

The analysis of left atrial function predicts the severity of functional impairment in chronic heart failure: The FLASH multicenter study[☆]

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ABSTRACT

Background: Heart failure (HF) patients present with a variety of symptoms at different stages of the disease, but the underlying pathophysiology still is unclear. Left atrial (LA) function might be tightly related to changes in patients' symptoms, more than morphological and anatomic heart features, measurable by ultrasound imaging technique. This study sought to investigate the correlation between LA function, assessed by Speckle Tracking Echocardiography (STE) and Quality of Life (QoL), assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ), in patients with chronic HF.

Methods: Clinically stable HF outpatients ($n = 369$) were enrolled from 7 different international centres and underwent echocardiographic studies. Patients >75 years old and with atrial fibrillation were excluded. LA strain during reservoir phase (LASr) by STE was measured in all subjects by averaging the 6 atrial segments. LA size was assessed using biplane volume and 4-chamber area acquisition.

Results: LASr strongly correlated with both MLHFQ total score ($r = -0.87$; $p < 0.0001$). Less significant correlations between MLHFQ and either LA volume or left ventricular global longitudinal strain (LV-GLS) were found ($r = 0.28$; $p = 0.05$ and $r = 0.30$; $p = 0.01$, respectively). No significant correlation was found between MLHFQ score, LVEF ($r = -0.15$; $p = \text{ns}$), E/E' ratio ($r = 0.19$; $p = \text{ns}$), and E/A ratio ($r = 0.20$; $p = \text{ns}$). Among all echocardiographic parameters analyzed, LASr presented the highest diagnostic accuracy (AUC = 0.74) in predicting a poor QoL (>45), when compared with LV-GLS (AUC = 0.61), LA volume (AUC = 0.54) and E/e' ratio (AUC = 0.51).

Conclusions: In patients with HF, irrespective of etiology, LA function strongly correlates with patients' QoL.

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Abbreviations: HRQoL, Health-related quality of life; HF, heart failure; LA, left atrium; LAS, left atrial strain; LASr, left atrial strain during reservoir phase; LV, left ventricle; LV-GLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal fragment of proB-type natriuretic peptide; QoL, Quality of Life; STE, Speckle Tracking Echocardiography.

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1. Introduction

Heart failure (HF) is a most common chronic disease worldwide, with an estimated prevalence of 1–2% in the adult population, which peaks up to 10% above the age of 70. [1–4] Improving the quality of life (QoL) of HF patients has become of crucial importance, with its impact on hospital admission rates and the cost of close monitoring. Health-related QoL (HRQoL) assessment is also of great importance in assessing patients' symptoms and for devising management plans [5]. Accordingly, many multidimensional questionnaires have been designed with the currently disease-specific ones being the most reliable

and easily usable. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) enables assessing HRQoL for both physical and emotional sides [6], since depressive and physical symptoms are the best predictors of HRQoL in these patients [7]. It consists of 21 items, each scaled from 0 to 5, with the higher score indicating poorer QoL. MLHFQ total score has been shown as a prognostic predictor in patients with HF [8,9]. Although the pathophysiological relationship among the different factors involved in the development and the evolution of HF is known, what mainly impacts on symptoms, i.e. on the subjective perception of the disease has still to be fully understood.

Left atrial (LA) changes are a well-established prognostic factor, but their role in the worsening of the symptoms has not been clearly established yet. LA dimensions have been shown as independent predictors of mortality in HF patients, with a prognostic impact that goes beyond the left ventricular (LV) systolic and diastolic function. [10] Nonetheless, LA function does not necessarily correlate with its structural measurements, since microscopic remodelling, e.g. interstitial fibrosis could occur before changes in volume and area. LA strain (LAS) enables quantification of longitudinal global and segmental LA myocardial deformation [11] thus, represents the best method for assessing LA function. [12] Clinically, LAS has been associated with NYHA functional class [13], functional capacity during exercise [14], peak oxygen consumption (peak VO₂) at cardiopulmonary exercise testing [15] and plasma levels of N-terminal fragment of proB-type natriuretic peptide (NT-proBNP) [16]. Moreover, when there is an increased filling pressure, atrial stretch receptors are stimulated and, through myelinated cardiac vagal afferent nerves [17,18], this information is conveyed to the medulla and limbic system, namely to the anterior insula, being implicated in the perception of dyspnea [19]. Thus, LA can be directly involved in the subjective feeling of breathing discomfort. In addition, LAS during LA reservoir phase (LASr) has been shown to hold the highest diagnostic accuracy in the non-invasive estimation of LV filling pressures among all other echocardiographic parameters [20].

The aim of this multicentre study was to investigate whether LA longitudinal deformation, determined by STE, is related to the QoL, assessed by MLHFQ, in chronic HF patients. The main hypothesis is that irrespectively of LA volume, LA function might play a significant role in maintaining the hemodynamic balance that determines severity of symptoms in patients with chronic LV dysfunction.

2. Methods

2.1. Study design

The FLASH (the analysis of left atrial function predicts the severity of functional impairment in chronic heart failure) study is an international, multicentre, observational study, coordinated by the Department of Cardiovascular Diseases of the University of Siena. The other involved centres with experience in heart failure and advanced imaging were:

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- Cardiovascular Diseases Section, Department of Emergency and Organ Transplantation, Bari (Italy)
- Cardiology Institute of Rio Grande Do Sul, Porto Alegre (Brasil)

2.2. Study population

A total of 369 clinically stable outpatients with chronic HF (with AHA HF Stage $\geq$ B) were enrolled between February 2016 and November 2016. Inclusion criteria required the patients to have chronic HF of any etiology, AHA Stage $\geq$ B irrespectively of LVEF, stable

medical therapy for at least 6 months, ability to understand and answer a MLHFQ. All subjects gave a written informed consent for participation in the study. The research design complied with the Declaration of Helsinki. Patients were excluded if over 75 years of age, had atrial fibrillation, previous heart transplantation, previous valve surgery, congenital heart disease, acute decompensation of HF, recent (< 3 months) hospitalization for cardiovascular causes, or inadequate acoustic window. All subjects underwent a transthoracic echocardiographic examination, and all conventional parameters of myocardial function were obtained including strain value assessed by STE. Moreover, patients were required to answer to MLHFQ, in order to obtain the total score and the physical and emotional ones.

2.3. Standard echocardiography

In all centres, the echocardiographic examination was performed by an expert cardiologist, using a high-quality echocardiograph (Vivid E9, GE, USA) equipped with a 3-MHz transducer, and images were analyzed in each center. Patients were studied in the left lateral recumbent position, in order to acquire conventional images using standard echocardiographic parameters; pulsed wave transmitral Doppler flow velocities and myocardial tissue Doppler velocities according to the ASE recommendations. [21]

Standard echocardiographic measures included: LV end-diastolic (EDD) and end-systolic (ESD) diameters from the parasternal long-axis, LV end-diastolic (EDV) and end-systolic (ESV) volumes, LV ejection fraction calculated by Simpson's method, mitral annular plane systolic excursion, peak early (E) and late (A) diastolic transmitral flow velocity and E/A ratio, pulsed wave Tissue Doppler systolic (S') and diastolic (E', A') velocities at both septal and lateral mitral annulus, E/E' ratio as an estimate of LV filling pressure. LA area and volume were measured using the biplane method of discs (modified Simpson formula) at end-systole in the 4- and 2-chamber apical views and average values were calculated.

2.4. Speckle tracking echocardiography

Speckle tracking analysis was performed from the apical 4- and 2-chamber images using conventional 2-dimensional grey scale echocardiography, during a brief breath hold and with a stable ECG recording. The frame rate was set between 60 and 80 frames per second, in order to combine a high temporal resolution with an acceptable spatial resolution [15]. The analysis of the recorded images was performed off-line by a single experienced and independent echocardiographer in each centre, who was not directly involved in the image acquisition and had no knowledge of the clinical parameters. Three consecutive heart cycles were recorded and their measurements were averaged. A semi-automated two-dimensional strain software (EchoPac, Ge, Milwaukee, WI, USA) was used; it allowed tracing the displacements of the speckles in the myocardial tissue frame by frame during the whole cardiac cycle. As stated in the consensus document of the EACVI-ASE Task Force [22], the LA endocardial border was manually traced in the 4- and 2-chamber views delineating a region of interest which consisted of 6 segments. After segmental tracking quality analysis and eventual manual adjustments of the region of interest, longitudinal strain curves were generated by the software for each atrial segment and the global value was calculated by the software resulting in LASr as an index of atrial reservoir function. Mean LASr values from 2- and 4-chamber views were calculated to obtain global LASr. Inadequate segments image quality disqualified them from the overall analysis. Time to peak longitudinal strain was also measured as the average of all 12 segments (global time to peak longitudinal strain) and by separately averaging values observed in the 2 apical views (4- and 2-chamber average times to peak longitudinal strain). In the same way, LV longitudinal strain, measured at the end of the ventricular systole, has been evaluated, taking into account 4-, 2-chamber views and parasternal long axis.

2.5. Minnesota Living with Heart Failure Questionnaire

Most of MLHFQ items regarding patient's ability to achieve daily normal activities can be considered as an instrument to measure the perceived health-related QoL. Each of the 21 items is presented on a graduated scale from 'not at all impactful' to 'highly impactful'. The total score ranges from 0, the best QoL, to 105, the worst QoL. MLHFQ includes two subscales: physical (range 0–40) and emotional (range 0–25). It also includes items assessing socio-economic status. In clinical practice, the global score is often used [8], although the original version aimed to evaluate separately 2 sub-scales, the physical and the emotional one. [6]

2.6. Statistical analysis

Data are shown as mean $\pm$ SD or median and interquartile range. P-value <0.05 was considered statistically significant. Pearson's correlation coefficients were calculated to assess the relationships between continuous variables in data with normal distribution and Spearman's correlation coefficients were calculated in case of data without normal distribution. Receiving operating characteristics (ROC) curve analyses were used to analyze the diagnostic accuracy in predicting a Minnesota score above 45. All analyses were performed using SPSS (Statistical Package for the Social Sciences, Version 20.0, SPSS Inc., Chicago, IL, USA).

Table 1
Clinical and echocardiographic features of the study population (n = 369).

	(n, %)		
Males	233 (63)	Age	65.6 ± 10.8
Females	136 (37)	BMI (kg/m ²)	27 ± 4.6
Diabetes	125 (34)	LV End-diastolic diameter (mm)	53.8 ± 9.7
Hypertension	273 (74)	LV End-systolic diameter (mm)	38.9 ± 12.5
Dyslipidemia	214 (58)	LV End-diastolic volume (ml)	128.7 ± 54.3
Ex/Current smokers	166 (45)	LV End-systolic volume (ml)	71.6 ± 48.6
CAD in first degree relatives	110 (30)	EF (%)	47 (34–60)
Previous episodes of Atrial fibrillation	96 (26)	LA volume (ml)	82.7 ± 38.5
Antiplatelets	206 (56)	LA area (cm ²)	23.8 ± 7.6
ACE-Inhibitors	173 (47)	MAPSE (mm)	13.4 ± 3.7
ARBs	162 (44)	RV End-diastole diameter (mm)	33.3 ± 6.9
β-blockers	140 (38)	TAPSE (mm)	20.1 ± 4.5
Aldosterone antagonists	88 (24)	PAPs (mmHg)	34 ± 12.2
Diuretics	240 (65)	E/E' Ratio	12.2 ± 6.4
Anticoagulants	48 (13)	LASr (%)	20.5 ± 8.7
Ivabradine	55 (15)	LV-GLS (%)	−13.4 ± 5.9
Statins	151 (41)		

Values are expressed as mean ± standard deviation (for continuous variables with Gaussian distribution) or median and interquartile range (for continuous variables with non-Gaussian distribution) and as percentage (for discrete variables).

ACE-Inhibitors, Angiotensin converting enzyme – Inhibitors; ARBs, Angiotensin II receptor blockers. BMI, Body Mass Index; CAD, coronary artery disease; LA, Left Atrium; LASr, left atrial strain during reservoir function; LV, Left Ventricle; LV-GLS, left ventricular global longitudinal strain; MAPSE, Mitral annular plane systolic excursion; PAPs, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

3. Results

3.1. Clinical and echocardiographic characteristics of the study population

Clinical and echocardiographic data are summarized in Table 1. The study population included 369 patients (141 females and 239 males). The sample included patients with preserved LVEF (46%), mid-range (14%) and reduced LVEF (40%), with a mean value of $45.6 \pm 14.2\%$. During off-line strain analysis, in the overall study population, 12 subjects were excluded due to the impossibility of obtaining an adequate tracking quality in more than three LA or LV segments. Among a total of 10,710 segments analyzed in the remaining 357 subjects a strain curve was obtained in 10,303 segments (96.2%). A great variability of MLHFQ total score was found in the population, with a median of 29. MLHFQ total score, as well as physical and emotional sub-scores, tended to increase with higher NYHA classes, implying a good correlation between subjective questionnaire answering and severity of symptoms.

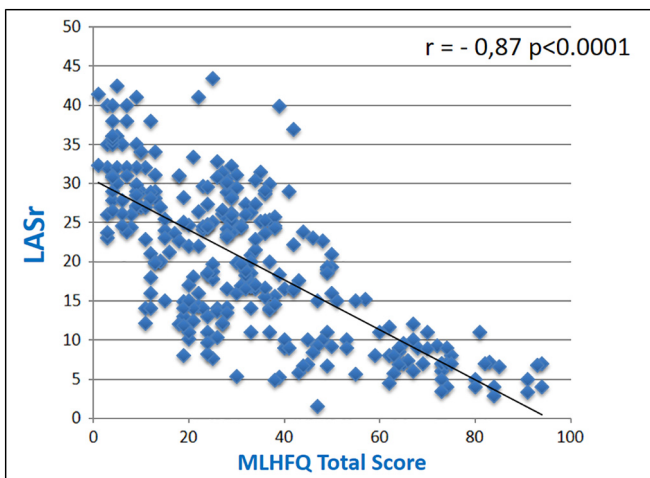


Fig. 1. Linear regression between Minnesota Living with Heart Failure (MLHFQ) total score and left atrial strain during reservoir function (LASr). The graph shows the strong inverse correlation that was found between left atrial strain during reservoir function (LASr) and Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score.

3.2. Correlation between MLHFQ score and clinical and echocardiographic parameters

Global LASr and MLHFQ total score strongly inversely correlated ($r = -0.87$; $p < 0.0001$) (Fig. 1), suggesting higher LA dysfunction in patients with worst perceived QoL. In contrast, LA volume and MLHFQ total score only poorly correlated ($r = 0.28$; $p = 0.05$) (Fig. 2). There was no relationship between MLHFQ total score and LVEF ($r = -0.15$; $p = \text{ns}$) (Fig. 2) and E/E' ratio ($r = 0.19$; $p = \text{ns}$) (Fig. 2), irrespective of LVEF. Moreover, MLHFQ total score did not correlate with E/A ratio either ($r = 0.20$; $p = \text{ns}$). Finally, a weak correlation between MLHFQ total score and LV global longitudinal strain (LV-GLS) ($r = 0.30$; $p = 0.01$) was also found (Fig. 2).

3.3. Diagnostic accuracy of echocardiographic indices

To further investigate the value of these echocardiographic indices in predicting poor QoL, we performed receiving operating characteristics (ROC) curve analyses. According to the available literature [23,24], MLHFQ total score of 45 was considered the cut-off value to predict impaired QoL, therefore ROC curve was performed to assess diagnostic accuracy of analyzed parameters to predict a MLHFQ Score > 45. Among all echocardiographic parameters analyzed, global LASr had the highest diagnostic accuracy (AUC = 0.74), in predicting poor QoL using a cut-off value <16% (Fig. 3). LV-GLS was less accurate (AUC of 0.61), at a cut-off value greater than −10.8%. Also, LA volume had limited diagnostic accuracy (AUC of 0.54), at a cut-off value >111 ml, as did mean E/E' ratio (AUC = 0.51) at a cut-off value of 14.5 in predicting QoL.

4. Discussion

Our findings indicate that in patients with HF, irrespective of the cause that led to HF, LA function strongly correlates with patients' QoL.

Both LV anatomical and functional changes occur in parallel with HF progression. However, the mechanisms underlying the improvement or the worsening of the symptoms are not well defined yet, and they probably go beyond the evaluation of a single cardiac chamber function/morphology. In recent years, LA has been proven to play a central role, since it appears to be involved in symptoms progression. [25] However, it is important to stress the fact that LA and LV are both anatomically and functionally tightly connected, therefore LA dilatation and an earlier LA

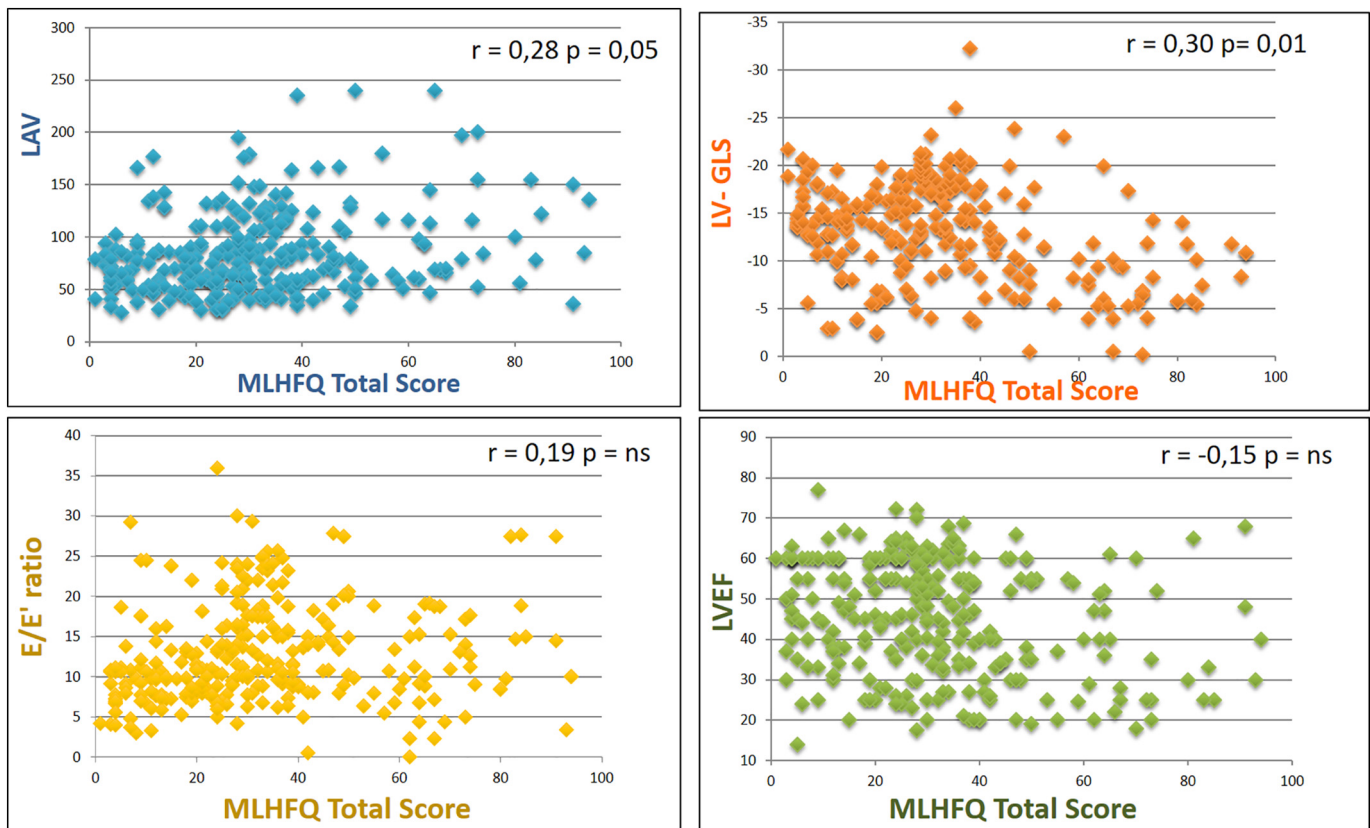


Fig. 2. Linear regression between Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score and Left Atrial (LA) Volume, Left ventricular Global Longitudinal Strain (LV-GLS), E/E' Ratio and Left Ventricular (LV) Ejection Fraction, respectively. In the upper graphs there is shown the poor correlation between the total Minnesota Living with Heart Failure Questionnaire (MLHFQ) score and Left Atrial (LA) volume and Left ventricular global Longitudinal Strain (LV-GLS). Whereas the lower graphs show the absence of a significant correlation with MLHFQ total score and E/E' Ratio and Left Ventricular (LV) Ejection Fraction. None of these correlations were found statistically significant.

dysfunction might be a consequence of LV dysfunction and at the same time be an important step towards the onset of symptoms. It would be particularly relevant to study and assess all of these connections and cause-effect relationships, in order to evaluate their clinical impact. On the other hand, patients' self-evaluation of QoL according to perceived burden of symptoms has proved to be related to hospital readmissions and mortality. [26] A questionnaire that investigates QoL, such as MLHFQ, is a valuable instrument to assess symptoms according to patients' experience and adds readily usable quantification. LA is localized

between LV, a high-pressure system, and the pulmonary venous circulation, a low-pressure system; in fact, one of its function is to cushion pressure changes. [27] It is evident, then, that LA dilation and dysfunction accompany an asymptomatic LV dysfunction shift to overt HF, since both are two of the most common prerequisites of pulmonary congestion. [28]

LA function is efficiently evaluated through STE, assessing global LASr, which estimates LA reservoir function, with an important prognostic impact. [29] It is important to stress that LASr reflects the real myocardial capacity of deformation independently of size parameters, thus indicating the real atrial ability to cushion volume and pressure changes and prevent overload. This is confirmed by the evidence of a good correlation between LA deformation and LV filling pressures [20]. Despite this pathophysiological rationale, the relationship between LASr and symptoms burden has not been totally investigated. The present study demonstrates that in chronic HF patients with a poor QoL an early index of LA function is a more sensible tool of atrial dysfunction than atrial dilation.

For this reason, we suppose that the assessment of LAS, together with other echocardiographic indexes of LV filling pressure, could represent an added tool for the evaluation of the patients' volume overload. Nowadays, one of the main target of therapy in HF patients is to improve QoL, and innovative care strategies are on study. [30] In this context, it is essential to have new independent parameters that can correlate to symptoms and experience of the disease, especially when other classical variables appear to be in the range, although the patient reports worsening QoL. LASr evaluation may thus represent a suitable tool in the daily evaluation of chronic HF patients, and it would be particularly useful to design prospective studies in order to prove the possible correlation between pulmonary congestion and indexes of LA function, such as LASr.

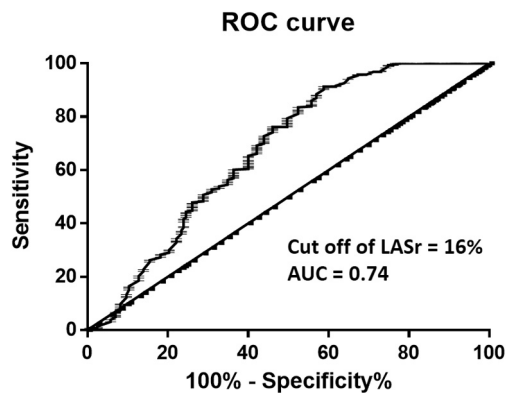


Fig. 3. Receiver operating characteristic (ROC) curve for left atrial strain during reservoir phase (LASr) for prediction of Minnesota Living with Heart Failure Questionnaire (MLHFQ) score > 45. This ROC curve shows the performance of multiple cut-off values for left atrial strain during reservoir function (LASr) to identify subjects with an MLHFQ > 45. The cut-off value of 16% showed the best diagnostic accuracy (AUC = 0.74) in predicting poor Quality of Life.

4.1. Study limitations

The measurement of LA strain requires adequate apical views and experience for a more reliable delineation of LA endocardial border. It is important to highlight the fact that this study focused on the reservoir phase of LA, which is evaluated through LASr, since it has the highest feasibility and reproducibility, whereas it did not assess the conduit phase nor the atrial systole. Furthermore, our preliminary results should be demonstrated in a wider prospective study, to verify their significance and their clinical impact. It would be also important to have serial testing of both echocardiographic parameters and MLHFQ in the same patients over time, in order to strength the correlation between LA function and the patient's volume status and symptoms.

5. Conclusion

The FLASH study examined the correlation between LA structure and function and QoL in HF patients, by analyzing STE. LASr resulted to be inversely correlated with QoL self-evaluated by MLHFQ. On the other hand, we found only a weak correlation between MLHFQ total score and LA volume and LV-GLS. Instead, no correlation was demonstrated either between MLHFQ score and LVEF or between MLHFQ score and E/E' ratio. Finally, STE confirmed to be a good, non-invasive tool for the evaluation of atrial dysfunction, whose clinical impact has to be proven yet.

In reference to the study results, LASr could be considered an echocardiographic parameter which strongly correlates with HF patients' self-evaluated QoL. For this reason, also considering the fact that it is a non-invasive and well-accessible method, it might be integrated in the current serial evaluation of chronic HF patients, for adding to the current decision-making approach.

Conflict of interest

The authors declare that they have no conflict of interest.
Compliance with ethical standards.

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