SYSTEMATIC REVIEW

The importance of integrated left atrial evaluation: From hypertension to heart failure with preserved ejection fraction

Matteo Beltrami¹,² | Alberto Palazzuoli³ | Luigi Padeletti⁴ | Elisabetta Cerbai⁵ | Stefano Coiro⁶ | Michele Emdin⁷,⁸ | Rossella Marcucci⁹ | Doralisa Morrone¹⁰ | Matteo Cameli¹¹ | Ketty Savino⁶ | Roberto Pedrinelli¹² | Giuseppe Ambrosio⁶ | on behalf of Società Italiana di Cardiologia, Sezione Regionale Tosco-Umbra

¹Cardio-Thoracic and Vascular Department, University of Florence, Florence, Italy
²Department of Medical Biotechnologies, University of Siena, Siena, Italy
³Department of Internal Medicine, Cardiovascular Diseases Unit, S. Maria alle Scottie Hospital, University of Siena, Siena, Italy
⁴IRCCS MultiMedica, Sesto San Giovanni, Milan, Italy
⁵Department of NeuroFarBa, C.I.M.M.B.A., University of Florence, Florence, Italy
⁶Division of Cardiology, University of Perugia School of Medicine, Perugia, Italy
⁷Division of Cardiology and Cardiovascular Medicine, Fondazione Toscana Gabriele Monasterio, Pisa, Italy
⁸Institute of Life Sciences, Scuola Superiore Sant’Anna, Pisa, Italy
⁹Department of Experimental and Clinical Medicine, Center for Atherothrombotic diseases, University of Florence, Florence, Italy
¹⁰Surgery, medicine, molecular and critical area Department-Cardiovascular disease Section 2, Pisa, Italy
¹¹Department of Cardiovascular Diseases, University of Siena, Siena, Italy
¹²Department of Surgery, Medical, Molecular, and Critical Area Pathology, University of Pisa, Pisa, Italy

Correspondence
Alberto Palazzuoli, Department of Internal Medicine, Cardiology Unit, Le Scotte Hospital, Siena Italy.
Email: palazzuoli2@unisi.it

Summary

Aim: Functional analysis and measurement of left atrium are an integral part of cardiac evaluation, and they represent a key element during non-invasive analysis of diastolic function in patients with hypertension (HT) and/or heart failure with preserved ejection fraction (HFpEF). However, diastolic dysfunction remains quite elusive regarding classification, and atrial size and function are two key factors for left ventricular (LV) filling evaluation. Chronic left atrial (LA) remodelling is the final step of chronic intracavitary pressure overload, and it accompanies increased neurohormonal, proarrhythmic and prothrombotic activities. In this systematic review, we aim to propose a multi-modality approach for LA geometry and function analysis, which integrates diastolic flow with LA characteristics and remodelling through application of both traditional and new diagnostic tools.

Methods: The most important studies published in the literature on LA size, function and diastolic dysfunction in patients with HFpEF, HT and/or atrial fibrillation (AF) are considered and discussed.

Results: In HFpEF and HT, pulsed and tissue Doppler assessments are useful tools to estimate LV filling pressure, atrio-ventricular coupling and LV relaxation but they need to be enriched with LA evaluation in terms of morphology and function. An integrated evaluation should be also applied to patients with a high arrhythmic risk, in whom eccentric LA remodelling and higher LA stiffness are associated with a greater AF risk.

Conclusion: Evaluation of LA size, volume, function and structure are mandatory in the management of patients with HT, HFpEF and AF. A multi-modality approach could provide additional information, identifying subjects with more severe LA remodelling. Left atrium assessment deserves an accurate study inside the cardiac imaging approach and optimised measurement with established cut-offs need to be better recognised through multicenter studies.
1 | INTRODUCTION

Left atrial (LA) activity consists of three components with respect to cardiac cycle: The first is the "reservoir" function, in which left atrium receives blood from pulmonary venous return; then a "conduit" phase ensues during early ventricular diastole after mitral valve opening, where blood passively flows into the left ventricle (LV); finally, during late diastole active contractile component takes place. This latter phase is called "booster pump." In patients with normal diastolic function, the three phases account for about 40%, 35%, and 25% of LV filling, respectively. Relaxation, stiffness and contractility of LA influence these three phases. The late phase plays an important role to increase ventricular volume, mostly in patients with LV dysfunction. Patients with atrial fibrillation (AF) lack the "booster pump" phase, and this leads to reduced late LV filling. LA function is coupled to LV compliance and they are strictly related each other. In healthy individuals, LA performance remains stable until the sixth decade, and then begins to decrease and leads to the initial phase of diastolic dysfunction. Diastolic dysfunction is due to both alterations of LA and LV properties in terms of ionic channels, cellular energy, neurohormonal expression and inflammatory response. Current dysfunction encompasses similar stressors such as, hypertension, diabetes, myocardial ischaemia and valvular disease. (Figure 2) Moreover, the diastolic filling impairment depends on the abnormal isovolumetric ventricular relaxation, the decrease of LV compliance, elevated end-diastolic ventricular filling pressure, LA and LV pressure intracavitary difference, and inadequate output of LV. Therefore, abnormal LV stiffness contributes to increased end-diastolic pressure during effort, and decreased stroke volume during atrial pacing. The aim of the review is to discuss a potential multi-modality approach for LA geometry and function in several clinical settings such as Hypertension (HT), Heart Failure with Preserved Ejection Fraction (HFrEF) and AF, through application of both traditional and new diagnostic tools.

2 | INTEGRATED IMAGING EVALUATION

2.1 | Multimodality approach in LA assessment

Multidisciplinary approach and imaging are helpful to better characterise LA anatomy, size, and function in terms of LA myocardial tissue, diastolic dysfunction and atrial remodelling. In practice, echocardiography still remains the most cost-effective tool to assess LA size and function. The LA volume index (LAVI) by 2D echocardiography may not always accurately estimate the severity of LA dilatation, especially in the enlarged left atrium, as the biplane methods using 2D echocardiography significantly underestimate LA volume when compared to Cardiac Magnetic Resonance (CMR) or Cardiac Computed Tomography (CCT). However, LA volumes assessed by 3D echocardiography display a better agreement with CMR imaging. The clinical value of LAVI-3D echocardiography is superior to LAVI-2D echocardiography, because LA volumes depend on the LA phase and various atrial events. In fact, 3D echocardiography has automated border detection, and it can permit the measurement of LAVI in the different phases of the cardiac cycle. Recently, Authors have provided reference values for LA volumes and function by 3D echocardiography from a group of healthy subjects with a wide age range. CMR is recognised as the gold standard technique to measure ventricular volumes and function; however, its specificity is extended also to left atrium through the use of the short-axis approach that is more reproducible than the biplane area-length method. The strength of CMR is its high spatial resolution and definite myocardial border identification throughout the cardiac cycle. CMR with late gadolinium enhancement (LGE) and feature-tracking are the most important tools to achieve non-invasive quantification of LA anatomy, function, fibrosis and tissue characterisation. Therefore, CMR has been proposed as the reference method to measure atrial volumes. (Figure 3) Increased LGE positivity of LA is associated with decreased LA reservoir, conduit and booster pump functions. In fact, CMR with LGE is the gold standard technique to assess the extent of LA fibrosis. Chronically elevated LA volumes and decreased LA emptying fractions lead to structural changes in the left atrium; the progression of LA remodelling is independently associated with the incidence of AF in asymptomatic subjects. Recent studies have demonstrated the utility of CMR LGE to detect abnormal atrial tissue before catheter ablation: LA myocardium with increased LGE signal has lower local conduction velocity, and the identification of such regions may facilitate targeting of the substrate for re-entrant arrhythmias. In recent years, CCT has emerged as a new technique to evaluate LA anatomy. It is the preferred tool to assess pulmonary vein anatomy, and it provides a real anatomical roadmap of left atrium before and
after ablation of AF.\textsuperscript{21,22} LA dilatation and remodelling, evaluated by CCT, are associated with AF recurrence and poorer long-term outcome.\textsuperscript{23} CCT imaging of left atrium is also useful to identify the risk of cardiovascular diseases in general populations, such as those at risk of AF, stroke and heart failure (HF) progression.

### 2.2 Dynamic measurement of LA volume and diastolic function

Currently, LAVI is the gold standard method to measure LA size.\textsuperscript{24} It demonstrates a higher powerful prognostic value over LA area or antero-posterior diameter. Increased LAVI is an expression of duration and severity of increased LA pressure caused by LV diastolic dysfunction, and it is a predictor of mortality in patients with HF.\textsuperscript{25} Biplane Simpson’s method and biplane area length by four and two-chamber views are both validated tools to measure LA volume.\textsuperscript{26} However, LAVI measured by 2D echo apical views is superior to 4-chamber area to predict AF, congestive HF, neurological disorders, acute myocardial infarction and cardiovascular death.\textsuperscript{27} Minimum left atrial volume (LAV\textsubscript{min}) measured by real-time 3D echocardiography is better correlated to LV diastolic function and LV filling pressure (E’/E) than maximum left atrial volume (LAV\textsubscript{max}). LV longitudinal systolic function impacts the LA reservoir function and could be the reason for the weaker relation between LAV\textsubscript{max} and LV diastolic function. For these reasons, LA volume at end-diastole may be a better marker of diastolic dysfunction and LA remodelling than LAV\textsubscript{max}.\textsuperscript{28} Moreover, 3D echocardiography is a useful tool to measure LA stroke volume (LAV\textsubscript{max}−LAV\textsubscript{min}) and LA ejection fraction (LA stroke volume/maximum LA volume × 100) and correlates well with parameters of LV diastolic function (transmitral flow pattern and E/E’). The evaluation of LA function by LA stroke volume and LA ejection fraction represents a viable alternative method for the accurate assessment of LV diastolic function.\textsuperscript{29}

The ratio between pulsed Doppler transmural flow velocity during early diastole velocity (E wave) and late diastole velocity (A wave) (E/A), the deceleration time (DT) of E, and the isovolumetric relaxation time (IVRT), do not represent direct measurements of LV relaxation, filling pressure and stiffness; only 57% of patients with impaired diastolic function have been identified by E/A ratio determination.\textsuperscript{30,31} Tissue Doppler Imaging (TDI) of LV remains mandatory with analysis of three major deflections: peak ventricular systolic velocity (S’), peak early ventricular diastolic velocity (E’), and during atrial contraction (A’). All these parameters correlate with LA ejection fraction, LA ejection force and LA kinetic energy in patients with LV diastolic dysfunction.\textsuperscript{32} TDI measurements should be obtained during end-expiration with an average of three sinus beats. E/E’ plays a pivotal role in echocardiographic diagnosis of Heart Failure with Preserved Ejection Fraction (HFrEF), as it gives greater diagnostic accuracy and it is one of the most
important non-invasive parameters for estimation of LV filling pressure.\textsuperscript{23} Echocardiographic parameters including lateral E/E’, LAVI, and the difference between the duration of reversed pulmonary vein atrial systolic flow and the duration of mitral A wave flow>30 ms (Ard-Ad) have the greatest value in diastolic dysfunction assessment. A strategy that includes these three parameters is simple to use in clinical practice and gives a greater diagnostic value than evaluation of left ventricular hypertrophy (LVH), concentric geometry, and NT-proBNP.\textsuperscript{34}

LA work is assessed by echocardiography through the calculation of LA kinetic energy (LAKE) from the formula: \(0.5 \times m \times A(2)\) where \(m\) is LA stroke volume \(\times\) blood density, and \(A\) is transmitral Doppler peak atrial velocity. The increase of LA work depends on LVH and diastolic dysfunction. LAKE is five times higher in patients with chronic HF (CHF) than in healthy controls. It depends on LV performance and renal function, and it is a strong predictor of cardiovascular events and hospitalisation for HF.\textsuperscript{35} Independently of HF aetiology, diastolic dysfunction is the strongest stimulus to increase LA size and work.

3 | ATRIAL REMODELLING IN HYPERTENSION

Hypertensive heart disease leads to atrial enlargement and diastolic dysfunction, and the progressive increase of LA size occurs with the degree of LV diastolic dysfunction.\textsuperscript{25} LV volume and geometry are significantly associated with LA dimensions, and patients with LV hypertrophy (LVH) show a more advanced diastolic dysfunction according to mitral valve regurgitation. Moreover, LV mass is a predictor of LA volume, impaired LV relaxation and compliance, which initially leads to improvement of LA contractility to maintain normal LV filling. The consequent change of LA shape leads to diastolic dysfunction. HFpEF patients share many abnormalities of systolic, diastolic and vascular functions with non-failing LVH patients, but display accentuated LVH and LA dilation/failure. LAV\textsubscript{max}, measurement by 2D echocardiography may help to clarify pathophysiology and better define HFpEF population from patients with LVH without HF. Higher LA volume, increased LV mass, E/E’ and IVRT differed between HFpEF and LVH.

About 30% of patients with HT actually show “white-coat hypertension”, and the impact on total and cardiovascular morbidity and mortality has not been established yet in this subgroup. Interestingly, authors demonstrate the association between white coat hypertension and LA phasic function assessed by the volumetric and speckle-tracking method. White coat hypertension interacts with LA phasic function and stiffness, and all patients with a clinic rise in systolic blood pressure show a functional and mechanical LA remodelling independent of hypertension type.\textsuperscript{37} LA function has been shown to be a predictor of adverse cardiovascular outcome, both in the general population and in patients with HT. For this reason, we need an imaging tool to highlight subtle LA dysfunction in the early stages of HT. In this context, strain and strain-rate regional myocardial deformation may be a new technique to assess phasic atrial functions in patients with HT. Mild HT leads to LA conduit volume abnormality, although LA volume remains unchanged.\textsuperscript{38} Moreover, asymptomatic hypertensive patients have altered LA strain despite normal LA size, that reflect preclinical LA myocardial dysfunction. LA functional index and peak atrial longitudinal strain are very sensitive parameters to assess LA function and potent predictors of LV diastolic dysfunction in hypertensive patients. Furthermore, LA strain parameters show their usefulness to unmask apparently normotensive patients with hypertensive response to exercise.\textsuperscript{39} Identification of early signs of hypertensive heart disease is the goal to prevent the progression of the disease. In grade 2 to grade 3 hypertension, LA size is significantly larger in patients with metabolic syndrome than those without. Tadic et al investigated the relationship between blood pressure (BP) variability and LA phasic function by volumetric and speckle-tracking method in normal-weight, overweight and, obese hypertensive patients. BP variability parameters were associated with LA remodeling in the whole study population. LA reservoir function and LA pump function are related to BP variability indices, obesity significantly impacts BP variability and LA phasic function in untreated hypertensive subjects.\textsuperscript{40} These results highlight the importance of early recognition of LA impairment that could identify patients with HT at risk of developing HF.\textsuperscript{41} Mordi et al demonstrate that echocardiography by speckle tracking and CMR are able to independently discriminate between hypertensive heart disease and HFpEF. Extracellular volume measured by CMR is an excellent discriminator between HFpEF and hypertension and could be used as a surrogate endpoint for therapeutic studies.\textsuperscript{42} Speckle tracking and CMR are also able to identify patients with prognostically significant reduction of exercise capacity.

3D echocardiography identifies early structural and functional LA changes better than conventional 2D echocardiography. Atrial volume analysis using 3D echocardiography may recognise earlier the target organ damage, which is an essential determinant of cardiovascular mortality and morbidity in patients with systemic HT. Patients with more advanced stages of retinal alterations show larger LA maximal volume, LA minimal volume, preatrial contraction volume, LA total
stroke volume and LA active stroke volume. CMR shows its utility also in patients with hypertension; arterial stiffness, assessed by pulse wave velocity in the thoracic aorta by velocity-encoded imaging, correlates with left atrial enlargement in hypertensive patients. CMR can accurately measure both LA volume and arterial stiffness, and this relation reflects the systemic arterial stiffness. Unfortunately, most of the above methods are currently confined to research settings and not extensively applied. The integrated evaluation of all these tools could achieve a more comprehensive risk assessment in hypertensive patients: more specifically dynamic evaluation with new echo techniques appear to become indicators of supraventricular arrhythmic burden, whereas volume measurement by CMR and 3D seem to be more related to HF occurrence and embolic events. In the future, a detailed comparison of several methods in specific population should clarify the best indicator with most accurate clinical value.

4 | LEFT ATRIAL DYSFUNCTION IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

4.1 | HFpEF diagnosis

The actual prevalence of HFpEF remains underestimated due to the absence of a universally accepted definition of the disease. HFpEF has a different pathophysiological mechanism and phenotype with several underlying conditions; such as hypertension, diabetes, metabolic syndrome and renal dysfunction. All these conditions lead to cardiac and vascular collagen deposition, myocardial fibrosis and hypertrophy, inflammatory activation, endothelial dysfunction with increased oxidative stress. In this context, additional parameters for both diagnostic and prognostic assessment may facilitate HF diagnosis, identifying the pathophysiological process responsible for the disease as well as its prognostic assessment. The transition from asymptomatic diastolic dysfunction to HF occurrence needs to be deeply investigated in order to recognize specific subset of patients with higher risk for HF development. Overall, patients with HFpEF display an LV ejection fraction (EF) within the normal range, although LA systolic function and pressure are both altered. Change in LA size and function may represent an expression of pathophysiological mechanisms of HFpEF. Patients may show a prolonged exercise tolerance. Moreover, LA size could be a marker of the hemo-dynamic severity of HF. Patients hospitalised with HFpEF have an average left atrial pressure (Lap) >24 mm Hg; conversely, only <5% of stable patients with less advanced HF class show those pressure values. Patients with Lap >24 mm Hg display a higher risk of HF decompensation and pulmonary oedema. Patients with HFpEF have impaired LA reservoir, conduit and pump function. CMR feature-tracking based on atrial performance analysis quantifies LA longitudinal strain and discriminates patients with impaired LV relaxation. Von Roeder et al demonstrated that the abnormal LA conduit function is a distinct feature of HFpEF, independent of LV stiffness and relaxation. Authors applied a CMR-derived feature tracking to measure LA strain and strain rate: by current analysis, it appears that LA function is a load-independent marker of LV stiffness and load-dependent marker of LV relaxation. This analysis displays that conduit function is not significantly related to LV stiffness and relaxation, arguing that LA conduit function reflects intrinsic LA pathology, not completely explained by ventricular pathology. Although the LA endocardial border is better delineated by CMR imaging compared with echocardiography, its lower temporal resolution could affect the accuracy of strain measures. Yet, the results of the study showed a high correlation between LA conduit strain and peak oxygen consumption; calculation of LA strain by CMR feature-tracking is a new emerging technique for left atrium evaluation in HFpEF.

Key points

- Left atrium play an integral role in cardiac performance. An integral evaluation of LA size, volume, function and structure are mandatory in the management of patients with HT, HFpEF and AF.
- LA dysfunction is linked to the severity of LV diastolic dysfunction and LA fibrosis. In HFpEF, LAVI and LA function are associated with more advanced symptomatic status as well as worse prognosis.
- Assessment of LA geometry and function can be performed with different imaging techniques; each imaging tool provides additional information particularly in subjects with more severe LA remodelling.

Left atrial (LA), Left ventricle (LV), atrial fibrillation (AF), Heart Failure and preserved ejection fraction (HFpEF), Hypertension (HT, Left atrial volume index (LAVI)).

4.2 | LA assessment in HFpEF and AF

During the course of HFpEF the majority of patients experience AF. The natural history of HFpEF is characterised by an increase in LV relaxation time, myocardial stress and mass. The altered diastolic filling, together with reduced elastic force, are backward transmitted to left atrium with consequent increase in the chamber pressure and volume. All these processes cause impaired LA reservoir, conduit and booster pump function, thus increasing the risk of AF development. Patients with LA dilation have an increased risk of stroke and death, but also patients with isolated LA dysfunction, even though still having normal LA size, show a higher risk for cardiovascular events. AF identifies a HFpEF cohort with more advanced disease and significantly reduced exercise capacity. AF is an indicator of poor prognosis and it has a more significant impact in patients with HFpEF than Heart Failure and Reduced Ejection
Fraction (HFpEF). For these reasons, it is recommended to evaluate several echocardiographic indexes of diastolic dysfunction to estimate the risk of AF development among patients with HFpEF. In particular, the risk of AF decreases with increasing peak A wave velocities and it is not substantially altered when peak A wave velocity is further adjusted for LAVI. Currently, diastolic parameters of LA function seem to be a more reliable marker of AF risk than LA dilation in HFpEF.

**Key points**
- Two thirds of HFpEF patients experienced AF at some point during natural history of the disease and it represent an indicator of poor prognosis.
- Eccentric LA remodelling and higher LA stiffness contribute to greater AF risk in HFpEF.
- LA enlargement and function abnormalities are linked with atrial remodelling and consequent initiation or maintenance of AF.
- Left atrial (LA), atrial fibrillation (AF), Heart Failure and preserved ejection fraction (HFpEF)

### 4.3 | Outcome

Increased LV mass, LA size and LA EF are associated with an increased risk of adverse outcome. Detecting LA remodelling due to diastolic dysfunction may be helpful to make the diagnosis and give prognostic information in patients with HFpEF, independently of potential clinical factors. LA function is associated with pulmonary vascular disease and right HF in both HFpEF and HFrEF, but it is more closely associated with outcome in HFpEF. HFrEF patients have larger LA volumes, whereas HFpEF patients have higher LA peak pressures, LA stiffness and wall stress variations and lower LA minimal pressures. In patients with HFpEF, lower systolic LA strain is associated with higher prevalence of HF hospitalisation and history of AF. Santos et al in a large trial of patients with HFpEF confirmed that systolic LA strain is decreased independently of LA size or history of AF and is associated with higher prevalence of HF hospitalisation as well as worse LV systolic function and LA remodelling. Atrial diastolic wall strain index is a marker of progressive impairment of diastolic filling, and it is associated with worse outcomes. Finally, Kaneko et al demonstrated that cardiopulmonary exercise testing and LA dilatation are associated with hospital readmission for HF, highlighting the importance of LA remodelling in acute decompensation of chronic HFpEF patients. For all these reasons, LA size and function are now considered a potential therapeutic target and an end-point to reduce morbidity and mortality in patients with HFpEF.

### 5 | INTEGRATED IMAGING EVALUATION FOR DECISION MAKING

LV diastolic dysfunction is the key of pathophysiological mechanism in patients with HFpEF, and therefore its assessment plays an important role in diagnosis. In clinical practice, the diagnosis of HFpEF, especially in elderly patient with comorbidities and no clear signs of fluid overload, is challenging. The specificity of the diagnosis of HFpEF can be improved by the evaluation of diastolic dysfunction at rest and during exercise. Additionally, cardiovascular risk conditions including systemic hypertension, diabetes, BMI > 25, cause LA enlargement and increase the risk of developing HF and/or AF. Early diagnosis and optimal management of these conditions by clinical evaluation and imaging studies may delay and sometimes reverse LA remodelling with reduced rate of AF development or recurrence. LA size and function represent a morphologic and pathophysiological dynamic marker of cardiovascular disease status useful to estimate structural and functional remodelling. Several factors, including genetic predisposition and metabolic, electrical, mechanical stressors are the leading cause of atrial remodelling. Diastolic dysfunction with increased LV end-diastolic pressure and decreased LV relaxation result in pressure and volume overload of the left atrium. LA remodelling is assessed in clinical practice using various noninvasive imaging modalities. Nevertheless, a careful specific monitoring of LA remodelling has not been included into clinical decision-making and disease management. Moreover, a combination of structural and functional remodelling may add prominent information in monitoring diseases stage. Currently, 2D echocardiography is the first imaging technique to use for the diagnosis of diastolic dysfunction and to demonstrate structural abnormalities of the heart, even though 2D echocardiography alone is not accurate enough to assess diastolic dysfunction, particularly in patients with AF. The diagnosis of HFpEF in patients with AF is often less clear. LAVI is increased in patients with HFpEF and AF, but the evaluation of diastolic dysfunction is less well established in these patients with the need of new cut-off and new parameters to assess diastolic impairment. However, a first line echocardiographic examination evaluating all relevant two-dimensional and Doppler data is recommended. LAVI > 34 mL/m² LV mass index ≥ 115 g/m² for males and ≥ 95 g/m² for females, E/E’ ≥ 13, the mean of E’ of septal and lateral wall<9 cm/s and the tricuspid regurgitation velocity are the major diagnostic points of HFpEF. Moreover, in HFpEF a diastolic stress test by echocardiography could be indicated in case of uncertainty, to evaluate LV filling pressure and pulmonary artery pressure during effort. Recently, speckle-tracking echocardiography has been used to evaluate regional and global LA function. Atrial strain is studied in multiple cardiovascular disorders including hypertension, diabetes, HF and AF. Increased LA volume and impaired LA function by strain analysis are associated with AF progression. LA indexed volume > 34 ml/m² and LA strain ≤ 30.9% is an independent predictor to develop persistent AF in patients with paroxysmal AF. LA strain could be also useful to facilitate stroke risk calculation and to estimate prognostic information in patients with AF. Finally, CMR and CCT provide accurate anatomical data of pulmonary veins prior to the isolation of pulmonary veins for AF electrical treatment. Moreover, LA fibrosis assessed with CCT or CMR, quantified by electrical mapping, can be used to characterise indirectly the extent of electrical remodelling of patients who would benefit from ablation for AF (Figure 4).
5.1 | The weakness of different imaging techniques in left atrial assessment

Several cardiac imaging modalities are able to visualise the left atrium and both structural and functional properties of this cardiac chamber. However, each technique displays some limitations: The most important disadvantage of 2D echocardiography is poor acoustic window, mostly in obese patients due to the presence of attenuated signal over the longer distance. In patients with chronic obstructive pulmonary disease, the lungs may expand with air trapping and chest window impairment. With lung disease (also in pneumothorax), the heart could be pushed towards the diaphragm, so sometimes parasternal view or subcostal window can be the only place where you have an acceptable acoustic window. Moreover, the major limitation of 2D echocardiography is the two-dimensional view, instead of 3D echocardiography does not require any geometric assumption and it seems to be more precise for measuring LA volume in patients with optimal acoustic window.\textsuperscript{74} CMR has some important limitations, such as high cost, limited availability and long timing scan: it also contraindicated in patients with pacemakers or other devices. These concerns are due to the potential magnetic field induced cardiac lead heating and eventually the myocardial thermal injury and alterations of pacing properties. Recently an important publication demonstrates that in subjects with last generation devices these problems do not occur using 1.5 tesla MRI.\textsuperscript{77} Finally, CCT show some limitations linked to radiation exposure and the need of contrast, which limits its wide utilisation mostly in patients with renal insufficiency.

5.2 | LA function in AF

During echocardiographic assessment of HFpEF patients, AF represents the major limitation to evaluate LV filling pressure by current Doppler and TDI analyses. The lack of a rhythmic timing course, together with R-R interval discordance, leads to a different haemodynamic profile for each cardiac cycle. Time interval measurements are performed from different cardiac cycles, and high variability of E wave represents the major limitation of LV filling pressure assessment. These concerns are the major limitation of LA function assessment during AF, particularly in those subtypes with elevated high rate response. Patients with AF have lost the “booster pump” phase; hence A wave
and its derivate measurement cannot be assessed. Indeed, such an approach is not completely able to define the precise diastolic dysfunction and atrial contribution in these patients. In particular, it appears hard to distinguish whether atrial enlargement is the "chicken or the egg". Atrial remodelling could be due to increased LV filling pressure or it could be a primary defect, independent of haemodynamic alteration. Flow analysis by Doppler images remains the only method to assess LA contribution, in patients with AF and lower heart rate an average of E wave of 5 continuous beats could be a surrogate measurement of E/E’ ratio, but it still remains inaccurate. However, diastolic parameters such as DT<150 ms, IVRT<65 ms, velocity deceleration time on pulmonary venous flow<150 ms, and the ratio of mitral E to colour M-Mode flow propagation velocity>1.4 can be used to evaluate LV filling pressure in patients with AF. Overall, the LA functional analyses in the most common arrhythmias disease, such as AF, remain an unmet need to characterise and identify patients with elevated LV pressure.

5.3 | The organisation of health care resources

Given the high proportion of older people being hospitalised due to HF with substantial associated diseases, concomitant cognitive, mood and functional disorders, it seems to be important to perform a comprehensive assessment in such HF patients. In this light, we feel that many readmissions are preventable through organised care programmes (ie, ambulatory visit after hospital discharge) with the aim to prevent re-hospitalisations. Moreover, detecting an early LA remodelling due to diastolic dysfunction may be helpful to anticipate the diagnosis and give prognostic information in asymptomatic patients with HFP EF. In the same way, the assessment of diastolic function by echocardiography in patients with hypertension could identify patients at increased risk of developing HF and/or AF and subsequent hospitalisation.

6 | CONCLUSIONS

The left atrium plays an integral role in cardiac performance. Evaluation of LA size, volume, function and structure are mandatory in the management of patients with HT, HFP EF and AF. LA dysfunction is linked to the severity of LV diastolic dysfunction and LA chamber pressure. Moreover, in the HFP EF setting, increased LAVI and LA dysfunction are associated with a more advanced symptomatic status as well as worse prognosis. Therefore, assessment of LA size, shape and function, could be performed with different imaging techniques, and may be the key to prognostic stratification of such patients. A multi-modality approach could provide additional information, identifying subjects with more severe LA remodelling. An integrated evaluation should be also applied to patients with a high arrhythmic risk, in whom eccentric LA remodelling and higher LA stiffness are associated with a greater AF risk. For these reasons, left atrium assessment deserves an accurate study inside the cardiac imaging approach and optimised measurement with established cut-offs need to be better recognised through multicenter studies. A universal multimodality evaluation could identify patients with a real impairment of atrio-ventricular pressure with increased arrhythmic and HF risk.

ACKNOWLEDGEMENTS

We thank all the members of Società Italiana di Cardiologia, Sezione Regionale Tosco-Umbra.

DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTIONS

MB, AP, GA and LP contributed to the concept/design, drafting, critical revisions and the approval of the article; while EC, SC, ME, RM, DM, MC, KS, and RP performed critical revisions of the article.

ORCID

Matteo Beltrami https://orcid.org/0000-0001-7161-3224
Alberto Palazzuoli https://orcid.org/0000-0002-6235-984X
Ketty Savino https://orcid.org/0000-0003-3494-0298

REFERENCES

1. Prioli A, Marino P, Lanzoni L, et al. Increasing degrees of left ventricular filling impairment modulate left atrial function in humans. Am J Cardiol. 1998;82:756-761.
2. Kagawa K, Arakawa M, Miwa H, et al. Left atrial function during left ventricular diastole evaluated by left atrial angiography and left ventriculography. J Cardiol. 1994;24:317-325.
3. Thomas L, Levet K, Boyd A, et al. Compensatory changes in atrial volumes with normal aging: Is atrial enlargement inevitable? J Am Coll Cardiol. 2002;40:1630-1635.
4. Gerstenblith G, Frederiksen J, Yin FC, et al. Echocardiographic assessment of a normal adult aging population. Circulation. 1977;56:273-278.
5. Yoshida N, Okamoto M, Makita Y, et al. Determinants of enhanced left atrial active emptying with aging: Left atrial preload, contractility or both? Intern Med. 2009;48:987-992.
6. Casaclang-Verzosa G, Gersh BJ, et al. Structural and functional remodeling of the left atrium: Clinical and therapeutic implications for atrial fibrillation. J Am Coll Cardiol. 2008;51:1-11.
7. Westermann D, Kasner M, Steendijk P, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. Circulation. 2008;117:2051-2060.
8. Hoit BD. Left atrial size and function: Role in prognosis. Am Coll Cardiol. 2014;63:493-505.
9. Vassiliou VS, Patel HC, Rosen SD, et al. Left atrial dilatation in patients with heart failure and preserved ejection fraction: Insights from cardiovascular magnetic resonance. Int J Cardiol. 2016;210:158-160.
10. Maceira AM, Cosin-Sale J, Roughton M, et al. Reference left atrial dimensions and volumes by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2010;12:65.
11. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update
from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16:233-270.

12. Poutanen T, Ikonen A, Vainio P, et al. Left atrial volume assessed by transthoracic three dimensional echocardiography and magnetic resonance imaging: Dynamic changes during the heart cycle in children. Heart. 2000;83:537-542.

13. Badano LP, Miglioranza MH, Mihăilă S, et al. Left atrial volumes and function by three-dimensional echocardiography: Reference values, accuracy, reproducibility, and comparison with two-dimensional echocardiographic measurements. Circ Cardiovasc Imaging 2016;9:https://doi.org/10.1161/CIRCIMAGING.115.004229

14. Hudsmith LE, Cheng AS, Tyler DJ, et al. Assessment of left atrial volumes at 1.5 tesla and 3 tesla using FLASH and SSFP cine imaging. J Cardiovasc Magn Reson. 2007;9:673-679.

15. Appelbaum E, Manning WJ. Left atrial fibrosis by late gadolinium enhancement cardiovascular magnetic resonance: Prediscrecurrence of atrial fibrillation after pulmonary vein isolation: Do you see what I see? Circ Arrhythm Electrophysiol. 2014;7:2-4.

16. Caudron J, Fares J, Bauer F, et al. Evaluation of left ventricular diastolic function with cardiac MR imaging. Radiographics. 2011;31:239-259.

17. Habibi M, Samiei S, Ambale Venkatesh B, et al. Cardiac magnetic resonance-measured left atrial volume and function and incident atrial fibrillation: Results from mesa (multi-ethnic study of atherosclerosis). Circ Cardiovasc Imaging. 2016;9:https://doi.org/10.1161/CIRCIMAGING.115.004299

18. Fukumoto K, Habibi M, Ipek EG, et al. Association of left atrial local conduction velocity with late gadolinium enhancement on cardiac magnetic resonance in patients with atrial fibrillation. Circ Arhythm Electrophysiol. 2016;9:e002897.

19. Oakes RS, Badger TJ, Kholmovski EG, et al. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. Circulation. 2009;119:1758-1767.

20. McGann C, Akoum N, Patel A, et al. Atrial fibrillation ablation outcome is predicted by left atrial remodeling on MRI. Circ Arhythm Electrophysiol. 2014;7:23-30.

21. To AC, Flamm SD, Marwick TH, et al. Clinical utility of multimodality LA imaging: Assessment of size, function, and structure. JACC Cardiovasc Imaging. 2011;4:788-798.

22. Shah A, Hocini M, Haissaguerre M, et al. Non-invasive mapping of cardiac arrhythmias. Curr Cardiol Rep. 2015;17:60.

23. Nédjos S, Kosiuk J, Koutalas E, et al. Comparison of left atrial dimensions in CT and echocardiography as predictors of long-term success after catheter ablation of atrial fibrillation. J Interv Card Electrophysiol. 2015;43:237-244.

24. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr. 2009;10:165-193.

25. Tamura H, Watanabe T, Nishiyama S, et al. Increased left atrial volume index predicts a poor prognosis in patients with heart failure. J Card Fail. 2011;17:210-216.

26. Thomas L, Levett K, Boyd A, et al. Compensatory changes in atrial volumes with normal aging: Is atrial enlargement inevitable? J Am Coll Cardiol. 2002;64:160-1635.

27. Tsang TS, Abbaharadish WP, Barnes ME, et al. Prediction of cardiovascular outcomes with left atrial size: Is volume superior to area or diameter? J Am Coll Cardiol. 2006;47:1018-1023.

28. Russo C, Jin Z, Homma S, et al. Left atrial minimum volume and reservoir function as correlates of left ventricular diastolic function: Impact of left ventricular systolic function. Heart. 2012;98:813-820.

29. Murata M, Iwanaga S, Tamura Y, et al. A real-time three-dimensional echocardiographic quantitative analysis of left atrial function in left ventricular diastolic dysfunction. Am J Cardiol. 2008;102:1097-1102.

30. Kasner M, Westermann D, Steendijk P, et al. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: A comparative Doppler-conductance catheterization study. Circulation. 2007;116:637-647.

31. Lubien E, DeMaria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: Comparison with Doppler velocity recordings. Circulation. 2002;105:595-601.

32. Blume GG, McLeod CJ, Barnes ME, et al. Left atrial function: Physiology, assessment, and clinical implications. Eur J Echocardiogr. 2011;12:421-430.

33. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation. 2000;102:1788-1794.

34. Shuai XX, Chen YY, Lu YX, et al. Diagnosis of heart failure with preserved ejection fraction: Which parameters and diagnostic strategies are more valuable? Eur J Heart Fail. 2011;13:737-745.

35. Mazzone C, Cioffi G, Faganello G, et al. Left atrial work in patients with stable chronic heart failure: Factors associated and prognostic role. Echocardiography. 2014;31:123-132.

36. Matsuda M, Matsuda Y. Mechanism of left atrial enlargement related to ventricular diastolic impairment in hypertension. Clin Cardiol. 1996;19:954-959.

37. Tadic M, Cuspidi C, Piccini P, et al. The influence of white-coat hypertension on left atrial phasic function. Blood Press. 2017;26:102-108.

38. Eshoo S, Boyd AC, Ross DL, et al. Strain rate evaluation of phasic atrial function in hypertension. Heart. 2009;95:1184-1191.

39. Aung SM, Güler A, Güler Y, et al. Two-dimensional speckle-tracking echocardiography-based left atrial strain parameters predict masked hypertension in patients with hypertensive response to exercise. Blood Press Monit. 2017;22:27-33.

40. Tadic M, Cuspidi C, Ilic I, et al. The relationship between blood pressure variability, obesity and left atrial phasic function in hypertensive population. Int J Cardiovasc Imaging. 2016;32:603-612.

41. Su G, Cao H, Xu S, et al. Left atrial enlargement in the early stage of hypertensive heart disease: A common but ignored condition. J Clin Hypertens (Greenwich). 2014;16:192-197.

42. Mordi IR, Singh S, Rudd A, et al. Comprehensive echocardiographic and cardiac magnetic resonance evaluation differentiates among heart failure with preserved ejection fraction patients, hypertensive patients, and healthy control subjects. JACC Cardiovasc Imaging. 2017;https://doi.org/10.1016/j.jcmg.2017.05.022

43. Kanar B, Kanar HS, Karataş A, et al. Relationship between left atrium and hypertensive retinopathy in patients with systemic hypertension: A real-time three-dimensional echocardiography-based study. Eur Heart J Cardiovasc Imaging. 2016;11:17.

44. Janvanishtaporn S, Boonyasirinant T. Correlation between aortic stiffness and left atrial volume index in hypertensive patients. Clin Exp Hypertens. 2016;38:160-165.

45. Chioncel O, Lainscak M, Seferovic PM, et al. Epidemiology and one year outcomes in patients with chronic heart failure and preserved ejection fraction: Which parameters and diagnostic strategies are more valuable? Eur J Heart Fail. 2017;https://doi.org/10.1002/ejhf.813.

46. González A, López B, Querejeta R, et al. Filling pressures and collagen metabolism in hypertensive patients with heart failure and normal ejection fraction. Hypertension. 2010;55:1418-1424.

47. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: Pathophysiology, diagnosis, and treatment. Eur Heart J. 2011;32:670-679.

48. Lim TK, Ashrafian H, Dwivedi G, et al. Increased left atrial volume index is an independent predictor of raised serum natriuretic peptide in patients with suspected heart failure but normal left ventricular...
ejection fraction: Implication for diagnosis of diastolic heart failure. *Eur J Heart Fail*. 2006;8:38-45.

49. Crawley SF, Johnson MK, Dargie HJ, et al. LA volume by CMR distinguishes idiopathic from pulmonary hypertension due to HFrEF. *JACC Cardiovasc Imaging*. 2013;6:1120-1121.

50. Rossi A, Gheorghiade M, Triposkiadis F, et al. Left atrium in heart failure with preserved ejection fraction: Structure, function, and significance. *Circ Heart Fail*. 2014;7:1042-1049.

51. Kurt M, Wang J, Torre-Amione G, et al. Left atrial function in diastolic heart failure. *Circ Cardiovasc Imaging*. 2009;2:10-15.

52. Kowallick JT, Kutty S, Edelmann F, et al. Quantification of left atrial strain and strain rate using cardiovascular magnetic resonance myocardial feature tracking: A feasibility study. *J Cardiovasc Magn Reson*. 2014;12:60.

53. Van Roeder M, Rommel KP, Kowallick JT, et al. Influence of left atrial function on exercise capacity and left ventricular function in patients with heart failure and preserved ejection fraction. *Circ Cardiovasc Imaging*. 2017;10:https://doi.org/10.1161/CIRCIMAGING.116.005467

54. Freed BH, Shah SJ. Stepping out of the left ventricle’s shadow: Time to focus on the left atrium in heart failure with preserved ejection fraction. *Circ Cardiovasc Imaging*. 2017;10:https://doi.org/10.1161/CIRCIMAGING.117.006267

55. Conen D, Glynn RJ, Sandhu RK, et al. Risk factors for incident atrial fibrillation with and without left atrial enlargement in women. *Int J Cardiol*. 2013;168:1894-1899.

56. Abhayaratna WP, Fatema K, Barnes ME, et al. Left atrial reservoir function as a potent marker for first atrial fibrillation or flutter in persons > or = 65 years of age. *Am J Cardiol*. 2008;101:1626-1629.

57. Hirose T, Kawasaki M, Tanaka R, et al. Left atrial function assessed by speckle tracking echocardiography as a predictor of new-onset non-valvular atrial fibrillation: Results from a prospective study in 580 adults. *Eur Heart J Cardiovasc Imaging*. 2012;13:243-250.

58. Zakeri R, Borlaug BA, McNulty SE, et al. Impact of atrial fibrillation on exercise capacity in heart failure with preserved ejection fraction: A RELAX trial ancillary study. *Circ Heart Fail*. 2014;7:123-130.

59. Cheng M, Lu X, Huang J, et al. The prognostic significance of atrial fibrillation in heart failure with a preserved and reduced left ventricular function: Insights from a meta-analysis. *Eur J Heart Fail*. 2014;16:1317-1322.

60. O’Neal WT, Sandesara P, Patel N, et al. Echocardiographic predictors of atrial fibrillation in patients with heart failure with preserved ejection fraction. *Eur J Heart Cardiovasc Imaging*. 2017; https://doi.org/10.1093/ehjci/jex038.

61. Pellicori P, Zhang J, Lukaschuk E, et al. Left atrial function measured by cardiac magnetic resonance imaging in patients with heart failure: Clinical associations and prognostic value. *Eur Heart J*. 2015;36:733-742.

62. Santos AB, Rocca GQ, Claggett B, et al. Prognostic relevance of left atrial dysfunction in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2016;9:e002763.

63. Melenovsky V, Hwang SJ, Redfield MM, et al. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail*. 2015;8:295-303.

64. Santos AB, Kraigher-Krainer E, Gupta DK, et al. Impaired left atrial function in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2014;16:1096-1103.

65. Ohtani T, Mohammed SF, Yamamoto K, et al. Diastolic stiffness as assessed by diastolic wall strain is associated with adverse remodelling and poor outcomes in heart failure with preserved ejection fraction. *Eur J Heart J*. 2012;33:1742-1749.

66. Kaneko H, Koike A, Senoo K, et al. Role of cardiopulmonary dysfunction and left atrial remodeling in development of acute decompensated heart failure in chronic heart failure with preserved left ventricular ejection fraction. *J Cardiol*. 2012;59:359-365.

67. Zile MR, Gottsdiener JS, Hetzel SJ, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation*. 2011;124:2491-2501.

68. Reant P, Lafitte S, Jais P, et al. Reverse remodeling of the left cardiac chambers after catheter ablation after 1 year in a series of patients with isolated atrial fibrillation. *Circulation*. 2005;112:2896-2903.

69. Thomas L, Abhayaratna WP. Left atrial reverse remodeling: Mechanisms, evaluation, and clinical significance. *JACC Cardiovasc Imaging*. 2017:10:65-77.

70. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC). Developed with the special contribution of the heart failure association (HFA) of the ESC. *Eur J Heart Fail*. 2016;18:891-975.

71. Erdei T, Smiseth OA, Marino P, et al. A systematic review of diastolic stress tests in heart failure with preserved ejection fraction, with proposals from the EU-FP7 MEDIA study group. *Eur J Heart Fail*. 2014;16:1345-1361.

72. Pathan F, D’Elia N, Nolan MT, et al. Normal ranges of left atrial strain by speckle-tracking echocardiography: A systematic review and meta-analysis. *J Am Soc Echocardiogr*. 2017;30:59-70.e8.

73. Liu Y, Wang K, Su D, et al. Noninvasive assessment of left atrial phasic function in patients with hypertension and diabetes using two-dimensional speckle tracking and volumetric parameters. *Echocardiography*. 2014;31:727-735.

74. Yoon YE, Oh IY, Kim SA, et al. Echocardiographic predictors of progression to persistent or permanent atrial fibrillation in patients with paroxysmal atrial fibrillation (E6P Study). *J Am Soc Echocardiogr*. 2015;28:709-717.

75. Obokata M, Negishi K, Kurosawa K, et al. Left atrial strain provides incremental value for embolism risk stratification over CHA2DS2-VASc score and indicates prognostic impact in patients with atrial fibrillation. *J Am Soc Echocardiogr*. 2014;27:e4.

76. Suh IW, Song JM, Lee EY, et al. Left atrial volume measured by real-time 3-dimensional echocardiography predicts clinical outcomes in patients with severe left ventricular dysfunction and in sinus rhythm. *J Am Soc Echocardiogr*. 2008;21:439-445.

77. Russo RJ, Costa HS, Silva PD, et al. Assessing the risks associated with MRI in patients with a pacemaker or defibrillator. *N Engl J Med*. 2017;376:755-764.

78. Donal E, Lip GY, Galderisi M, et al. EACVI/EHRA expert consensus document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. *Eur Heart J Cardiovasc Imaging*. 2016;17:355-383.

How to cite this article: Beltrami M, Palazzuoli A, Ambrosio G, et al; The importance of integrated left atrial evaluation: From hypertension to heart failure with preserved ejection fraction. *Int J Clin Pract*. 2018;72:e13050. https://doi.org/10.1111/ijcp.13050