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Editorial

New Perspective in Atrial Fibrillation

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Despite a large number of publications on this subject, the pathophysiological mechanisms involved in atrial fibrillation (AF) onset and recurrence are uncertain. Moreover, though several thrombo-embolic and bleeding prediction [1] scores for AF patients have been developed, their performance is still limited [2]. Taken together, these facts suggest that we are still missing a global theory of atrial fibrillation pathophysiology (or at least some parts of it).

A better understanding of AF pathophysiology could come from the integration of all the cardiac environment modulators, including "Coumel triangle" components [3]. Indeed, apart from the pulmonary vein triggers that have been extensively studied [4], the relationship between other triggers (inflammation as in acute AF [5–7], stable coronary artery disease [8], or post-operative AF [9]), the modulator (mainly autonomic nervous system dysregulation [10]) and substrate alterations (fibrosis but also changes in the conduction properties of the atrial cells even in the absence of a quantifiable "scar" [11]) have been recently brought to light by several papers [12,13]. The interplay between cardiovascular risk factors, mainly high blood pressure [14] and obesity [6], atrial epicardial fat, and atrial ganglionated plexi [15], is complex and critical for the understanding of AF, but also in the search for new treatments. In this regard, a particular focus should be placed on the new anti-diabetic therapies (SGLT-2 inhibitors [16] and GLP-1 receptor agonists [17]) that have not only proven a benefit for major cardiovascular events (MACE) occurrence but also a decrease in AF burden. These treatments do not act so much as glycemia regulators, as Hb1Ac is usually only slightly decreased, but on the complex metabolic pathways involved in diabetic cardiomyopathy and possibly also in metabolic syndrome patients without diabetes. Thus, a fascinating field of research is open for the characterization of the metabolism's role in AF onset and persistence and perhaps also as a therapeutic target, as suggested by the major results obtained through weight loss in obese patients suffering from AF [18].

In the past few years, the concept of atrial cardiopathy has emerged as a promising lead to connect AF to stroke, heart failure, and inflammatory processes; indeed, all of the mechanisms associated with atrial remodeling and the development of atrial cardiopathy are also likely to promote the development of AF [19]. An international expert consensus defined atrial cardiopathy as "any complex of structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations" [20]. This recent concept suggests that the real trigger of stroke may be an abnormal atrial substrate rather than the atrial rhythm itself. Indeed, evidence from studies analyzing the data obtained from implantable cardiac devices has recently demonstrated that there is no temporal correlation between AF and stroke [21]. This finding is in line with current thinking on the pathophysiology of the relationship between AF and cardioembolic stroke [22]: AF seems to be more of a risk marker than the cardioembolic risk vector itself. It is, therefore, only a symptom

of underlying atrial cardiomyopathy, which, even in sinus rhythm, increases thromboembolic risk. For now, however, the lack of a clinically validated definition of atrial cardiopathy limits its clinical applications and the reproducibility of the results obtained using these various definitions. Indeed, several clinical, electrocardiographic, biological, and imaging markers [23] have been suggested [24], but few of them have been correlated to atrial tissue abnormalities as defined by the international expert consensus [20].

The aim of this Special Issue is to gather basic research, as well as pathophysiological and epidemiological papers, focused on the relationship between atrial substrate and atrial fibrillation onset, recurrence, and outcomes.

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