EDITORIAL COMMENT

The “Second Factor”: A First Step Toward Diagnosing the Substrate of Atrial Fibrillation?*

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In this issue of the Journal, Stiles et al. (1) publish a report titled “Paroxysmal Lone Atrial Fibrillation Is Associated With an Abnormal Atrial Substrate: Characterizing the ‘Second Factor’.” In 25 patients with paroxysmal lone atrial fibrillation (AF), atrial electrophysiological abnormalities were found, characterized by loss of myocardial voltage, conduction slowing, altered sinus node function, and prolonged refractoriness. The authors postulate that these abnormalities are essential contributors to the “second factor” that promotes progression of AF and explains why sinus rhythm does not beget sinus rhythm in patients with AF.

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The term “second factor” originally stems from observations in the goat in which AF was artificially maintained by a fibrillation pacemaker (2). It was found that after electrical remodeling was complete (the “first factor”), the duration of induced AF-paroxysms still continued to prolong with time. Actually, whereas the atrial refractory period already reached a new steady state within 2 to 3 days, it usually took another 1 to 2 weeks before AF became self-sustained (2). This led to the conclusion that other more slowly developing factors, like atrial dilation, enlargement of atrial myocytes, loss of myofilaments, changes in expression of connexins and gap junctions, and altered composition of the extracellular matrix, must be important for the development of a substrate of AF (3–6). Although initial experiments of repetitive episodes of 5 days of AF, separated by 2 days of sinus rhythm, failed to show any cumulative effect on AF inducibility or stability (3), a later study by Todd et al. (7) demonstrated that longer episodes of repetitive AF (1 month of AF separated by 1 week of sinus rhythm) did result in a substrate that became more and more susceptible to persistent AF. These observations strongly suggest that indeed a slower “second factor” is involved in the atrial remodeling process that finally leads to a substrate in which AF is no longer self-terminating and with time becomes more and more resistant to pharmacological and nonpharmacological therapies.

The present study of Stiles et al. (1) addresses the clinically important question whether the term “lone” or “idiopathic” AF, in fact, expresses our inability to diagnose the early stage of atrial remodeling, rather than indicating the absence of electrophathological changes in the atria. They hypothesized that patients with paroxysmal “lone” AF already have an abnormal atrial substrate, and that the transition from paroxysmal to persistent AF is primarily determined by the progression of these atrial abnormalities. Of 215 consecutive highly symptomatic patients undergoing first-time ablation for paroxysmal AF, 25 patients fulfilled strict criteria of having no signs of structural heart disease, coronary artery disease, pulmonary disease, stroke, hypertension, hyperthyroidism, or diabetes. To avoid any confounding effects of AF-induced electrical remodeling, patients in whom in the week before ablation, an AF episode of >30 s was detected by continuous monitoring were excluded from the study. Before the ablation procedure, an extensive electrophysiological study was carried out to quantify abnormalities in refractoriness and conduction both in the right and left atrium. The data clearly showed the presence of bi-atrial structural and electrophysiological abnormalities in patients with paroxysmal “lone” AF. Compared with a reference group of 25 patients subjected to ablation of a left-sided accessory pathway, the following differences were documented: left and right atrial volumes were enlarged by respectively 27% and 36%, the P-wave was prolonged by 35%, atrial refractoriness was lengthened by 10%, right atrial and left atrial voltages were lowered by respectively 41% and 48%, various parameters of intra-atrial conduction were decreased between 21% and 45%, the proportion of fractionated electrograms was more than tripled, and the corrected sinus node recovery time was prolonged by 43%. All of these changes were highly statistically significant. No areas of electrical scar were found in patients with paroxysmal “lone” AF.

Early Diagnosis of Atrial Remodeling

The considerable changes in atrial structure and electrophysiological properties that Stiles et al. (1) report in a patient cohort with paroxysmal “lone” AF strongly support the option that the atrial changes that will eventually lead to persistent AF can already be detected at an early stage. Given the disappointing effects of the use of antiarrhythmic drugs, and the extensive ablation procedures that are required for effective modification of the substrate of long-standing persistent AF, the role of upstream therapies...
becomes more and more obvious. However, to implement a prevention program for AF, the development of sensitive and specific diagnostic tools that can detect early signs of atrial remodeling is a conditio sine qua non. In order to select individuals that will benefit from upstream therapies, one must be able to identify patients with a pre-disposition or high risk in developing a substrate of persistent AF. Diagnosis of the electropathological substrate is also necessary to decide whether secondary prevention measures are indicated. Based on monitoring of the time course of atrial remodeling, one could consider limited atrial ablation at an earlier stage, not only to treat symptoms, but also to help prevent or delay the further development of a substrate of AF.

A first step toward diagnosis of the various stages of atrial remodeling is to know which are the vulnerable parameters that determine the susceptibility of the atria to sustain AF. As pointed out by Stiles et al. (1), it seems that atrial dilation and intra-atrial conduction disturbances are the key features to consider. High-density mapping during cardiac surgery and standardized electrophysiological evaluation of atrial conduction disturbances during atrial catheterization can provide a gold standard of the atrial changes underlying the development of a substrate of AF. Especially detailed analysis of fractionated fibrillation electrograms, recorded from different sites during paroxysmal and persistent AF, may provide a sensitive and specific description of the atrial substrate. For a more standardized evaluation of (the progression of) atrial remodeling, the value of various surrogate parameters that can be obtained from noninvasive recordings should be evaluated. Characteristics of the averaged P-wave, pre-cordial AF electrograms, and transesophageal recordings from the posterior left atrium may provide promising noninvasive markers of the substrate of AF. Likewise, detailed echocardiographic determination of right and left atrial function, and the use of tissue Doppler for noninvasive determination of the temporal and spatial variation in local AF cycle lengths might provide useful information about the electropathological status of the atria. Novel enhanced magnetic resonance imaging techniques for high-resolution visualization of structural changes in the atrial wall are quickly emerging (8).

The scenario as noted in the previous text may seem rather futuristic, and, in the eyes of some, quite unrealistic and naïve. However, the past decade has shown an unprecedented development in technologies enabling accurate imaging and extensive catheter-based ablation of the atria. There is no reason to believe that we cannot accomplish a similar progress in AF diagnostics. This is of crucial importance, because without a good match between therapeutic and diagnostic tools, ablation of AF will remain a purely empirically based therapy. The present study by Stiles et al. (1) gives a strong impetus in this direction. It provides support and inspiration to redirect part of our efforts to find a “cure” for AF, toward the development of new techniques that can diagnose the stage of progression of the underlying atrial disease.

**REFERENCES**


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