

## ORIGINAL ARTICLE

# Circumferential Pulmonary-Vein Ablation for Chronic Atrial Fibrillation

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## ABSTRACT

**BACKGROUND**

We conducted a randomized, controlled trial of circumferential pulmonary-vein ablation for the treatment of chronic atrial fibrillation.

**METHODS**

A total of 146 patients with a mean ( $\pm$ SD) age of  $57\pm 9$  years who had chronic atrial fibrillation were randomly assigned to receive amiodarone and undergo two cardioversions during the first three months alone (the control group) or in combination with circumferential pulmonary-vein ablation. Cardiac rhythm was assessed with daily telephonic transmissions for one year. The left atrial diameter and the severity of symptoms were assessed at 12 months.

**RESULTS**

Among the 77 patients assigned to undergo circumferential pulmonary-vein ablation, ablation was repeated because of recurrent atrial fibrillation in 26 percent of patients and atypical atrial flutter in 6 percent. An intention-to-treat analysis showed that 74 percent of patients in the ablation group and 58 percent of those in the control group were free of recurrent atrial fibrillation or flutter without antiarrhythmic-drug therapy at one year ( $P=0.05$ ). Among the 69 patients in the control group, 53 (77 percent) crossed over to undergo circumferential pulmonary-vein ablation for recurrent atrial fibrillation by one year and only 3 (4 percent) were in sinus rhythm without antiarrhythmic-drug therapy or ablation. There were significant decreases in the left atrial diameter ( $12\pm 11$  percent,  $P<0.001$ ) and the symptom severity score ( $59\pm 21$  percent,  $P<0.001$ ) among patients who remained in sinus rhythm after circumferential pulmonary-vein ablation. Except for atypical atrial flutter, there were no complications attributable to circumferential pulmonary-vein ablation.

**CONCLUSIONS**

Sinus rhythm can be maintained long term in the majority of patients with chronic atrial fibrillation by means of circumferential pulmonary-vein ablation independently of the effects of antiarrhythmic-drug therapy, cardioversion, or both. The maintenance of sinus rhythm is associated with a significant decrease in both the severity of symptoms and the left atrial diameter.

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CIRCUMFERENTIAL PULMONARY-VEIN ABLATION is reported to be effective for paroxysmal and chronic atrial fibrillation.<sup>1-5</sup> However, patients with chronic atrial fibrillation typically receive temporary antiarrhythmic-drug therapy after ablation and often require one or more cardioversions to restore sinus rhythm. These are confounding variables that may inflate the efficacy of catheter ablation. Furthermore, prior studies have not systematically monitored patients for asymptomatic recurrences of atrial fibrillation on a frequent basis. Therefore, we conducted a randomized, controlled study to determine the long-term efficacy of circumferential pulmonary-vein ablation in patients with chronic atrial fibrillation while taking into account the confounding variables of antiarrhythmic-drug therapy and cardioversion.

## METHODS

### STUDY POPULATION

Between November 2002 and February 2004, 146 patients with chronic atrial fibrillation were randomly assigned to receive amiodarone and undergo two cardioversions during the first three months alone (the control group) or in combination with circumferential pulmonary-vein ablation. Chronic atrial fibrillation was defined as atrial fibrillation that had been present for more than six months without intervening spontaneous episodes of sinus rhythm and that recurred within one week after cardioversion. Exclusion criteria are listed in Table 1. The clinical characteristics of the two groups of patients are described in Table 2.

### STUDY DESIGN

The study was designed to determine the efficacy of circumferential pulmonary-vein ablation in maintaining sinus rhythm in the absence of antiarrhythmic-drug therapy in patients with chronic atrial fibrillation. To prevent short-term recurrences of atrial fibrillation that could interfere with the reverse remodeling process, patients received amiodarone for three months after undergoing circumferential pulmonary-vein ablation. In addition, if atrial fibrillation recurred within the first three months after ablation and persisted, cardioversion was performed. Because the combination of short-term treatment with amiodarone and cardioversion may result in atrial re-

modeling that promotes long-term sinus rhythm even after treatment with amiodarone is discontinued, patients in the control group also received amiodarone for three months and underwent cardioversion. The study design and flow are presented in Figure 1.

### STUDY PROTOCOL

The study was conducted at the San Raffaele Hospital in Milan and the University of Michigan Medical Center in Ann Arbor. The study protocol was approved by the institutional review board at each institution. Written informed consent was

**Table 1. Exclusion Criteria.**

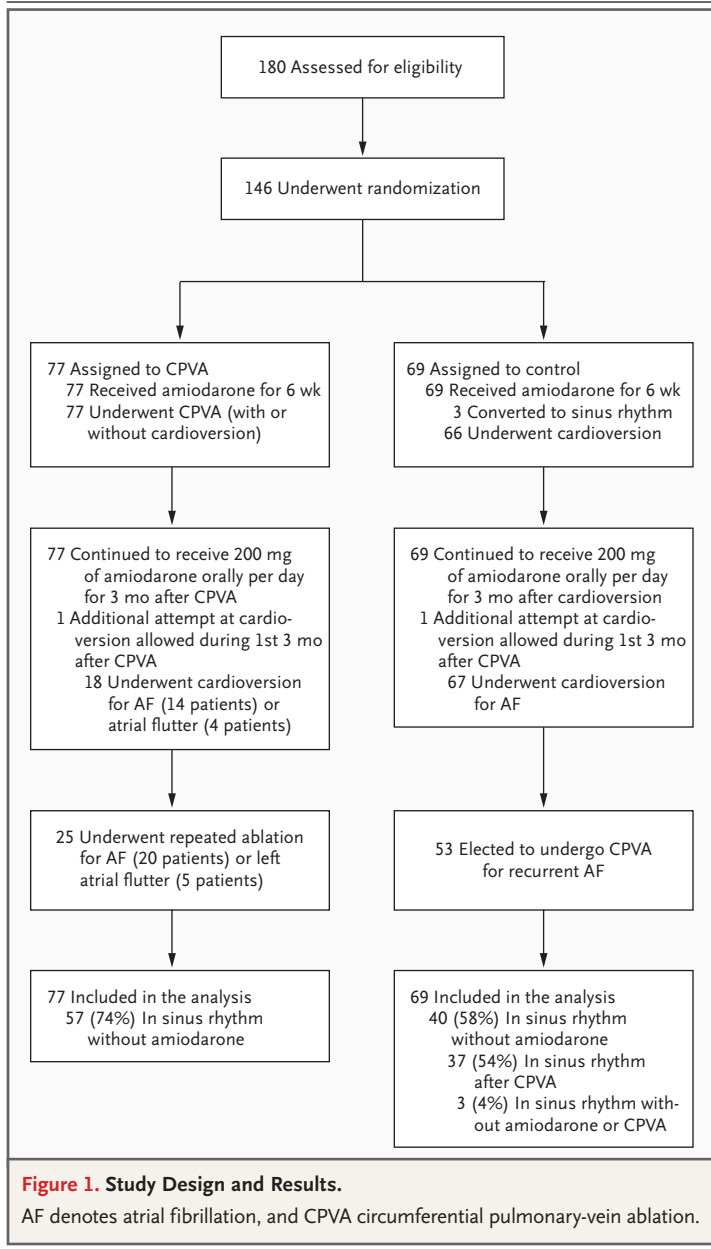
Age <18 or >70 yr
Left atrial diameter >55 mm
Left ventricular ejection fraction <30 percent
Contraindication to amiodarone therapy or anticoagulation with warfarin
Presence of a mechanical prosthetic valve
History of a cerebrovascular accident
Presence of left atrial thrombus on transesophageal echocardiography
Prior attempt at catheter or surgical ablation for atrial fibrillation

**Table 2. Characteristics of the Patients.\***

Characteristic	Control (N = 69)	Circumferential Pulmonary-Vein Ablation (N = 77)
Age (yr)	58±8	55±9†
Sex (no. of patients)		
Male	62	67
Female	7	10
Duration of atrial fibrillation (yr)	4±4	5±4
Left atrial diameter (mm)	45±5	45±6
Left ventricular ejection fraction (%)	56±7	55±7
Structural heart disease (no. of patients)	6	6
Nonischemic cardiomyopathy	1	2
Coronary artery disease	4	3
Valvular heart disease	0	1
Congenital heart disease	1	0
No. of previously ineffective antiarrhythmic drugs	2.1±1.2	2.0±1.2
No. of prior cardioversions	1.7±1.0	2.2±1.7

\* Plus-minus values are means ±SD.

† P=0.03.



All patients were given an event monitor (LifeWatch) for one year and were asked to record their rhythm at least five days a week for three minutes and whenever they had symptoms suggestive of atrial fibrillation. All rhythm tracings were interpreted in a blinded fashion by two physicians at the University of Michigan who did not otherwise participate in the study. Rhythms were classified as atrial fibrillation, atrial flutter, sinus rhythm, or indeterminate. An arrhythmia had to last more than three seconds to be classified as atrial fibrillation or atrial flutter. Indeterminate rhythms (which represented a mean [±SD] of 1.0±0.8 percent of all transmissions per patient) were reviewed by the investigators, and a consensus was reached. Rhythm transmissions were available in all patients for 85±8 percent of the days of follow-up.

**CIRCUMFERENTIAL PULMONARY-VEIN ABLATION**

Treatment with 200 mg of amiodarone orally per day was initiated six weeks before circumferential pulmonary-vein ablation. A transesophageal echocardiogram was obtained immediately before the procedure to rule out the presence of atrial thrombi. An electrode catheter in the coronary sinus was used to record left atrial electrical activity and for pacing. After transeptal puncture, intravenous heparin was infused to maintain an activated clotting time of at least 300 seconds.

Ablation was guided by an electroanatomical mapping system (CARTO, Biosense Webster) and performed with a temperature-controlled, quadripolar, deflectable catheter with an 8-mm tip (Navistar, Biosense Webster) to encircle the left and right pulmonary veins 1 to 2 cm from their ostia, with additional lines in the posterior left atrium or roof and along the mitral isthmus (Fig. 2). Contiguous applications of radiofrequency energy were delivered at a target temperature of 55°C and a maximal power output of 70 W for 20 to 40 seconds at each site. The end point of ablation was an 80 percent reduction in the amplitude of the electrogram or a total of 40 seconds of energy application. Additional ablation was performed within the circles, outside the pulmonary veins, where the local electrogram amplitude exceeded 0.2 mV. If atrial fibrillation was still present at the end of circumferential pulmonary-vein ablation, either ibutilide or transthoracic cardioversion was used to restore sinus rhythm (some patients received both treatments).

obtained from all patients. A computer-generated randomization table was used for randomization.

Patients were seen in the clinic before randomization and at 3, 6, and 12 months. An electrocardiogram and transthoracic echocardiogram were obtained during these visits, and patients completed a questionnaire to assess the severity of symptoms of arrhythmia (maximum possible score, 25, with higher scores indicating more severe disease; details are provided in the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)).

Patients were hospitalized overnight. Heparin was infused and warfarin therapy was started the same day. On discharge, patients received low-molecular-weight heparin until their international normalized ratio was at least 2.0. Patients received 200 mg of amiodarone orally per day for three months. Transthoracic cardioversion was permitted for recurrent atrial fibrillation during the first three months after circumferential pulmonary-vein ablation. When necessary because of recurrent atrial fibrillation, circumferential pulmonary-vein ablation was repeated.

#### CONTROL GROUP

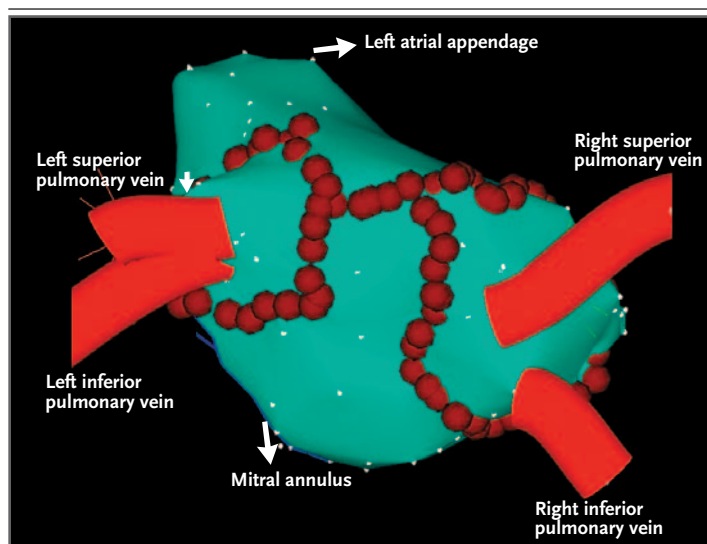
Patients in the control group received 200 mg of amiodarone orally per day for at least six weeks after randomization and then underwent transthoracic cardioversion. Amiodarone was discontinued after three months. Patients with recurrent atrial fibrillation were allowed to undergo cardioversion a second time within three months after the first cardioversion. Patients in whom recurrent atrial fibrillation developed more than three months after the first cardioversion were allowed to resume amiodarone therapy or to undergo circumferential pulmonary-vein ablation.

#### FOLLOW-UP

All patients had 12 months of follow-up. In both study groups, warfarin was discontinued at six months if there was no evidence of atrial fibrillation on daily rhythm tracings.

#### END POINTS

The primary end point of the study was freedom from atrial fibrillation and atrial flutter in the absence of antiarrhythmic-drug therapy one year after ablation in the group that underwent circumferential pulmonary-vein ablation or one year after cardioversion in the control group. The results were analyzed on an intention-to-treat basis. Because the control group was designed to control for confounding variables and not to compare circumferential pulmonary-vein ablation with a pharmacologic treatment strategy, we also analyzed the data according to the treatment actually received. Secondary end points were the incidence of complications, changes in the diameter of the left atrium and the left ventricular ejection fraction, and changes in the severity of symptoms.



**Figure 2. Circumferential Pulmonary-Vein Ablation.**

A three-dimensional electroanatomical depiction of the left atrium and the pulmonary veins is shown in a right posterior oblique projection with cranial angulation. The two encircling lesions were connected with an ablation line in the roof. Another ablation line was created along the mitral isthmus, between the left inferior pulmonary vein and the lateral mitral annulus.

#### STATISTICAL ANALYSIS

Assuming that sinus rhythm would be present at one year in 70 percent of patients who underwent circumferential pulmonary-vein ablation and 40 percent of patients in the control group, we estimated that a minimum of 56 patients was required in each group to give the study a statistical power of 90 percent with a two-tailed alpha value of 0.05. We determined the prevalences of sinus rhythm, atrial fibrillation, and atrial flutter each month. Even if only one rhythm recording in a given month demonstrated atrial fibrillation or atrial flutter, the patient was classified as having had atrial fibrillation or atrial flutter in that month.

Continuous variables are expressed as means  $\pm$ SD and were compared with use of Student's t-test. Categorical variables were compared with use of chi-square analysis or Fisher's exact test. All P values were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

#### CIRCUMFERENTIAL PULMONARY-VEIN ABLATION

Circumferential pulmonary-vein ablation was performed in 77 patients with the use of a mean of

37±11 minutes of radiofrequency energy. Atrial fibrillation was terminated during circumferential pulmonary-vein ablation in 12 of the 77 patients (16 percent). In the remaining 65 patients, sinus rhythm was restored after the ablation by the administration of ibutilide or transthoracic cardioversion. The mean duration of the procedure was 96±77 minutes. At the discretion of the operator, cavotricuspid isthmus ablation was also performed in 55 patients to prevent typical atrial flutter.

Transthoracic cardioversion was performed in 18 of the 77 patients (23 percent) a mean of 78±45 days after circumferential pulmonary-vein ablation, because of recurrent atrial fibrillation in 14 and atrial flutter in 4. Except for one patient who continued to take amiodarone for recurrent atrial fibrillation, patients discontinued amiodarone therapy a mean of 72±71 days after undergoing circumferential pulmonary-vein ablation. The ablation procedure was repeated in 20 patients (26 percent) because of recurrent atrial fibrillation and in 5 patients (6 percent) because of left atrial flutter, a mean of 204±82 days after the first procedure.

#### CONTROL GROUP

After the initiation of treatment with amiodarone, 3 of the 69 patients in the control group converted to sinus rhythm. In the other 66 patients, sinus rhythm was restored by transthoracic cardioversion. Atrial fibrillation recurred within two months in 67 patients (97 percent), and these patients underwent a second cardioversion a mean of 72±25 days after the first cardioversion. Except in 25 patients who elected to resume therapy, amiodarone was discontinued permanently a mean of 135±42 days after the first cardioversion in all patients.

#### FREEDOM FROM RECURRENT ATRIAL FIBRILLATION AND FLUTTER

According to the intention-to-treat analysis, 12 months after the first circumferential pulmonary-vein ablation, 57 of 77 patients in the group that underwent circumferential pulmonary-vein ablation were in sinus rhythm and free of atrial fibrillation and atrial flutter in the absence of antiarrhythmic-drug therapy (74 percent). At 12 months, atrial fibrillation was present in 22 percent of patients and atrial flutter was present in 4 percent of patients.

According to the intention-to-treat analysis, in the control group, 40 of 69 patients were free of atrial fibrillation 12 months after the first cardioversion in the absence of antiarrhythmic-drug therapy (58 percent,  $P=0.05$  by Fisher's exact test for the comparison with the group that underwent circumferential pulmonary-vein ablation) (Fig. 1). Seven patients (10 percent) had resumed treatment with amiodarone and were in sinus rhythm at 12 months of follow-up.

#### CROSSOVER TO CIRCUMFERENTIAL PULMONARY-VEIN ABLATION IN THE CONTROL GROUP

In the control group, 53 patients (77 percent) with recurrent atrial fibrillation crossed over to undergo circumferential pulmonary-vein ablation a mean of 128±57 days after cardioversion. Sinus rhythm was present in 37 of these 53 patients (70 percent) in the absence of antiarrhythmic-drug therapy at 12 months of follow-up. Only 3 of the 69 patients in the control group were free of recurrent atrial fibrillation 12 months after the first cardioversion in the absence of antiarrhythmic-drug therapy and circumferential pulmonary-vein ablation (4 percent,  $P<0.001$  for the comparison with the group that underwent circumferential pulmonary-vein ablation) (Fig. 3).

#### LEFT ATRIAL FLUTTER

Five of the 77 patients underwent an ablation procedure for atypical atrial flutter at a mean of 139±123 days. The atrial-flutter circuit used the mitral isthmus in two of these patients, gaps along the right or left circles in two patients, and multiple left atrial sites in one patient.

#### DIAMETER OF THE LEFT ATRIUM

Among patients without recurrent atrial fibrillation in the group that underwent circumferential pulmonary-vein ablation, the diameter of the left atrium was smaller at 12 months than before the procedure (40±6 mm vs. 45±6 mm,  $P<0.001$ ). There was no significant difference in the left atrial diameter among patients with recurrent atrial fibrillation.

#### LEFT VENTRICULAR EJECTION FRACTION

Among the patients who remained in sinus rhythm, the left ventricular ejection fraction was higher 12 months after circumferential pulmonary-vein ablation than before the procedure (0.62±0.08 vs. 0.55±0.06,  $P<0.001$ ). There was no

significant difference in the left ventricular ejection fraction values among patients with recurrent atrial fibrillation ( $P=0.47$ ).

#### SEVERITY OF SYMPTOMS

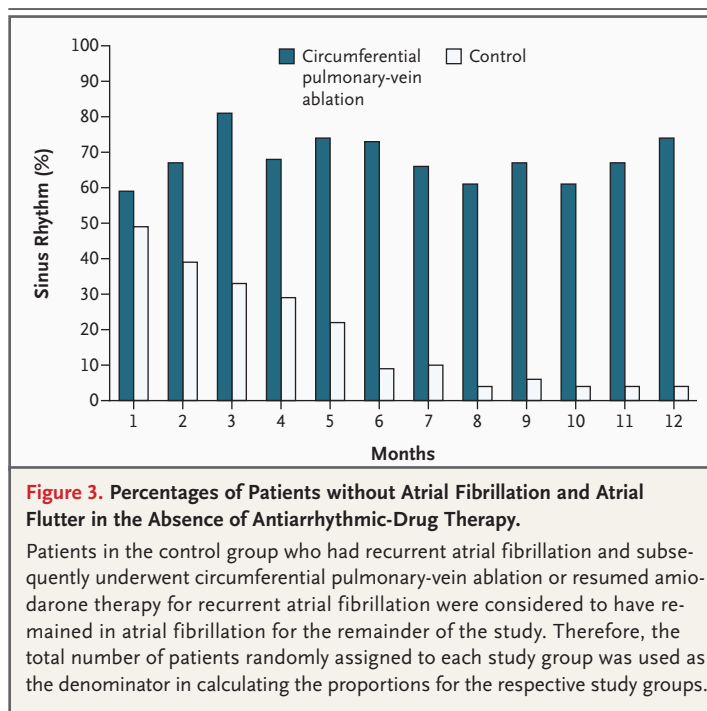
Among the patients who remained in sinus rhythm, the symptom severity score was  $17\pm 4$  at baseline and  $6\pm 2$  points at 12 months after circumferential pulmonary-vein ablation ( $P<0.001$ ). Among the patients who had recurrent atrial fibrillation or atrial flutter, the symptom severity score was  $17\pm 4$  at baseline and  $12\pm 4$  at 12 months after circumferential pulmonary-vein ablation ( $P=0.02$ ). Patients who were in sinus rhythm had a greater improvement in the symptom severity score than did patients with recurrent atrial fibrillation or atrial flutter ( $10\pm 5$  vs.  $5\pm 7$ ,  $P=0.002$ ).

#### COMPLICATIONS AND OTHER EVENTS

Other than the atypical flutters in the group that underwent circumferential pulmonary-vein ablation, there were no complications in either group. One patient in the group that underwent circumferential pulmonary-vein ablation and one patient in the control group received a permanent pacemaker for the sick sinus syndrome unrelated to ablation or drug therapy. Another patient in the group that underwent circumferential pulmonary-vein ablation who had recurrent atrial fibrillation underwent atrioventricular-junction ablation and received a pacemaker. A 66-year-old patient with a nonischemic cardiomyopathy died of pneumonia seven months after undergoing circumferential pulmonary-vein ablation.

#### DISCUSSION

We found that circumferential pulmonary-vein ablation resulted in long-term maintenance of sinus rhythm without the need for antiarrhythmic-drug therapy in 74 percent of patients with chronic atrial fibrillation. Because sinus rhythm was maintained in only 4 percent of patients in the control group in the absence of antiarrhythmic-drug therapy or circumferential pulmonary-vein ablation, the efficacy of ablation cannot be attributed to transient therapy with amiodarone, cardioversion, or both. The maintenance of sinus rhythm after circumferential pulmonary-vein ablation was associated with a decrease in the diameter of the left atrium, an improvement in the left ventricular ejection fraction, and a reduction in



the severity of symptoms. Atypical atrial flutter was the only complication attributable to circumferential pulmonary-vein ablation in this study. In addition, the procedure took less than two hours in most patients.

Many prior studies of ablation in patients with atrial fibrillation have been uncontrolled or have not systematically looked for asymptomatic episodes of recurrent atrial fibrillation on a frequent basis. Our study demonstrates that catheter ablation is reasonably efficacious in chronic atrial fibrillation independently of antiarrhythmic-drug therapy and cardioversion and with the use of a rigorous end point involving intense telephonic monitoring during follow-up. However, our study was not designed to demonstrate the superiority of circumferential pulmonary-vein ablation over pharmacologic therapy. Furthermore, we present no evidence that early circumferential pulmonary-vein ablation has any advantage over a deferred procedure.

Circumferential pulmonary-vein ablation may exert its beneficial effects by eliminating “driver tachycardias” or “rotors” that could play a role in the genesis of atrial fibrillation,<sup>6,7</sup> autonomic denervation of the left atrium,<sup>8</sup> isolation of the pulmonary veins,<sup>9</sup> atrial debulking,<sup>10</sup> and elimination of arrhythmogenic foci outside the pulmonary veins.<sup>11</sup> Recurrent atrial fibrillation and

atrial flutter were most common within the first weeks after circumferential pulmonary-vein ablation and were often transient. Early arrhythmias after circumferential pulmonary-vein ablation may be due to proarrhythmic effects of radiofrequency ablation within the left atrium or to residual mechanisms of atrial fibrillation that resolve as a result of maturation and progressive fibrosis of the ablation lesions. Late recurrences of atrial fibrillation may have been due to the emergence of new mechanisms of atrial fibrillation that were not eliminated by circumferential pulmonary-vein ablation, the recovery of conduction at previously ablated sites, or the washout of amiodarone, which was discontinued three months after ablation.

It is consistent with prior reports of the effect of circumferential pulmonary-vein ablation on the diameter of the left atrium<sup>4,12</sup> that we found a significant decrease in the diameter in patients who remained in sinus rhythm after ablation. This finding suggests that maintenance of sinus rhythm after circumferential pulmonary-vein ablation resulted in the resumption of atrial transport function and reverse atrial anatomical remodeling.

Patients who remained in sinus rhythm after undergoing circumferential pulmonary-vein ablation also had an improvement in the left ventricular ejection fraction. This improvement may have been due to the elimination of tachycardia-mediated ventricular dysfunction or the resumption of atrioventricular synchrony with regular RR intervals, or to both mechanisms.

As expected, there was a marked decrease in the severity of symptoms in patients who remained in sinus rhythm after they had undergone circumferential pulmonary-vein ablation. Patients with recurrent atrial fibrillation after they had undergone circumferential pulmonary-vein ablation had a smaller improvement. This may have been due to a placebo effect or to a decrease in the burden of atrial fibrillation (i.e., atrial fibrillation may have become less frequent and the episodes may have become shorter after ablation). It is also possible that regular clinic visits resulted in improved control of the ventricular rate during the study.

No complications other than left atrial flutter were attributable to circumferential pulmonary-vein ablation. However, atrioesophageal fistula was recently reported to be a rare complication of

catheter ablation in the posterior left atrium.<sup>13,14</sup> A reduction in the power output, target temperature, and duration of radiofrequency-energy applications and avoidance of sites on the posterior wall of the left atrium overlying the esophagus should prevent esophageal injury. Real-time, direct visualization of the esophagus may also be helpful.<sup>15</sup> The risk of atrioesophageal fistula should be carefully considered when one is selecting an ablation strategy for patients with atrial fibrillation.

Patients with a low left ventricular ejection fraction or a markedly dilated left atrium (more than 55 mm) were excluded from the study. Furthermore, the age cutoff was 70 years. Therefore, our findings are not applicable to all patients with chronic atrial fibrillation.

Many patients in the control group who had recurrent atrial fibrillation resumed therapy with amiodarone or underwent circumferential pulmonary-vein ablation after three months of follow-up. Ideally, outcomes in the two study groups would have been compared during 12 months of follow-up. However, the patients in this study were referred because they had symptoms despite drug therapy, and a requirement for 12 months of follow-up without further intervention despite the presence of recurrent atrial fibrillation would have severely limited our ability to recruit subjects.

We demonstrated that circumferential pulmonary-vein ablation can restore and maintain sinus rhythm in approximately 75 percent of patients with symptomatic, chronic atrial fibrillation, with a concomitant decrease in both the severity of symptoms and the diameter of the left atrium. Therefore, patients with chronic atrial fibrillation who otherwise would be destined to remain in atrial fibrillation for the rest of their lives can be offered the option of radiofrequency catheter ablation, even when chronic atrial fibrillation has been present for several years.

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial demonstrated that the use of a rhythm-control strategy does not have any advantages over the use of a rate-control strategy in patients with atrial fibrillation.<sup>16</sup> However, the patients in that trial were elderly (mean age, 70 years) and did not have that many symptoms, and the rhythm-control strategy consisted of antiarrhythmic drugs that had not been very effective and had the potential for serious adverse effects. Therefore, the results of

the AFFIRM trial should not be applied to all patients with atrial fibrillation. Our findings demonstrate that circumferential pulmonary-vein ablation is a reasonable option in patients with symptomatic, chronic atrial fibrillation.

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Drs. Oral and Morady are founders of Ablation Frontiers, report being major stockholders in Ablation Frontiers, and report having served as consultants to Ablation Frontiers and Biosense Webster. Dr. Pappone reports having received grant support from Biosense Webster, St. Jude Medical, Guidant, and Medtronic and having served as a consultant to Biosense Webster. Dr. Chugh reports having received lecture fees from Biosense Webster. No other potential conflict of interest relevant to this article was reported.

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