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REVIEW TOPIC OF THE WEEK

Catheter Ablation of Atrial Fibrillation

How to Modify the Substrate?

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ABSTRACT

A frequent need for re-ablations and limited overall success rates are still major limitations of catheter ablation procedures for the treatment of atrial fibrillation (AF). These limitations include not only the durability of the pulmonary vein isolation (PVI) lines, but also the pathophysiological understanding of the arrhythmia's substrate. Long-term single procedure success rates in non-paroxysmal AF are disappointingly low for current stepwise ablation approaches adding the placement of linear lines and electrogram-based ablation after circumferential PVI isolation. In the future, substrate modification in AF ablation should move toward individualized patient-tailored ablation procedures. Magnetic resonance imaging could play a major role for noninvasively describing the localization and extent of fibrotic areas. Specific new strategies that could be used include precise localization and ablation of rotors that maintain the arrhythmia using multielectrode mapping during AF and box isolation of fibrotic areas guided by electroanatomic voltage mapping during sinus rhythm. (J Am Coll Cardiol 2015;65:196–206) © 2015 by the American College of Cardiology Foundation.

Percutaneous catheter ablation is widely used as an interventional tool for rhythm control in patients with atrial fibrillation (AF) (1). Circumferential pulmonary vein isolation (PVI), with confirmation of the entrance block, anchors this procedure. However, this intervention produces a frequent need for re-ablations and has limited overall success rates. This is caused by limitations not only in the durability of PVI lines, but also in our current understanding of the pathophysiology, especially of the arrhythmia's substrate.

A better understanding of the human atrial substrate that maintains AF has led to the concept of pre-existing specific fibrotic atrial cardiomyopathy (FACM), in which AF manifests from an individually localized substrate (2,3). This may help explain why circumferential PVI is effective in many, but not all, patients with paroxysmal AF, and is also effective in some patients with long-standing, persistent AF. In addition, the extent and localization of an individual patient's AF substrate must be understood to find effective ablation targets in the relatively small group of people with paroxysmal AF who experience AF recurrences despite durable PVI, as well as in the larger group of patients with persistent AF who obviously need more than PVI.

HUMAN AF SUBSTRATE

In a substantial subgroup of patients, evidence suggests that there is a genetic predisposition for development of AF based on the identification of multiple genes and genetic loci that appear to affect AF susceptibility (4). Although familial AF may be a monogenetic disorder, nonfamilial AF may be a multigenetic disease in which genetic factors interact with environmental variables. We are beginning to see research that focuses on primary fibrotic atrial changes. A recent study described a rare autosomal recessive atrial cardiomyopathy that clinically presented with atrial arrhythmias, including AF, bi-atrial dilatation, and potential electrical standstill over

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time, all of which were characterized by progressive fibrosis and/or scarring of the atrial myocardium (5).

Fibrotic atrial structural remodeling has been consistently described in AF patients in histological and autopsy studies (6–8) (**Figure 1**). The presence of (micro)fibrosis leading to changes in cellular coupling results in spatial "nonuniform anisotropic" impulse propagation, which is a potential cause of atrial activation abnormalities underlying the initiation and perpetuation of re-entrant arrhythmias like AF (9,10). Recent clinical research has highlighted the presence of atrial tissue fibrosis using delayed-enhancement magnetic resonance imaging (DE-MRI) and electroanatomic voltage mapping (EAVM) (11–14). Importantly, fibrotic atrial changes vary in localization and extent, and are principally bi-atrial findings. A higher mean value of fibrosis was detected in patients with persistent AF versus paroxysmal AF; however, variability in the extent of fibrosis among patients with AF is very high (7). In addition, patients with so-called "lone" AF may exhibit a substantial fibrotic substrate before and/or at the clinical advent of AF, whereas other patients with a decades-long history of AF do not develop a significant fibrotic substrate (3). The most frequent manifestation combination of bi-atrial FACM was described as bradycardia/tachycardia syndrome with sick sinus node plus paroxysmal AF (2) (**Figure 2**). Importantly, the extent of the fibrotic atrial substrate is variable and has been classified as FACM 0 to 3 (2,3) (**Figure 3**), which corresponds to the DE-MRI study Utah classification of 1 to 4 (12). Furthermore, the regional distribution of patchy fibrotic atrial areas varies significantly from patient to patient (**Figures 4 and 5**).

In other patients, the fibrotic atrial substrate leading to increased AF susceptibility may result from severe underlying structural heart disease (e.g., mitral stenosis or hypertrophic obstructive cardiomyopathy). An EAVM study in patients with rheumatic mitral stenosis who underwent commissurotomy and who did not have a history of AF described a significantly reduced bi-atrial voltage (15). Conversely, in an EAVM series of patients with systemic hypertension plus left ventricular hypertrophy, but no history of AF, the mean right atrial voltage was identical in the hypertension and control groups (16). In general, the impact of "classic comorbidities" among patients undergoing catheter ablation of AF seems to be overestimated, as is the role of age on the fibrotic substrate (3). In an MRI study that compared left atrial (LA) structural changes in patients with lone AF versus those with classic comorbidities, the substrate was independent of comorbidities (17). This corresponds well with a recent autopsy study in which negligibly low amounts of fibrosis were found in older patients with a high CHA_2DS_2-VASc score (4.3), but who did not have a history of AF; patient age was not correlated with an increase in the extent of atrial fibrosis (8).

In addition to "substrate makers" like FACM or mitral stenosis, "modulators" influence the susceptibility of AF occurrence (e.g., obesity and/or cardiometabolic syndrome, infections and/or inflammation, surgery, and cancer). Weight reduction with intensive risk factor management substantially changed these modulators in 1 study, and reduced AF symptom burden and severity. Changing these modulators was also beneficial for cardiac remodeling (18). With respect to surgery, pre-operatively elevated serum markers of collagen synthesis were associated with post-surgical AF in patients without a history of AF (19). Importantly, pre-existing LA fibrosis was significantly higher in patients who developed post-surgical AF compared with those who stayed in sinus rhythm (19), which indicates toward the modulating effects of cardiac surgery on previously subclinical LA fibrosis and/or FACM.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BIFA = box isolation of fibrotic areas

CFAE = complex fragmented atrial electrogram

CT = computed tomography

DE-MRI = delayed enhancement magnetic resonance imaging

EAVM = electroanatomic voltage mapping

FACM = fibrotic atrial cardiomyopathy

FIRM = focal impulse and rotor mapping

LA = left atrial

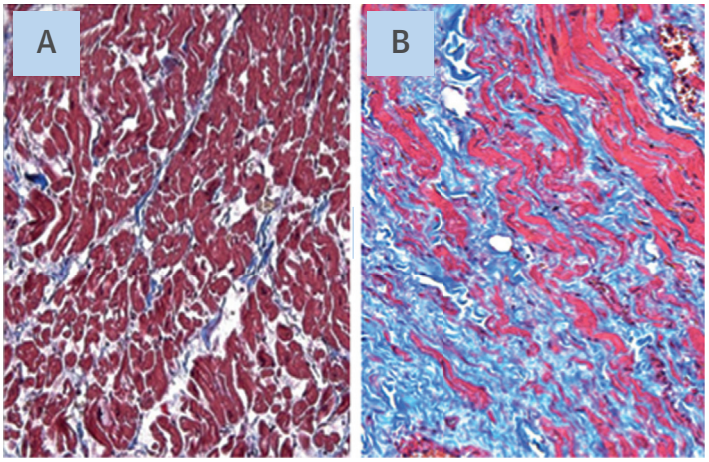
PV = pulmonary vein

PVI = pulmonary vein isolation

ATRIAL SUBSTRATE MODIFICATION STRATEGIES

CIRCUMFERENTIAL PV ISOLATION. Within the evolution of AF catheter ablation, circumferential PVI

FIGURE 1 Light Microscopy of Crista Terminalis Specimen



Light microscopy of a crista terminalis specimen in a patient in **(A)** sinus rhythm and without a history of atrial fibrillation (AF) showing no significant fibrosis, and **(B)** persistent AF showing a high level of fibrosis. Courtesy of Pyotr Platonov, MD, and Lubov Mitrofanova, MD.