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GUEST EDITORIAL

Atrial remodelling in heart failure: recent developments and relevance for heart failure with preserved ejection fraction

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Introduction to atrial function

As specialized compartments of the heart, the atria feature unique mechanical and structural properties that differ considerably from those of the ventricular myocardium. Beyond their contribution to cardiac output as a reservoir, conduit, and booster pump at different phases of the cardiac cycle, the atria determine heart rhythm, regularity, and rate (chronotropy). They also function as mechanical sensors and exert relevant endocrine activity (e.g. natriuretic peptides). Atrial remodelling is often observed in association with ventricular remodelling in heart failure (HF) but by itself adds to the complexity of the disease.

Atrial remodelling—types and classifications

In a recent consensus statement, atrial remodelling has been defined as 'any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations' and giving rise to an atrial cardiomyopathy.[1] The authors have further proposed a novel classification to differentiate histological changes European Heart Rhythm Association (EHRA I–IV). In clinical settings, characterization and understanding of atrial remodelling in the context of HF and comorbidities currently remain dependent on cardiac imaging-derived read-outs, as outlined later.

Left atrial (LA) enlargement (LAE) is frequently used synonymously with atrial remodelling. However, also in HF, hypertrophy and fibrosis of the atrial wall, atrial fibrillation (AF; suggesting electrical remodelling), and atrial contractile dysfunction all may occur in the absence of LAE,[2–5] indicating the necessity for a more comprehensive assessment of the atrial phenotype.

Clinical diagnosis of atrial remodelling

Size and function

Individual electrocardiogram (ECG) criteria (P-wave morphology) are not a reliable measure for LAE and right atrial (LA) enlargement (RAE) but may serve as a screening tool.[6] LA size or volume by echocardiography, corrected for body size [i.e. LA volume index (LAVI)] are commonly used to describe LAE, with 2D echocardiography underestimating volumes as measured by 3D echocardiography, cardiac computed tomography, or cardiac magnetic resonance.[7] Volumes relate to the reservoir function of the LA. Neither LA size nor LAVI is gender dependent, yet they increase with age.[8] Measurement of atrial volumes additionally allows to calculate atrial contractility (i.e. LA emptying fraction and LA expansion index), but without differentiating between passive (conduit and reservoir) and active (booster pump) function. Atrial strain and atrial strain rate based on speckle tracking echocardiography have been recently implemented for the differentiation of LA reservoir and conduit function. Methodically more challenging, LA strain rate allows to measure active LA contraction (i.e. booster pump).[9] In experimental settings, in analogy to the ventricle, pressure-volume catheters have been used to quantify LA stiffness and atrioventricular coupling.[10]

Tissue composition

Cardiac magnetic resonance late gadolinium enhancement regions are used to characterize atrial fibrous remodelling.[11] Magnetic resonance imaging (MRI) T1 mapping allows to assess the degree of fibrosis in ventricular remodelling; however, it has failed to convincingly do so in the LA.[12] Finally, in selected patients, electro-anatomical mapping

allows the quantification and localization of low-voltage areas to assess an additional local functional parameter of atrial remodelling. However, to date, the exact relation between the extent and severity of low-voltage regions and the degree of LA fibrosis/remodelling needs further clarification. Biomarkers have been used as a surrogate for atrial remodelling, reflecting mechanical stress, fibrosis, or inflammation; but individual markers to date lack atrial specificity.[13–15]

Prevalence of atrial remodelling in heart failure

Left atrial enlargement as a sign of atrial remodelling is observed in about half of the patients with stable chronic HF with large variations between studies, likely reflecting heterogeneous disease aetiologies and stages (*Table 1*).

Atrial contractile dysfunction

In HF with reduced ejection fraction (HFrEF), LA emptying fraction has been shown to be significantly decreased.[23] LA emptying fraction and LA strain are also reduced in HF with preserved ejection fraction (HFpEF) in clinical studies[9,24,25] and randomized controlled trials [e.g. Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure with Preserved Ejection Fraction (RELAX trial) substudy[26] and Candesartan in Heart failure - Assessment of moRtality and Morbidity (CHARM trial)-preserved]. Regional differences in LA strain may also be an early sign of electrical remodelling leading to AF.[27]

Atrial fibrosis

In HFrEF, LA fibrosis has been reported to range from 13% to 27% of the LA area as compared with 1.4% in control.[28] In HFpEF, LA fibrosis as assessed using histology and MRI imaging was shown to be 30.1 ± 4.6% of the LA area (n = 18 HFpEF patients).[29] However, aetiology-dependent differences in prevalence of atrial fibrosis in HF have not been systematically studied.

Electrophysiological remodelling

Signs of LA electrical remodelling in HF (HFrEF) include conduction abnormalities (as reflected by P-wave morphology in ECG), prolonged refractoriness (in contrast to AF-induced remodelling), and sinus node dysfunction.[30] Incidental AF serves as a marker of electrophysiological remodelling. The prevalence of AF in HF has been reported from 5% in New York Heart Association (NYHA) I to 25–50% in NYHA III/IV,[31,32] with higher prevalence in HFpEF vs. HFrEF (see subsequent discussion).

Clinical impact of atrial remodelling and relevance in heart failure with preserved ejection fraction

Atrial remodelling as risk biomarker

Left atrial volume index is strongly associated with cardiovascular disease[33] and a predictor of new HF

Table 1 Atrial enlargement in heart failure

Study	HF type (EF %)	*n* patients	Measure of LA size	Non-failing group	HF group	Cut-off abnormal LA	HF and LAE (% patients)
TOPCAT[16]	HFpEF (≥45%)	935	LAVI (mL/m^2)	n/a	29.8 ± 12.5	≥29	46%
PARAMOUNT[5]	HFpEF (≥45%)	175	LAVI (mL/m^2)	21.1 ± 5.3	33.4 ± 11.5	≥29	61%
ARIC (Jackson)[17]	HFpEF (≥50%)	85	LA diam. (cm)	3.4 (3.0, 3.7)	3.4 (3.1, 3.8)	≥4.0	19%
ARIC (Jackson)[17]	HFrEF (<50%)	31	LA diam. (cm)	3.4 (3.0, 3.7)	3.8 (3.3, 4.3)	≥4.0	39%
i-PRESERVE Echo Substudy[18]	HFpEF (≥45%)	745	LA area (cm^2)	n/a	23 ± 6	≥20 mild, ≥31 mod./sev.	66% (51% mild)
Cioffi *et al*.[19]	HFrEF (<50%)	194	LA max vol. (mL/m^3)	7.1 ± 2.1	11.0 ± 4.0	11.3	41%
Rossi *et al*.[20]	HFpEF (>45%)	310	LA diameter (cm)	3.7 ± 0.6	4.6 ± 1.0	5.0	34%
Zivlas *et al*.[21]	HFrEF (<35%)	40	LAVI (mL/m^2)	n/a	66.6 ± 1.7	≥29	n/a
Almodares *et al*.[22]	HFpEF/HFrEF (NYHA III–IV)	289	LAVI (mL/m^2)	n/a	58 ± 22.7	≥29	n/a

EF, ejection fraction; HF, heart failure; HFpEF, HF with preserved EF; HFrEF, HF with reduced EF; LA, left atrial; LAE, LA enlargement; LAVI, LA volume index; NYHA, New York Heart Association.

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irrespective of systolic left ventricular (LV) function.[18,34,35] LAE is also an independent predictor for the development of early [American Heart Association (AHA) stage B] non-ischaemic HF.[36] With regard to secondary events, LAVI correlates with a higher incidence of congestive HF recurrence[37] and sudden cardiac death.[38] LA size is used as an independent marker of risk in several HF risk scores, such as the Coronary Artery Revascularization in Diabetes (CARDIA) risk score [based on the Framingham 10 year global cardiovascular (CV) Framingham risk score (FRS)[39]], the Redin-SCORE,[40] and the MUerte Subita en Insuficiencia Cardiaca (MUSIC) Risk score. Indexed LA diameter is increasingly being used as predictor of long-term outcomes in patients evaluated for aortic valve replacement, and its assessment may guide patient management.[41] LA function (at rest) is a predictor of exercise capacitance in HFrEF,[42] and LA contractile dysfunction has been shown to be associated with a higher risk of HF hospitalization independent of potential clinical confounders.[43]

Atrial remodelling is of particular interest in patients with HFpEF,[44] where it has been associated with increased mortality[45] and has been recognized as a hallmark feature of the disease.[44] Melenovsky *et al*. have shown that preserved LA function was significantly associated with lower mortality in HFpEF.[46] Moreover, in HFpEF, impaired LA conduit function is associated with exercise intolerance, independent of LV stiffness and relaxation.[47] On the other hand, in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, contractile LA dysfunction (reduced peak LA strain) in HFpEF was not associated with a higher risk of HF hospitalizations when also accounting for LV systolic and diastolic function.[43] This is explained by the robust interrelation between peak LA strain, LV global longitudinal strain, and E/e′.[25]

Atrial contribution to ventricular function

The role of atrial contraction in different aetiologies and stages of HF is quantitatively not very well explored. Modelling suggests that a timely atrial contraction significantly improves LV stroke work.[48] In a recent report from a cohort of HF patients (51% HFpEF), atrial remodelling in HFrEF was characterized by increased LA volumes and lower contraction amplitude (pulsatility) as compared with HFpEF, whereas HFpEF was associated with higher LA pressures and increased LA wall stiffness.[46] Vice versa, in patients with HFrEF receiving cardiac synchronization therapy (CRT), a reduction in LA strain induced by atrial pacing resulted in a significant reduction in global LV strain.[49] Atrial contribution to ventricular filling can decline with the progression of HF, as increased atrial mechanical load leads to atrial dysfunction.[50] HFpEF is characterized by impaired LV diastolic filling, and LA ejection volume contributes to LV filling. Clearly, more work is needed to dissect the relative contribution of atrial dysfunction to impaired LV filling in different HFpEF phenotypes.

Atrial fibrillation and fibrosis

Atrial fibrillation is common HF, with reported prevalences of 21–65% in HFpEF, which is higher than what has been reported in HFrEF (<10–50%).[51] AF is often linked to the presence of fibrotic remodelling, as fibrosis creates conduction obstacles that perpetuate the genesis of re-entry circuits.[52] Fibrosis is especially prevalent in atrial remodelling in patients with HFpEF.[29] In the RELAX trial, HFpEF patients with AF (37%) had more advanced disease and a significantly reduced exercise capacitance, which might be also related to the development of tachy-cardiomyopathy.[53] Likewise, others reported that AF is independently associated with greater exertional intolerance, natriuretic peptide elevation, and left anterior descending artery remodelling in HFpEF.[53,54] Vice versa, in Framingham Heart Study participants, pre-existing AF tended to be more strongly associated with new-onset HFpEF (hazard ratio 2.34) than did HFrEF (hazard ratio 1.32), highlighting the relevance of atrial function in HFpEF.[55]

Endocrine activity

Physiologically, endocrine function of the heart is mainly located to the atria.[56] Natriuretic peptides [e.g. atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP)] and vasopressin are secreted by atrial myocytes (and possibly fibroblasts) in response to acute stretch and neurohumoral activation (angiotensin, endothelin, and catecholamines)[57,58] and have a pivotal role in volume regulation.[56] In HF, ANP and BNP production increases in the atria, and BNP is also produced in the ventricle.[59] As reviewed elsewhere, atrial myocyte ANP secretion is impaired in HFrEF.[60] Fibrotic atrial remodelling may contribute to the reduced amount of natriuretic peptides secreted from the atria.[61]

Interestingly, the increase of natriuretic peptides is less pronounced in HFpEF than in HFrEF.[62] Increased BNP clearance by adipose tissue (in HFpEF) and decreased BNP production due to ‘cardiac cachexia’ have been proposed as mechanisms,[62] but an impaired production or secretion in the atrial (or ventricular) myocardium in HFpEF remains to be explored.[63] Beta-blockade with metoprolol increases plasma BNP levels in HFrEF.[64] BNP given subcutaneously can improve the haemodynamic response to acute volume load in patients with HFpEF,[65] corroborating a relative deficit of natriuretic peptides. Likewise, increasing natriuretic peptide availability by neprilysin inhibition with simultaneous angiotensin II receptor blockade and neprilysin inhibition has been shown to be beneficial (see below ‘Atrial Reverse Remodeling with Therapy’). The role of atrial remodelling in the disproportionate levels of natriuretic peptides and their precursors in response to chronic and acute stress in particular in HFpEF warrants further research.

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Chronotropic incompetence

Chronotropic incompetence is a common and likely undervalued cause of reduced exercise capacitance in HFrEF and HFpEF.[66] Borlaugh *et al*. demonstrated that in particular in HFpEF patients, an attenuated increase in heart rate rather than inappropriate stroke volume was the cause of a reduced cardiac output reserve during exercise.[67] While in patients with HFrEF, down-regulation of myocardial beta-adrenergic receptors and sinus node remodelling and dysfunction have been demonstrated as potential causes of chronotropic incompetence,[68] its pathophysiology in HFpEF has not yet been studied in detail. As published recently in this journal, 3D echocardiography-based assessment of stroke volume and heart rate during exercise may allow differentiating patients with reduced chronotropic reserve from others in a heterogeneous HFpEF population.[69]

Hypercoagulability

Left atrial enlargement has been shown to predict the risk for stroke even when adjusted for the prevalence of AF.[70] The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) and Anticoagulation Guided by Remote Rhythm Monitoring in Patients With Implanted Cardioverter-Defibrillator and Resynchronization Devices (IMPACT) trials also suggested that stroke risk is increased in remodelled atria even if patients are in sinus rhythm. Vice versa, hypercoagulability itself may promote atrial remodelling by activation of pro-fibrotic signalling molecules like TGF-beta increasing thrombin. Inhibition of thrombin has been associated with attenuated atrial remodelling.[71]

The right atrium

Similar to the LA, RA size is strongly correlated to right ventricular end-diastolic pressure and is thereby linked to pulmonary artery hypertension and right HF.[72] RA dysfunction and the severity of right HF can be assessed using RA longitudinal strain by speckle tracking echocardiography.[73] As a biomarker, an RA larger than LA is associated with increased mortality in elderly HF patients,[22] and systolic blood pressure to RA pressure ratio is a marker that identifies a spectrum of complications after hospitalization of patients with decompensated systolic HF.[74]

Risk factors and pathophysiology of atrial remodelling in heart failure

Mechanical load

In HF, increased pressure or volume load in the ventricle is a strong trigger for atrial enlargement and remodelling. In chronic conditions, LA volume and strain correlate with LV end-diastolic pressures irrespective of EF.[75,76] Mechanical stress induces stretching and stiffening of the atria.[77] Atrial fibrosis is perpetuated by atrial distention[78–80] and related to activation of pro-fibrotic signalling cascades and apoptosis/necrosis of cells as well as activation of a foetal gene programme.[81] This in turn negatively impacts atrial reservoir function (through stiffening) and active atrial kick (through over-stretching and Frank–Starling mechanism). Increased ventricular pressures may contribute to remodelling of the LA (as in arterial hypertension) or the RA (as in pulmonary hypertension secondary to chronic pulmonary disease). Mechanical load is a strong confounder in investigating other load-independent mechanisms for atrial remodelling in HF and arguably may diminish the role of other co-morbidities in shaping atrial remodelling in later HF stages. On the other hand, even in advanced HFrEF, the impact of reducing mechanical load (e.g. by CRT) on myocardial remodelling is lower in the presence of other co-morbidities, suggesting (but not proving) load-independent effects of relevant co-morbidities on atrial remodelling in HF.[82] In early-stage hypertensive HFpEF, LA cardiomyocyte hypertrophy, titin hyperphosphorylation, and microvascular dysfunction occur in association with increased systolic and diastolic LA chamber stiffness, impaired atrioventricular coupling and decreased LV stroke volume.[10]

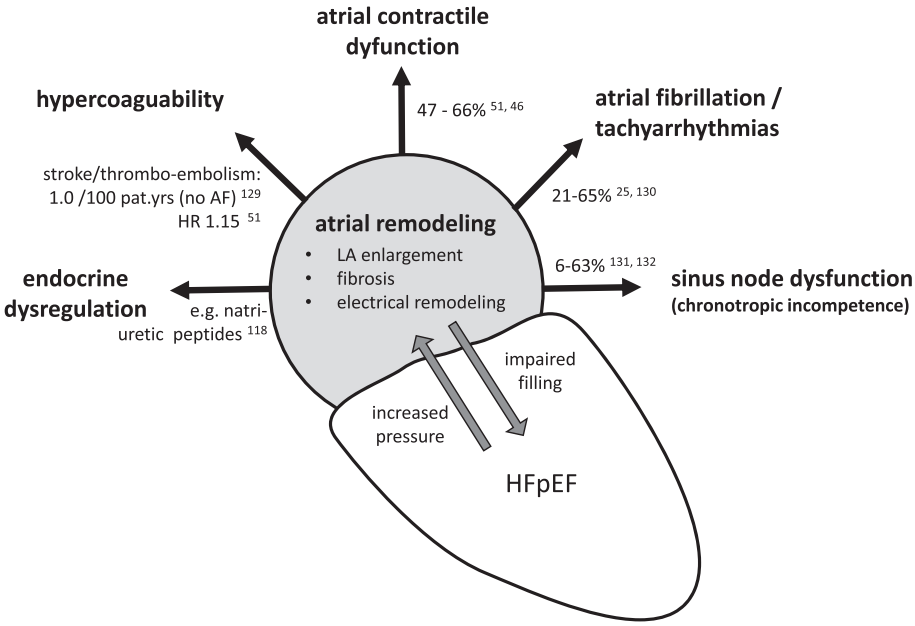
Neuroendocrine activation triggered by low cardiac output is a hallmark of HFrEF but likely also plays a role in HFpEF.[83,84] Systemic and myocardial levels of catecholamines, aldosterone, and angiotensin are increased in HF and perpetuate atrial remodelling owing to their prohypertropic and pro-fibrotic effects.[85,86]

In HFpEF, chronic kidney disease (CKD) is highly prevalent with the majority of patients suffering mild to moderate renal impairment.[87] Others have reported similar prevalence of CKD in HFpEF and HFrEF.[88] CKD-associated renal arterial hypertension has been identified as a trigger of maladaptive LA remodelling in a model of early-stage HFpEF.[10]

The prevalence of diabetes is similar in HFpEF and HFrEF[88] and independently associated with LAE.[89] A higher prevalence of *obesity* has been reported in HFpEF (51%) vs. HFrEF (37%[88]). LA enlargement correlates with epicardial fat thickness[90] and visceral fat mass.[91] In patients undergoing AF ablation (n = 236), low-voltage areas suggestive of atrial fibrosis were much more common (46% of patients) in patients with metabolic syndrome than in those without (8%[92]). The pathomechanisms of atrial remodelling in metabolic syndrome are unclear and, as in ventricular metabolic remodelling, may be multifactorial including inflammation, oxidative stress, pro-fibrotic pathways, and others.[93]

Atrial fibrillation in HF is a result of atrial remodelling (*Figure 1*). Mechanical stretch facilitates arrhythmia initiation[94] and structural changes (e.g. fibrosis), thus providing the substrate for sustained arrhythmias.[95] At the same time, AF itself is a strong promoter of tachyarrhythmia-induced atrial

Figure 1 Clinical features of atrial cardiomyopathy in HFpEF. AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; LA, left atrial



cardiomyopathy. Electrical atrial remodelling during AF, however, differs from HF-related atrial remodelling.[7] The current understanding of the pathomechanisms underlying AF-induced remodelling has been extensively reviewed.[1,52]

Cumulative cardiovascular risk factors

The aforementioned common risk factors and other cardiovascular risk factors, including age and vascular disease, may synergistically promote atrial remodelling. Indeed, the CHA_2DS_2-VASc risk score established to evaluate stroke risk in AF also reflects the risk of incidental AF[96] and correlates with LA enlargement.[97]

Atrial reverse remodelling with therapy

Reverse atrial remodelling in patients with HF or at risk of HF has been shown to improve clinical endpoints like the incidence of AF[98] and is independently associated with decreased mortality.[99] Weight reduction with intensified risk factor management induces reverse atrial remodelling and reduces AF prevalence.[100] Exercise training was also associated with a reduction in LA volume in HFpEF.[101]

Medical therapy

Several classes of classical HFrEF drugs [e.g. angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, and spironolactone] have been associated with a reduction in LAE in patients with structural heart disease[102] in part related to their blood-pressure-lowering effect.[103] Treatment with ACE inhibitors and angiotensin receptor blockers also positively affects contractile function of the LA in HF.[104,105] In the absence of HF, quinapril effectively reduced LA volume independent of its effects on systolic blood pressure, suggesting direct effects on the atrial myocardium. Similarly, increasing the levels of natriuretic peptides, e.g. with neprilysin inhibition, has had beneficial effects on LA size in HFrEF[106] and in HFpEF [Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT trial[107])] independent of the drug's blood-pressure-lowering effects.[108] Lowering heart rate could improve atrial contribution to LV filling in HF. Interestingly, recent data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF trial) registry suggest that lowering heart rate (<70 b.p.m.) has beneficial effects in HFpEF independent of atrial contribution (i.e. sinus rhythm vs. AF[109]).

Cardiac synchronization therapy was associated with a significantly increased LA strain, suggestive of reverse function atrial remodelling.[110] Of note, maintaining intrinsic electrical atrial activation and contraction (as opposed to AV-sequential pacing) significantly improves cardiac output with CRT.[49]

Specifically targeting AF as a result of atrial remodelling in HF has been proposed with the aim of reversing electrical remodelling induced by AF and preserve/restore contribution of the LA to ventricular filling in sinus rhythm.[53] Indeed, surgical and catheter-based AF ablation was associated with

reverse atrial remodelling in non-failing[111–113] and also failing hearts (HFrEF[114]). Restoration of atrial function may contribute to the observations of the yet-to-be-published Catheter Ablation vs. Conventional Therapy For Patients With AFib and LV Dysfunction (CASTLE-AF) trial,[115] where AF ablation significantly decreased the composite of all-cause mortality and unplanned hospitalization for worsening HFrEF. In addition, in the Prevention of Early Atrial Fibrillation in Heart Failure (RACE 3) trial (n = 250), presented at the ESC Congress 2017, an early upstream therapy consisting of physical activity, dietary restrictions, statins, and ACE inhibitors or angiotensin receptor blocker was superior to conventional therapy in maintaining sinus rhythm in HF patients with AF (http://clinicaltrials.gov Identifier: NCT00877643).

Hypercoagulability is currently treated mainly in the presence of AF. In HF(rEF) alone, i.e. in the absence of AF, anticoagulation with warfarin is not recommended based on randomized trials.[116] Additional risk factors such as previous stroke,[117] the CHA_2DS_2-VASc score,[118] or LAE[119] may identify HF patients at increased risk for future stroke, but further studies are needed to refine the tools for patient selection and evaluate the novel oral anticoagulants.

Outlook

Atrial function and remodelling are strongly influenced by LV haemodynamics, and atrial size may even serve as biomarker of chronically elevated LV pressure. As outlined earlier, however, accumulating evidence suggests that atrial remodelling independently adds to the complexity of the systemic dysregulation characterizing HF. The role of different co-morbidities for atrial remodelling at later stages of HF in the context of increased mechanical load needs to be defined. The recently proposed EHRAS classification for atrial cardiomyopathy[1] is a first step in establishing an aetiology-dependent and stage-dependent understanding of atrial remodelling as a basis for novel selective therapeutic approaches. Advanced clinical imaging, mainly MRI based, will add detailed *in vivo* information on function, fibrosis, inflammation, and metabolism for a better characterization of the atrial substrate. In addition, a combination of established biomarkers elevated during HF and associated with atrial remodelling might contribute to the development of risk scores: e.g. BNP[54] and Galectin-3[120] have been shown to be markers of atrial remodelling and to directly correlate with the extent of LA fibrosis.[121] Only recently has TNF-alpha been suggested as a biomarker for increased fibrosis, cardiomyocyte apoptosis, and AF.[122] Increases in TNF-alpha are also associated with an increased risk of HF: in Framingham per tertile increment in TNF-alpha, HF risk was increased by 68%.[123,124]

Novel treatment approaches for atrial remodelling associated with HF have been tested in animal models. Direct thrombin inhibition has been shown to prevent HF-related and AF-related atrial remodelling in rats.[125] Currently, following the landmark trials Amiodarone for Treatment of persistent Atrial fibrillation in patients with Congestive heart failure and an implanted device (AATAC) and CASTLE-AF, a number of studies evaluate the role of catheter-based AF ablation on clinical endpoints in different HF populations, and it is reasonable to assume that reverse atrial remodelling will be a key for a sustained success of AF ablation.

However, the process of reverse atrial remodelling is poorly quantified. More advanced imaging technologies like MRI-based quantification of atrial remodelling[126] and novel algorithms are needed to address this issue. The first attempts to further characterize the state of atrial remodelling using advanced imaging techniques but also basic clinical tools like resting ECGs[127,128] have been made and were able to report the degree of electrophysiological changes in the atria owing to structural remodelling.

In summary, enhancing atrial contribution to ventricular filling, preventing atrial tachyarrhythmias (restoring sinus rhythm), and improving atrial endocrine and regulatory function are equally important approaches that need to be further explored in HF.

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