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INVITED EDITORIAL

Proteomic insights into bi-atrial remodelling in persistent atrial fibrillation

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This editorial refers to 'Mass spectrometric proteome profiling using a deep spectral library reveals homogenization of right and left atrial proteomes in persistent atrial fibrillation patients', by A. Liutkute *et al.*, https://doi.org/10.1093/cvr/cvag076.

Atrial fibrillation (AF) is typically initiated by ectopic activity within the pulmonary veins, leading to electrical remodelling of the left atrium (LA), characterized by shortened refractoriness and altered conduction. Sustained high-rate activity promotes structural remodelling, including fibrosis and atrial dilation, resulting in contractile dysfunction. Progressive extracellular matrix (ECM) deposition increases tissue anisotropy, further destabilising electrical conduction. Although remodelling is initially predominant in the LA, remodelling of the right atrium (RA) occurs during persistent AF (PersAF). Consistent with bi-atrial involvement, cardiac magnetic resonance data demonstrate a strong correlation between LA and RA fibrosis.[1] Bi-atrial involvement in AF leads to convergent remodelling, with similar fibrosis burden, entropy, and voltage characteristics at arrhythmogenic sites in both the RA and LA. Supporting this, a cardiac magnetic resonance-derived bi-atrial digital twin model suggests that up to two-thirds of arrhythmogenic sites in PersAF are located in the RA.[2] While this highlights a potential limitation of pulmonary vein isolation in PersAF, the procedure can induce reverse remodelling in both atria, reinforcing the concept that they function as an interconnected unit rather than separate chambers.[3] Accordingly, electrical, functional, and structural (fibrotic) remodelling affect both atria. However, whether the atrial proteome reflects this convergence remains poorly understood.

In this issue of *Cardiovascular Research*, Liutkute *et al.*[4] used proteomics to compare the RA in 15 patients in sinus rhythm (SR) and 16 patients with PersAF to define a core RA-specific remodelling signature. They then analysed a subset of patients with paired LA-RA samples, enabling direct assessment of atrial chamber homogenization in PersAF. For the first time, paired RA–LA samples were quantified at the protein level across SR and PersAF using data-independent acquisition mass spectrometry, a technique that systematically fragments all detectable peptides to enable comprehensive protein quantification. The RA in PersAF recapitulated remodelling signatures classically attributed to the LA: ECM expansion (including increased collagens and basement membrane glycoproteins); myofibrillar loss with downregulation of sarcomeric proteins; proteostasis stress marked by activation of ER/Golgi secretory pathways; and metabolic remodelling involving shifts in mitochondrial and cytosolic enzymes. Consistent with this, proteomic profiling of paired samples showed that the LA–RA molecular divergence observed in SR is markedly reduced in PersAF, supporting a model of bi-atrial convergence.

An important strength of the study is the use of paired human RA–LA samples. Previous studies focused on single atria or exclusively on diseased samples. For example, using glycoproteomics, we demonstrated that differences in ECM glycoproteins between LA and RA appendages are not pronounced in SR, but ECM glycoprotein accumulation and processing are important in AF.[5] Similarly, region-resolved proteomics shows that the RA and LA, although distinct, cluster more closely to each other than to other cardiac regions.[6] Foundational chamber-specific markers such as PITX2c, enriched in the LA, and BMP10, confined to the RA, remain strongly polarized independently of AF status, as demonstrated by Hsu *et al.* using RNA sequencing in paired human atria.[7] Notably, BMP10 also appears as an RA-enriched protein in the deep proteome generated by Liutkute *et al.*[4] Thus, bi-atrial convergence in PersAF does not reflect a loss of fundamental chamber identity, but rather shared pathological remodelling superimposed on intrinsic molecular asymmetries. However, an important limitation is that proteomic data from bulk atrial tissue do not allow attribution of changes to specific cell types. For example, shifts in protein abundance within myofibrillar, mitochondrial, or ER/Golgi compartments may reflect changes in cellular composition, including increased fibroblast content, immune cell infiltration, or cardiomyocyte loss. While ECM expansion can be confidently attributed to fibroblasts, the structural signatures underlying the bi-atrial convergence in PersAF cannot be fully deconvoluted in this study, highlighting the need for future single-cell or spatially resolved omics approaches.

The comparison with DCM ventricles is exploratory. The long-standing observation that MYH6 down-regulation and MYH7 induction occur in PersAF reflects a non-specific stress response common across cardiac diseases. This reflects foetal reprogramming and metabolic stress,[8] two phenomena that parallel increases in NPPA/NPPB in AF rather than a chamber-specific drift towards ventricle-like proteomic profiles (*Figure 1*). In fact, the atrial and ventricular markers used in this study are derived from two external proteomics datasets and represent only a small subset of the >6000 proteins identified, potentially biasing the analysis towards compartment- and cell-type effects. The concept of a ventricular-like shift in AF is not new. Barth *et al.* previously reported a 'ventricularization' of the RA transcriptome in permanent AF, based on large-scale mRNA profiling.[8] The present study revisits this question in a more nuanced manner, suggesting that the RA-PersAF

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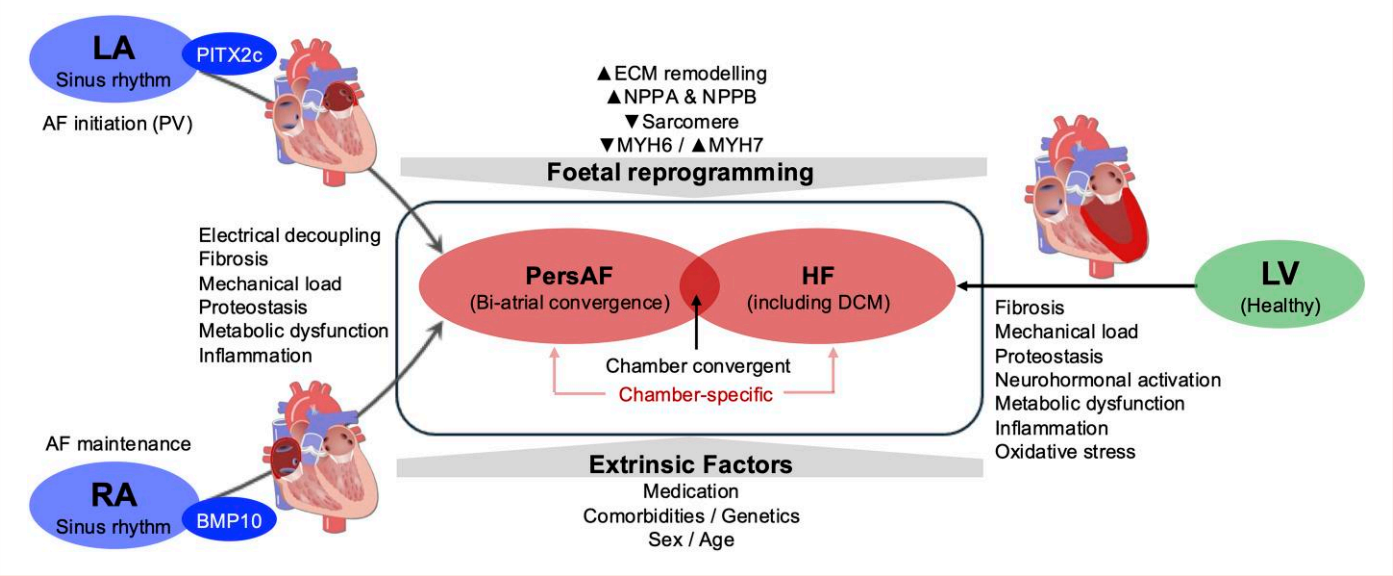

Figure 1 Schematic overview of the principal drivers of atrial and ventricular remodelling in disease. Shared pathways, including ECM expansion, metabolic remodelling, and stress-response signalling, contribute to partially convergent proteomic profiles.

proteome reflects shared stress-response pathways that overlap with DCM signatures. Importantly, the comparison between RA-PersAF and failing ventricles relies on an external DCM dataset,[9] introducing potential confounding. The authors assessed medication and comorbidity profiles for their atrial-only comparisons, but these are expected to differ substantially between AF and DCM patients, and they are known modifiers of proteomic profiles, in particular ECM proteins (see *Figure 1*).[10] Thus, the results reported by Liutkute *et al.*[4] are an important contribution to the study of atrial remodelling in AF; however, given that ECM deposition and metabolic down-regulation are common features across many cardiac pathologies,[9] the apparent convergence towards ventricle-like or DCM-related profiles may instead reflect shared stress-response pathways.

A major challenge for the proteomics field remains ensuring that cross-study comparisons are conducted with sufficient methodological homogeneity. Notably, normalization strategies such as the histone ruler may be confounded in cardiac tissue, where variations in cell-type composition, cardiomyocyte multinucleation, and ECM expansion violate the assumption of a constant nuclear-to-protein ratio. As increasingly deep datasets emerge, harmonisation of sample preparation, acquisition parameters, and data-processing pipelines will be essential. Equally important is access to detailed metadata (age, sex, genetics, comorbidities, and medication), which profoundly shape cardiac proteomes.[9,10] Future collaborative efforts, including shared repositories with complete metadata and harmonized analytical standards, will be essential; without these, cross-cohort comparisons risk conflating treatment effects with disease signatures.

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