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EDITORIAL COMMENT

The Substrate in "Early Persistent" Atrial Fibrillation

Arrhythmia Induced, Risk Factor Induced, or From a Specific Fibrotic Atrial Cardiomyopathy?*

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Catheter ablation of atrial fibrillation (AF) has undergone considerable improvement within the last years. As a result, catheter ablation may even be indicated as a primary therapy in selected patients in experienced centers (1). By achieving more proximal plus durable pulmonary vein (PV) isolation, the success rate has substantially increased in patients with paroxysmal AF. The situation is still different in nonparoxysmal AF patients. In this population, PV isolation alone results in successful rhythm control in approximately 50% of the patients only, and, even more frustratingly, additional placement of "traditional" linear lines or ablation of complex fragmented atrial electrograms did not result in any additional benefit in a recent prospective randomized multicenter study (2).

Interestingly, in some patients with nonparoxysmal AF, PV isolation only results in perfectly stable sinus rhythm over time, whereas AF or atrial tachycardia recur in others despite very extensive ablation far beyond PV isolation. Recently, 2 new concepts have evolved for more individualized ablation of nonparoxysmal AF beyond or even without PV isolation. Using the FIRM (Focal Impulse and Rotor Modulation) concept, localized rotors are mapped within the left and/or right atrium using a 64-pole basket catheter and are subsequently targeted for ablation (3). In the same direction, noninvasive driver domain mapping was introduced using 252 body surface electrodes for identification of driver domains (4). Recently, we applied a new substrate modification concept according to the individual fibrotic substrate as estimated from electroanatomic voltage mapping during sinus rhythm using so-called box isolation of fibrotic areas (5,6).

In this issue of the *JACC: Clinical Electrophysiology*, Lim et al. (7) sought to characterize the clinical characteristics, atrial substrate, and ablation outcome in a very interesting subgroup of nonparoxysmal AF patients: those with "persistent AF from the onset" (PsAFonset). In this 3-center study from Bordeaux, Toulouse, and Adelaide, 129 consecutive patients with PsAFonset were compared with 231 control patients with "typical" persistent AF that progressed

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from previous paroxysmal AF. Patients with PsAFonset were found to be more obese (body mass index 29 vs. 27 kg/m^2), to have a higher proportion of hypertension (50% vs. 39%), and larger left and right atria. In a subgroup of patients from Bordeaux, additional noninvasive panoramic mapping using a 252-electrode vest was applied. PsAFonset patients had a higher number of extra-PV regions harboring re-entrant drivers and a higher absolute number of re-entrant driver regions, and, in addition, the biatrial endocardial voltage was lower as measured during AF. With respect to catheter ablation outcome, acute AF termination rate was lower in the PsAFonset patients and AF/atrial tachycardia recurrence rate after the last procedure was substantially higher (7).

It might be argued that it is difficult to prove that the very first AF episode was indeed directly

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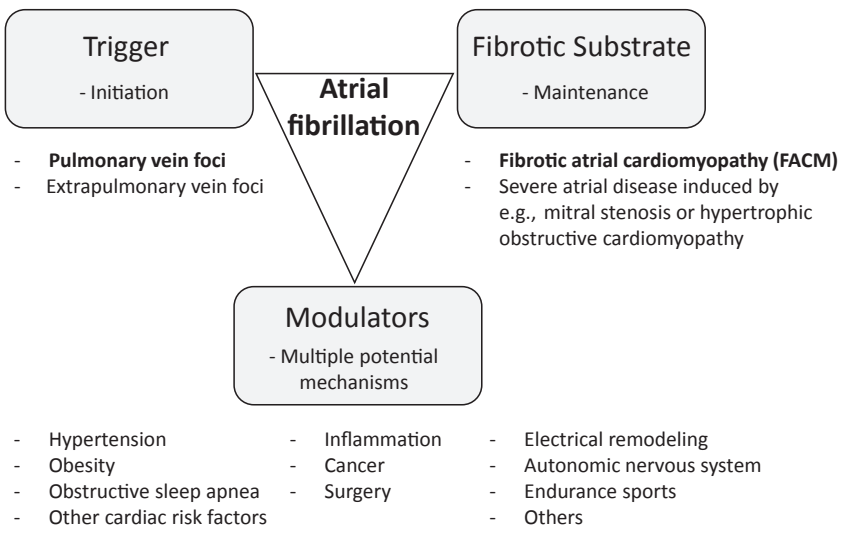
persistent without at least a few preceding episodes of paroxysmal or persistent but self-terminating AF that might have been asymptomatic. However, this is not an important limitation in our eyes because it seems very reliable from the applied methods that a subgroup of patients with at least "early persistent" AF have been investigated.

Lim et al. (7) draw conclusions about the role of obesity and other risk factors for their group of patients with "early persistent" AF. The important modulating role of risk factors for the occurrence of AF in general is now widely accepted (**Figure 1**) (8). We have no doubt that—besides oral anticoagulation for prevention of thromboembolism and antiarrhythmic drugs/ablation for rate/rhythm control—risk factor management will become the additional new pillar for the treatment of AF with respect to primary as well as secondary prevention. But are risk factors more important in the subgroup of patients with "early persistent" AF? In a recent study on the same topic, Konrad et al. (9) compared "early persistent" AF patients with control persistent AF patients and also found worse outcome in the "early persistent" AF patients but no differences at all with respect to obesity (body mass index 28 vs. 28 kg/m^2), hypertension (70% vs. 76%), and the Hatch score (1.6 vs. 1.6). In addition, the difference, for example, in obesity described in the present study by Lim et al. (7) was statistically significant but also not particularly pronounced (body mass index 29 vs. 27 kg/m^2).

The striking finding in this subgroup seems to be the diffuse/severe substrate and the poor outcome after ablation (7,9). What is the pathophysiological question/clue behind this subgroup with "early persistent" AF? The group is clinically defined from the early/direct appearance of persistent AF in contrast to the "typical" AF history with months, years, or even decades of paroxysmal AF before establishment of persistent AF. But is this clinically defined subgroup also principally different from a pathophysiological aspect? Obviously, we cannot apply the "old conventional wisdom" that "AF begets AF" where the arrhythmia itself is thought to induce structural/fibrotic changes because persistent AF occurs "early" or even "directly from the onset" in this subgroup. Furthermore, arrhythmia-induced fibrosis is also questioned by findings of a very high variability in the amount of fibrosis in AF patients, with some paroxysmal AF patients having massive fibrosis and some persistent AF patients showing mild fibrosis (10). The specific role of age and risk factors as atrial fibrosis makers has also been questioned in an autopsy study, where "negligibly" low amounts of fibrofatty tissue were described in atrial specimens from patients with a high CHA_2DS_2-VASc (age, sex, congestive heart failure history, hypertension history, stroke/transient ischemic attack/thromboembolism history, vascular disease history, diabetes mellitus) score of 4.3 but no AF (11). In addition, we recently described a low correlation of risk factors with respect to the fibrotic

FIGURE 1 The Pathophysiological Triangle in AF



AF = atrial fibrillation; FACM = fibrotic atrial cardiomyopathy.

substrate as estimated from electroanatomic voltage mapping in patients with nonparoxysmal AF (6). In the same direction, cardiovascular risk factors were found to be equally distributed in different classes of left atrial fibrosis as described by magnetic resonance imaging studies, and structural atrial remodeling was the same in patients with and without cardiovascular risk factors (12).

Therefore, if the results in the present study by Lim et al. (7) with obviously diffuse and extensive biatrial substrate in the patients with "early persistent" AF obviously cannot be explained as arrhythmia-induced and also not by the extent of risk factors, then, in our opinion, the fibrotic atrial substrate is a result of a specific disease that we have named/described as "fibrotic atrial cardiomyopathy" (FACM) (**Figure 1**) (13,14). FACM is described as a specific disease with different expressions from mild, moderate, to severe atrial fibrosis and with a potentially progressive disease process. Consequently, we understand AF—and other arrhythmias such as re-entrant atrial tachycardia and sinus node disease—as a manifestation of the pre-existing FACM (13,14). This concept can explain the different clinical manifestations of AF, e.g., the appearance of relatively short episodes of paroxysmal AF over decades or "forever" in mild forms of FACM with a limited and stable fibrotic substrate, but also the appearance of "early persistent" AF in patients with severe FACM with a fast progressing and diffuse substrate. In addition, interactions of active "modulators" on previously subclinical left atrial fibrosis/FACM have been described in a surgical scenario where pre-operatively elevated serum markers of collagen synthesis were associated with post-surgical AF compared with those who stayed in sinus rhythm (15). In the other direction, aggressive risk factor management may substantially reduce the burden of AF and has been shown to significantly improve catheter ablation outcome (16).

In summary, Lim et al. (7) add important new data on a subgroup of patients with "early persistent" AF revealing an extensive substrate and high AF recurrence rate after ablation. We need to shed further light on the individual substrate in our AF patients, especially, but not exclusively, in those with nonparoxysmal AF. As a consequence of the individual extent and localization of the fibrotic substrate, catheter ablation needs to be an individualized ablation. In contrast, the time for "traditional" lines or any other nonindividualized substrate modification for us seems over. However, we might also need to accept that in some patients with massive plus diffuse atrial fibrosis, rhythm control will not be achievable.

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