Catheter Ablation of Atrial Fibrillation
On the Pathophysiology of the Arrhythmia and the Impact of Cardiac Risk Factor Management*

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Catheter ablation of atrial fibrillation (AF) has undergone considerable development within the last 15 years. Originally, the procedure was predominantly reserved for relatively young patients with no significant structural heart disease. Subsequently, more elderly patients and patients with significant structural heart disease and substantial numbers of cardiac risk factors have been treated with catheter ablation. For example, within the last 10 years, the mean age of patients undergoing AF ablation in our laboratory increased from 54 to 67 years. Recommendations for patient selection, procedural techniques, patient management, and follow-up were recently updated in the expert consensus statement (1).

In addition to further reductions in the complication rate, another major target for improving this relatively invasive catheter procedure is reduction of the necessity for redoing procedures. In the young and otherwise healthy patient population undergoing AF ablation, the typical reason for arrhythmia recurrences (although not always) is reconnection of the initially isolated pulmonary veins. With inclusion of patients who have significant structural heart disease and substantial numbers of cardiac risk factors, this scenario is more complex and combined with our still-limited understanding of AF pathophysiology. Besides the well-accepted role of pulmonary vein foci in triggering the arrhythmia, the nature of the substrate maintaining AF is still under debate and was recently called the “unknown species” in an editorial (2). Within the last decade, data on the relationship between AF and obesity, obstructive sleep apnea (OSA), alcohol consumption, and cardiometabolic risk factors have emerged (3-6). Furthermore, in a recently published randomized clinical study (7), weight reduction plus intensive general risk factor management (RFM) resulted in reduced AF symptom burden and severity. AF also has a genetic component, and a primary fibrotic atrial cardiomyopathy was described as a specific disease supplying substrates for AF, atrial tachycardia, sinus node disease, AV node disease, and thromboembolic complications (8,9).

In this issue of the Journal, Pathak et al. (10) report the results of the ARREST-AF Cohort Study (Aggressive Risk Factor Reduction Study for Atrial Fibrillation) and their implications for catheter ablation outcomes. This study comprised consecutive patients with body mass index ≥27 kg/m² and ≥1 risk factor (hypertension, glucose intolerance/diabetes mellitus, hyperlipidemia, OSA, smoking, or alcohol excess) undergoing catheter ablation for symptomatic AF, despite use of antiarrhythmic drugs. Patients in the RFM group (n = 61) attended an intensive physician-directed program in a RFM clinic, according to American College of Cardiology/American Heart Association guidelines (11). The control group subjects (n = 88) continued RFM under the direction of their treating physician. RFM resulted in significantly greater weight and blood pressure reductions, and better glycemic control and lipid profiles. Reviews were every 3 months for the first year and then every 6 months thereafter, including ambulatory 7-day monitoring at each review. At follow-up after catheter

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ablation, arrhythmia-free survival after single and multiple procedures was significantly greater in RFM patients compared with control subjects. On multivariate analysis, RFM was an independent predictor of arrhythmia-free survival, with an impressive hazard ratio of 4.8 (10).

This report from Pathak et al. (10) confirms and extends the growing body of evidence that a variety of cardiac risk factors affect procedural outcomes in patients with AF undergoing catheter ablation (12-15). The “aggressive” RFM used in the study by Pathak et al. was, indeed, impressive and comprehensive, including blood pressure control, weight management, lipid management, glycemic control, sleep-disordered breathing management, smoking cessation framework, and alcohol reduction. Furthermore, the improvement in long-term success of AF ablation was significant and seems substantial, even given the limitation that the study was nonrandomized.

It is also impressive that of 281 consecutive patients referred for catheter ablation of symptomatic AF, 165 had a body mass index ≥27 kg/m² plus ≥1 risk factor. In other words, almost 60% of the patients referred for catheter ablation of symptomatic AF qualified for RFM because of obesity plus additional risk factors. This finding confirms recent estimations that almost 70% of U.S. adults are either overweight or obese, with ~35% being obese (16).

The clinical implications of the data presented by Pathak et al. (10) seem clear and important. First, “aggressive” RFM in patients with obesity and other cardiac risk factors substantially improved outcomes after catheter ablation of AF. Second, given the biomedical and socioeconomic consequences of obesity on morbidity and mortality, the high prevalence of obesity needs to be generally addressed with a higher social priority.

The scientific implications with respect to the human AF substrate, or the pathophysiology of AF in general, seem less clear. In this study (10), because a comprehensive RFM was performed, the relative contribution of each risk factor cannot be assessed. In addition, even the single risk factor, obesity, can promote AF from different directions. For incident AF, analysis demonstrated that left atrial enlargement was one critical mediating factor for obesity (2). Furthermore, increased systemic inflammation marker levels (17), changes in neurohumoral activation (18), increased arterial stiffness (19), and increased OSA incidence (5), indicate that the interaction of obesity with different aspects of AF pathophysiology is complex. Conversely, the vast majority of overweight and obese patients do not have AF. Therefore, it may be argued that rather than acting as a primary “substrate maker,” obesity modulates or promotes AF. Atrial fibrosis seems the common endpoint of atrial structural remodeling, forming the substrate for AF maintenance. But where does this fibrosis come from? Originally, aging and general cardiac disease, as well as the arrhythmia itself, were assumed to underlie the structural remodeling process leading to the progression of AF from paroxysmal to persistent forms. However, an autopsy study in which no correlation could be detected between patient age and increased extent of fibrosis (20) called the importance of age itself into question. Results from analysis of intraoperatively obtained specimens, autopsy findings, electroanatomic mapping studies, and magnetic resonance imaging investigations showed high variability in the extent of fibrosis, with some patients with paroxysmal AF having massive fibrosis (even very early after the first AF episode) and some patients with persistent AF showing mild fibrosis, with recent analyses suggesting a specific underlying structural atrial disease, fibrotic atrial cardiomyopathy (8,9). In contrast, little clinical evidence was found that AF itself significantly produces fibrosis, in the sense of “AF begets AF” (9).

In a surgical scenario, pre-operatively elevated serum markers of collagen synthesis were recently reported to be associated with post-surgical AF in patients with no history of AF (21). Importantly, pre-existing left atrial fibrosis was significantly higher in patients who developed post-surgical AF, compared with those who stayed in sinus rhythm, suggesting modulating effects of cardiac surgery on pre-existing and, thus far, subclinical left atrial fibrosis/fibrotic atrial cardiomyopathy.

In summary, the authors (10) are to be commended for rigorously applying “aggressive” RFM and demonstrating its beneficial effects on long-term success after catheter ablation of AF. Their study sheds further light on the substantial clinical role of modifiable factors, such as obesity and other cardiac risk factors, and has significant clinical implications. Certainly the “unknown species” human AF substrate as well as the specific roles of promoters/modulators of AF pathophysiology (e.g., cardiac risk factors, inflammation, surgery, cancer) deserve further evaluation.

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