

Circumferential Pulmonary-Vein Ablation for Atrial Fibrillation

TO THE EDITOR: In their study of circumferential pulmonary-vein ablation in patients with chronic atrial fibrillation, Oral et al. (March 2 issue)¹ do not mention evaluation or discuss the potential complication of pulmonary-vein stenosis. In their definition of ostial stenosis, they rely on the electroanatomical “tube depiction” method as a guide; this is a suboptimal method for exact ostial demarcation since the tubes are automatically centralized around the acquired points. Any movement by the patient can also make electroanatomical mapping even more inaccurate.

Although the authors report no follow-up for the assessment of pulmonary-vein stenosis, a recent study involving magnetic resonance imaging detected a variable degree of stenosis in 38 percent of pulmonary veins ablated with the use of the electroanatomical approach.² A recent worldwide survey has shown that pulmonary-vein stenosis occurs in about 1.3 percent of patients.³ In addition, the authors mention that a patient died of pneumonia after ablation. However, they give no details about any further diagnostic investigation. Many reports, including one by Salamon et al.⁴ in the same issue of the *Journal*, have emphasized that pulmonary-vein stenosis is associated with symptoms that may mimic common lung diseases, which can lead to unnecessary diagnostic and therapeutic procedures.⁵

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TO THE EDITOR: Oral et al. report that “there were no complications” in a trial of catheter ablation for atrial fibrillation. This conclusion lacks meaning without consideration of the limited power of the study to detect rare but clinically significant events. The incidence of atrioesophageal fistula associated with this procedure has been estimated at less than 1 percent.¹ Even if the incidence were as high as 2 percent, the study by Oral et al. had less than 5 percent power to detect such a difference. Moreover, the authors followed patients for only 12 months after the procedure — a period that may be insufficient for the detection of occurrences of pulmonary-vein stenosis.²

The determination of the efficacy of a treatment with the use of a superiority design does not allow investigators to conclude that rates of adverse events are equivalent.³ Guidelines for the reporting of adverse events have been proposed that emphasize the need to discuss the limited power of trials to detect rare occurrences.⁴ This generally relevant consideration⁵ takes on increased importance when an adverse event is already recognized and potentially catastrophic.¹

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TO THE EDITOR: In the study by Oral et al., the mean age of patients who were randomly as-

signed to undergo pulmonary-vein ablation was 55 years, and about 92 percent of them did not have structural heart disease. The study population was highly selected and was not representative of the general population of patients with chronic atrial fibrillation.¹ Thus, it is premature to conclude that sinus rhythm can be maintained in the long term in the majority of patients with chronic atrial fibrillation by means of pulmonary-vein ablation. Such a conclusion can be misleading, considering that most patients with chronic atrial fibrillation are elderly and that thromboembolism is one of the leading causes of complications and death associated with atrial fibrillation.¹

The results of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial² should be applied to the majority of patients with chronic atrial fibrillation, and appropriate antithrombotic strategies should not be replaced by attempts to maintain sinus rhythm by catheter ablation. On the basis of currently available data, highly selected younger patients whose condition is refractory to medical treatment and who do not have structural heart disease³ may be most likely to benefit from catheter ablation for paroxysmal or chronic atrial fibrillation.

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2. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825-33.

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THE AUTHORS REPLY: The risk of pulmonary-vein stenosis depends on the ablation technique, en-

ergy source, maximum power and temperature, and whether energy was delivered within pulmonary veins. Circumferential pulmonary-vein ablation is performed outside the pulmonary veins. A previous study demonstrated that the procedure was not associated with any significant pulmonary-vein stenosis.¹ However, we do understand the concern of Wazni et al. regarding pulmonary-vein stenosis.² In the study by Dong et al.,³ unlike this study, linear lesions were created between the ipsilateral superior and inferior pulmonary veins, which increased the risk of stenosis. Dong et al. reported in the same study that stenosis occurred only when this line was created. The worldwide survey included patients from 100 centers that used a variety of techniques between 1995 and 2002. Therefore, these findings may not be representative of current practice, particularly when the rapid evolution of ablation strategies and techniques is considered. In our study, the 66-year-old man who died had a fatal case of *Stenotrophomonas maltophilia* pneumonia after surgical intervention for an aortic aneurysm seven months after the ablation.

Aberegg and Majure point out that our study did not have sufficient power to assess safety. However, as indicated, the primary end point was efficacy. Because the incidence of atrioesophageal fistula is very low, more than 1700 patients would be required in each group for a study to detect a difference at a power of 0.90. Because atrioesophageal fistula is a rare but often fatal complication, it was discussed in detail. Nevertheless, large-scale multicenter trials with an extended duration will be necessary to determine the ultimate safety of ablation in the treatment of atrial fibrillation. However, because ablation strategies are still evolving, such trials may not be feasible in the near future.

We agree with Auer et al. that the study population was not representative of all patients with chronic atrial fibrillation. However, we strongly disagree that the AFFIRM results should be applied to the majority of patients with atrial fibrillation. As discussed, there are important differences between the subjects of the AFFIRM trial and those in our study, since patients in the AFFIRM study were older (mean [\pm SD] age, 70 \pm 9), had at least one risk factor for stroke, and were unlikely to have debilitating symptoms caused by the atrial

fibrillation. Furthermore, sinus rhythm was maintained in only one third of the rhythm-control group. We believe that our study has demonstrated that catheter ablation is a reasonable option for younger patients whose quality of life is disturbed by chronic atrial fibrillation and whose condition has not responded well to drug therapy or cardioversion.

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THE EDITORIALISTS REPLY: In our editorial¹ accompanying the study by Oral et al., we stated, “According to the latest guidelines of the American Heart Association [AHA], the American College of Cardiology [ACC], and the European Society of Cardiology [ESC], catheter ablation is considered standard therapy for patients who have symptomatic paroxysmal atrial fibrillation

after having had no response to a single antiarrhythmic drug.” This statement is incorrect, since the only approved guidelines on this topic are those from 2001, rather than those we cited as being currently “in press.” Although a revision is under development, it has not been completed. The current policy of the organizations regarding this issue can be found in the 2001 ACC–AHA–ESC guidelines on atrial fibrillation.²

In addition, our statement and the accompanying citation violate the confidentiality policies of these three organizations for the development of guidelines — policies that are specifically designed to prevent premature distribution of draft recommendations that are not yet approved, as was done in this case. We deeply regret the inclusion of misleading information about the position of the organizations in our editorial and our erroneous citation of the guidelines as being “in press,” as well as our violation of the policies of the organizations regarding the development of guidelines.

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Urinary *FOXP3* Messenger RNA and Renal-Allograft Rejection

TO THE EDITOR: The observations of Muthukumar et al. (Dec. 1 issue)¹ regarding the clinical usefulness of *FOXP3* messenger RNA (mRNA) in predicting the outcome of renal-allograft rejection are thought-provoking, but we believe caution is needed. Although data from their study suggest that levels of *FOXP3* mRNA in urine are the best prognostic indicator of reversal of acute rejection, there is substantial overlap in values be-

tween the patient groups (as shown in Fig. 2 of the article). In addition, the overlapping confidence intervals for the areas under the receiver-operating-characteristic (ROC) curves (shown in Fig. 3 of the article) suggest the need for larger group sizes to establish the superiority of this marker definitively.

It is not known whether *FOXP3* mRNA levels in urine can be influenced by factors other than