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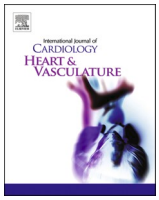

Editorial

Collagen type V, interstitial fibrosis and the substrate for atrial fibrillation

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Links between a history of atrial fibrillation (AF) and increased atrial fibrosis have long been appreciated. In an elegant quantitative histology study reported in 1982, Ih and Sato compared the histologic properties of 12 patients with long-term (persistent) AF with 43 patients with no history of arrhythmia; the authors reported "severe fibrosis and lipomatosis of atria were common precipitating factors" of AF [1]. With respect to the control group, the authors reported that "fibrosis and lipomatosis of atria were more prominent in the majority of the older group than that of the younger" subjects. They concluded that the pathological lesions of the SA node and atrial myocardium in AF reflected "exaggerated aging changes, and (that) these lesions may be the main anatomic substratum for AF" [1].

Fibrosis is a common response of organs or vessels to increased mechanical stress, ischemia and/or metabolic stress. In the setting of AF, these stressors lead to increased production of inflammatory cytokines and peptide hormones, most notably endothelin-1 [2,3] and angiotensin-II [4,5]. Endothelin-1 and angiotensin-II production by endothelial cells, fibroblasts and myocytes promotes TGF-β1 signaling that activates fibroblasts from a quiescent state transforming them into myofibroblasts that have a propensity to secrete a variety of collagen isoforms into the extracellular matrix (ECM) [6]. Accumulation of collagen in chambers of the heart increases chamber stiffness and attenuates dilatation of the heart. However, by interfering with the lateral connectivity between atrial myocytes, interstitial fibrosis promotes conduction heterogeneity and slowing.

In this issue, Kostin and colleagues use a quantitative immunohistochemistry approach to provide new insights into the composition of the ECM in right and left atrial biopsies from patients in sinus rhythm (SR, n = 35), with a history of paroxysmal AF (pAF n = 35), and patients with long-standing persistent AF (ls-peAF, n = 27) [7]. While fibrosis is very abundant in the hearts of patients with mitral valve disease (MVD), it is notable that only 1–2 patients per group had significant MVD. Here they focused on measurement of collagen V, vimentin positive fibroblasts and the abundance of TGFβ1. In contrast to collagens I, III and IV, very little is known about collagen V. The authors note that collagen types I and III account for >95 % of the atrial ECM, but that collagen V is critical for the normal nucleation fibril assembly of collagens type I and III fibrils. The authors provide new data showing that collagen type V fibers surround individual atrial muscle cells and blood vessels (perivascular fibrosis). Perivascular fibrosis increased from ~25 % in SR to 57 % in pAF and 85 % in ls-peAF. Replacement fibrosis had a similar trajectory, present in 11 % of SR atria, 37 % of atria from pAF patients to 82 % with ls-peAF. [7] Interstitial fibrosis is thought to be most significantly associated with heterogeneity and slowing of conduction. The authors reported that collagen type V occupied ~7 % of atrial tissues from patients in SR and increased to ~12 % of patients with pAF and 21 % of patients with ls-peAF. While this sounds small, it may have an important functional impact due to its deposition immediately around the working myocytes.

The authors further evaluated the abundance of vimentin positive fibroblasts (V + FBs) that likely contributed to the deposition of collagen in these specimens) [7]. For the patients in SR, the V + FBs were detected at a density of ~32 fibroblasts/mm^2 and increased to ~76 fibroblasts/mm^2 in pAF and ~99 fibroblasts/mm^2 in ls-peAF. Double labeling of tissue sections for TGFβ and collagen V showed that TGFβ was mostly localized in the interstitial cells (V + FBs), and that relative to SR patients, the abundance of TGFβ increased by 77 % in pAF and 300 % in ls-peAF atria. Staining was validated by qPCR which confirmed a 3x increase of TGFβ in pAF and ls-peAF (not significantly different between groups). Overall, the authors have shown that the abundance of each of the histologic markers increased in a stepwise fashion from SR to pAF to ls-peAF and suggest that this may be useful for staging the progression of

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AF [7]. While the associations are novel and plausible, the utility of efforts to routinely assess these targets remains unclear. Although collagen type V is easily detectable, it remains a relatively small fraction of the overall burden of collagen in the ECM. It may be of interest in future studies to assess the relative abundance collagen type V in the atria of patients with underlying valvular disease, and to evaluate the upstream regulators of collagen V. The conventional wisdom in this field suggests that fibrosis, once established, is difficult or impossible to reverse. The authors cite a mouse study in which the minor expression of collagen type V had an oversized impact on scar size following myocardial infarction. Loss of collagen V was associated with increased scar size in an integrin dependent manner [8]. This study suggests that efforts to decrease the abundance of collagen V in the atria are likely contraindicated.

Overall, this well-written paper from Kostin and colleagues provides new insights into our understanding of the relative abundance and possible roles of collagen V in human atria. The confocal imaging is impressive. It will be of interest to determine if this protein represents a target for therapeutic intervention, or an ECM protein whose abundance is critical. It notable that some patients with advanced valvular heart disease (4 + mitral valve prolapse) have extreme dilatation of the left atrium, while dilatation is modest in others. The role of collagen type V in the dilatation process is unclear, as is the balance between increased interstitial fibrosis and overall atrial dimensions on AF progression.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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David R. Van Wagoner

Department of Cardiovascular and Metabolic Sciences, Cleveland Clinic, M/S ND50, 9500 Euclid Avenue, Cleveland, OH 44195, USA

E-mail address: vanwagd@ccf.org.