Atrial disease and heart failure: the common soil hypothesis proposed by the Heart Failure Association of the European Society of Cardiology

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Introduction

Abnormal atrial structure and function, also termed atrial myopathy or atrial disease, is common in patients with heart failure (HF) and may be an integral aspect of its development. A frequent clinical consequence of atrial disease is atrial fibrillation (AF) that is also closely linked with HF with a bidirectional relationship, the one increasing the likelihood and worsening the prognosis of the other.

A consensus document defined atrial myopathy as ‘any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations’. The recognition of atrial disease as an entity has long appeared in the literature while its diagnosis and management may potentially impact the pathogenesis of both HF and AF. However, the concept of identifying coincident AF and HF as a specific entity remains poorly defined and has therefore not been a target of specific clinical strategies or recommendations.

The aim of this article is to summarize the deliberations of a dedicated workshop of experts brought together by the Heart Failure Association of the European Society of Cardiology. Our intentions were to provide a conceptual framework for the medical community to consider atrial disease as a manifestation of the HF syndrome and also discuss the gaps in evidence concerning the epidemiology, diagnosis, and management of this entity.

Conceptual framework for atrial disease

The risk factors and pathogenetic mechanisms leading to HF and AF are similar, and these conditions often co-exist, while good management of one condition requires good management of the other. Recognizing this overlap and promoting awareness of atrial dysfunction and disease as an entity within the spectrum of the HF syndrome will stimulate research into the prevention and management of both AF and HF.

Atrial disease results from a complex interplay of risk factors, comorbidities, and genetic susceptibilities that underly both HF and AF.
The onset of AF causes additional cardiovascular stress, which may precipitate the development of clinically overt HF in a predisposed individual with asymptomatic cardiac dysfunction or exacerbate pre-existing HF. Similarly, HF will increase the stress on the atria and precipitate AF in susceptible individuals. Susceptibility to the onset of AF will vary according to the atrial myocardial substrate, particularly in the vicinity of the pulmonary veins. Patients with a high-risk atrial substrate may develop AF with a relatively minor haemodynamic stress but other patients with a low-risk substrate may be relatively resistant. Similarly, the risk of AF precipitating HF will depend on the duration of AF, the sustained speed of ventricular contraction, and the extent to which loss of atrial contraction impairs haemodynamic function.

Gaps in evidence and perspectives

Epidemiology
Because atrial disease is not a well-defined entity, epidemiological data are limited. However, atrial dilatation, fibrosis, and functional impairment are common if not universal accompaniments of both HF and AF. All forms of AF—paroxysmal, persistent, or permanent—are associated with atrial structural, functional, and electrical changes. The ‘AF begets AF’ phrase has been coined to account for the self-perpetuation of AF, which alternatively could be explained by atrial disease underlying the vast majority if not all AF syndromes. Similarly, HF has been associated with both atrial remodelling and dysfunction, including atrial dilatation, abnormal left atrial (LA) reservoir, conduit and booster functions, and interatrial dyssynchrony with conduction delays. Evidence of atrial disease commonly precedes the development of AF and HF, being an independent predictor of incident AF and HF, and potentially driving the pathogenesis and progression of both conditions. However, the close relationship between AF and HF is often underestimated since the recognition of co-existing HF, particularly of HF with preserved ejection fraction (HFpEF), is frequently missed in patients with AF.

Pathophysiology
The precise pathophysiological processes involved in the generation and progression of atrial disease remain unclear. Key open issues concern the drivers and mechanisms underlying AF initiation and progression (e.g. changes in electrical properties or conduction, inflammation). Whether these mechanisms are distinct in different patient populations is also unknown. Regarding rhythm control, further data are needed on whether there is a point of no-return for improvement in heart function, particularly considering the differences in recent large outcome trials. The pathophysiology of thromboembolism also remains unclear, while the concept of changes in atrial endocardium, termed prothrombotic endocardial remodelling, has attracted some attention. The differences in the remodelling process between atrial and ventricular myocardium in the context of AF and HF are further relevant, given the finding that although atrial and ventricular myocytes may respond differently, they may also adopt each other’s phenotypes. The severity of atrial structural remodelling is exaggerated by the presence of HF, but the question remains as to which of the two comes first. For a better understanding of both conditions, studies should focus on ventricular structure and function in AF and on atrial structure and function in HF.

Diagnosis
A proper definition of atrial disease is lacking. The identification of atrial disease has hitherto been based primarily on markers of LA size and function, obtained by two- and three-dimensional echocardiography, deformation imaging, computed tomography, and cardiac magnetic resonance. Cardiac troponins and natriuretic peptides are also useful in assessing pathophysiologic aspects of atrial disease under the understanding that are not atrial-specific markers. Blood biomarkers associated with fibrotic pathways are of interest but reflect the systemic activity rather than being cardiac specific. Monitoring atrial electrical activity may contribute to the identification of atrial disease in combination with imaging and biomarkers.

More precise clinical and pathophysiological profiling of patients with atrial disease will allow for better understanding, more timely diagnosis, and more individualized management. One proposed scheme categorizes atrial disease into four groups defined by histological criteria alone. A more comprehensive profiling, which combines clinical features, specific imaging, and biomarkers may be more clinically relevant. In this context, identification of atrial-specific biomarkers using gene expression profiles may be helpful. Novel molecular imaging technologies also seem promising in the assessment of atrial disease. Candidate targets for molecular imaging in atrial disease include collagen synthesis and degradation, autonomic innervation, activated platelets and coagulation factors, and inflammatory pathways.

Treatment
The development of atrial fibrosis is believed to play a key role in the pathogenesis of atrial dysfunction leading to AF and possibly HFpEF. Features of atrial dysfunction in HFpEF in the absence of AF include increased LA volume, decreased LA emptying fraction, and decreased LA contractile reserve (reduced response of A’ mitral annular velocity to handgrip) compared both to controls but also to hypertensive patients with left ventricular hypertrophy. Atrial disease should be considered as a potential therapeutic target, either for existing treatments or for new agents. However, this would require reliable diagnostic methods to identify atrial disease.

Conclusions
The appreciation of the close convergence of AF and HF, HFpEF, in particular, based on clinical and epidemiological evidence, allows for a paradigm change. According to this, the two conditions do not result from a sequential relationship in which the one condition provokes the other, but rather from parallel trajectories activated by a common underlying myopathy that affects both the atrial and the ventricular myocardium. The atrial component of this myopathy is atrial disease. The detection of subclinical atrial disease with imaging, biomarkers, and other modalities offers a window of opportunity for interventions that could prevent deterioration to clinical disease, including AF, stroke, and HF with preserved/reduced ejection fraction and could potentially allow the reversal of subclinical disease (Graphical Abstract).
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References