Transvenous Radiofrequency Catheter Ablation for Atrial Flutter and Atrial Fibrillation

The End of the Beginning?

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Now this is not the end. It is not even the beginning of the end, but it is, perhaps the end of the beginning.
—Winston Churchill, November 10, 1942

Transvenous radiofrequency catheter ablation (RFA) for treatment of atrioventricular (AV) reentrant tachycardia and AV nodal reentrant tachycardia is remarkably successful. To the best of my knowledge, there has not been a large randomized trial comparing RFA with other treatments for these tachycardias. The lack of such trials is due at least in part to the self-evident efficacy of RFA in this setting. In turn, the efficacy of RFA for these tachycardias is in large part due to the fact that the anatomy and pathophysiology of these two tachycardias are well understood. The success of RFA for treating AV reentrant tachycardia and AV nodal reentrant tachycardia quite rightly led to a large effort to expand this success, and thereby the indications for RFA, to other tachyarrhythmias.

Among the supraventricular tachyarrhythmias, the atrial flutter (AFL)/atrial fibrillation (AF) family is an obvious but challenging target for RFA. The early results are promising. AF is numerically the largest member of this family of tachyarrhythmias. The other family members are atrial tachycardia and AFL. These tachyarrhythmias can be closely related anatomically, can share a common pathophysiology, and can be found in the same patient.1

There are probably several different anatomies and pathophysiologies for these tachyarrhythmias. Inability to fully understand the anatomy and pathophysiology of a tachyarrhythmia in an individual patient makes RFA more difficult and to some extent empiric. Among the various AFLs, one is well understood. So-called classic, typical, common, or isthmus AFL has a characteristic but not unique surface ECG pattern: a “saw-tooth” pattern of p waves in the inferior leads (II, III, and aVF). It is a reentrant atrial tachyarrhythmia that is dependent on unidirectional block and slow conduction through the isthmus of right atrial tissue between the tricuspid annulus and the inferior vena cava. The critical importance of this region is demonstrated by the concealed entrainment seen when this area is paced. This maneuver distinguishes it from other AFLs that may look similar in the surface ECG. RFA to produce a line of bidirectional conduction block across this isthmus is a highly effective treatment for this AFL. The procedure is not always easy, given the valleys and ridges created by the pectinate atrial muscle in this region. Again, however, detailed understanding of the anatomy and pathophysiology has led to a very useful RFA procedure for this particular AFL. The main weakness of the procedure is that during extended follow-up, AF will emerge in about half of the patients, mostly in those with previous AF.2 It is in this particular setting that the Loire-Ardèche-Drôme-Isère-Puy-de-Dôme (LADIP) trial investigators have chosen to study the efficacy of RFA compared with amiodarone.3

The LADIP Trial: A Perspective

The major strength of the LADIP trial is that it is a randomized controlled trial. It enrolled a selected subset of patients with right atrial isthmus AFL: elderly patients presenting with their first symptomatic episode. Studying this patient group allows comparison of both the recurrence of AFL and the emergence of AF because AF is more common in the elderly.4

The place of RFA relative to antiarrhythmic drug therapy in treating the AFL/AF family of arrhythmias remains incompletely defined. RFA for AV reentrant tachycardia or AV nodal reentrant tachycardia can be offered as first-line therapy without prior drug therapy.5 Although there has been a pilot study for a trial of RFA treatment after the first episode of paroxysmal AF,6 it is more widely believed that RFA for AF is currently indicated for selected patients after the failure of antiarrhythmic drugs.7 The place for RFA in the treatment of isthmus AFL is somewhat intermediate, with some experts believing that it is a first-line alternative to drug therapy.8 The LADIP trial therefore partly intends to address the question of whether RFA should be first-line therapy for isthmus AFL in elderly patients. A major issue in this instance, however, is the emergence of AF.

The LADIP investigators concluded that their study demonstrated 2 main findings: RFA is “superior” to amiodarone for the prevention of recurrence of AFL, and RFA is “equivalent” to amiodarone for the prevention of AF.
Superiority is based on finding lower recurrence of AFL in the RFA group compared with that in a comparator group when that finding has a low probability of a type I error (declaring a difference when in fact there is none). The end point in this case is recurrence of AFL. In LADIP, AFL (and AF) was sought in an identical manner in both groups using 1-week-long event recorder monitoring at regular intervals during follow-up. Regular event recordings are important because the occurrence of asymptomatic events is common in patients like those enrolled in the LADIP study. It is not mentioned whether the readers of these recordings were blinded to treatment assignment. Blinded interpretation of monitoring is critical to optimizing unbiased ascertainment of the end point, especially when it is not possible to blind treatment assignment, such as is the case in LADIP. It should be noted, however, that differentiating AFL from AF with such recordings is subject to error.

The question being addressed in LADIP is comparative antiarrhythmic efficacy of the treatments. Examination of the results at first glance suggests a clear superiority of RFA, and the authors present statistical calculations to buttress their first conclusion. Although one might accept the overall conclusion, the magnitude of difference is surprising. The uncertainty around this conclusion emerges in examination of the appropriateness of the period of comparison for the treatments.

One expects an antiarrhythmic effect of RFA from completion of the ablation procedure on, which corresponds closely to time 0. In contrast, setting electrical cardioversion and starting amiodarone as time 0 does not allow for the fact that the full effect of amiodarone will take some time, particularly with a loading dose of 400 mg/d. In other settings and using substantially larger loading doses, the pertinent electrophysiological effects of amiodarone are not complete until >2 and up to 10 weeks have passed. The authors understand this limitation but dismiss it too lightly by noting few recurrences of AFL in the amiodarone-treated group in the first week. The contentious time period is much longer than a week, and examination of their Figure 1 shows that most recurrences in the amiodarone group were in the first 40 days, a period during which the antiarrhythmic effect of amiodarone would be diminished. With this point taken into consideration, their first conclusion is less convincing than the authors imply. In passing, it should be noted that with an average follow-up of 13±6 months, the uncertainties in the Kaplan-Maier plots beyond 400 days are quite large.

Claims of equivalence for emergence of AF, on the other hand, are based on finding no difference (or a clinically unimportant small difference) in the occurrence of AF in the RFA group in relation to that in the comparator group and on that finding having a low probability of a type II error (declaring no difference when in fact there is one). Equivalence is not quite the same as finding no difference after applying a test for type I error and typically requires larger sample sizes to be accepted. The end point in this case is occurrence of AF. Of course, the same argument about the appropriateness of the period of comparison during follow-up discussed above also applies in this case. Furthermore, this finding is more surprising than the first for other reasons. The biological plausibility for a right atrial isthmus ablation to prevent AF seems tenuous. RFA could be effective through preventing tachycardia-induced tachycardia (AFL degenerating into AF), but ablation in the right atrium is known to have little effect on AF itself. On the other hand, amiodarone has been compared with placebo and certainly has efficacy for the prevention of AF. Finally, with respect to the emergence of AF, the follow-up period was quite short (see Hsieh et al). Therefore, the second conclusion of the LADIP investigators is even less convincing than the first.

**Moving Ahead With Trials of RFA**

Randomized controlled trials are a useful and powerful tool for the study and comparison of treatments with one another and with placebo. So far, the trials of RFA for AFL/AF such as the LADIP trial have focused on antiarrhythmic efficacy. Similarly, when a new antiarrhythmic drug for AFL/AF is first tested, the focus is also on antiarrhythmic efficacy, and one of the main criteria for registration of a drug with regulatory agencies is demonstration of such efficacy. Eventually, it is important to move on and demonstrate that the treatment has more tangible clinical benefits. In contrast to life-threatening ventricular arrhythmias in which death is the obvious benefit and the primary clinical end point for clinical trials, the most appropriate benefits and end points for clinical trials of treatments for AFL/AF are not so obvious and vary, depending on the population being studied. This topic has been reviewed recently.

In an elderly population such as that enrolled in LADIP, relief of symptoms or improved functional capacity or quality of life is a potentially useful clinical end point but presents a problem with unbiased ascertainment because of the unblinded nature of treatment assignment. On the other hand, in the elderly, hard clinical end points such as death and stroke may be viable end points. Cost-effectiveness is always a useful end point, and recent modeling of this end point for RFA for AF suggests that its economic advantage is driven largely by the impact of the treatment on the risk of stroke. Of course, the difficulty is that conducting trials with such end points is much more difficult, and they need to be much larger. It is noteworthy that when trials of antiarrhythmic drugs for treatment of AFL/AF moved on from simple antiarrhythmic efficacy studies to studies of other clinical end points, the benefits of pharmacological rhythm control were quite meager.

The benefits of rhythm control have often been argued on the basis of a post hoc subanalysis of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial. It has invariably been overlooked when this AFFIRM publication has been quoted that there are many potential explanations for the observed results, including the possibility that being able to maintain sinus rhythm in itself may portend a good outcome with respect to death as a result of factors that were not measured or accounted for in that analysis. Although the presence of sinus rhythm may be associated with improved survival in various cohorts, it remains unproven that any antiarrhythmic treatment (drugs or RFA) for AFL/AF reduces the risk of death. The real test of the impact of a
treatment on death, when death is a valid end point, is to do the experiment.

**Conclusions**

The LADIP trial enrolled a selected type of patient and compared RFA with amiodarone for treatment of a specific type of AFL. The main finding is that RFA was superior to amiodarone for preventing the recurrence of AFL and the emergence of AF, particularly the latter, may be attributable largely to trial design issues rather than true differences. The major issue is that events contributing to the end points were accumulated during a time in which RFA would be expected to be efficacious but amiodarone would not. In a more general sense, it is time that trials of RFA for the treatment of AFL/AF move on from testing the simpler question of antiarrhythmic efficacy to testing the treatment using robust and clinically relevant end points. Although testing for antiarrhythmic efficacy is important at the beginning, perhaps we are nearing the end of the beginning.

**Disclosures**

Dr Wyse has received research grants from Cardiome/Astellas and Medtronic; has served on Scientific Advisory boards for Boehringer Ingelheim and Novartis; has been a speaker for Chugai, Cardiome/Astellas, Daiichi, and Eisai; and has served on Steering Committees or Data and Safety Monitoring boards for Cardiome/Astellas, Medtronic, Sanofi Aventis, and Boehringer Ingelheim.

**References**


**Key Words**: Editorial | ablation | antiarrhythmia agents | arrhythmia | atrial flutter | randomized controlled trials
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_Circulation_. 2006;114:1670-1672
doi: 10.1161/CIRCULATIONAHA.106.653519

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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