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Review

Assessment of atrial fibrosis for the rhythm control of atrial fibrillation

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ABSTRACT

Rhythm control of atrial fibrillation (AF) remains challenging, with modest long-term success rates. Atrial fibrosis has been associated with AF, but the clinical utility of assessment of this fibrosis has yet to be fully elucidated. In this paper we review the current state of understanding of the pathophysiology of atrial fibrosis in AF, and its impact upon the instigation and propagation of the arrhythmia. Fibrosis causes an increase in volume of dysfunctional extracellular matrix, and is associated with cellular alterations such as hypertrophy, apoptosis and membrane dysfunction within the atrial myocardium. In turn, these cause pathological alterations to atrial conduction, such as increased anisotropy, conduction block and re-entry, which can lead to AF. We review current methods of assessing atrial fibrosis and their impact upon the prediction of success of interventional rhythm control strategies such as ablation and cardioversion. We focus particularly on circulating biomarkers of fibrosis and scar formation; their role in the fibrotic process, and their value in the prediction of rhythm control success. We also review imaging and invasive electrocardiographic mapping techniques that may identify fibrosis, and again assess their potential predictive value. In this area there exist many unanswered questions, but further work will help to refine techniques to reliably identify and treat those patients who are most likely to benefit from rhythm control treatment strategies.

1. Introduction

Reliable prediction of treatment success for a rhythm control strategy for atrial fibrillation (AF) is highly desirable, to minimise unnecessary exposure to procedural risk and improve outcomes. Clinical factors favouring rhythm control strategies such as ablation include younger age, shorter duration of AF, paroxysmal AF, a structurally normal heart, and little comorbidity. Inflammatory disorders, valvular disease, left atrial dilatation, cardiomyopathy, and obesity are all considered clinical predictors of AF recurrence in individual trials, although a meta-analysis found no definitive clinical predictors of recurrent arrhythmia [1].

Circulating biomarkers may serve as surrogate indicators for advanced atrial pathology that may reduce the likelihood achieving rhythm control. If such markers could be identified and used in conjunction with clinical and imaging criteria, patient selection could be improved, leading to improved success rates from rhythm control.

Left atrial fibrosis has been associated with AF, and shown to be a poor prognostic marker for maintenance of sinus rhythm. Circulating markers of fibrosis may therefore be used as markers of left atrial remodelling.

This review focuses on the pathophysiology of atrial fibrosis, the use of serological, electrophysiological, and imaging methods to identify this fibrosis, and the ability of such methods to predict or improve the success of rhythm control treatment of AF.

1.1. Selection criteria

We searched *Medline* (up to November 2015) using the terms "atrial fibrillation" and "fibrosis". The abstracts were screened and full articles relevant to the review were selected. In total, 87 articles were selected for inclusion.

2. The extracellular matrix, collagen turnover, and fibrosis

Cardiac extra-cellular matrix (ECM) consists predominantly of type I (80%) and type III collagen and plays an important role in maintaining tissue architecture [2]. Furthermore, through interaction with fibroblasts and cardiomyocytes, involving TGF-β and angiotensin II paracrine signalling, the ECM has an important role in the detection of myocardial stretch [3]. Normal ECM is also important for intercellular signalling as well as electrical conduction.

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Procollagen is synthesised in the fibroblast endoplasmic reticulum and then converted to collagen in the extracellular space by cleavage of the amino and carboxyl terminal groups [4]. The ECM is in a constant state of flux. A number of mechanisms regulate collagen turnover (Fig. 1), and involve transforming growth factor β (TGF-β), angiotensin II, platelet-derived growth factor, insulin-like growth factor-1, growth hormone, and endothelins 1 and 3 [3,5–8]. Matrix metalloproteinases (MMPs) are primarily responsible for collagen degradation and IL-1, prostaglandin, tumour necrosis factor α (TNF-α), and brain natriuretic peptide (BNP) upregulate MMP production [8–10]. Tissue inhibitors of MMPs (TIMPs) are the primary inhibitors of MMPs. MMPs 1, 2, 7, 8, 9, 10, and 13 have major roles in degrading type I and III collagen.

In AF, inflammatory changes in the ECM result in fibrosis [11]. Left atrial biopsy samples in patients with AF undergoing cardiac surgery have higher levels of collagen compared controls without AF with increased collagen crosslinking [12,13]. In addition, fibroblast and lymphomononuclear cells proliferate and infiltrate atrial tissue. Fibroblasts differentiate into activated myofibroblasts and secrete paracrine factors and extracellular membrane proteins [14,15]. This has been shown to cause cardiomyocyte de-differentiation into embryonic precursor cells [16]. Cardiomyocyte structure and function across the atrial myocardium become heterogenous, with varying levels of hypertrophy, necrosis, apoptosis and proliferation. This heterogeneity, in animal models, provides a substrate for AF initiation and perpetuation by interrupting cellular conduction and signalling.

Recent evidence suggests that epicardial adipose tissue may play a major role in cardiac inflammation and fibrosis potentially explaining why obesity is a risk factor for AF (although it is important to note that epicardial fat does not necessarily correlate with BMI) [17]. Definitions of epicardial adipose tissue vary (many studies include fat in the pericardial space), but the largest such study in humans – involving the Framingham cohort – found a strong relationship between pericardial fat (measured by CT) and AF [18]. Other studies have associated pericardial/epicardial fat with recurrent AF after ablation [19,20]. Adipose tissue is known to stimulate the production of proinflammatory TNF-α, IL-6, TGF-β and MMPs. Thus, a paracrine effect on atrial myocardium, resulting in inflammation and fibrosis, has been postulated as a mechanism for the generation of AF substrate, as well as the direct effects of adipose infiltration into the myocardium [21]. Clinical assessment of these processes could help determine left atrial health and may serve as useful prognostic markers.

3. Fibrosis as a therapeutic target — is there any benefit?

Reducing left atrial fibrosis could have important clinical implications. A number of animal studies have shown the adverse effects of left atrial fibrosis. Li et al. showed that angiotensin II signalling and atrial fibrosis were increased by ventricular tachypacing but this could be attenuated with enalapril [22]. In a rabbit model of heart failure, inhibition of angiotensin II with pioglitazone and candesartan reduced atrial fibrosis, conduction delay and levels of TGF-β1 and TNF-α [23]. Clinical studies have shown similar promise. The TRACE study reported a reduction in AF incidence in patients with LV impairment treated with trandalopril after myocardial infarction – reduction in angiotensin signalling perhaps leading to a reduction in atrial fibrosis [24]. Furthermore, Vermes et al. showed that enalapril could prevent AF in heart failure patients [25]. Treatment with irbesartan in addition to amiodarone after electrical cardioversion appears to prevent AF recurrence in the absence of heart failure [26]. A potential anti-fibrotic role of ACE inhibition was supported in a study by Boldt et al. who showed a reduction collagen deposition in ACEI-treated patients [27]. However, in meta-analysis and in studies which used AF as a pre-determined endpoint, evidence was less convincing – particularly in patients without heart failure – that inhibition of the renin–angiotensin system prevents AF [28,29]. The clinical utility of ACE inhibition for AF remains debatable.

Statins may exert anti-inflammatory, anti-oxidant and endothelium-stabilising effects that could reduce formation of fibrotic tissue. In animal histological experiments, statins have shown beneficial effects on atrial remodelling, and a reduction in fibrosis, likely as a result of reduced inflammation [30,31]. Subsequent trials in humans have been mixed, and the largest meta-analysis revealed no benefit of statins for

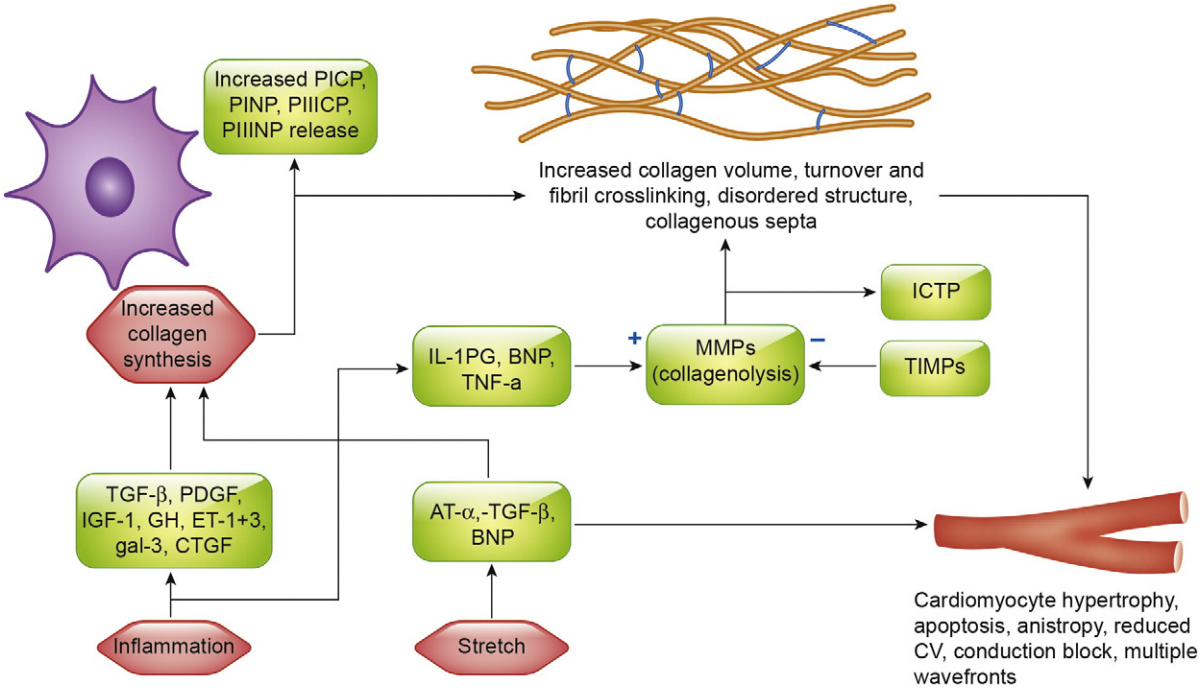

Fig. 1. Biomarkers in fibrosis. Green boxes indicate substances measurable in the circulation. PICP—procollagen I C peptide, PINP—procollagen I N peptide, PIIICP—procollagen III C peptide, PIIINP—procollagen III N peptide, TGF—transforming growth factor, PDGF—platelet-derived growth factor, IGF—insulin-like growth factor, GH—growth hormone, ET—endothelin, Gal—galectin, CTGF—connective tissue growth factor, IL—interleukin, BNP—brain-type natriuretic peptide, TNF—tumour necrosis factor, AT—angiotensin, MMP—matrix metalloprotein, ICTP—collagen I C telopeptide, TIMP—tissue inhibitor of MMP, CV—conduction velocity.