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ORIGINAL ARTICLE

Potential role of left atrial strain in estimation of left atrial pressure in patients with chronic heart failure

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Abstract

Aims In a large proportion of heart failure with reduced ejection fraction (HFrEF) patients, echocardiographic estimation of left atrial pressure (LAP) is not possible when the ratio of the peak early left ventricular filling velocity over the late filling velocity (E/A ratio) is not available, which may occur due to several potential causes. Left atrial reservoir strain (LASr) is correlated with LV filling pressures and may serve as an alternative parameter in these patients. The aim of this study was to determine whether LASr can be used to estimate LAP in HFrEF patients in whom E/A ratio is not available.

Methods and results Echocardiograms of chronic HFrEF patients were analysed and LASr was assessed with speckle tracking echocardiography. LAP was estimated using the current ASE/EACVI algorithm. Patients were divided into those in whom LAP could be estimated using this algorithm (LAPe) and into those in whom this was not possible because E/A ratio was not available (LAPne). We assessed the prognostic value of LASr on the primary endpoint (PEP), which comprised the composite of hospitalization for the management of acute or worsened HF, left ventricular assist device implantation, cardiac transplantation, and cardiovascular death, whichever occurred first in time. We studied 153 patients with a mean age of 58 years of whom 76% men and 82% who were in NYHA class I-II. A total of 86 were in the LAPe group and 67 in the LAPne group. LASr was significantly lower in the LAPne group as compared with the LAPe group (15.8% vs. 23.8%, $P < 0.001$). PEP-free survival at a median follow-up of 2.5 years was 78% in LAPe versus 51% in LAPne patients. An increase in LASr was significantly associated with a reduced risk of the PEP in LAPne patients (adjusted hazard ratio: 0.91 per %, 95% confidence interval 0.84–0.98). An abnormal LASr ($<$18%) was associated with a five-fold increase in reaching the PEP.

Conclusions In HFrEF patients in whom echocardiographic estimation of LAP is not possible due to due to unavailability of E/A ratio, assessing LASr potentially carries added clinical and prognostic value.

Keywords Heart failure with reduced ejection fraction; Left atrial strain; Left atrial pressure

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Introduction

Elevated left atrial pressure (LAP) in patients with heart failure with reduced ejection fraction (HFrEF) is common and can be a sign of disease progression or trigger of worsening HF.[1] The main reason to noninvasively estimate LAP in HFrEF is that it can be used to guide medical treatment and can affect clinical outcomes.[2,3] Currently, echocardiographic estimation of LAP in HFrEF is performed by evaluating a combination of parameters related to left ventricular (LV) diastolic function.[4]

Potential complicating factors in estimating LAP in HFrEF, are that the algorithms as proposed by the ASE/EACVI guide-

lines are relatively complex and that crucial parameters, such as the ratio of the early (E) to late (A) ventricular filling velocities (E/A ratio), are often affected by heart rhythm abnormalities and/or mitral valve disease.[4] An emerging echocardiographic parameter that may be used to estimate LAP in HFrEF, is left atrial reservoir strain (LASr).[5–7] Previous studies have shown that LASr is impaired in HFrEF,[8,9] and that an abnormal LASr is associated with increased LAP, as measured invasively in patients with moderately and severely reduced LV ejection fraction (EF).[10] An important advantage of measuring LASr, as opposed to traditional echocardiographic estimation of LAP, is that LASr is not affected by atrial fibrillation (AF) and mitral valve disease, conditions that are frequently present in patients with HFrEF.[11,12] Therefore, assessment of LASr in HFrEF patients in whom estimation of LAP cannot be performed due to these comorbidities and in whom E/A ratio is subsequently missing, could help to estimate LAP and herewith to guide treatment and provide prognostic information.

The algorithm as proposed by the ASE/EACVI guidelines for estimation of LAP is not applicable in HFrEF patients in whom E/A ratio is not available. It is unknown whether LASr may be of added value in these patients. Therefore, the aim of this study is to determine whether LASr may be a useful parameter in this specific patient group.

Methods

Study design

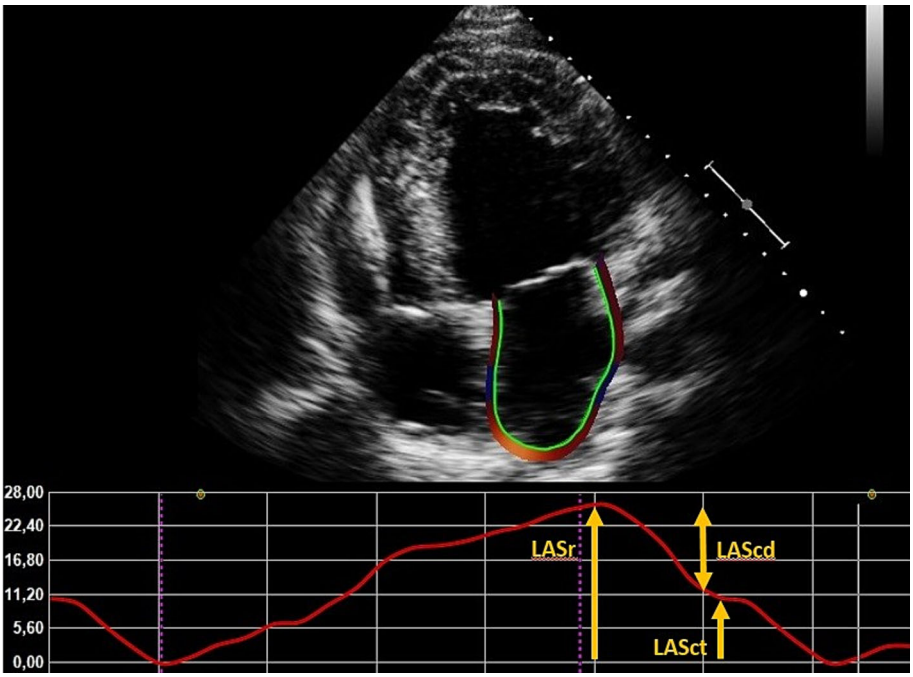
For this study, data was used from the Bio-SHiFT study (Serial Biomarker Measurements and New Echocardiographic Techniques in Chronic Heart Failure Patients Result in Tailored Prediction of Prognosis). Details on the design of the Bio-SHiFT study have been published previously.[13] In short, Bio-SHiFT is a prospective, observational cohort of stable patients with chronic heart failure (CHF), conducted in the Erasmus MC, Rotterdam, and Northwest clinics, Alkmaar, the Netherlands. The main inclusion criteria were diagnosis of HF according to the then prevailing guidelines of the European Society of Cardiology[14,15] and age $\geq$18 years. Ambulant patients were recruited during their regular outpatient visits while in clinically stable condition (i.e. they had not been hospitalized for HF in the 3 months prior to inclusion). Patients were followed for a maximum of 30 months by tri-monthly study visits. During the study, the routine outpatient follow-up by the treating physician also continued for all patients. A total of 398 patients were included in the entire Bio-SHiFT cohort. Out of these, 175 patients were included in an echocardiography substudy at the Erasmus MC[16] of whom 2 patients had insufficient image quality, leaving a total of 173 patients for the substudy. All the patients from the Erasmus MC were eligible to enter the echocardiographic substudy. The study was approved by the medical ethics committees, conducted in accordance with the Declaration of Helsinki, and registered in ClinicalTrials.gov (NCT01851538). All patients signed informed consent for the study.

Echocardiography measurements and evaluation

Two-dimensional grey-scale harmonic images were obtained in the left lateral decubitus position. Conventional and speckle tracking echocardiography was performed on all participants. Standard apical four-, three-, and two-chamber views were recorded. A commercially available ultrasound system was used (iE33, Philips, Best, The Netherlands), equipped with a broadband (1–5 MHz) S5–1 transducer (frequency transmitted 1.7 MHz, received 3.4 MHz). Images were stored in the echo core lab of Erasmus MC. All acquisitions, and measurements were performed according to the ASE/EACVI guidelines[17] using Philips Excellera version R4.1 (Philips Medical Systems, The Netherlands) or TomTec Imaging Systems. Diastolic parameters were assessed, and grading occurred according to the ASE/EACVI guidelines.[4] All echocardiographic measurements were performed blinded to biomarker and clinical event data.

LA strain was measured with speckle tracking and analysed offline with dedicated software (2D Cardiac Performance Analysis version 4.5; TomTec Imaging Systems, Unterschleissheim, Germany). Measurement of LA strain was performed retrospectively by a single operator who was trained and experienced in strain analysis. Intra-observer variability was assessed by re-measuring 20 echocardiograms and calculating the intraclass correlation coefficient. A second operator measured LASr in 20 echocardiograms in order to assess the inter-observer variability. The apical 4-chamber view was used preferably for the analysis. LA endocardial borders were automatically traced using end-diastole as reference. When tracking was suboptimal, fine-tuning was performed manually. If the 4-chamber view was of poor image quality, the 2-chamber view was used. Patients with images of insufficient quality to perform LA strain analysis or patients with an atrial pacemaker were excluded. LA strain was assessed according to the three phases of the LA cycle: LA reservoir strain (LASr) which starts at the end of ventricular diastole (mitral valve closure) and continues until mitral valve opening, LA conduit strain (LAScd) which occurs from the time of mitral valve opening through diastasis until the onset of LA contraction, and LA contractile strain (LASct) which occurs from the onset of LA contraction until the end of ventricular diastole (mitral valve closure). LASr was used for the analysis. All strain values are reported as absolute

Figure 1 Example of left atrial strain measurement. LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contractile strain.



values for improved readability and data interpretation.[18] An example of a LA strain curve is provided in *Figure 1*.

Classification based on available or not available left atrial pressure estimation

Patients in whom E/A ratio was available, were pooled in the group 'LAP estimation available' (LAPe). Patients in whom E/A ratio was not available to estimate LAP (lack of an A-wave due to AF, fusion of E- and A-wave, and/or moderate/severe mitral valve disease) were pooled in the group 'LAP estimation not available' (LAPne). General and echocardiographic characteristics were compared between the LAPe and LAPne group to provide information on severity of disease.

Clinical study endpoints

The primary endpoint (PEP) comprised the composite of hospitalization for the management of acute or worsened HF, LV assist device (LVAD) implantation, cardiac transplantation, and cardiovascular death, whichever occurred first in time. All events were adjudicated by a clinical event committee blinded for the echocardiographic assessments and biomarker measurements, after reviewing corresponding hospital records and discharge letters.

Statistical analyses

Distributions of continuous variables were tested for normality using the Shapiro–Wilk test. Normally distributed continuous variables are presented as mean ± standard deviation (SD), and nonnormally distributed variables as median and 25th–75th percentile. Categorical variables are presented as numbers and percentages. Differences in baseline characteristics between patients in the different LAP groups were tested using ANOVA and the Kruskal–Wallis test, according to variable distributions, for continuous variables, and χ^2 tests and Fisher's exact tests, when appropriate, for categorical variables.

In order to evaluate the association between LASr and the PEP, Cox proportional hazards regression was performed. First, we studied the unadjusted association between LASr (model 1) as well as conventional diastolic echocardiographic parameters and the incidence of the PEP (Supplementary material). Next, we used multivariable models to adjust for age, sex, HF duration, and NT-proBNP[19,20] (model 2), additionally for left atrial volume index (LAVI) and the E/e' ratio (model 3), and additionally for global longitudinal strain (GLS) and EF (model 4).

We report our findings as hazard ratios (HRs) and the corresponding 95% confidence intervals (CI). The HRs are given per one unit increase in LASr. In addition, we dichotomized LASr to study the effect of a normal versus abnormal LASr. For this purpose, we used a cut-off value of 18%.[7] All analyses

were performed with R Statistical Software using package survival.[18] All tests were two-tailed, and *P* values $< .05$ were considered statistically significant.

Results

Baseline characteristics

From October 2011 to January 2018, 175 patients were included in an echocardiography substudy at the Erasmus MC[15] of whom 2 patients had insufficient image quality, leaving a total of 173 patients for the substudy. Twenty patients had an atrial pacemaker and were therefore excluded from the analysis. The remaining 153 patients were used for this analysis of whom 86 patients (56%) were assigned to the LAPe group. In the remaining 67 patients (44%), E/A ratio was not available and these patients formed the LAPne group. In the LAPne group, in 31 patients had moderate/severe mitral regurgitation, 20 patients had AF during the echocardiogram, and 16 patients had unmeasurable A wave due to fusion of the E and the A wave. None of the patients had mitral stenosis. *Figure 2* provides an overview of the included patients and their categorization.

Baseline and echocardiographic characteristics of the study population are shown in *Tables 1 and 2*. In the total study population, 76% patients were male, mean age was 58.0 years ± 11.1 years, and mean LVEF was 28.6% ± 10.2%. Most patients were often in NYHA class I or II (26% and 56% respectively), and ischemic heart disease was the most common HF aetiology (44%).

When comparing the LAPe and LAPne groups, a similar proportion was male, and the groups did not significantly differ in age. However, patients in the LAPne group did have a higher NT-proBNP (233 pmol/L (122 pmol/L–419 pmol/L) vs. 73 pmol/L (27 pmol/L–188 pmol/L), $P < 0.001$), and were in a higher NYHA class (NYHA III 29% vs. 10%, $P = 0.009$). Also, mean systolic blood pressure was lower (104 mmHg ± 17.9 mmHg vs. 110 mmHg ± 17.1 mmHg, $P = 0.039$) and the proportion of prior occurrence of atrial fibrillation was higher (43% vs. 20%, $P = 0.003$). As for medication use, in the LAPe group there was a higher proportion of ACE-inhibitor use (77% vs. 60%, $P = 0.037$) (*Table 1*).

Conventional echocardiographic parameters

The echocardiographic characteristics are shown in *Table 2*. Patients in the LAPne group had a lower mean LVEF (25% ± 9.9% vs. 31% ± 9.9%, $P = 0.001$) and a lower mean GLS (−7.8% ± −3.6% vs. -9.8% ± −3.5%, $P < 0.001$). As for diastolic parameters, patients in the LAPne group had a higher median E/e' ratio (18.7 (12.5–21.6) vs. 14.1 (7.8–19.2), $P = 0.007$), and a larger mean LAVI (46.2 mL/m^2 ± 19.6 mL/m^2 vs. 35.3 mL/m^2 ± 14.6 mL/m^2, $P < 0.001$). The intraclass correlation coefficients for intra-observer and inter-observer variability were 0.93 and 0.89, respectively.

Figure 2 Overview of the study population. LAP, left atrial pressure.

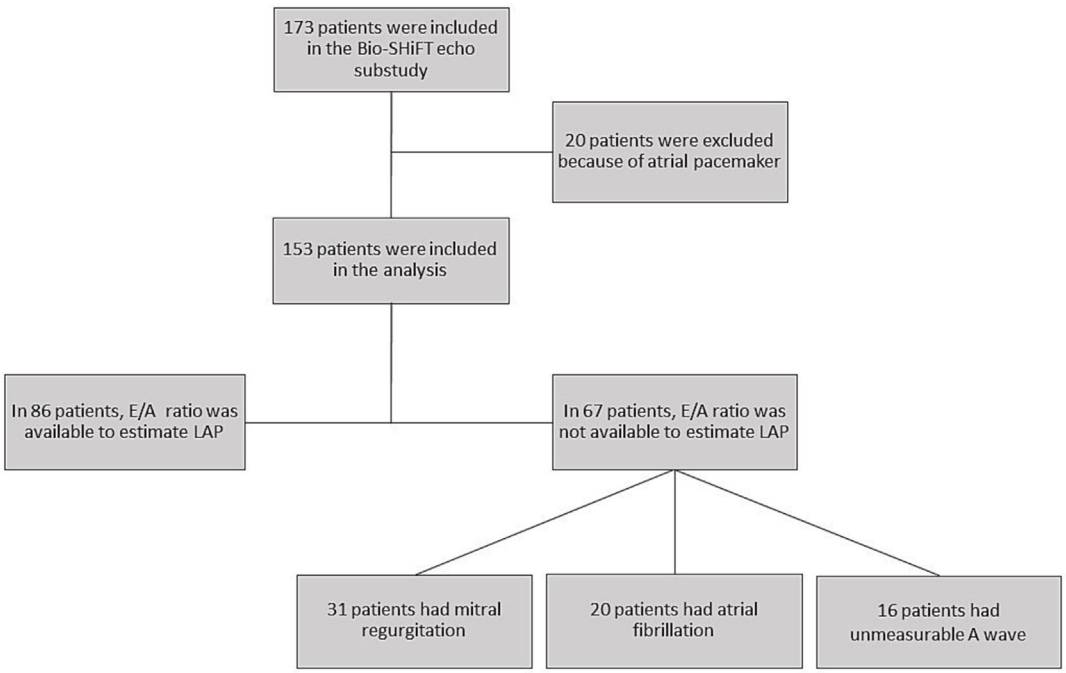


Table 1 Clinical characteristics of the study population

	Total (n = 153)	LAPe (n = 86)	LAPne (n = 67)	P value
Male, n (%)	116 (76)	67 (78)	49 (73)	0.6
Age, years	58.0 ± 11.1	56.9 ± 11.4	59.3 ± 10.7	0.2
BMI, kg/m^2	27.6 ± 4.6	27.8 ± 4.9	27.2 ± 4.3	0.5
Mean heart rate, b.p.m.	68 ± 13	68 ± 15.4	67 ± 10.5	1
Systolic BP, mmHg	107 ± 18.1	110 ± 17.1	104 ± 17.9	0.039
Diastolic BP, mmHg	67 ± 9.6	69 ± 9.9	66 ± 9.6	0.2
NYHA class, n (%)				0.009
NYHA class I	40 (26)	25 (29)	15 (22)	
NYHA class II	84 (56)	52 (61)	32 (49)	
NYHA class III	27 (18)	8 (10)	19 (29)	
NT-proBNP, pmol/L	140 (39–262)	73 (27–188)	233 (122–419)	<0.001
HF aetiology				
Ischemic heart disease, n (%)	67 (44)	38 (44)	29 (43)	1
Hypertension, n (%)	2 (1)	2 (2)	0 (0)	0.6
Cardiomyopathy, n (%)	58 (38)	32 (37)	26 (39)	1
Valvular heart disease, n (%)	4 (3)	2 (2)	2 (3)	1
Unknown, n (%)	9 (6)	6 (7)	3 (5)	0.8
Medical history				
Myocardial infarction, n (%)	65 (43)	38 (44)	27 (40)	0.8
PCI, n (%)	58 (38)	33 (38)	25 (37)	1
CABG, n (%)	15 (10)	8 (9)	7 (10)	1
Atrial fibrillation, n (%)	46 (30)	17 (20)	29 (43)	0.003
Diabetes Mellitus, n (%)	37 (24)	20 (23)	17 (25)	0.9
Chronic renal failure, n (%)	61 (40)	30 (35)	31 (46)	0.2
COPD, n (%)	22 (14)	11 (13)	11 (16)	0.7
Medication				
Beta-blockers, n (%)	145 (95)	81 (94)	64 (96)	1
ACE inhibitors, n (%)	106 (70)	66 (77)	40 (60)	0.037
ARB, n (%)	43 (28)	21 (24)	22 (33)	0.3
Loop diuretics, n (%)	143 (94)	77 (90)	66 (99)	0.059
Aldosterone antagonists, n (%)	110 (72)	58 (67)	52 (78)	0.2

Normally distributed data are presented as mean ± SD, non-normally distributed data are presented as median (25th–75th percentile). P-values represent overall comparison between LAPe and LAPne.
Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HF, heart failure; LAPe, left atrial pressure grading available; LAPne, left atrial pressure grading not available; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Table 2 Echocardiographic characteristics of the study population

	Total (n = 153)	LAPe (n = 86)	LAPne (n = 67)	P value
LASr, %	20.6 ± 11.3	23.8 ± 11.4	15.8 ± 9.7	<0.001
LAScd, %	10.9 ± 5.8	12.5 ± 6.0	8.6 ± 4.8	<0.001
LASct, %	8.8 (3.2–14.0)	11.0 (4.9–15.8)	4.2 (2.1–11.0)	<0.001
LV GLS, %	−8.9 ± 3.7	−9.8 ± 3.5	−7.8 ± 3.6	<0.001
LVEF, %	28.6 ± 10.2	31.1 ± 9.9	25.1 ± 9.9	0.001
E/e' ratio	15.7 (9.5–19.7)	14.1 (7.8–19.2)	18.7 (12.5–21.6)	0.007
TR velocity, m/s	2.5 (2.1–2.8)	2.4 (2.0–2.7)	2.7 (2.4–3.2)	0.01
LAVI, mL/m^2	39.6 ± 17.4	35.3 ± 14.6	46.2 ± 19.6	<0.001
Mitral regurgitation, n (%)				<0.001
None	48 (31)	40 (47)	8 (14)	
Mild	61 (40)	46 (54)	15 (27)	
Moderate	25 (16)	0 (0)	25 (45)	
Severe	8 (5)	0 (0)	8 (14)	

Normally distributed data are presented as mean ± SD, non-normally distributed data are presented as median (25th–75th percentile). P-values represent overall comparison between LAPe and LAPne.
Abbreviations: LAPe, left atrial pressure estimation available; LAPne, left atrial pressure estimation not available; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; LASr, left atrial reservoir strain; LAVI, left atrial volume indexed; LV GLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation.

Left atrial strain parameters

In the total study population, mean LASr was 20.6% ± 11.3%, mean LAScd 10.9% ± 5.8%, and median LASct 8.8% (3.2%–14.0%). Patients in the LAPne group had significantly lower LASr, LAScd, and LASct compared with patients in the LAPe group (resp. 15.8% ± 9.7% vs. 23.8% ± 11.4%, $P < 0.001$; 8.6% ± 4.8% vs. 12.5% ± 6.0%, $P < 0.001$; 4.2% (2.1% - 11.0%) vs. 11.0% (4.9–15.8%), $P < 0.001$).

Clinical endpoints

Median follow-up time was 2.5 years (25^{th}–75^{th} percentile: 2.3–2.6 years). In total, 50 patients reached the PEP, out of whom 37 patients were re-hospitalized for acute or worsened HF, six patients received a heart transplantation, four patients received an LVAD implantation, and three patients died due to cardiovascular causes. The number of PEPs in the LAPe group was 19 (22%). In the LAPne group, a total of 31 patients (46%) reached the PEP (*Figure 3*). The LAPne group had a significantly lower event-free survival time compared with the LAPe group ($P < 0.001$). The event-free survival probability at the median follow-up time was 78% for the LAPe group and 51% for the LAPne group.

Association of left atrial reservoir strain with the composite endpoint

In LAPne patients, LASr was significantly associated with reduced incidence of the PEP (unadjusted HR was 0.84 per 1% absolute increase; 95% CI 0.78–0.90). After adjustment for age, sex, HF duration and NT-proBNP (model 2) the association remained statistically significant, as well as after additional adjustment for conventional diastolic (model 3) and systolic (model 4) echocardiographic parameters (*Table 3*). Abnormal LA strain was associated with a five-fold increase in risk of reaching the PEP (HR 5.2, 95% CI 1.4–18.9). An overview of the associations of LASr with the PEP is presented in *Table 3*.

Table S1 shows the univariable associations of echocardiographic parameters with the PEP in the LAPne group. LASr showed the strongest association (HR 0.84, 95% CI 0.78–0.90).

Discussion

In the present study, we have demonstrated that assessment of LASr has added clinical and prognostic value in the large proportion of HFrEF patients in whom estimation of LAP is not possible with conventional echocardiographic parameters due to unavailable E/A ratio. A decrease in LASr was associated with an increased risk of the PEP, even after adjusting for potential confounders. Therefore, in HFrEF patients with limited prognostic information due to missing E/A ratio and consequently unavailable LAP estimation, LASr can provide important information on prognosis, which may help monitor HF severity and guide medical treatment.

Figure 3 Kaplan–Meier survival curves displaying the survival probabilities for both groups (logrank test). LAPe, left atrial pressure estimation available; LAPne, left atrial pressure estimation not available.

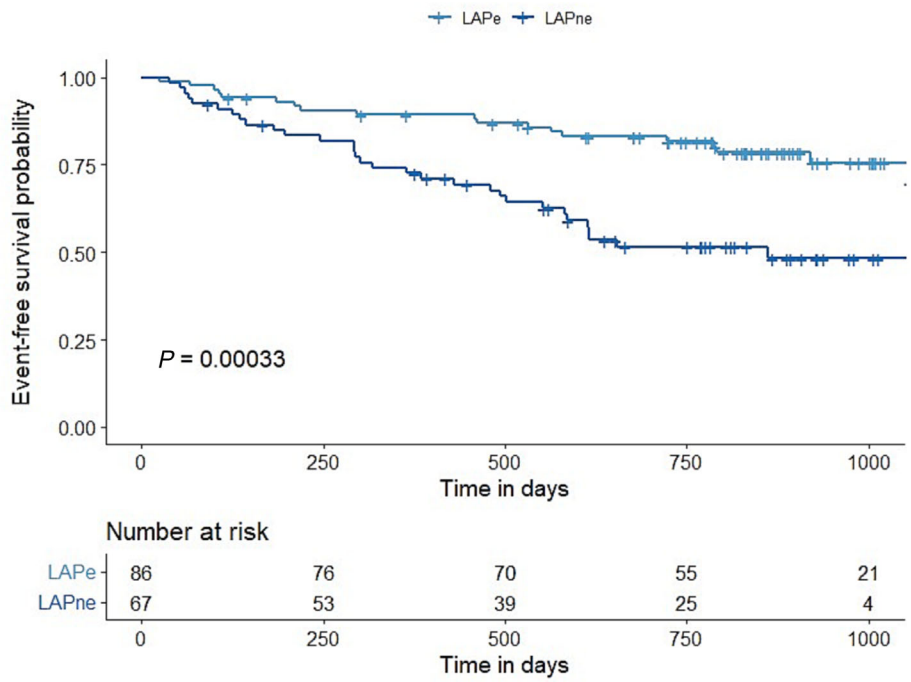


Table 3 Associations of left atrial reservoir strain with the primary endpoint

	LAPe (n = 86) HR (95% CI)	LAPne (n = 67) HR (95% CI)
Model 1	0.90 (0.85–0.97)	0.84 (0.78–0.90)
Model 2	0.85 (0.77–0.93)	0.91 (0.85–0.97)
Model 3	0.87 (0.79–0.96)	0.91 (0.84–0.98)
Model 4	0.88 (0.79–0.97)	0.88 (0.79–0.98)

Model 1: univariable analysis. Model 2: corrected for age, sex, HF duration, and NT-proBNP. Model 3: corrected for age, sex, HF duration, NT-proBNP, left atrial volume index, E/e' ratio (log transformed). Model 4: corrected for age, sex, HF duration, NT-proBNP, global longitudinal strain, left ventricular ejection fraction.

Assessing left atrial pressure in heart failure with reduced ejection fraction

Although the treatment of HF has improved over the last decade, the mortality due to HF remains high and repeated hospitalizations for HF occur frequently.[20] Categorization of HF is mainly based on systolic function, and less on diastolic determinants.[21] However diastolic determinants are essential in HFrEF, as they can provide information on LAP that can be used to guide prognosis.[2,3,22,23] Cardiac catheterization remains the gold standard for assessing LV pressure and subsequent LAP. Nevertheless, cardiac catheterization is less attractive for routine assessment of LAP because its invasive nature carries a non-negligible risk and adds significant costs.[24] Using echocardiography, a rough estimation of LAP can be made along with grading of diastolic function, using a combination of several echocardiographic parameters.[4] A limitation of this approach is that a large number of HFrEF patients may remain uncategorized because of the absence of a reliable E/A ratio. A common comorbidity in HFrEF that limits measurements of the E/A ratio, is AF during the echocardiogram. The prevalence of concomitant AF in HFrEF patients is high, and assessment of diastolic determinants in AF is limited by the variability in cycle length, the absence of organized atrial activity and subsequent missing A wave, as well as the frequent occurrence of LA enlargement regardless of filling pressures.[4,25] The co-existence of mitral valve disease also restrains the usability of echocardiographic assessment of LAP. Moderate to severe mitral regurgitation (MR) or stenosis (MS) leads to an elevation in peak E velocity and LA enlargement and thus the evaluation of LAP is hindered.[4,26]

LASr is not affected by these conditions and could therefore provide a clinical solution to estimate LAP in these HFrEF patients.[10–12] Our study is the first to investigate the potential role of LASr in HFrEF patients in whom echocardiographic assessment of LAP is not possible due to lack of one or more of the required echocardiographic parameters. The importance of measuring LAS in patients with HFrEF is illustrated by the observation that LAS is associated with invasively measured LV filling pressure.[7,10] In a study consisting of 322 patients with various cardiovascular diseases, LASr and LASct predicted LV filling pressure better than conventional echocardiographic markers.[7] In the same study, LASr <18% supported elevated LV filling pressure in patients with reduced HFrEF. In our cohort, LASr was 15.8% in the LAPne group, while in the LAPe group this was 23.8%. Because LASr has been shown to correlate with LAP,[5,7,10] this observation indicates that in the LAPne group LAP was more increased, a finding in-line with several other clinical and echocardiographic parameters that pointed at a more severe disease stage in these patients.

Role of conventional diastolic parameters and left atrial reservoir strain in clinical outcomes of heart failure with reduced ejection fraction patients

Only a few studies have previously investigated the role of parameters of LV diastolic function on outcomes in HFrEF patients.[27,28] In a study consisting of 2018 HFrEF and HF patients with mid-range EF (HFmrEF), severe diastolic dysfunction was associated with increased all-cause mortality.[28] A study by Benfari et al. investigated the mortality associated with diastolic echocardiographic measures in patients with HFrEF, and found that elevated E/e' was associated with substantially reduced short-term survival.[27] However, these studies did not include LASr in their analysis, and focused specifically on patients in whom estimation of LAP was possible with conventional echocardiographic parameters.

Studies that have focused on the prognostic value of LASr in HFrEF, have demonstrated that measurement of LASr is predictive of clinical outcomes in these patients.[9,29,30] The strength of our study is that it is the first to investigate the potential role of LASr specifically in patients in whom grading of LAP with the current guideline algorithm is not possible due to conditions such as AF and MR. We demonstrated that in this LAPne group, a decrease in LASr was associated with an increased risk of PEP, even after adjusting for multiple confounders. Moreover, an abnormal LASr <18% was associated with a five-fold increased risk in reaching the primary endpoint in the LAPne group. In addition, we showed that LASr was significantly associated with the primary outcome, while conventional echocardiographic parameters, such E/e' and LAVI, were not. We also found that LASr was associated with the PEP in the LAPe group, which suggests that LASr also carries prognostic information in this group. However additional prognostic information is essential for the LAPne group, while sufficient prognostic information may already be available in the LAPe group by using the ASE/EACVI algorithm.

Study limitations

Treating physicians were not blinded to the echocardiograms and conventional parameters derived from the echocardiograms. Therefore, echocardiographic characteristics may have influenced treatment. However, LAS values were not available to the treating physicians because they were measured after completion of follow-up. Strain analysis were performed by a single operator. However, to assess the inter-observer variability, a second operator measured LASr in 20 echos, and correlation was shown to be high. In addition, the sample size of this study was modest and so was the number of endpoints, which limits statistical power. Also, consequently, the number of variables that could be entered into the Cox models was limited, and therefore residual confounding may be present. However, we adjusted for the most important confounders, we also adjusted for the duration of HF at baseline, to control for possible lead time or length time bias. Furthermore, the patients in this echo sub-study were mostly men and relatively young and there was a relatively high proportion of HF patients in NYHA classes I and II. This may be because older patients with worse condition were less likely to participate in the echo sub-study of Bio-SHiFT. The results may therefore not be extrapolated to patients in more advanced stages of HF. Finally, inherent to the design of this study, patients in the LAPne group were in worse condition than those in the LAPe group. Nonetheless, there is currently no estimate for LAP in this group of patients, further stressing the importance for an appropriate parameter for LAP estimation in this group and underscoring the relevance of our study.

Conclusion

In patients with HFrEF in whom LAP cannot be estimated using the conventional algorithm due to an unavailable E/A ratio, LASr is able to provide clinical and prognostic information that may help monitor HF severity and guide medical treatment.

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Conflict of interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Univariable associations of conventional echo parameters with the primary endpoint.

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