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Biomarkers and atrial fibrillation: A new paradigm for assessing the progression of left atrial endocardial remodelling

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ABSTRACT

Atrial fibrillation is a heterogeneous disorder that is usually characterized by paroxysmal onset, particularly in patients without structural heart disease. Defining biological markers of atrial remodelling would help identify patients at high risk who would benefit most from prophylactic treatment and careful monitoring. Biomarkers of atrial fibrillation progression would be helpful for following patients that present with asymptomatic atrial fibrillation. Notably, the roles of such markers in the pathophysiology of atrial fibrillation must be determined. Some markers may indicate the presence, complications or progression of the disease, while others may be involved in key pathological processes and thus represent novel therapeutic targets. Although a number of markers have been reported as potential predictors of paroxysmal atrial fibrillation progression towards persistent arrhythmia, their usefulness and clinical value need further validation. This report reviews several newly identified markers of atrial fibrillation progression.

Keywords: Atrial Fibrillation; Biomarkers; Progression

1. INTRODUCTION

Atrial fibrillation is a heterogeneous disorder that varies in terms of clinical presentation, natural history, and response to therapy [1-3]. This cardiac arrhythmia is usually characterized by paroxysmal onset, particularly in patients without structural heart disease, but the natural history of the arrhythmia is to worsen [4]. Experiments in goats have shown that "atrial fibrillation begets atrial fibrillation" and that over the long term, atrial fibrillation progresses in frequency and duration to become persistent and finally permanent [5,6].

However, it remains unclear whether paroxysmal, persistent and permanent atrial fibrillation represent three different stages of the same pathophysiological process or whether they represent three distinct disorders. Markers that predict the clinical progression of atrial fibrillation and its complications are yet to be defined.

2. PREDICTORS OF ATRIAL FIBRILLATION PROGRESSION

A number of clinical variables, such as valvular disease, alcohol consumption, age, left atrial dimension, and the occurrence of stroke or heart failure, have been proposed as predictors of atrial fibrillation progression [7]. In a retrospective study, Jahangir *et al.* identified older age at diagnosis and the presence of QRS abnormalities on ECG (prolonged QRS duration of 110 to 120 ms, notching or slurring of the QRS complex, or low anterior forces with small R waves in the precordial leads) as predictors of progression towards permanent atrial fibrillation. However, age was the sole independent predictor of progression in multivariable analysis [8].

Several other parameters were also identified as predictors of the transition from paroxysmal to persistent atrial fibrillation, including duration of the arrhythmia [9], left ventricular dysfunction [10], enlarged left atria, prolonged filtered P-wave duration, and a low root mean square voltage for the last 30 ms of the filtered P wave [11].

The CARAF study showed that a more rapid heart rate during atrial fibrillation at baseline is associated with a lower risk of developing permanent atrial fibrillation [12].

3. BIOMARKERS OF ATRIAL FIBRILLATION PROGRESSION

Biomarkers are defined as measurable components, such as cells, proteins and/or metabolic products that reflect, either directly or indirectly, one or more biological processes involved in a disease state [13]. Such markers help

establish a diagnosis and may themselves be involved in subsequent pathobiological events.

3.1. Inflammatory Burden and Atrial Fibrillation Progression

Higher C-reactive protein levels have been observed in patients with persistent atrial fibrillation than in patients with paroxysmal atrial fibrillation, suggesting that C-reactive protein levels may be related to the burden of atrial fibrillation [14].

Higher levels of YKL-40, a new biomarker of inflammation, have recently been documented in individuals with permanent atrial fibrillation compared to patients with persistent atrial fibrillation, further supporting the concept of an association between the chronicity of atrial fibrillation and the inflammatory burden [13].

Although there is abundant data suggesting a link between inflammation and atrial fibrillation, several studies failed to show elevated levels of C-reactive protein, interleukin-6, or interleukin-8 in atrial fibrillation patients [15-19].

A recent study was conducted in our department that included 81 subjects, 72 atrial fibrillation patients (39 with paroxysmal atrial fibrillation and 33 with persistent atrial fibrillation) and 9 control patients with Wolff-Parkinson-White syndrome. In the study, the levels of several inflammatory markers were determined in peripheral, coronary sinus, left atrial and pulmonary veins. There were no significant differences among the three groups regarding interleukin-8, soluble intercellular adhesion molecule-1 or transforming growth factor β1 levels at any of the sampling sites. Similarly, C-reactive protein levels, which were only measured in the peripheral blood, did not differ in the three groups. These results suggest that the high inflammatory marker levels reported in atrial fibrillation patients could be due to associated comorbidities rather than to atrial fibrillation *per se* [20].

3.2. Markers at the Crossroads of Several Mechanisms

In the same study that compared paroxysmal and persistent atrial fibrillation patients with controls without any history of atrial fibrillation [20], the peripheral levels of vascular endothelial growth factor (VEGF) were higher in both paroxysmal and persistent atrial fibrillation patients compared to controls (**Figure 1**). In the left atrium, VEGF levels were higher in the paroxysmal atrial fibrillation group compared to the control group; however, there was no significant difference between persistent atrial fibrillation patients and controls (**Figure 1**).

A number of pathological conditions induce VEGF secretion, including oxygen deficiency, inflammation, and pulsatile mechanical stretch [21]. Patients with atrial fibrillation showed low levels of several inflammatory markers, regardless of the clinical form of the arrhythmia. This suggests that the inflammatory process is low grade, if present at all, in these patients. Therefore, it seems unlikely that inflammation alone could account for the high peripheral VEGF levels in atrial fibrillation patients. Despite the absence of evidence of accelerated angiogenesis in paroxysmal atrial fibrillation patients, we found high levels of VEGF in the left atrium in this population. Histopathological studies report a high incidence of atrial ischemia in up to 17% of autopsied patients with a history of atrial fibrillation and isolated atrial infarctions in more than 20% of them [22]. A transient increase in hypoxia inducible factor α (HIF1α) gene expression, which is a known trigger for VEGF secretion, is reported in cardiac myocytes in the early onset of atrial fibrillation [23]. On the other hand, the inverse relationship is also a possibility, with ischemia favouring atrial fibrillation occurrence.

A fibrillating atrium leads to irregular blood flow and may induce pulsatile vascular stretch and impaired blood rheology with subsequent VEGF secretion in the peripheral blood [24-26]. Pulsatile mechanical stretch, recently postulated to be a potent trigger for VEGF secretion from cardiac myocytes [21,27], could lead to the high intracardiac VEGF levels observed in paroxysmal atrial fibrillation.

Nevertheless, it appears that left atrial secretion of VEGF is a transient event in the natural history of atrial fibrillation. Persistent atrial fibrillation is associated with more important fibrotic changes than the paroxysmal form (**Figure 2**) [28,29].

VEGF itself may be involved in these fibrotic changes, probably through the induction of angiogenesis [30-32]. The spreading of cardiac fibrosis may cause progressive

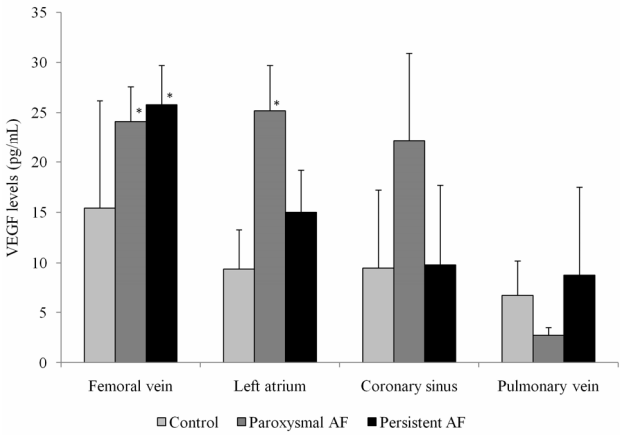

Figure 1. Mean levels of vascular endothelial growth factor (VEGF) in the femoral vein, left atrium, coronary sinus, and pulmonary vein in paroxysmal atrial fibrillation patients, persistent atrial fibrillation patients and in control patients with Wolff-Parkinson-White syndrome [20]. $^{*}p < 0.05$ vs. control.

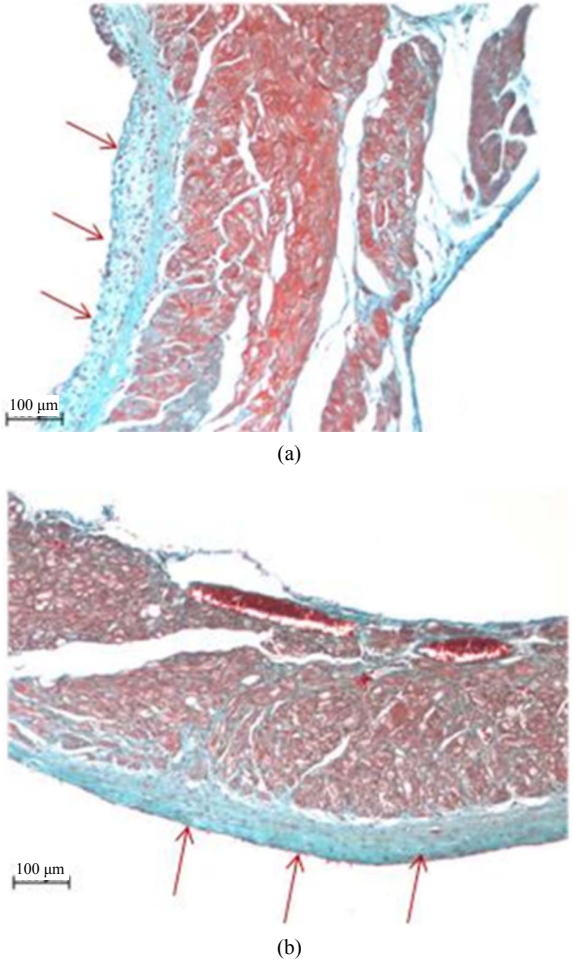

Figure 2. Left atrial samples (10×, Masson's trichrome staining) from aging spontaneously hypertensive rats presenting with atrial fibrillation. The samples show two stages of left atrial fibrosis, (a) Progressive, stratified endocardial fibrosis, and (b) Stable, evolved endocardial fibrosis. Red arrows indicate the endocardial layer.

cardiac stiffening, thereby reducing the degree of pulsatile stretch and subsequently diminishing intracardiac VEGF levels, as observed in patients with persistent atrial fibrillation. Thus, newly identified biomarkers, such as VEGF, may serve as predictors of atrial fibrillation progression.

4. CONCLUSIONS

Atrial fibrillation and related complications result from complex interactions of systemic conditions such as atherosclerosis, obesity, hypertension, and inflammation [15,33-38]. The progression of the arrhythmia towards more refractory forms seems to be related both to underlying conditions and to the extent of atrial remodelling [39]. Identifying biomarkers of atrial fibrillation progression would most benefit patients who present with asymptomatic atrial fibrillation. Preliminary results are encouraging, but prospective studies are needed to validate these indexes of worsening atrial disease.

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