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VIEWPOINT

Ablation for Atrial Fibrillation: Are Cures Really Achieved?

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During the past 10 years numerous studies on the treatment of paroxysmal atrial fibrillation (AF) by right and left atrial ablation procedures have been published. The results of studies based on follow-up periods of a few months have been repeatedly interpreted as providing evidence for curative therapy. However, insufficient focus on the variability of the natural history of paroxysmal AF, the inadequate detection of silent arrhythmic events, the eclectic post-interventional use of antiarrhythmic drugs, and the lack of appropriate control groups make the reports unconvincing. Randomized controlled trials are needed to confirm postulated long-term cure rates for AF. (J Am Coll Cardiol 2004;43:1940–2) © 2004 by the American College of Cardiology Foundation

The limited success of drug therapy for the prevention and treatment of atrial fibrillation (AF) has incited clinical investigators to explore alternative treatments (1–3). Various preventive electrophysiologic strategies ranging from multisite atrial pacing to rate smoothing, antitachycardia pacing, and atrial defibrillators have been proposed, but these therapies remain largely investigational (4). A common therapy for "drug-refractory" AF is ventricular pacing after atrioventricular nodal ablation, a palliative treatment still requiring anticoagulation (5). But perhaps the most intriguing nonpharmacologic therapy is that seeking to cure AF by the targeted destruction of atrial muscle. Working in the footsteps of arrhythmia surgeons, electrophysiologists have devised during the past decade catheter-based ablation procedures inspired by the Corridor and Maze operations. In their most recent work on "pulmonary vein isolation," they interpreted their interventions to *cure* AF in more than 85% of the patients (6–9). These cure rates published in peer-reviewed journals have put considerable pressure on practicing electrophysiologists to make ablation for AF available to their patients. Consequently, the procedure has been adopted widely, but registries documenting the efficacy and safety of atrial ablation as applied in the community are not available. Some operators have failed to achieve high cure rates (10). One investigator wondered whether looking for curative atrial scars was "hype or hope" (11), and another felt that ablation for AF was "not a reality" (12).

Although surgeons and interventionalists like to debate whether clinical research based on randomized controlled trials should or could be implemented in their fields, there is really no doubt that new treatments require comparison with established treatments or no treatment (placebo or sham operations) (13). Momentarily forgetting the trialists' special criteria-guided assembly of cohorts, randomization with the generation of control groups, masking (blinding), power estimates, and survival statistic applying the intention-to-treat principle, the simplest and most modest evaluation of therapeutic efficacy is to compare patients receiving a new experimental treatment with those who have previously received either no therapy or another therapy. Describing patients who received no therapy in the past are historical controls that help us define the natural history of a disease. In a recent meta-analysis summarizing 91 randomized trials of the drug treatment of AF (total number of patients 8,563), the maintenance of sinus rhythm over follow-up periods lasting <1 to 1,096 days (mean ± SD, 46 ± 136) ranged in the placebo group between 0% and 90% (mean, 32%) and in the drug group between 0% and 100% (mean, 52%; $p < 0.0001$ vs. placebo) (1). The extensive meta-analysis suggests two points: 1) overall treatment efficacy with drug versus placebo is highly significant although modest in magnitude; and 2) the relapse rate over relatively short periods both with and without antiarrhythmic drug treatment is spectacularly variable, ranging essentially between 0 and 100%. In their review of paroxysmal AF (PAF), Lip and Li Saw Hee (3) emphasized the difficulty in delineating a natural history of this disease. One of the major problems in the assessment of PAF is that its episodes are very frequently silent (14,15). In patients receiving implantable devices with long-term Holter memory function, more than 50% of the patients exhibit unsuspected PAF (14,15). A seeming cure of PAF may simply represent the conversion of early symptomatic to subsequent asymptomatic disease (14). Therapeutic efficacy of atrial ablation critically depends upon the use of special tools for the detection of asymptomatic arrhythmias (15,16). Patients seek medical help selectively during periods of *symptomatic* exacerbations, not periods of symptomatic remission. There is evidence that the initial episodes of AF are most likely to produce anxiety and be poorly tolerated, whereas increasing chronicity of AF may favor asymptomatic episodes, espe-

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cially in the elderly population (14). Post-interventional symptom modification in patients willing to submit themselves repeatedly to hazardous invasive procedures such as AF ablation may importantly depend upon a placebo effect (13), a phenomenon strikingly illustrated in recent *sham- or placebo-controlled* trials of myocardial revascularization (17,18). Post-interventional appraisal of PAF is most difficult and requires special methodological precautions that have been extensively evaluated for other chronic relapsing-remitting diseases with erratic clinical course, multiple sclerosis in particular (19).

Claiming cure or palliation in the absence of randomized controlled trials ignores modern evidence-based medicine. Concurrent nonrandomized control groups do not eliminate selection bias and inequalities between groups. Prospective epidemiologic studies and observational registries have demonstrated that AF in industrialized societies is a highly age-dependent disease. Groups younger than 60 years of age may amount to no more than 10% of the total AF population (5,20,21). Therefore, reports on AF ablation involving patients younger than a mean age of 60 years (for example, 7,22,23) or indeed 50 years (6) are examples of patient selection. Furthermore, if patients are also stated to exhibit no signs of structural heart disease (7,22), they may be viewed as suffering from "lone AF," a controversial type of AF that may be associated with low long-term relapse rates (24). Another major drawback of assessing therapeutic efficacy without appropriate controls is the failure to consider concomitant therapy. In most AF ablation studies, authors used eclectically antiarrhythmic agents on top of ablation therapy without prospective specification of drug indication, type, or dosage. Knowing that drug therapy for AF is partly effective over short periods (1) makes the evaluation of superimposed ablation therapy virtually impossible. A minimal requirement would be to obtain quantitative Holter type assessments of AF burden serially before and after invasive intervention while keeping *pharmacologic treatment invariant*.

The literature on ablation for AF suffers in part from the same shortcomings as that on arrhythmia surgery for AF. In both cases, uncontrolled studies often describe single-center experiences with *repeatedly modified procedures and newly tested instrumentation* that make the evaluation of sequential studies from single institutions or comparisons between institutions impossible. Over recent years, single groups prematurely claimed success, for instance, success with right atrial ablation or ostial pulmonary vein ablation (22,23,25), a procedure that invites pulmonary vein stenosis (26). In two studies reported by one group, the mean age of *consecutive* atrial ablation patients collected "from all over Italy" (8) during *completely overlapping* study periods differed between a typical 65 years in one study (8) and an atypical young age (~50 years) in the other (7). This epidemiologically unlikely event suggests eclectic grouping rather than the reporting of *consecutive* patients. The second of these two studies (8) was called "controlled," although the indication for ablation was determined by *either* the patient's preference *or* the electrophysiologist's judgment, arguably not exemplary control. This study reported a remarkable reduction in sudden cardiac death (SCD) rate (and total cardiovascular mortality) by atrial ablation. During a mean observation of approximately 2.4 years, there were no SCDs among 589 ablated patients, but 12 among 582 non-ablated controls (no statistical analysis provided) (8). The apparent protection against SCD occurred in patients exhibiting an elevated left ventricular mass (138 g/m^2) estimated by an unknown echocardiographic method. In a recent Italian multicenter study (MAssa Ventricolare sinistra nell'Ipertensione arteriosa [MAVI]), this degree of left ventricular hypertrophy was associated with a high SCD risk (27). Intimating that such studies provide controlled data demonstrating the reduction of mortality and morbidity by atrial ablation cannot be accepted without reservations. Another pervasive problem in recent atrial ablation reports is a variable or absent definition of the term *cure* of AF. As with earlier reports on Maze operations, there is after approximately 10 years of clinical experimentation with continually modified procedures a lack of randomized studies providing convincing survival-statistical information on therapeutic gains, risks, and complications. Important possible complications, such as high radiation doses from single or repeated procedures or postprocedural cognitive deficits from silent embolic brain injury (28,29), have been largely ignored.

We recognize that ablation for AF, if successful, would represent an important advance in cardiovascular therapeutics and we truly applaud research in this field. However, it is the responsibility of peer-reviewed cardiology journals to provide a critical and balanced assessment of the work performed in this field. Editors and reviewers should make an effort to resolve uncertainties arising from contradictory reports. Recently, one group of authors (30) concluded in the abstract of their report that "isolation of pulmonary veins is not crucial for curing AF." Four months later, in the same journal, another group (31) concluded in their abstract that "total electrical isolation of the pulmonary venous region. . .appeared necessary for success." The second paper (31) did not relate to the preceding one (30). Methodological research and feasibility appraisals should be described as such without claims to achieve cure rates as evaluated in phase III clinical trials. Also, claims of cure should be based on adequate follow-ups of at least two years. Knowing the epidemiology of AF, in particular its association with advanced age and cardiovascular risk factors (5,20,21), and considering the diffuse structural alterations affecting the atria (atrial and pulmonary vein enlargement, apoptosis of cardiomyocytes, deposition of matrix proteins, and extensive genetic reprogramming) (32), the postulate that the placement of a few scars can truly cure venoatrial disease remains provocative. Previous experience with ablation therapy for ventricular tachyarrhythmias has documented the difficulties arising from diffuse myocardial disease (33). Nonvalvular

AF is a tenacious erratic disease evolving over a lifetime, and brief post-interventional follow-ups over periods of months should be interpreted cautiously.

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