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ORIGINAL PAPER

Left atrial remodeling in heart failure: the role of sphericity index (the SPHERICAT-HF study)

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Abstract

Left atrial sphericity index (LASI) is an echocardiographic index easily obtained; its use in patients with heart failure (HF) has never been investigated so far. This single-centre study aimed to investigate the usefulness of LASI in an unselected cohort of patients hospitalized for acute HF, and its potential correlation with the amino-terminal portion of pro-B-type natriuretic peptide (NT-proBNP) levels and with New York Heart Association (NYHA) functional class. Ninety-four consecutive HF patients underwent a transthoracic echocardiogram with a detailed study of the left atrium (LA) including LASI (calculated from the apical four-chamber view as the ratio between the transverse and longitudinal diameters), and blood tests (including NT-proBNP) on the same day. Median age was 75.5 (interquartile range-IQR 62–82) years and 55% were males, 58.5% had a NYHA class III–IV, and median NT-proBNP was 3284 (IQR 1215–7055) pg/ml. The LA was dilated in 94%, and median biplane LA volume index was 62 ml/m^2. Patients with advanced NYHA class showed more advanced LA remodeling. Mean LASI was 0.78 ± 0.09 and did not correlate with NT-proBNP levels (r 0.03; p 0.75) or with patient NYHA class (R^2 0.011; p 0.287). None of the echocardiographic indices of LA structural and functional remodeling proved to be independently associated with a high NYHA class on multivariate regression analysis. In conclusion, LA remodeling is almost invariably present in patients with HF. LASI does not correlate with NT-proBNP levels or with NYHA functional class. Further studies are needed to describe the complex patterns of atrial remodeling in HF.

Keywords Heart failure · Left atrial sphericity index · NT-proBNP · NYHA functional class

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Introduction

In patients with heart failure (HF), left atrial (LA) size provides incremental prognostic information over left ventricular (LV) function [1, 2]. Increased LA dimensions and volume indicate a higher risk of adverse cardiovascular outcomes for patients with HF with either a reduced or normal left ventricular ejection fraction (LVEF) [3]. LA function indices may provide further information, especially when morphological features do not yet suggest the presence of advanced LA pathology and remodeling [4, 5].

The availability of cardiovascular magnetic resonance (CMR) and computed tomography, or the use of advanced echocardiography (e.g. three-dimensional and speckle-tracking imaging), has shifted attention to more sophisticated and detailed study of the LA and its function [3]. However, standard transthoracic echocardiography remains the simplest routinely available method of assessing the LA in daily clinical practice. Physicians managing HF patients in a busy setting (e.g. intensive care unit—ICU, cardiology ward, outpatient clinic) without easy, direct access to complex imaging facilities, require accurate, simple and fast parameters able to provide answers to their clinical queries.

In recent years left atrial sphericity, defined as the variation between actual LA shape and a perfect sphere, has been used to define LA remodeling in different conditions [6–9]. More specifically, left atrial sphericity index (LASI) has been studied in atrial fibrillation (AF) [6, 8, 9]. Of note, a more spherical LA seems to be associated with an increased risk of AF recurrence after successful direct-current cardioversion or arrhythmia ablation procedures [8, 9]. Moreover, data suggest that the LA becomes more spherical with increasing severity of mitral regurgitation (MR) [7]. The role of LASI in HF has not been extensively investigated so far, although in a recent CMR study LA sphericity resulted an independent predictor of hospitalization for HF in patients with dilated cardiomyopathy (DCM) [10]. We hypothesized that HF patients with a more spherical LA have greater LA reservoir and booster function impairment associated with a worse clinical status. To test this clinical hypothesis, we designed the SPHERICAT-HF (SPHERICity index of the left atrium in patients with HF) study. Aims of the study were: (1) To describe the morphological and functional characteristics, and the patterns of LA remodeling in an unselected cohort of inpatients with acute HF; (2) To investigate the usefulness of echocardiographic LASI, particularly its potential relationship with New York Heart Association (NYHA) functional class and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Materials and methods

Study population

Consecutive inpatients admitted to our hospital (Sassari University Hospital, Sassari, Italy) due to acute HF (new-onset—"de novo" or decompensated chronic HF) were enrolled in the present observational cross-sectional study. HF was carefully diagnosed and defined according to the international guidelines by the contemporary presence of cardiac dysfunction plus congestion (i.e. signs and symptoms and NT-proBNP elevation) [11]. Patients were subdivided based on LVEF in three main categories, according to contemporary guidelines: HF with reduced (HFrEF), mid-range (HFmrEF) and preserved (HFpEF) ejection fraction (EF) [11]. In order to comprehensively explore the usefulness of LASI in HF, we decided to include a wide range of HF etiologies including: ischemic heart disease, cardiomyopathy, valvular heart diseases etc. The case-mix reflected the hospital admissions in order to limit any potential external bias. Exclusion criteria were: age < 18 years, prior mitral valve surgery (due to potentially confounding effects on mitral annular dynamics), poor acoustic echocardiographic window, denial of informed consent.

The study protocol conformed to the principles outlined in the Declaration of Helsinki and was approved by the local Research Ethics Committee. Written informed consent was obtained from the patients or their legal guardians.

Patients provided a detailed clinical history and had blood tests (including serum creatinine and NT-proBNP), ECG and a complete transthoracic echocardiogram done on the same day. The enrollment time varied between 12-h after hospital admission and the day of discharge, in accordance with patients' ability to maintain an appropriate left lateral decubitus for the echocardiographic examination. Anthropometric (height, weight, body mass index—BMI and body surface area—BSA) and clinical data (blood pressure, heart rate and rhythm, medications administered), as well as NYHA functional class, were collected at the moment of the echocardiographic examination by a clinical cardiologist (E.M.) and recorded for all patients. The information was systematically recorded in a dedicated electronic database stored on a secure National Health Service computer with restricted access. The consultant cardiologist performing the echocardiographic examinations was blinded to blood results, including NT-proBNP, in order to reduce potential sources of bias, while a complete blinding to NYHA functional class was not achievable in the most critically ill patients (i.e. those in NYHA class IV).

Echocardiographic measurements

Echocardiography was performed by an experienced operator (G.D.S.) using a Vivid E9 ultrasound system (GE Healthcare, US) equipped with a 1.5–4.6 MHz transducer. All the study patients underwent a comprehensive transthoracic examination in the left-lateral decubitus position [12, 13]. Doppler tracings and two-dimensional images were obtained from parasternal long- and short-axis, apical and subcostal views. In the presence of irregular heart rhythm (e.g. atrial fibrillation—AF), multiple loops (at least five) and averaged measurements were obtained.

Stored images and loops were reviewed by the same operator who repeated all the measurements offline. Standard cardiac chamber quantification was performed in accordance with current American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) recommendations [14]. LV volumes were calculated from apical four-chamber and two-chamber views. LVEF was measured using the biplane modified Simpson's rule. LV global longitudinal strain (GLS) values were obtained from apical three-chamber, four-chamber and two-chamber views, using the commercially available Automated Function Imaging—AFI (GE Medical Systems).

Assessment of left atrial (LA) size and function

LA anteroposterior diameter was measured in the parasternal long-axis view from the trailing edge of the posterior aortic wall to the leading edge of the posterior LA wall.

Maximal and minimal LA volumes were calculated from dedicated apical four- and two-chamber views using the biplane area–length method just before mitral valve opening, and at mitral valve closure, respectively. These views were acquired avoiding foreshortening, in order to maximize LA length and base, so that the difference between LA lengths in the two apical views was minimal (< 10%), as previously described [15]. All the measurements were indexed to body surface area (LAVi) [14].

From LA volumes, biplanar assessment of the LA function was performed and the following parameters derived: LA emptying fraction (LAEF) calculated as biplane $[(LAVi_{max} - LAVi_{min})/LAVi_{max}] \times 100$; and LA expansion index (LAEI) calculated as biplane $[(LAVi_{max} - LAVi_{min})/LAVi_{min}] \times 100$ [2].

LASI was calculated from the apical four-chamber view as the ratio between the transverse and longitudinal diameters, excluding the left atrial appendage and the insertion of the pulmonary veins; measurements were done just before the opening of the mitral valve (Fig. 1) [8]. In patients with AF we used average measurements over 5 beats.

LASI measurements were repeated by two experienced and blinded operators (G.D.S. and M.C.) in order to limit potential sources of bias. Average measurements were considered.

LA speckle-tracking analyses were performed offline by an experienced operator (C.S.) using an EchoPAC station (GE Medical Systems), as already described, and peak atrial longitudinal strain (PALS) values were obtained when feasible [4].

Assessment of functional capacity

To describe the impact of HF on patients' daily activities and functional status we used the NYHA classification [16]. Originally developed in 1928 and subsequently revised, the classification subdivides patients with HF into four categories (I, II, III, IV), with higher class indicating more severe symptoms, limitation in physical activity, and worse health [16, 17]. Clinicians assigned NYHA class on the basis of their indirect interpretation of reported patients' symptoms, medical history, and results from clinical tests [16].

Evaluation of amino-terminal portion of pro-B-type natriuretic peptide (NT-proBNP)

Fasting venous blood samples were collected in ethylendiaminetetraacetic acid containing tubes and centrifuged within 1 h. The analytic range of the NT-proBNP assay (The Stratus® CS Acute Care™ NT-proBNP assay, Siemens Healthineers) extended from 5 to 35×10^3 pg/mL. A cut-off value of NT-proBNP < 300 pg/mL was used for ruling out HF, according to guidelines [11].

Statistical analysis

Based on an estimated LASI difference between NYHA functional class I–II *vs* NYHA III–IV of 0.07, keeping into consideration the increasing risk of AF with worse NYHA class, an alpha and beta error of 0.05 and 0.2, respectively, a total sample size of 56 patients was estimated to be recruited (n = 28 per single group) [8].

Statistical analyses were performed using Stata13 software (StataCorp, College Station, Texas) and SPSS 25.0 statistical package (IBM Corp, Armonk, NY, USA). All the variables were tested for normality by Shapiro–Wilk test. Results were expressed as mean ± SD (or median and interquartile range) for continuous variables or as number of cases and percentage for categorical variables. The Student's t-test and Mann–Whitney U test or the χ-square test were used to compare the differences between groups. One-way analysis of variance (ANOVA) was used to test the differences in terms of LASI between HF categories (i.e. HFrEF, HFmrEF, HFpEF). $P < 0.05$ values were considered statistically significant.

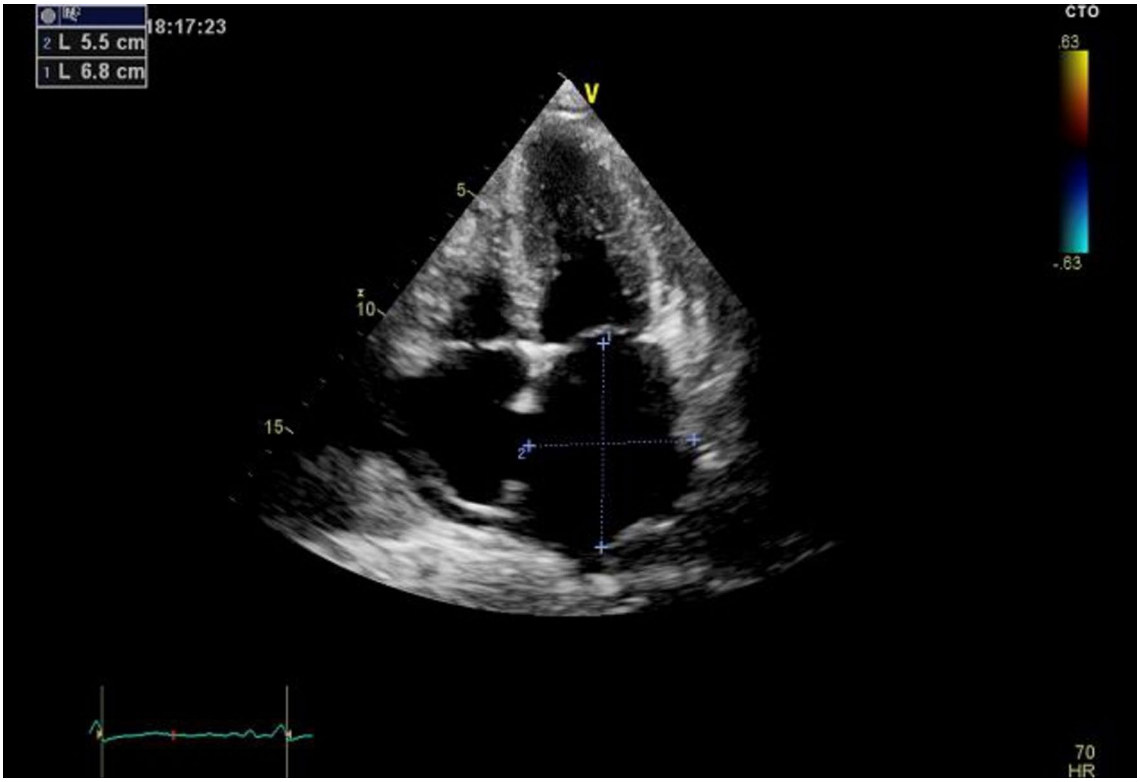

Fig. 1 Echocardiographic measurement of left atrial sphericity index (LASI). The measurement is calculated from the apical 4-chamber view as the ratio between the transverse and longitudinal diameters, excluding the left atrial appendage and the insertion of the pulmonary veins

Interobserver reliability for LASI measurements was assessed by Intraclass Correlation Coefficient (ICC) with cut-off values > 0.7, > 0.8 and > 0.9 indicating good, optimal and excellent agreement, respectively (Supplemental Table 1).

The relationship between echocardiographic indices of left atrial remodeling and NT-proBNP levels were analyzed, and Pearson's (r) or Spearman's (ρ) correlation coefficients obtained. Bearing in mind the wide range and NT-proBNP level distribution with no skew, the peptide values were log-transformed to reduce the effects of extreme values and to obtain a normal distribution for some analyses, as already described [18].

The relationship between echocardiographic indices of left atrial remodeling and NYHA functional class were analyzed with linear regression analysis, and results were expressed as R^2 (i.e. the proportion of variance in the dependent variable—NYHA class that can be explained by the independent variable—any index of left atrial remodeling).

Logistic regression analysis was performed to assess the independent determinants of a high (i.e. III and IV) NYHA functional class by entering into the model a set of 9 clinical and echocardiographic variables with potential pathophysiological relevance based on existing literature and the results of univariate analyses (age, gender, NT-proBNP levels, LV end-diastolic volume—LVEDV, LVEF, E/e′ ratio, LASI, left atrial emptying fraction—LAEF, left atrial expansion index—LAEI).

Results

Clinical characteristics

The enrolled patients' (n = 94) clinical characteristics are summarized in Table 1. Fifty-two (i.e. 55%) were males. Median age was 75.5 (IQR 62–82) years. Arterial hypertension was found to be the most common cardiovascular risk factor (62%). The majority of patients (69.15%) were diagnosed as having an HFrEF (i.e. LVEF < 40%). Based on NYHA classification, classes II and III were the largest group (41.5% and 41.5%, respectively); overall, 55 (59%) patients presented with an advanced III or IV NYHA functional class. Median plasma NT-proBNP was 3284 (IQR 1215–7055) pg/ml.

The most frequent causes of HF were: AF (31%), DCM (28%), coronary artery disease (23%), severe mitral valve regurgitation (20%), and severe aortic stenosis (14%).

Table 1 Clinical characteristics of the study population

Variable	Entire cohort n = 94
Males n (%)	52 (55)
Age (years)	75.5 (62–82)
Body mass index (kg/m^2)	25 (22.4–27.4)
Arterial hypertension n (%)	58 (62)
Diabetes mellitus n (%)	28 (30)
Smokers n (%)	15 (16)
Hypercholesterolemia n (%)	54 (58)
GFR (ml/min)	63 ± 23
Serum creatinine (mg/dl)	1.07 (0.83–1.43)
Coronary artery disease (CAD) n (%)	
No	42 (45)
Yes	36 (38)
Unknown	16 (17)
HFrEF n (%)	65 (69.15)
HFmrEF n (%)	7 (7.45)
HFpEF n (%)	22 (23.4)
NYHA (New York Heart Association) functional class n (%)	
II	39 (41.5)
III	39 (41.4)
IV	16 (17)
Coronary artery disease (CAD) n (%)	22 (23) (CAD primary or concomitant primary cause of HF)
Severe mitral regurgitation n (%)	19 (20)
Severe aortic stenosis n (%)	13 (14)
Severe aortic regurgitation n (%)	4 (4)
Severe mitral stenosis n (%)	1 (1)
Dilated cardiomyopathy (DCM) n (%)	26 (28)
Hypertrophic cardiomypathy (HCM) n (%)	3 (3)
Infiltrative myocardial disease (e.g. amyloidosis) n (%)	2 (2)
Myocarditis n (%)	0 (0)
Other unspecified forms of heart disease (e.g. LBBB-induced cardiomyopathy; hypertensive heart disease with afterload mismatch; etc.)	9 (10)
Diastolic heart failure n (%)	6 (6)
Tachycardia-induced cardiomyopathy n (%)	5 (5)
Atrial fibrillation (AF) n (%)	29 (31)
Left bundle branch block (LBBB) n (%)	20 (22)
Right bundle branch block (RBBB) n (%)	4 (4.4)
Pacemaker n (%)	2 (2)
Automatic implantable cardioverter defibrillator (AICD) n (%)	6 (6)
CRT-D/CRT-P device n (%)	3 (3)
ACE-I or ARB n (%)	70 (74)
Beta-blockers n (%)	74 (79)
Diuretics n (%)	86 (91)
MRA antagonists n (%)	73 (78)
ARNi n (%)	9 (10)
Ivabradine n (%)	10 (11)
Digoxin n (%)	5 (5)
Calcium channel blockers n (%)	10 (11)
NT-proBNP (pg/ml)	3284 (1215–7055)

GFR glomerular filtration rate, *HFrEF* heart failure with reduced ejection fraction, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *ACE*-I ACE inhibitors, *ARB* angiotensin receptor inhibitors, *MRA* mineralcorticoid receptor antagonists, *CRT-D/CRT-P* cardiac resynchronization therapy-defibrillator/pacing

Echocardiographic features

The echocardiographic characteristics of the study population are reported in Table 2. Median LVEF was 34% (IQR 26–45). Nearly all the enrolled patients (94%) showed LA dilation. Median max and min LAVi were 62 and 45 ml/m^2, respectively. Mean LASI was 0.78 ± 0.09. LASI did not significantly differ across the three different HF categories (0.79 ± 0.09, 0.76 ± 0.04, 0.76 ± 0.08, $p = 0.42$ respectively for HFrEF, HFmrEF and HFpEF). Regarding the volumetric indices of LA function, mean LAEF was 0.25 ± 0.13, and median LAEI was 0.32 (IQR 0.16–0.52). Median PALS was 9.12%.

Correlation between LA remodeling indices and NT-proBNP values and NYHA functional class

Correlations between the different LA remodeling indices and NT-proBNP levels were generally weak (Supplemental Table 2). To be specific, LASI did not show any correlation with the plasma levels of natriuretic peptides (r 0.03; p 0.75). LAEF and LAEI showed a weak negative correlation with NT-proBNP (r − 0.36, p 0.0004; and ρ − 0.32, p 0.0015 respectively) (Supplemental Fig. 2A, B). Subgroup analyses in patients with AF or severe MR confirmed no correlation between LASI and NT-proBNP.

Linear regression analysis did not show any significant relationship between LA remodeling indices and NYHA functional class (Supplemental Table 3). Again, LASI did not show any relation with NYHA class (R^2 0.011; p 0.287). The only parameters showing a statistically significant correlation, although weak, with NYHA class were LAEF (R^2

Table 2 Echocardiographic characteristics of the study population

Variable	Entire cohort n = 94
Heart rate (bpm)	76 ± 14
Systolic blood pressure (mmHg)	110 (100–125)
Diastolic blood pressure (mmHg)	66 ± 13
Interventricular septum thickness (mm)	11 (9–12)
End-diastolic diameter (mm)	58 ± 9
End-systolic diameter (mm)	46 ± 12
Left ventricular end-diastolic volume index (ml/m^2)	84 (62–104)
Left ventricular end-systolic volume index (ml/m^2)	60 (31–73)
Left ventricular ejection fraction (EF) (%)	34 (26–45)
Left ventricular global longitudinal strain (GLS) (%)	-8.15 (-12.1/-6.4)
Left atrial anterior–posterior diameter (2D method APLAX) (mm)	48 (42–53)
Left atrial volume index max (biplane A–L method) (ml/m^2)	62 (48–76)
Left atrial emptying fraction [$(LA_{max} - LA_{min})/LA_{max}$]	0.25 ± 0.13
Left atrial expansion index [$(LA_{max} - LA_{min})/LA_{min}$]	0.32 (0.16–0.52)
Peak left atrial longitudinal strain (PALS) (%)	9.12 (5.6 / 11.9) over 53 obs
Left atrial dilation n (%)	88 (94)
Left atrial sphericity index	0.78 ± 0.09
Right atrial volume index (4CH view) (ml/m^2)	30 (22–44)
Right atrial dilation n (%)	50 (53)
Tricuspid annular plane systolic excursion (TAPSE) (mm)	17 ± 4
Mitral E wave velocity (m/s)	0.98 (0.73–1.23)
Mitral E/A ratio	1.64 (0.79–2.2)
e′ septal velocity (m/s)	0.04 (0.03–0.05)
e′ lateral velocity (m/s)	0.06 (0.05–0-09)
E/e′ ratio (average)	17 (13–23)
Diastolic dysfunction n (%)	
Abnormal relaxation	13 (14)
Pseudonormal pattern	17 (18)
Restrictive filling pattern	13 (14)
Undetermined	51 (54)
Pulmonary arterial systolic pressure (PASP) (mmHg)	42 (37–53)

0.107, p 0.0003), LAEI (R^2 0.093, p 0.0007), and PALS (R^2 0.067, p 0.019). Again, subgroup analyses in patients with severe MR or AF did not show any significant relationship between LASI and NYHA functional class.

LA echocardiographic characteristics according to NYHA functional class

Table 3 shows LA echocardiographic characteristics in the study patients subdivided into two groups according to NYHA functional class. The first group included patients (n = 39) with NYHA class II, while the other group (n = 55) included those with advanced NYHA classes III and IV. LAVi proved to be significantly higher in patients with an advanced NYHA class (68 vs 56 ml/m^2, p 0.00159). Similarly, LAEF and LAEI were significantly lower (i.e. impaired) in patients with NYHA functional classes III and IV (0.20 vs 0.31, p 0.02; and 0.22 vs 0.41, p 0.0003) suggesting more advanced LA remodeling and pathology. LASI did not show statistically significant differences between the two groups, despite a trend toward increased sphericity in patients with lower NYHA classes.

Echocardiographic predictors of a high (i.e. III and IV) NYHA functional class and potential LA role

The multivariate regression analysis showed that only age (OR 1.08, 95% CI 1.03–1.13; p 0.001) and the E/e′ ratio evaluated with pulsed-wave Tissue Doppler Imaging (OR 1.09, 95% CI 1.01–1.18, p 0.02) were independent determinants of a high NYHA functional class (Supplemental Table 4).

Discussion

Emerging data suggest that the LA is much more than simply a conduit for LV filling, and its anatomical and functional remodeling is recognized as a predictor of poor outcomes in HF [19–21]. LA dilation was highly prevalent (94%) in our cohort, suggesting that LA remodeling is almost invariably present in HF. Moreover, our data suggest that LA remodeling is somehow a progressive phenomenon, and patients with more advanced disease states or symptoms (i.e. NYHA classes III and IV) exhibit significantly larger LA volumes together with reduced emptying fraction and expansion index. In our cohort LASI did not correlate with NT-proBNP levels or with NYHA functional class, thus allowing falsification of the clinical hypothesis underlying the study. Previous studies have shown that a more spherical LA is associated with an increased risk of AF recurrence after successful cardioversion or first ablation procedure, and with the severity of MR [7–9]. However, these studies were not specifically used to investigate HF patients [7–9]. More recently, Yazaki et al. found that LASI assessed by CMR has a prognostic value in DCM; in their study patients with a high LASI had a significantly higher risk of hospitalization for HF than those with a low LASI [10]. Looking carefully at our results, it is noteworthy that the majority of patients had advanced HF or severe impairment of functional capacity with congestion, and LASI showed a trend toward higher values in patients with NYHA class II. These results could suggest that LASI possibly reflects an earlier stage of LA remodeling. The spherical shape has the most convenient volume/surface ratio, thus LA spherical remodelling might be the initial way to accommodate the increased volume/pressure overload with lesser LA wall stress/tension. A more spherical LA might be more compliant, and this could be the response to the increased pulsatility (LA max–min pressure) and wall stress variation observed by Melenovsky et al. in HFpEF [21]. Our study findings suggest that no single echocardiographic parameter is able per se to correctly catch and comprehensively describe the complex phenomenon of atrial remodeling (Supplemental Fig. 3).

Another interesting finding of our study is the relatively scarce informative value of PALS. Carluccio et al. showed that reduced PALS was associated with poor outcomes in a cohort of 405 stable patients with HFrEF [20]. Although outcomes were not evaluated in our cohort, thus enabling a direct comparison between the two studies, we should underline some important differences in terms of enrolled patients. In our study we recruited patients with acute HF, as demonstrated by a high median value of NT-proBNP (3284 pg/ml vs 497 pg/ml in the Carluccio et al. study). Therefore, it is possible that PALS, whose potential usefulness has been described in high cardiovascular risk patients without LA

Table 3 Differences in left atrial remodeling according to the NYHA functional class

Variable	NYHA class II (n 39)	NYHA class III–IV (n 55)	P value
Left atrial volume index (ml/m^2)	56 (44–65)	68 (54.5–83)	**0.0015**
Left atrial emptying fraction	0.31 ± 0.13	0.20 ± 0.12	**0.02**
Left atrial expansion index	0.41 (0.27–0.69)	0.22 (0.14–0.4)	**0.0003**
Peak atrial longitudinal strain	10 (5.6–21.6) 18 obs	7.1 (5.3–11.1) 35 obs	0.14
Left atrial sphericity index	0.81 (0.73–0.84)	0.76 (0.72–0.81)	0.099

p value < 0.05 to emphasize the variables with statistical significance dilation as an early marker of atrial disease [4], loses its strong additive diagnostic value in the advanced stages of HF and atrial remodeling.

The only echocardiographic indices of LA remodeling showing some (although weak) relationship with NT-proBNP levels and NYHA functional class in our study were the volumetric LAEF, LAEI and PALS. Prastaro et al. found a similar correlation between LAEF and NT-proBNP in a cohort of 101 patients with congestive HF [18]. The concomitant use of two or more indices and their wise use at different moments and different stages (early vs late) of the disease could probably be the key for decoding the riddle of LA remodeling in HF.

Limitations

Our findings should be evaluated in light of some limitations. First, this was a single-centre study with a relatively small sample size. The majority of patients had HFrEF, while HF with mid-range ejection fraction (HFmrEF) and HFpEF categories were less represented; this provides general results but does not allow further analyses to be performed identifying any differences between HF subgroups potentially characterized by distinct hemodynamic behaviours which may affect LA size, shape and function in a different way. However, although HFpEF currently represents approximately 50% of HF cases, hospitalizations in this subgroup are often due to non-cardiovascular causes [11]. These patients with several noncardiac comorbidities are usually admitted to the internal medicine or geriatric units, and only the more critically ill or with new-onset HF are admitted to the cardiology ICUs. This might explain the imbalance between HF phenotypes based on LVEF. Anyway, the distribution of LVEF in our study is somewhat similar to that of previous large trials conducted on acute decompensated HF [22]. However, single subgroups related to disease severity could be not adequately represented in the current sample affecting the inference of the findings.

Moreover, we enrolled in-patients with acute HF; most of them presented with severe HF states (i.e. marked congestion and NYHA class III or IV), or advanced stages of the disease. Thus, we cannot definitely exclude some differences in the results in terms of LA remodeling when considering early stages or chronic HF.

In our study the timing of the echocardiographic examination varied during patients' hospital-stay due to the need of obtaining a comprehensive study. This could certainly have had an impact on NT-proBNP levels and on some echocardiographic parameters (e.g. E/e′ ratio, pulmonary artery systolic pressure, etc.). However, aim of the study was to test the performance of several echocardiographic indices of LA size/function (mainly LASI) in the acute setting of HF (regardless of the patients' loading/congestion state), and the ability of simple and easily available measurements to provide useful information on LA remodeling.

To the best of our knowledge, this is the first and largest study systematically investigating the role of LASI and comparing it with other echocardiographic indices in HF, also coupled with a detailed and comprehensive clinical and biomarker evaluation of congestion.

Our study was observational in nature and a prospective follow-up evaluation would be useful to establish the prognostic significance of the observed features in terms of LA remodeling. According to previous investigations, LA reservoir and booster function, while severely impaired during immediate decompensation, significantly improve with decongestive therapy; poor LA reservoir function after decongestion is associated with worse outcome [23].

In our study LASI did not provide significant additional information in terms of LA remodeling. However, a two-dimensional echocardiographic parameter is probably insufficient to describe the complexity of LA geometry. CMR [6] and 3D-echo may overcome this limitation, at the expense of reduced simplicity with increased costs in terms of time and money.

Another potential limitation of our study is the method used for the assessment of functional status. Although the reliability and validity of the NYHA classification have been widely debated, and more objective measures of HF severity (such as the 6-min walk distance—6MWD, and cardiopulmonary exercise testing—CPET) have been proposed [24], we should acknowledge that: (1) The ease of application of NYHA classification has resulted in its widespread use in many HF studies/trials and international guidelines [24]; (2) The NYHA classification performs well in more symptomatic patients (NYHA III and IV) [24]; (3) There are significant logistical and financial barriers limiting the routine use of CPET albeit regarded as the gold standard for assessment of aerobic functional capacity [24]; (4) The role of 6MWD in NYHA classes I and II is yet to be clearly and fully established.

A possible alternative could be exercise echocardiography [25], although not really feasible in the more symptomatic patients.

Finally, LA strain analysis was not feasible in all the study patients. Although PALS did not show any significant correlation with NT-proBNP plasma levels or with NYHA functional class, the absence of its measurement in the entire cohort could have somehow introduced a potential source of bias. However, strain measurements are not feasible in all patients; atrial walls are usually very thin and echo dropouts may interfere with correct tracking by the software, thus rendering the strain measurements not feasible or at least less accurate and possibly unreliable [26, 27].

Conclusions

LA remodeling is common in HF patients and it seems to be a progressive phenomenon (patients with more advanced stages of the disease exhibit more marked degrees of LA remodeling). The study of LA in HF is of paramount importance, since parameters describing its phasic function and its close interconnection with LV (i.e. E/e′ ratio) together with patients' age are independent predictors of clinical and functional status. LASI, despite its underlying pathophysiological rationale and the fact that its measurement is easily obtainable and highly reproducible, does not correlate with NT-proBNP levels or with NYHA functional class in acute HF. LA sphericity could be more marked in the early stages of atrial remodeling, as suggested by some data from our study. Further larger studies are needed to describe the patterns of atrial remodelling in HF together with the potential therapeutic and prognostic implications.

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Code availability Not applicable.

Declarations

Conflict of interest The Authors have no conflict of interest to declare.

Ethical approval The study protocol conformed to the principles outlined in the Declaration of Helsinki and was approved by the local Research Ethics Committee.

Informed consent Written informed consent was obtained from the patients or their legal guardians.

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