Function over form? Assessing the left atrium in heart failure

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This editorial refers to ‘Left atrial function measured by cardiac magnetic resonance imaging in patients with heart failure: clinical associations and prognostic value,’ by P. Pellicori et al., on page 733.

The understanding of heart failure (HF) haemodynamics has traditionally focused on left ventricular (LV) structure and function, with the left atrium being viewed simply as a passive transport chamber that empties into the left ventricle. Over the last decade, there has been increasing recognition of the importance of left atrial (LA) structure and function in the pathophysiology of HF. LA volume was first to be established as a biomarker integrating the magnitude and duration of LV diastolic function, and a predictor of cardiovascular outcomes in HF. More recently, LA function has emerged as a novel determinant of clinical status and outcomes in HF, and perhaps an even more robust prognostic marker than LA volume (Table 1).

Pellicori et al. have now explored the prognostic relevance of one summary measure of LA function—LA emptying fraction (LAEF)—by magnetic resonance imaging (MRI) in HF. In this single-centre study of 759 patients with suspected HF and in sinus rhythm undergoing cardiac MRI, LAEF was lower on average among 664 patients with the confirmed diagnosis of HF. Lower LAEF correlated with larger LA maximal and conduit volumes, smaller LA reservoir volume, lower LV and right ventricular (RV) ejection fraction, greater LV and RV remodelling, and higher circulating N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Over a median follow-up of 3–4 years, LAEF, but not LA volume, was independently associated with incident HF hospitalization, cardiovascular mortality, all-cause mortality, and atrial fibrillation in multivariable models that included clinical predictors and NT-proBNP level. Importantly, LAEF provided incremental value in predicting these outcomes, beyond clinical variables alone but not in addition to NT-proBNP levels.

The left atrium modulates LV filling and cardiovascular performance by three distinct functions: (i) as a reservoir for pulmonary venous return during LV systole; (ii) as a conduit for passive flow of blood from the pulmonary veins into the ventricle during early LV diastole and diastasis, and (iii) as a pump during late LV diastole that augments LV stroke volume (by ~15–30% in healthy individuals and more in the presence of abnormal LV relaxation) (Figure 1). LA reservoir function is influenced by LA compliance as well as LV contraction via descent of the LV base during systole, and RV systolic pressure transmitted via the pulmonary circulation. LA conduit function is inversely related to reservoir function and strongly modulated by LV relaxation and compliance. LA pump function reflects LA contractility and is also dependent on both LA preload (venous return) and LA afterload (LV end-diastolic pressure). Of note, the Frank–Starling mechanism applies to LA mechanics (as with LV mechanics), wherein LA ejection volume increases as LA filling volume increases, but reaches a tipping point in severe LA dilation where LA contractility drops. Thus the assessment of LA function provides important information beyond LA volume alone.

Left atrial function can be assessed non-invasively by echocardiography, cardiac computed tomography (CT), and cardiac MRI. Importantly, differences in LA measurements have been reported between techniques. Echocardiography is most often used clinically because of its widespread availability, safety, convenience, low cost, ability to image in real time, and technical advancements which have enabled imaging with high temporal and spatial resolution as well as quantification of LA longitudinal deformation throughout the cardiac cycle (Supplementary material online, Table S1). Cardiac CT involves radiation exposure and need for iodinated contrast; however, it has an important adjunctive role in LA ablation procedures. Cardiac MRI provides accurate measurements of LA volume but is limited by high costs, decreased availability, inability to scan patients with intracardiac devices, and lack of data on LA phasic volumes with gated three-dimensional sequences. Pellicori et al. only obtained total LAEF, without distinguishing between the active and passive components of LA function. Concurrent echocardiographic assessments would have been extremely useful to study the different LA phasic functions in detail and determine the generalizability of their prognostic findings to the much more commonly used
Table 1  Clinical significance of left atrial function in heart failure

<table>
<thead>
<tr>
<th>Stage of HF</th>
<th>Clinical significance of LA function</th>
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<tr>
<td>A (Cardiovascular risk factors)</td>
<td>• ↓ peak longitudinal LA strain is independently associated with incident HF in a multiethnic population of asymptomatic individuals¹¹</td>
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<td>• ↓ LAEF (but not LA volume) is independently associated with mortality in the general population, and of incremental prognostic utility to clinical risk factors, LV mass, and LV ejection fraction¹³</td>
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<td>B (Asymptomatic structural heart disease)</td>
<td>• LA peak reservoir strain measured within 48 h of admission for acute myocardial infarction is associated with the composite outcome of death and HF¹³</td>
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<td>• LA function independently predicts HF hospitalization among patients with coronary artery disease and preserved LVEF¹⁴</td>
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<td>• LA pump function is the strongest predictor of major adverse cardiac events and all-cause mortality in patients with chronic hypertension¹⁵</td>
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<td>• ↓ LAEF is associated with risk of new-onset AF independent of clinical risk factors, LV systolic/diastolic function, and LA volume in elderly persons referred for echocardiography¹⁶</td>
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<td>• ↓ LA ejection force is associated with risk of cardiovascular events independent of age, risk factors, LV geometry, and LV diastolic function in a population with pre-clinical risk factors such as hypertension and diabetes¹⁷</td>
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<td>C (Symptomatic HF)</td>
<td>• ↓ LA strain occurs in hypertensive and diabetic patients even prior to development of overt LA dilatation¹⁸</td>
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<td>HFpEF</td>
<td>• LA kinetic energy predicts cardiovascular death and HF hospitalization in chronic HF regardless of EF, and has an incremental prognostic value over LA size¹⁹</td>
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<td>• Blunted increase in mitral annular A’ velocity during exercise distinguishes HFpEF from asymptomatic hypertensive patients²⁰</td>
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<td></td>
<td>• ↓ LAEF at rest and blunted LA systolic reserve with isometric handgrip distinguish HFpEF from asymptomatic hypertensive LV hypertrophy²¹</td>
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<td>• LA dysfunction relates to symptom onset in HFpEF²² and occurs even in the absence of overt LA enlargement²³</td>
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<td>HFrEF</td>
<td>• LA strain is independently associated with exercise capacity in HFpEF²⁴</td>
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<td></td>
<td>• LA pump function is an independent correlate of HF symptoms in hypertrophic cardiomyopathy⁵</td>
</tr>
<tr>
<td></td>
<td>• ↓ mitral annular A’ velocity is the most powerful predictor of cardiac death or HF hospitalization among clinical, haemodynamic, and echocardiographic variables in chronic HFrEF²⁵</td>
</tr>
<tr>
<td></td>
<td>• LAEF, but not LA volume, is associated with HF hospitalization, cardiovascular and all-cause mortality, and AF independent of clinical predictors and NT-proBNP level in stable HF regardless of ejection fraction¹⁹</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrial; LAEF, left atrial emptying fraction; LV, left ventricular; NT-proBNP, N-terminal pro brain natriuretic peptide.

Heart failure is now recognized as a progressive disorder in which asymptomatic risk factors (Stage A) progresses to a pre-clinical stage of LV dysfunction (Stage B) and finally to the clinically manifest stage of asymptomatic HF (Stages C and D) (Table 1). While the role of LV functional changes in the staged progression of HF has been well described, the role of LA dysfunction has received relatively little attention. Increases in LA preload initially enhance LA contractility by the Frank-Starling mechanism; thus the relative contribution of LA pump function increases, whereas conduit function decreases, in the presence of abnormal LV relaxation such as in Stage B patients. As LV filling pressures further increase in Stage C HF, LA enlargement reaches the limits of LA preload reserve, and LA conduit function becomes predominant, as shown in the study by Pellicori et al. In all stages of HF, a reduction in LA function has been identified to be an independent predictor of adverse events, including death and HF (Table 1). Given that the risk associated with impaired LA function has been shown in several studies to be independent of, or incremental to, LV diastolic function or LA volume, it is likely that mechanisms beyond increased LA afterload (impaired LV diastolic function) or increased LA preload (LA dilatation) are involved. Combined myopathy affecting both the atrium and ventricle may be involved, as suggested by the correlation of abnormalities in LV systolic longitudinal function with that of impaired LA contractile function.⁵ Activation of the renin–angiotensin–aldosterone and adrenergic systems in HF, or a pro-inflammatory milieu particularly in HF with preserved ejection fraction (HFpEF), may be common triggers for myocardial fibrosis in both the atrium and ventricle. Abnormal distribution of gap junctions and loss of cell to cell coupling in areas of fibrosis may lead to loss of cellular connectivity in the left atrium, predisposing to atrial fibrillation,⁶ a condition in which all components of LA function (reservoir, conduit, and pump) are severely impaired.

While measures of LA function are clearly promising novel prognostic markers in HF, we have some way to go before LA function will be established as a key biomarker in HF. The sheer number of measures of LA function (>20) generates confusion and hinders comparability of published studies. The reproducibility of these measures may also be an issue that threatens the robustness of these
measures as biomarkers. Adequate age- and sex-specific normal reference values for LA functional measures must be defined for these measures to have utility in an individual patient. Finally, robust outcome data from large prospective clinical trials are needed to confirm the incremental predictive utility of LA function compared with other measures.

Importantly, LA structural remodelling is reversible with effective therapies,\textsuperscript{7–9} and longitudinal improvements in LA structure are associated with improved cardiovascular clinical outcomes,\textsuperscript{10} thus validating LA size as a useful biomarker for patient selection and a surrogate measure of outcomes in HF clinical trials. Several recent studies, including that of Pellicori et al., raise the possibility that LA function may be a better prognostic marker than LA structure in HF. While tantalizing, the ability of therapeutic interventions to reverse LA dysfunction, and the impact of such LA functional improvements on clinical outcomes, remain to be demonstrated. Novel prognostic imaging biomarkers are particularly needed in HFpEF trials, where improvement in LV ejection fraction, a commonly used surrogate measure in HF with reduced ejection fraction (HFrEF) trials, is not applicable. Whether LA function will surpass form as a prognostic biomarker and surrogate endpoint in HF is yet to be seen.

Figure 1 Changes in left atrial (LA) pressure (A) and volume (B) are shown over time. At mitral valve closure (MVC), blood flows from the pulmonary veins into the left atrium, producing an increase in volume accompanied by a pressure rise (V wave). After mitral valve opening (MVO), LA volume decreases associated with a fall in left atrial (LA) pressure. During left ventricular (LV) diastasis, LA volume remains relatively constant and LA pressure increases. With active LA contraction, LA volume decreases associated with a new pressure rise (a’ wave). The LA pressure–volume loop shows instantaneous changes in LA pressure and LA volume during one cardiac cycle. Arrows indicate the temporal sequence throughout the ‘figure of eight’ loop describing changes in LA pressure and volume during LA reservoir (solid), conduit (dotted), and pump (dashed) phases.
**Supplementary material**

Supplementary material is available at *European Heart Journal* online.

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**References**


