A New Biomarker in Atrial Fibrillation: Monocyte Chemoattractant Protein-1-Induced Protein

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Atrial fibrillation (AF) has been recognized as the most common cardiac arrhythmia affecting both the aging population and younger individuals, with estimated 33.5 million individuals worldwide. It is an etiologically and pathophysiologically complex and diverse condition, with multiple knowledge gaps in understanding its determinants and mechanisms. There has been a surge in academic interest in AF in recent years, and much of the research focused on various biological pathways involved in structural, electrical, and autonomic remodeling, including atrial fibrosis and apoptosis, inflammation and oxidative stress, endothelial dysfunction, neurohumoral activity, and procoagulation state.

A plethora of blood-derived biomarkers engaged in the pathogenesis of AF have been investigated, and many have proven to be associated with AF or its sequelae. Some, such as high-sensitivity troponin and natriuretic peptide, have been incorporated in the risk stratification systems [1] and have been recommended for consideration for refining risk stratification for stroke and bleeding by the 2016 ESC Guidelines (class IIb recommendation, level of evidence B) [2].

Biomarkers of fibrosis and inflammation as significant pathophysiological determinants of atrial remodeling in AF have recently taken the center stage of research. In animal models and human tissue preparations, the amount of atrial fibrosis, including the fibrotic changes in the epicardial adipose tissue, was linked to increased collagen turnover biomarkers, proinflammatory cytokines, and growth factors [3]. Several markers have been explored as targets for pharmacological interventions [4, 5].

Monocyte chemoattractant protein-1 (MCP-1), a pro-inflammatory chemotactic cytokine which is synthesized in monocytes and macrophages, plays an important role in atherogenesis and thrombosis. Along with other chemokines, MCP-1 is upregulated in patients with AF. MCP-1 is involved in regulating the production of several matrix metalloproteinases. Genetically predetermined elevated MCP-1 levels have been associated with a 14% increased risk of cardioembolic stroke for each SD increase in MCP-1 levels [6].

The family of MCP-1-induced proteins (MCPIP) include several subtypes. MCPIP1 is expressed in several human tissues including the heart, and its primary

function is regulation of inflammatory responses through increased degradation of cytokine mRNAs and inhibition of the lipopolysaccharide- and interleukin-1-induced nuclear factor κ B signaling pathway [7]. MCPIP1 has been reported to act a transcription factor in the pathogenesis of atherosclerosis and cardiomyocyte apoptosis and as a differentiation factor in adipogenesis.

In their study published in *Cardiology*, Zhang et al. [8] have tested the hypothesis that the expression of MCPIP1 can be linked to AF using retrospective electronic medical data and stored blood samples of 542 patients with AF and age- and gender-matched controls. Target biomarkers were analyzed using commercially available ELISA kits. The authors have found that MCPIP1 circulating levels were elevated in the AF patients, being the highest in those aged 65 years and older, whereas no differences in MCPIP1 levels were found between younger patients with AF and elderly controls. MCPIP1 levels correlated with 2 established fibrosis biomarkers, PIIINP (procollagen type III N-terminal peptide) and ICTP (type I collagen C-terminal telopeptide).

While this study provides important further insights into the role of biomarkers in AF, it is exploratory analysis that may have been influenced by many factors, which are beyond control in this and similar design investigations. Peripheral circulating levels of biomarkers, such as ICTP and galectin-3, do not always match the intracardiac levels, and elevated peripheral blood biomarker levels do not necessarily mean that the origin of the biomarkers is the heart [9]. The authors did not employ advanced imaging modalities enabling the assessment of the extent and distribution of atrial fibrosis and only collected basic echocardiographic data on left atrial size and left atrial appendage function. Cardiac fibrosis is associated with an increase in the turnover of extracellular matrix which is principally comprised of type I and type III collagen, so PIIINP and ICTP are measurable products of this turnover [10]. However, the direct association between quantification of fibrosis by cardiovascular magnetic resonance imaging, electroanatomical mapping, and/or blood-derived biomarkers of fibrosis has not been uniformly confirmed, and the histologically proven evidence of their association with either atrial fibrosis is limited.

MCPIP1 is a mediator of cellular inflammatory responses, but no other proinflammatory biomarker, except for C-reactive protein, has been studied. There may be time-defined associations between proinflammatory

cytokines and markers of fibrosis and the risk of AF occurrence and AF type. Mediators of inflammation can be elevated before consolidation of structural changes or act as triggers of AF onset. MCPIP1 levels were higher in older patients who were more likely to have a persistent or permanent AF variety, but an association with the AF type has not been reported.

The study is hypothesis generating, but its design does not allow the assessment of the added incremental value of the biomarkers beyond clinical variables and thus establish causality. The biological significance and associations of biomarkers are altered in the presence of AF compared with the physiological state, and underlying cardiovascular pathology as well as pharmacological interventions (e.g., anticoagulation therapy) may further modify these associations. The results of the study suggest that that age and underlying heart conditions, which were more common in older patients, have been as significant as MCPIP1 circulating levels as determinants for the presence of AF.

The inherent limitation of such observational studies is their inability to assess all known biomarkers and the highly complex interplay of multiple pathophysiological pathways modulated by multiple intrinsic and extrinsic factors, with diverse biological effects. This would only be possible with the involvement of much larger patient populations with a full array of biomarkers, which would enable the determination of the clinical significance of individual biomarkers or a combination of the strongest biomarkers.

Biomarkers of multiple pathophysiological pathways have been investigated in large epidemiological databases and dedicated biomarker substudies of large randomized clinical trials. However, unlike in other clinical settings where biomarkers have been firmly established as valuable diagnostic tools, in AF, they remain to be regarded as a pure research tool with a limited direct clinical value. In the future, an individual biomarker profile may more accurately reflect the pathophysiological mechanisms of susceptibility to AF, identify predictors of the incident and recurrent arrhythmia, refine risk stratification for thromboembolic events, bleeding, and mortality, establish the potential therapeutic targets, and provide guidance for specific treatments and objective measurement of the treatment effects.

Disclosure Statement

There is nothing to disclose with regard to this work.

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