrium were analyzed to determine the mechanism of initiation of immediate recurrence of AF. Immediate recurrence of AF was defined as a recurrence of AF within 90 seconds after restoration of sinus rhythm. There were 124 episodes of immediate recurrence of AF at a mean of 18 ± 23 seconds after cardioversion. Recordings within the PV that triggered the immediate recurrence of AF were available in 23 (19%) of the 124 immediate recurrence of AF episodes. Among these 23 episodes of immediate recurrence of AF, all (100%) were triggered by a burst of PV tachycardia ($P < 0.001$). The coupling interval and prematurity index (coupling interval/preceding sinus cycle length) of the premature depolarizations that did and did not trigger immediate recurrence of AF were 246 ± 67 ms and 0.30 ± 0.11 vs 378 ± 117 ms and 0.49 ± 0.16 , respectively ($P < 0.01$). Immediate recurrence of AF was abolished by PV isolation. The mechanism of immediate recurrence of AF is a burst of PV tachycardia, not a single premature depolarization. Immediate recurrence of AF identifies patients with AF in whom the PVs may play a major role in the initiation of AF. (PACE 2004; 27:77-82)*

atrial fibrillation, cardioversion, pulmonary vein

Introduction

An immediate recurrence of atrial fibrillation (AF) may occur after restoration of sinus rhythm in patients with AF.¹⁻⁴ Some studies have suggested that immediate recurrence of AF is triggered by premature depolarizations, and that the probability of immediate recurrence of AF is dependent on the prematurity of the ectopic beat.^{5,6} A more recent study demonstrated that pulmonary vein (PV) isolation consistently abolishes the immediate recurrence of AF.⁴ However, the specific triggers of the immediate recurrence of AF have not been well described. The aim of this study was to determine the mechanism of initiation of the immediate recurrence of AF in patients with AF.

Patients and Methods

Patient Characteristics

The study included 89 consecutive patients who underwent PV isolation for paroxysmal ($n = 73$) or persistent ($n = 16$) AF. AF that had been present for >1 month without any intervening episodes of sinus rhythm and required cardioversion for restoration of sinus rhythm was considered persistent. There were 78 men and 11 women (mean age 53 ± 11 years). The mean left ventricular ejection fraction was 0.54 ± 0.04 , and the mean left atrial diameter was 41 ± 5 mm. AF was first diagnosed 7 ± 7 years before the PV isolation procedure. Among the 89 patients, 78 had no structural heart disease and 11 (12%) had structural heart disease (i.e., coronary artery disease $n = 4$, valvular heart disease $n = 4$, and a nonischemic cardiomyopathy $n = 3$).

Electrophysiological Study

All patients provided informed, written consent. Antiarrhythmic drug therapy was discontinued at least 5 half-lives before the procedure, except for amiodarone, which was discontinued at least 4 weeks previously. A quadripolar electrode

Supported in part by the Ellen and Robert Thompson Atrial Fibrillation Research Fund.

Address for reprints: Hakan Oral, M.D., Cardiology, TC B1 140, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0311. Fax: (734) 936-7026; e-mail: oralh@umich.edu

Received March 3, 2003; revised May 8, 2003; accepted May 29, 2003.

catheter (EP Technologies Inc., Mountain View, CA, USA) was inserted into a femoral vein and positioned in the coronary sinus. After transeptal catheterization, a decapolar ring catheter (Lasso, Biosense Webster, Inc., Diamond Bar, CA, USA) and a deflectable, quadripolar catheter (EP Technologies Inc.) with 2-5-2-mm interelectrode spacing and a 4-mm distal electrode were inserted into the left atrium. Systemic anticoagulation was achieved with intravenous heparin to maintain an activated clotting time of 250–350 seconds.

Bipolar intracardiac electrograms were filtered at band-pass settings of 30–500 Hz and were recorded digitally (EP MedSystems, Inc., West Berlin, NJ, USA). Atrial pacing was performed from the coronary sinus (EP MedSystems, Inc., Model EP-3 Clinical Stimulator).

Study Protocol

Among the 89 patients, 42 (47%) were in AF and 47 (53%) were in sinus rhythm at the onset of the procedure. In patients who presented in sinus rhythm, AF was induced by atrial pacing at a cycle length of 200–180 ms.

During AF, electrograms were recorded within each PV in sequence with the ring catheter. In a prior study, all episodes of immediate recurrence of AF were abolished by isolation of the PVs, indicating that the PVs are the source of triggers for immediate recurrence of AF.⁴ Therefore, to characterize the trigger of immediate recurrence of AF, the ring catheter was positioned within a PV during cardioversion. Because it was not feasible to place a ring catheter in each of the four PVs simultaneously, the catheter was positioned inside the left superior, right superior, or left inferior PV, within 5 mm of the ostium. In general, the ring catheter was positioned within the PV that had the most frequent bursts of rapid electrical activity consistent with a PV tachycardia.⁷ A quadripolar catheter was positioned in the left atrium, adjacent to the PV in which the ring catheter was positioned. To prevent catheter induced atrial depolarizations during cardioversion, firm contact of this catheter against the atrial wall was avoided.

Transthoracic cardioversion was performed after conscious sedation with midazolam and fentanyl. Adhesive electrodes were positioned on the anterior and posterior chest. Sinus rhythm was restored with a conventional defibrillator using monophasic shocks of 200–360 J (Hewlett-Packard, Andover, MA, USA). In 4 (4%) of the 89 patients, AF converted to sinus rhythm spontaneously.

Immediate recurrence of AF was defined as an episode of AF that occurred within 90 seconds after transthoracic or spontaneous cardioversion (Fig. 1).

Analysis of Intracardiac Electrograms

Intracardiac electrograms were analyzed offline to determine the mechanism of immediate recurrence of AF. Premature depolarizations recorded within a PV were considered to have originated in that PV if they preceded the atrial electrogram recorded in the adjacent left atrium (Fig. 1). PV depolarizations that occurred simultaneous with or after the adjacent left atrial electrogram were considered to represent passive activation of the PV. A PV tachycardia was defined as a burst of repetitive electrical activity within a PV that preceded left atrial activation, and that had a shorter cycle length than at the adjacent left atrium, or that had cycle length oscillations that preceded changes in the left atrial cycle length (Fig. 1).

The coupling interval of premature depolarizations was defined as the interval from the prior sinus depolarization to the onset of the premature depolarization. The prematurity index was defined as the ratio of the coupling interval of the premature depolarization to the preceding sinus cycle length (Fig. 2).

PV Isolation

Electrical isolation of the PVs was performed by segmental ostial applications of conventional radiofrequency energy, guided by PV potentials, as described previously.^{4,8,9}

Statistical Analysis

Continuous variables are expressed as mean \pm 1 SD. Continuous variables were compared with the Student's *t*-test. Categorical variables were compared by chi-square analysis or with the Fisher's exact test, as appropriate. A *P* value $<$ 0.05 indicated statistical significance.

Results

Prevalence of Immediate Recurrence of AF

Among the 89 patients, 50 (56%) experienced 124 episodes of immediate recurrence of AF. Immediate recurrence of AF occurred a mean of 18 ± 23 seconds after restoration of sinus rhythm. The prevalence of immediate recurrence of AF was similar in patients who had spontaneous (65%) or pacing induced AF (56%, *P* = 0.4). Immediate recurrence of AF occurred after 17 of 67 episodes of spontaneous termination of AF (25%) and after 107 of 192 successful transthoracic cardioversions (56%, *P* $<$ 0.01).

Premature Depolarizations After Restoration of Sinus Rhythm

In the 50 patients with an episode of immediate recurrence of AF, there were 301 premature

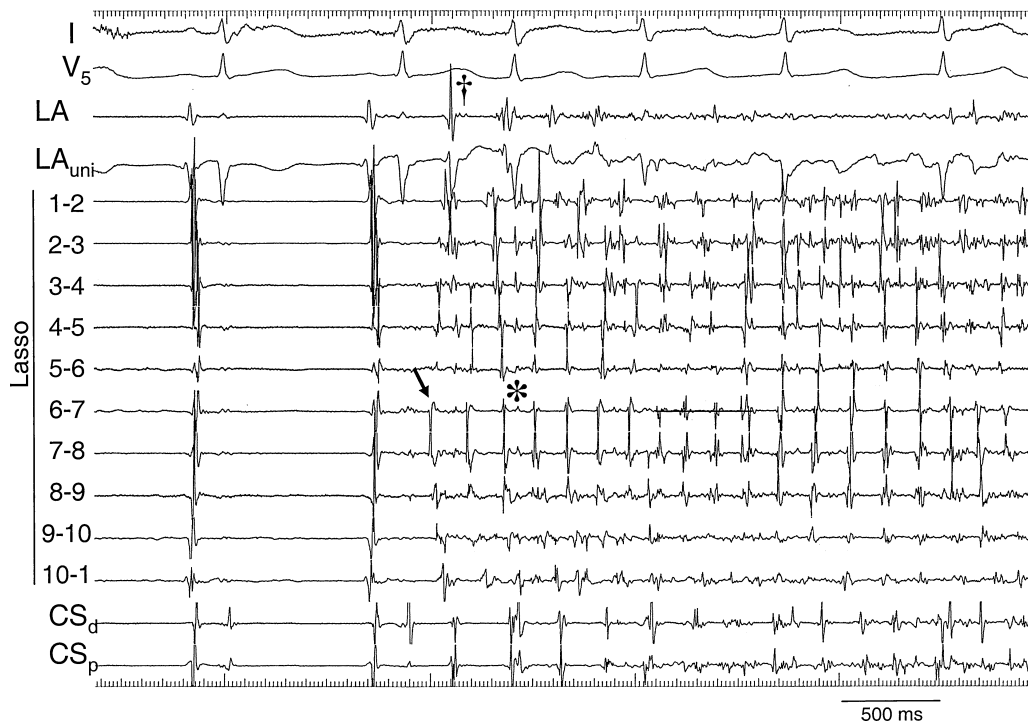


Figure 1. Pulmonary vein (PV) tachycardia and immediate recurrence of atrial fibrillation (AF) after transthoracic cardioversion. Shown are leads I, and V₅, bipolar, and unipolar recordings from the distal electrode pair of a mapping catheter positioned in the left atrium just outside the ostium of the left superior PV (LA, LA_{uni}), a decapolar Lasso catheter positioned within the left superior PV (L₁₋₂, . . . , L₁₀₋₁), and distal and proximal electrode pairs of a coronary sinus catheter (CS_d, CS_p). After transthoracic cardioversion, a PV tachycardia that has a mean cycle length of 125 ms (asterisk) triggers immediate recurrence of AF. The cycle length within the adjacent left atrium was 188 ms. The first premature PV depolarization (arrow) precedes the left atrial electrogram (dagger) recorded just outside the PV ostium.

atrial depolarizations that occurred within 90 seconds after restoration of sinus rhythm. Among these 301 premature atrial depolarizations, a PV was documented to be the source of the depolarization(s) in 120 (40%). Within the same PVs, 16 PV depolarizations that did not conduct to the left atrium also were recorded. The prematurity index of the first beat of the premature PV depolarizations that did and did not conduct to the left atrium were 0.45 ± 16 and 0.20 ± 0.08 , respectively, ($P < 0.01$).

Premature PV depolarizations occurred at a mean of 26 ± 23 seconds after restoration of sinus rhythm. Among the 136 premature PV depolarizations, 84 (61%) were single, 24 (18%) were double, 5 (4%) were triple, and 23 (18%) occurred in the form of a PV tachycardia.

Mechanisms of Initiation of Immediate Recurrence of AF

Among the 124 episodes of immediate recurrence of AF, the trigger was recorded by the

ring catheter that was positioned within a PV in 23 (19%). In all episodes (100%), the trigger of immediate recurrence of AF was a burst of PV tachycardia. The mechanism of initiation of immediate recurrence of AF was by a PV tachycardia regardless of whether AF was paroxysmal or persistent.

Among these 23 episodes of immediate recurrence of AF, 2 (9%) occurred in patients with persistent AF and 21 in patients with paroxysmal AF. During 23 episodes of immediate recurrence of AF recorded from a ring catheter, the catheter was positioned within the left superior PV in 16 (70%), the right superior PV in 4 (17%), and the left inferior PV in 3 (13%) patients.

Among 84 single premature PV depolarizations that were recorded after cardioversion, none initiated an episode of immediate recurrence of AF. Among 23 bursts of PV tachycardia that were recorded after cardioversion, 23 (100%) triggered an episode of immediate recurrence of AF (Fig. 2). The coupling interval and the prematurity index

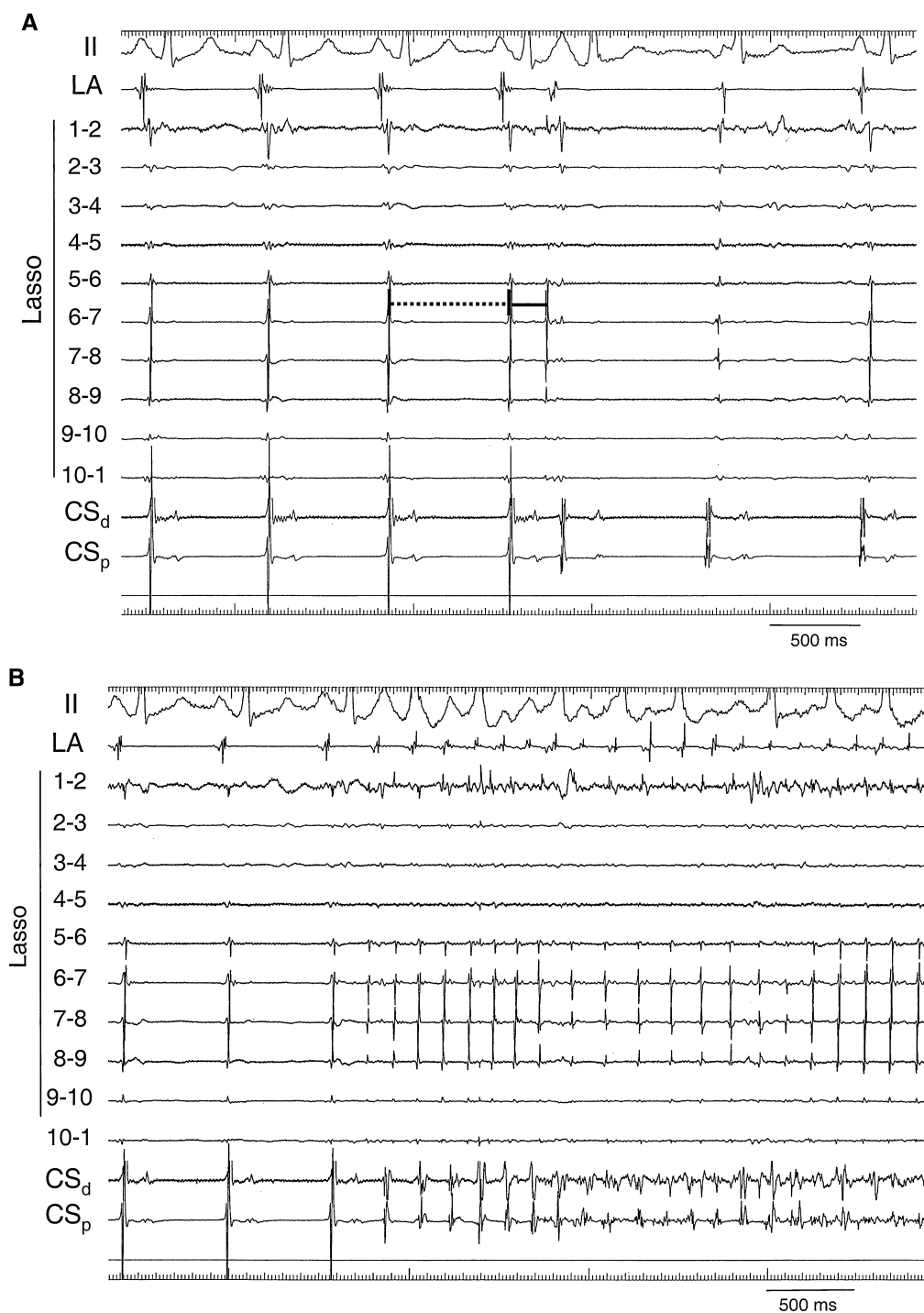


Figure 2. Immediate recurrence of atrial fibrillation (AF) triggered by a burst of pulmonary vein (PV) tachycardia, but not by a single premature depolarization. (Panel A) A premature PV depolarization with a coupling interval and prematurity index of 206 ms and 0.30 fails to trigger immediate recurrence of AF after electrical cardioversion. The coupling interval was defined as the interval from the prior sinus depolarization to the onset of the premature depolarization (solid line). The prematurity index was defined as the ratio of the coupling interval to the preceding sinus cycle length (dashed line). (Panel B) In the same patient, a burst of PV tachycardia with a coupling interval and prematurity index of 192 ms and 0.33, initiated an episode of immediate recurrence of AF. Catheter positions and abbreviations as in Figure 1.

of the bursts of PV tachycardia were 246 ± 67 ms, and 0.30 ± 0.11 , respectively.

The coupling interval and prematurity index of the PV depolarizations that did and did not trigger immediate recurrence of AF were 246 ± 67 ms and 0.30 ± 0.11 vs 378 ± 117 ms and 0.49 ± 0.16 , respectively ($P < 0.01$).

PV Isolation

Among 306 PVs, 293 (96%) were successfully isolated by segmental ostial applications of radiofrequency energy. After PV isolation, there were no further episodes of immediate recurrence of AF.

Discussion

Main Findings

A prior study demonstrated that immediate recurrence of AF is consistently abolished by PV isolation, indicating that the PVs are a common source of the trigger for immediate recurrence of AF. The present study demonstrates that the trigger of immediate recurrence of AF always is a burst of PV tachycardia, as opposed to a single premature depolarization.

Mechanisms of Immediate Recurrence of AF

Compared to a single premature depolarization, a burst of PV tachycardia may facilitate immediate recurrence of AF in several ways. First, consecutive premature stimuli may progressively shorten the PV fascicular and left atrial effective refractory periods so that subsequent stimuli with shorter coupling intervals can conduct to the left atrium and trigger AF. Second, AF usually may be more readily induced by rapid atrial burst pacing than a single extrastimulus. Rapid atrial pacing may facilitate the induction of AF by creating multiple sites of functional block that serve as a substrate for reentry. It is possible that bursts of PV tachycardia have a similar effect on the atrium.

Immediate Recurrence of AF After Spontaneous and Transthoracic Cardioversion

Immediate recurrence of AF occurred less often after spontaneous conversion than after transthoracic cardioversion. A possible explanation for this finding is that the trigger for immediate recurrence of AF is the same type of PV tachycardia that plays a role in maintaining AF,⁷ and that spontaneous conversion occurs only because PV tachycardia has become less frequent. Therefore, the immediate recurrence of AF may not have occurred as often because of the same reason that AF converted spontaneously. However, the higher prevalence of immediate recurrence of AF after transthoracic cardioversion may also be explained by a stimulatory

effect of transthoracic shocks on the PVs. Additional studies are required to determine which one of these explanations is more likely.

Clinical Significance of Immediate Recurrence of AF in Patients with AF

In a prior study, immediate recurrence of AF that occurred during an electrophysiological procedure in patients with paroxysmal AF was consistently abolished by complete electrical isolation of the PVs.⁴ This finding suggests that immediate recurrence of AF is primarily triggered by premature depolarizations that originate from the PVs.

Intermittent PV tachycardias have been shown to play a critical role in the initiation and perpetuation of AF.^{4,7,10} However, because the mechanism of AF is multifactorial,¹¹ PV isolation by itself does not always prevent AF. It would be helpful to be able to identify the patients who are most likely to benefit from a PV isolation procedure. A clinical variable that is predictive of a successful outcome after PV isolation is paroxysmal (as opposed to persistent) AF.^{9,12} The results of this study suggest that another clinical variable that may be helpful in selecting patients for PV isolation is an episode of immediate recurrence of AF after cardioversion.

Previous Studies

No prior studies have described the triggers of immediate recurrence of AF. A prior study in which immediate recurrence of AF was used to map arrhythmogenic foci within PVs suggested that immediate recurrence of AF was triggered by premature depolarizations from the PVs, but the characteristics of the triggers were not described.⁵

Study Limitations

PV recordings were available from only one PV at a time. Because there was no reliable method to predict which PV would be the source of immediate recurrence of AF, the ring catheter often was positioned in a PV that was not the source of the immediate recurrence of AF, and the trigger for immediate recurrence of AF could be characterized in only 19% of episodes of immediate recurrence of AF. The possibility that immediate recurrence of AF was triggered by a source outside the PVs cannot be excluded. However, this possibility is unlikely since immediate recurrence of AF was consistently abolished by PV isolation, as previously reported.⁴

Conclusions

In this study, all instances of immediate recurrence of AF were triggered by a burst of PV tachycardia, not simply a premature depolarization. An episode of immediate recurrence of AF

after transthoracic or spontaneous cardioversion of AF may identify the patients who are most likely

to benefit from a PV isolation procedure to prevent recurrent episodes of AF.

References

1. Daoud EG, Hummel JD, Augostini R, et al. Effect of verapamil on immediate recurrence of atrial fibrillation. *J Cardiovasc Electrophysiol* 2000; 11:1231–1237.
2. Van Noord T, Van Gelder IC, Schoonderwoerd BA, et al. Immediate reinitiation of atrial fibrillation after electrical cardioversion predicts subsequent pharmacologic and electrical conversion to sinus rhythm and amiodarone. *Am J Cardiol* 2000; 86:1384–1385. A5.
3. Yu WC, Lin YK, Tai CT, et al. Early recurrence of atrial fibrillation after external cardioversion. *PACE* 1999; 22:1614–1619.
4. Oral H, Knight BP, Ozaydin M, et al. Segmental ostial ablation to isolate the pulmonary veins during atrial fibrillation: Feasibility and mechanistic insights. *Circulation* 2002; 106:1256–1262.
5. Lau CP, Tse HF, Ayers GM. Defibrillation-guided radiofrequency ablation of atrial fibrillation secondary to an atrial focus. *J Am Coll Cardiol* 1999; 33:1217–1226.
6. Timmermans C, Rodriguez LM, Smeets JL, et al. Immediate reinitiation of atrial fibrillation following internal atrial defibrillation. *J Cardiovasc Electrophysiol* 1998; 9:122–128.
7. Oral H, Ozaydin M, Tada H, et al. Mechanistic significance of intermittent pulmonary vein tachycardia in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 2002; 13:645–650.
8. Haissaguerre M, Shah DC, Jais P, et al. Electrophysiological breakthroughs from the left atrium to the pulmonary veins. *Circulation* 2000; 102:2463–2465.
9. Oral H, Knight BP, Tada H, et al. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation* 2002; 105:1077–1081.
10. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998; 339:659–666.
11. Allesie MA, Boyden PA, Camm AJ, et al. Pathophysiology and prevention of atrial fibrillation. *Circulation* 2001; 103:769–777.
12. Pappone C, Oreto G, Rosanio S, et al. Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: Efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. *Circulation* 2001; 104:2539–2544.