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DISSERTATION

Die Bedeutung des linksatrialen Strain bei Herzinsuffizienz

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List of Abbreviations

2D	Two-dimensional
AECL	Academic Echo Core Lab
ASE	American Society of Echocardiography
AUC	Area under the curve
CAD	Coronary Artery Disease
DM	Diabetes Mellitus
EACVI	European Association of Cardiovascular Imaging
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HTN	Arterial hypertension
LA	Left atrial
LAVI	Left atrial volume index
LV	Left ventricular
LVDD	Left ventricular diastolic dysfunction
LVEF	Left ventricular ejection fraction
TR	Tricuspid regurgitation velocity

Abstract:

Aim: To examine the potential of left atrial (LA) strain to detect early cardiac alterations or elevated filling pressures in patients with cardiovascular risk factors and preserved left ventricular ejection fraction (LVEF) and in patients with symptomatic heart failure (HF).

Methods and results: 517 patients in sinus rhythm with cardiovascular risk factors and preserved LVEF and 300 patients with symptomatic HF were analyzed. In patients with cardiovascular risk factors and preserved LVEF, LA strain was the most affected parameter, when compared to other imaging parameters of LA function (rate of abnormal results: LA strain 18.8%; LA strain rate: 3.8%, LA emptying fraction: 7.3%, and LA expansion index: 3.8%). In line with these findings, an abnormal LA strain was significantly associated with HF hospitalizations at 2 years (OR: 6.6 [2.6 -16.6]), even after adjustment for age and gender and despite preserved LV or LA conventional measurements such as LV ejection fraction and LA volume index. In patients with HF, LA strain showed a high sensitivity to determinate left ventricular diastolic dysfunction (LVDD) (sensitivity 80%, specificity 77.8%), which was better than conventional parameters such as LA volume index and the mitral E/e´ ratio. Moreover, in both patient cohorts a high percentage of patients with normal left atrial volume index had an abnormal LA strain value (i.e., 29.4% of the patients in risk for cardiac alterations and 60.6% of patients with symptomatic HF).

Conclusion: The results of my analyses suggest that the use of new LA imaging parameter such as LA strain could be useful and clinically relevant in the evaluation of patients with cardiovascular risk factors and in those with established HF.

Abstrakt:

Ziel: Ziel meiner Arbeit war zu untersuchen ob der neue echokardiographische Parameter „linksatrialer (LA) Strain“ zur Früherkennung kardialer Veränderungen in Risikokonstellationen, sowie zur Erkennung erhöhter Füllungsdrücke bei Patienten mit symptomatischer Herzinsuffizienz (HF) beiträgt.

Methoden und Ergebnisse: 517 Patienten im Sinusrhythmus mit kardiovaskulären Risikofaktoren und normaler systolischer linksventrikulärer Funktion (LVEF) und 300 Patienten mit etablierter HF wurden analysiert. Bei Patienten mit kardiovaskulären

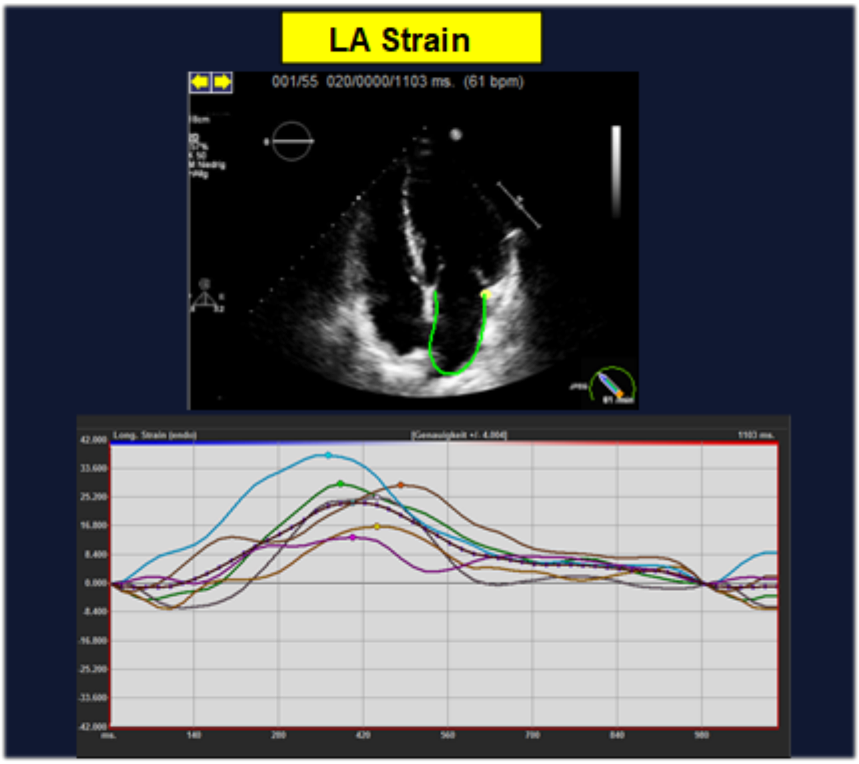
Risikofaktoren und normaler LVEF war LA Strain der am meisten beeinträchtigte Parameter im Vergleich zu anderen konventionellen LA-Parametern (Häufigkeit von abnomalen Befunden: LA-Strain 18.8%; LA Strain Rate 3.8%; LA-Entleerungsfraktion 7.3%; LA-Expansionsfraktion 3.8%). Ein abnormaler LA Strain zu Studienbeginn war im klinischen Follow-Up (2 Jahre) signifikant mit einem HF-Krankenhausaufenthalt assoziiert (OR: 6.6 [2.6–16.6]), selbst nach statistischer Korrektur für Alter und Geschlecht und trotz erhaltener konventioneller LV- oder LA-Bildgebungsparametern wie LV-Ejektionsfraktion und LA Volumen.
Darüber hinaus zeigte LA Strain bei Patienten mit HF eine gute diagnostische Wertigkeit zur Vorhersage schwerer diastolischer LV-Veränderungen (Sensitivität 80%, Spezifität 77.8%), besser als konventionelle echokardiographische Parameter wie LA-Volumenindex und E/e´ Verhältnis. Ferner, hatte in beiden Patientenkohorten ein hoher Prozentsatz der Patienten mit normalem Index des linken Vorhofvolumens (LAVI) einen abnormalen LA Strain-Wert (29.4% der asymptomatischen Patienten mit Risiko für Herzveränderungen und 60.6% der Patienten mit symptomatischer HF).
Schlussfolgerung: Die Ergebnisse meiner Untersuchungen legen nahe, dass die Verwendung neuer sensitiver LA-Parameter wie des LA Strain potenzielle Nützlichkeit und klinische Relevanz bei der Bewertung von Patienten mit kardiovaskulären Risikofaktoren und bei Patienten mit etablierter HF haben könnte.

1. Introduction

The left atrium (LA) plays a key role during the cardiac cycle, acting as a blood reservoir during cardiac systole, as a conduit for blood flow during early diastole and as booster pump during late diastole ("atrial kick").(1, 2) Despite the complexity of atrial passive and active function, only left atrial diameter and volume during left ventricular (LV) end-systole (assessed by 2D-echocardiography) are used in clinical practice to describe atrial alterations. (3)However, structural LA abnormalities may only be present in advanced stages of cardiac disease, and do not describe atrial function. In fact, disturbed atrial function may be an early and sensitive parameter to predict cardiac overload, elevated filling pressures, and ventricular dysfunction. (3) A relatively new imaging-based parameter which is used to assess cardiac mechanics is strain.(4, 5) Strain is a software-derived measure, which is expressed in percentage and reflects the fractional change of the length of a selected myocardial segment in the longitudinal, circumferential or radial direction, based on the orientation of the myocardial fibers.(4, 5) Regarding the LA, longitudinal strain can be measured for all three aforementioned functions of this chamber.(4, 5) Reservoir strain reflects the deformation of the LA after receiving the blood form the pulmonary veins during ventricular systole.(4, 5) During this phase LA reaches its maximum volume and thus LA reservoir strain represents the positive peak value of LA strain. This parameter was shown to be well correlated to LV longitudinal strain and LV diastolic function.(4, 5) Thus, LA strain is referring to LA reservoir strain (see Figure 1).(4, 5) LV diastolic dysfunction plays a fundamental role in the pathophysiology of heart failure and can be characterized by means of echocardiography. In clinical practice, Doppler-derived and volumetric echocardiographic parameters are used for the evaluation of the LV diastolic function. Previous studies have suggested that strain could be more sensitive than LAVI to detect LA or LV diastolic alterations.(6-8) Moreover, this parameter was shown to be well correlated with invasive measurements of end-diastolic LV filling pressures.(9-11) Nevertheless, the clinical and prognostic relevance of LA strain has not been comprehensively studied in early versus advanced stages of the HF continuum. Therefore, the purpose of my analyses was to examine the clinical and prognostic role of LA strain in patients with cardiovascular risk factors and preserved LVEF and in symptomatic HF patients, irrespective of LV ejection fraction.

Figure 1.

Example of left atrial reservoir strain measurement in apical 4-chamber view. LA reservoir strain was defined as the average value of the positive longitudinal strain peak during LA filling and LV contraction as indicated by the fragmented line using the onset of QRS as reference point (Software: Tomtec Arena; apical-four-chamber view).



2. Methods

2.1. Study populations

I included 2 patient cohorts in my analysis: 1) a cross-sectional retrospective study analyzed patients referred to the Echocardiography Laboratory of the Department of Internal Medicine and Cardiology (Director: Prof. Dr. med. Burkert Pieske) at Charité University Medicine, Campus Virchow Klinikum, Berlin, Germany. Patients were recruited between July 2009 and October 2014.(12) The inclusion and exclusion criteria for these patients cohort can be seen in Table 1.

Table 1. Inclusion and exclusion criteria for the Charité patient cohort.(3, 12)

Inclusion Criteria
Patients with preserved LV systolic (LVEF ≥52% in men or ≥54% in women) and LV diastolic function (see diagnostic algorithm, page 9) with or without risk factors for cardiac functional or structural alterations, defined as patients with arterial hypertension (HTN), diabetes mellitus (DM) or a history of coronary artery disease (CAD).

Exclusion Criteria
Elevated filling pressures according to the criteria of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI), LAVI>34 ml/m², mitral E/e' average>14, significant valvular stenosis, moderate or severe aortic or mitral regurgitation, severe pulmonary or tricuspid regurgitation, valvular heart surgery or intervention, and significant mitral annular calcification (≥ 5 mm), supraventricular arrhythmias or atrial fibrillation within 3 months before the echocardiographic examination, ventricular paced rhythm or left bundle branch block, hypermobile interatrial septum, interatrial septal aneurysm, poor 2D imaging quality in ≥ 1 LA segments, severe pulmonary disease, severe kidney disease, and severe liver disease.

For our next two cross-sectional, retrospective studies the same Charité patient cohort was analyzed, with the difference that the presence of LVDD was not an exclusion criterion. (13, 14)

Our fourth study was a retrospective study that analyzed a group of patients who were included in the SOCRATES-PRESERVED and SOCRATES-REDUCED trials.(15) These were two multi-center, randomized, double-blind, placebo-controlled, Phase 2 dose-finding trials, that tested the effects of the novel sGC stimulator vericiguat on surrogate imaging parameters and NTproBNP in patients after stabilization from a worsening chronic HF episode.(16) SOCRATES-REDUCED included 456 patients≥ 18 years old, with LVEF< 45%, NYHA class II–IV symptoms and treatment with guideline-directed medical HF therapy for 30 days or longer before hospitalization or intravenous diuretic administration without hospitalization, who were clinically stable prior to randomization (no intravenous vasodilator therapy for at least 24 hours and no intravenous diuretic therapy for at least hours; systolic blood pressure 110 mm Hg or greater and less than 160 mm Hg, and heart rate 50/min or greater and less than 100/min) and had a recent episode of worsening chronic HF defined by 3 components: worsening HF symptoms requiring either hospitalization or outpatient administration of intravenous diuretics; signs of congestion (clinical or chest radiograph findings); and elevated natriuretic peptide level (N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 1000 pg/mL or B-type natriuretic peptide (BNP) ≥ 300 pg/mL if in sinus rhythm, or NT-proBNP ≥1600 pg/mL or BNP ≥ 500 pg/mL if in atrial fibrillation.(16, 17) SOCRATES-PRESERVED trial included 477 patients ≥ 18 years old with LVEF ≥ 45%, NYHA class II–IV symptoms, elevated natriuretic peptide level and LA enlargement by echocardiography at randomization. (16, 18)The Charité ethics committee approved the locally generated cohorts informed consent was obtained from all included patients.(12-14) Likewise, institutional review board or ethics committee approval was obtained at each study site and all patients provided written informed consent for the SOCRATES trials.(16-18)

2.2. Echocardiography

Patients that were included in our first three studies were examined using a Vivid 7 or E9 (GE Healthcare, Horton, Norway) ultrasound system at the Laboratory of Echocardiography of the Charité University Hospital.(12-14) For each echocardiographic parameter, an average of three consecutive measurements was calculated.(12-14) 2D and Doppler measurements were conducted according to ASE and EACVI guidelines for chamber quantification and diastolic dysfunction.(3, 19) Moreover, in order to compare the ability of LA strain to detect DD in comparison to that of LAVI we excluded LAVI from the recommended diagnostic algorithm of DD.(12, 13) For this purpose, we used only Doppler parameters to define patients with diastolic alterations, who were divided into three groups (patients with mild diastolic dysfunction when septal e’<7cm/s or lateral e’<10 cm/s and average E/e’<10, patients with moderate diastolic dysfunction when septal e’<7cm/s or lateral e’<10 cm/s and average E/e’ 10 to 14 and patients with severe diastolic dysfunction (equivalent to elevated filling pressures) when septal e’<7cm/s or lateral e’<10 cm/s and average E/e’>14.(12, 13) Using the Nagueh’s formula for the estimation of pulmonary capillary wedge pressure (PCWP) (i.e., estimated PCWP=2+1.3 x mitral E/lateral e’ ratio), we analyzed the correlation of LA strain with PCWP.(13)
DD was assessed by means of 2D echocardiography according to the 2016 recommendations of ASE and EACVI.(3) Namely, for patients with reduced LVEF (i.e. LVEF <50%) or for patients with preserved LVEF and myocardial abnormalities (i.e. LVEF ≥50%) according to the mitral inflow measurements patients were classified to patients with normal left atrial pressure (LAP) or Grade I diastolic dysfunction when E/A≤0.8 and E≤50 cm/s, and patients with elevated LAP or Grade III diastolic dysfunction when E/A ≥2.(19) For patients with E/A ≤0.8 and E>50 cm/s or 0.8<E/A<2 three additional criteria [i.e. Average E/e’>14, Tricuspid regurgitation velocity (TR)> 2.8 m/s, LAVI>34 ml/m^2] were evaluated. In case of two negative criteria patients were classified as patients with Grade I diastolic dysfunction, in case one criterion was positive and one negative and the third could not be assessed during the examination patients could not be classified and finally patients with 2 positive criteria were classified as patients with Grade III diastolic dysfunction.(3)

Speckle tracking analysis (2DSTE) was performed offline by one cardiologist (reader), whose focus was echocardiography using the Echo-Pac version 113.0 GE Healthcare software package.(12-14) The reader was blind to the patient clinical-data. The onset of QRS was used as starting point of the cardiac cycle. LA strain was calculated by the software after depicting the region of interest (ROI) in apical 4- and 2-chamber view at frame rates of 50–80 frames/s. The positive peak value of LA reservoir strain during the cardiac systole (namely, LA strain) and the negative peak value of LA strain rate during LA contraction in late diastole (LASRa) were analyzed. Each analysis was conducted in three consecutive cardiac cycles and an average was calculated.
For the volumetric analysis we used the LA total emptying fraction (LAEF) [(maximal volume – minimal volume)/maximal volume] and the LA expansion index (LAEI) [(maximal volume − minimal volume)/minimal volume]. Furthermore, we calculated a new index defined as the ratio of mitral E velocity over LAS, which we named ‘LA filling index’. Mitral E velocity was derived by means of pulsed-wave Doppler, after expiration, at the tips of the mitral leaflets.
SOCRATES Preserved and Reduced patients received an echocardiogram at the participating centers by a sonographer certified by the academic echo core lab at Charité (AECL). Subsequently, the site-recorded echocardiography DICOM files were sent to the AECL for analysis. All AECL measurements and analyses were performed and saved as still images and the 2DSTE analyses as videos in the central server. Afterwards, each measurement and analysis was checked by a cardiologist of the AECL with long experience in echocardiography. In case of an error, the measurement or analysis was repeated by the over-reader and the result was replaced. Members of AECL were blinded to patients’ data. For the purpose of the 2DSTE analysis we used the same rules as in our previous studies, but this time TomTec 2D Cardiac Performance Analysis Software (Version 4.6) was used.(15)
Based on previously published studies, we used a cut-off of 23% as the lower limit of normality of LAS, -0,90 s^{-1} for LASRa, 50% for LAEF und 73% for LAEI in all our four studies. (20, 21)
The author of this thesis (A.F) received a sufficient 6-month-training in echocardiography in the AECL of Charite´ and was certified by the EACVI for adult transthoracic echocardiography after successfully passing the exam.

2.3. Statistical analysis:

The statistical analysis was performed with the use of SPSS (IBM), MedCalc (MedCalc Software bvba) or Statview. Mean ± standard deviation (SD) was used for continuous values and percentages for dichotomous data. For differences in continuous variables between two groups we used the Student´s t-test and between three groups the analysis of variance (ANOVA). Categorical variables were compared by using the Chi square test, Fisher exact-test, χ^2 and the McNemar test.

The association of the LA filling index and LA strain with continuous variables was analyzed using a simple linear regression analysis (with b coefficient as the main analysis), and with dichotomous variables using a logistic regression analysis [with the odds ratio (OR) as the main analysis].

In order to analyze the association and diagnostic performance of LA strain to detect LVDD as well as that of LA filling index to detect elevated LV filling pressures [by means of invasive measurements within 72h of the echocardiographic examination [(LVEDP > 16mmHg), test-cohort: n=31] we used the area under the curve (AUC) of receiver operating characteristic (ROC) curve analysis. The optimal cut-off value of LAS and LA filling index was defined by the Youden Index (Youden Index = sensitivity + specificity – 1) and ROC curves of LA strain and LA volumetric parameters were compared by the DeLong's method. Furthermore, the diagnostic performance of the cut-off of the LA filling index to determine elevated LV filling pressures in the test cohort was also verified in a validation cohort (cohort without patients with invasive LVEDP measurement, n=486) using the 2016 ASE/EACVI recommendations, as well as in the group of patients without cardiovascular diseases or cardiovascular risk factors (specificity-validation cohort, n=120).

Moreover, in order to test the association of an elevated LA filling index with the risk of heart failure (HF) hospitalization at 2 years after inclusion in the study, we searched retrospectively all the digital medical records of the study patients. Subsequently, a logistic regression analysis (with the OR and C-statistic as the main analysis) was performed.

Patients with DM and CAD had a high prevalence of HTN. Therefore, when analyzing the association of abnormal LAS with the presence of HTN, DM or the history of CAD separately, "CAD only" was used to indicate history of CAD without the presence DM and likewise "DM only" the presence of DM without the history of CAD. Unadjusted and adjusted logistic regression analyses were conducted with the purpose of evaluating the link between pathological LA strain and dyspnea, worse New York Heart Association functional class (NYHA), and elevated PCWP, whereas Pearson correlation analysis (with r correlation coefficient as the main analysis) was performed to test the association of LA strain with LV echocardiographic diastolic parameters.

The reproducibility of LA strain (for both the Charité patient cohort and the SOCRATES cohort) and LA filling index were analyzed on 20 randomly selected patients and the intra- and inter-observer variability of those parameters were calculated.

A P-value of < 0.05 was necessary in order to consider differences as statistically significant.

3. Results:

The clinical and baseline echocardiographic characteristic of the patients included in each cohort is shown in Table 2. For the SOCRATES echocardiography analysis, we focused on the echocardiographic data of the patients and no clinical data were used.

Table 2. Clinical and echocardiographic characteristics of each patient cohort(12-15)

	Charité patient cohort (n=517)	**SOCRATES echocardiography analysis (n=300)**
Age (years)	68.0 ± 13.0	n/a
Women (%)	46.0	n/a
Body mass index (kg/m2)	27.5 ± 4.8	n/a
Systolic blood pressure (mmHg)	135.9 ± 15.2	n/a
Diastolic blood pressure (mmHg)	80.3 ± 11.2	n/a
Heart rate (b.p.m.)	71.2 ± 9.3	n/a
Arterial hypertension (%)	95.0	n/a
Diabetes mellitus (%)	30.6	n/a
History of coronary artery disease (%)	33.8	n/a
LV ejection fraction (%)	62.1 ± 5.7	42.4 ± 16.6
LV mass index (g/m²)	100.3 ± 25.1	141.1 ± 41.9

Septal e' mitral annular velocity by TDI (cm/s)	5.5 ± 1.9	5.1 ± 2.1
Lateral e' mitral annular velocity by TDI (cm/s)	7.6 ± 2.4	7.5 ± 3.0
Mitral early-diastolic inflow velocity (E) (cm/s)	71.3 ± 21.9	86.8 ± 28.3
Mitral E/ e' septal-lateral average ratio (Av. E/ e')	11.9 ± 5.2	15.0 ± 6.5
LA volume index (LAVI) (mL/m²)	27.1 ± 10.0	43.1± 13.5
LA strain (%)	26.6 ± 9.7	17.5 ± 7.9
TR jet peak velocity (m/s)	2.24 ± 0.49	2.82 ± 0.54

Values are expressed in mean ±SD.

Concerning the potential usefulness of LA strain to detect early cardiac alterations, by analyzing the cohort of 234 patients with CV risk factors and preserved LVEF, LA strain showed the highest sensitivity to detect cardiac alterations in in comparison to conventional LA parameters (see Table 3). (12)

Table 3. Early left atrial mechanical alterations in patients in risk for cardiac abnormalities assessed by conventional and 2DSTE parameters (12)

Parameters	**Controls (n=48)**	**All patients with risk for cardiac abnormalities (n = 234)**	**HTN only (n = 132)**	**DM only (n=40)**	**CAD only (n=40)**
LA strain absolute values (%)	38.5 ± 12.6	29.2 ± 8.6	30.3 ± 8.2	29.9 ± 9.8	26.5 ± 7.5
LA strain <23%	0%	18.8%	11.4%	20%	26.3%
LSRa absolute values (s−1)	2.30 ± 0.7	1.73 ± 0.5	1.78 ± 0.5	1.78 ± 05	1.55 ± 0.4
LSRa< 0.90 s−1	0%	3.8%	2.3%	7.5%	5.3%
LAEF absolute values (%)	65.3 ± 7.2	63.1 ± 9.9	63.1 ± 8.9	63.0 ± 11.5	62.1 ± 11.4
LAEF<50%	2.1%	7.3%	5.3%	12.5%	5.3%
LAEI absolute values (%)	200.8 ± 62	192.3 ± 88	188.3 ± 79	199.8 ± 105	192.4 ± 104

LAEI<73%		0%	3.8%	3.8%	5%	2.6%
Normal GLS	**LA strain absolute values (%)**	38.1 ± 12.1	30.1 ± 8.5	31.1 ± 8.0	31.8 ± 9.5	26.4 ± 7.0
	LA stain <23%	0%	13.9%	7.6%	9.7%	24.2%
Abnormal GLS	**LA strain absolute values (%)**	n/a	23.7 ± 7.3	23.5 ± 6.2	23.4 ± 8.2	27.1 ± 11.0
	LA strain<23%	0%	48.5%	42.9%	55.6%	40%
Normal septal and lateral e'	**LAS absolute values (%)**	39.5 ± 12.7	32.5 ± 8.7a	32.5 ± 8.3	38.6 ± 10.5	27.2 ± 4.9
	LA strain <23%	0%	6.8%	5.9%	0%	10%
Abnormal septal or lateral e'	**LA strain absolute values (%)**	36.0 ± 12.7	27.7 ± 8.1a	28.9 ± 7.8	27.0 ± 7.7	26.2 ± 8.2
	LA strain<23%	0%	24.4%	14.8%	26.7	32.1%

Values are mean ± SD or %.

Moreover, we identified a group of patients with LA dysfunction detected by LA strain, despite a normal LAVI (see Figure 2).

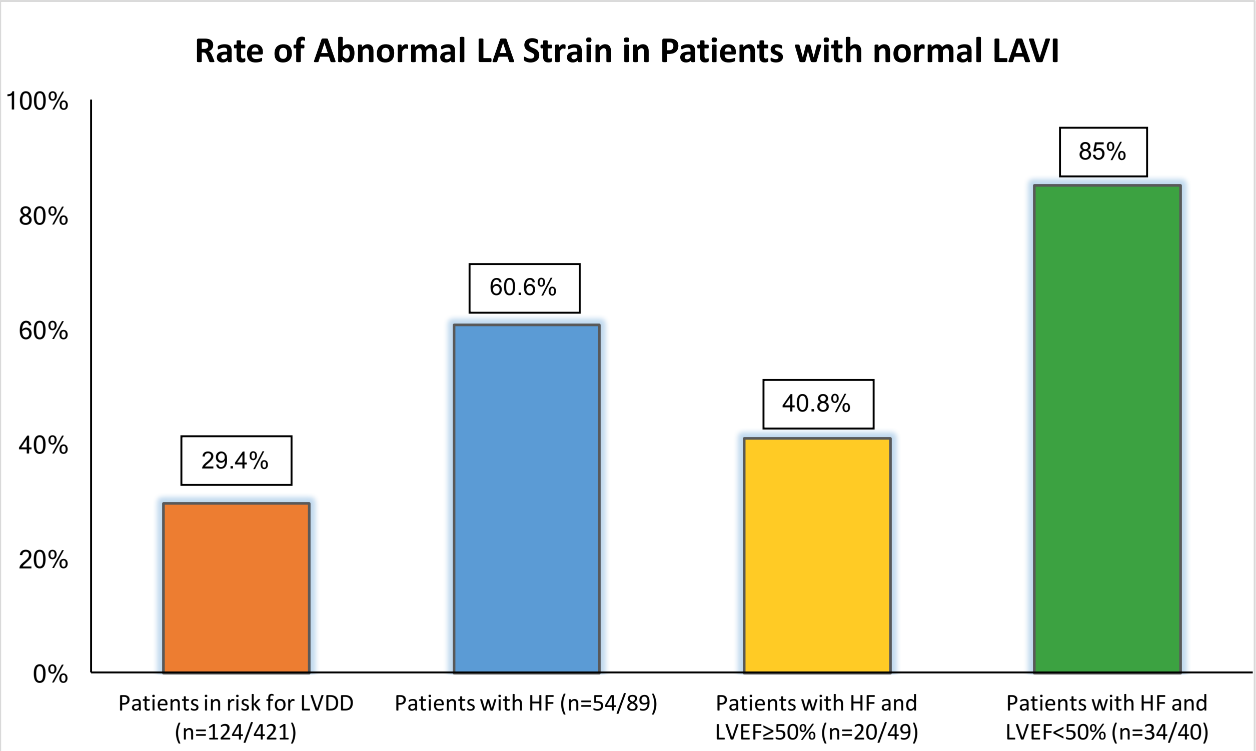


Figure 2. Rate of left atrial dysfunction detected by abnormal left atrial strain in patients with normal left atrial volume index.

In line with the previous mentioned findings, LA strain was well correlated with the severity of LVDD both in the Charité and in the SOCRATES cohort (see Table 4). (14, 15)

Table 4. Correlation between the Grade of LV diastolic dysfunction and LA strain(13, 15)

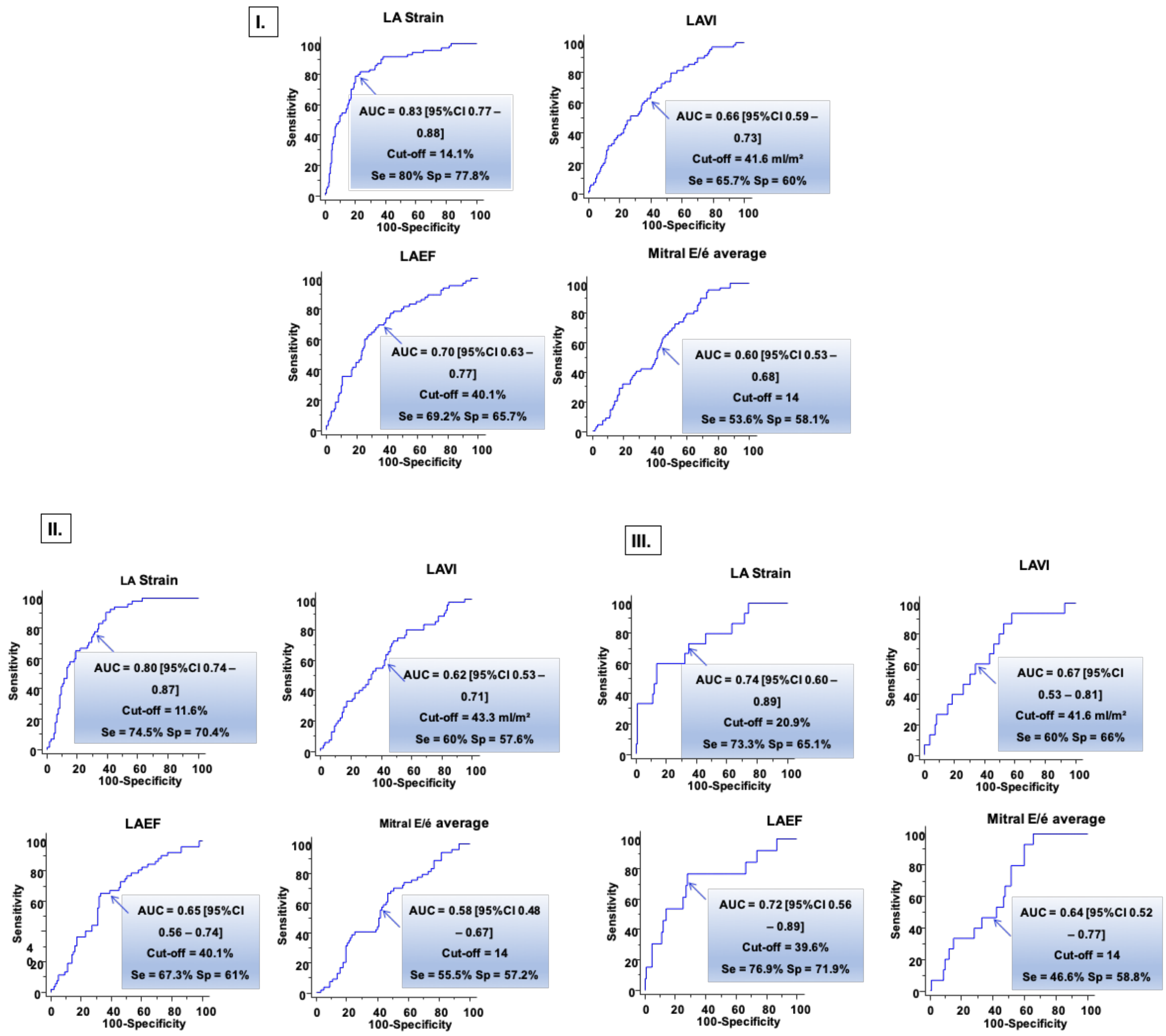
Charité cohort (n=517)	**LVDD Grade based on 2016 ASE recommendations**				
	Normal (n=337)	**Grade I (n=133)**	**Grade II or indeterminate (n=56)**	**Grade III (n=11)**	**p value ANOVA**
LA strain, %	28.8±9.8	24.0±8.3	20.3±6.4	17.7±7.2	<0.01
Abnormal LA strain	23.7	55.8	69.6	81.8	n/a
SOCRATES cohort (n=300)	**LVDD Grade based on 2016 ASE recommendations**				
	Normal (n=0)	**Grade I (n=116)**	**Grade II (n=114)**	**Grade III (n=70)**	**p value ANOVA**
LA strain, %	n/a	22.2 ± 6.6	16.6 ± 7.4	11.1 ± 5.4	<0.01

Abnormal LA strain	n/a	62.9%	88.6%	95.7%	n/a

Values are mean ± SD or %. Abnormal LA strain was defined as LA strain <23% and abnormal LAVI as >34 ml/m^2. ANOVA=analysis of variance; ASE= American Society of Echocardiography; n/a =not applicable.

Moreover, by analyzing the diagnostic performance (namely, the sensitivity and specificity) of LA strain to detect severe LV diastolic alterations or elevated LV filling pressures, LA strain had a significantly better diagnostic performance than conventional LA and LV parameters both in patients with preserved and reduced LVEF (see Figure 3)(15).

Figure 3. Detection of severe LVDD by means of LA strain vs. LAVI, LAEF and Mitral E/e' average in: I) symptomatic patients with HF, II) HFrEF patients, III) HFpEF patients.(15)



AUC comparison by DeLong’s method: LA strain vs. LAVI = p value < 0.01, LA strain vs. LAEF = p value < 0.01; LA strain vs. E/é average = p value < 0.01

Furthermore, we tested the diagnostic performance of another new LA parameter, the LA filling index (i.e. the ratio of the mitral E inflow on LA strain), to detect elevated LV filling pressures. In this respect, in a the test cohort (i.e., test cohort: n=31 patients with invasive measurements of LVEDP) LA filling index showed significantly better results than the other echocardiographic parameters (E/LA strain ratio: AUC 0.82, cut-off > 3.27 = sensitivity 83.3%, specificity 78.9%, Mitral E/e’: AUC 0.67, cut-off>14= sensitivity 41.6%, specificity 84.2%, Mitral E/A: AUC 0.78, cut-off≥2= sensitivity 16.6%, specificity 100%, LAVI: AUC 0.63, cut-off≥34ml/m²= sensitivity 25%, specificity 89.4%, TR maximum-velocity: AUC 0.55, cut-off>2.8m/s= sensitivity 27.2%, specificity 86.6%, LAS:AUC 0.77, cut-off ≤ 23.0%, sensitivity 66.7%, specificity 68.4%).(14) Likewise, In a validation cohort (n=486) LA filling index showed also a performance, sensitivity and specificity to detect elevated filling pressures (AUC=0.91 [95%CI 0.87-0.94] sensitivity 88.1% and specificity 77.6%). (14)

3.1. Clinical Relevance of left atrial strain

Regarding the potential clinical relevance of LA strain, in patients with risk factors for LVDD and preserved LVEF an abnormal LA strain was significantly linked to worse functional Class and HF hospitalization at 2 years [OR ratio (95% CI): 4.6 (2.6-8.3), 6.6 (2.6-16.6), respectively p < 0.01].(13) In line with these findings, an abnormal LA strain was significantly associated with HF hospitalization at 2 years even after adjustment by age>65 years and female gender [OR ratio (95% CI): 5.7 (2.2-14.7), p-value<0.01] and even when LA volume was normal [OR ratio unadjusted (95% CI): 10.1 (2.1-48.6), p-value<0.01; OR ratio adjusted for age and gender (95% CI): 9.5 (1.9-46.4), p-value<0.01].(13) Moreover, regarding the clinical relevance of the LA filling index (i.e. of the ratio of mitral E inflow / LA strain), E/LA strain ratio>3.27 was significantly associated with a symptomatic status (dyspnea), worse NYHA functional class and HF hospitalization at 2 years [OR ratio (95% CI): 4.4 (2.9-6.7), 4.5 (2.5-8), 4.3 (1.8-10.5), p < 0.01, respectively].(14)

4. Discussion

The findings of these studies suggest that the use of a new sensitive LA parameter such as LA strain could have potential usefulness and clinical relevance in the evaluation of patients with CV risk factors and in those with established HF. Previous studies have shown that early LA impairment caused by LA fibrosis can be found in patients with cardiovascular risk factors or history of CAD, with normal LV systolic and diastolic function. (22, 23)What is more, when analyzing the heart as an entire entity the effect of the LV subtle alterations on the LA should be taken into consideration, for these two chambers are in contact and function together. In line, our study findings suggest that LA strain can be impaired in those patients in risk for cardiac abnormalities.(12)

In patients at risk for LVDD and preserved LVEF, LA strain could be a more useful parameter than LAVI for the detection of early LV diastolic alterations.(12) The findings of our study are supported by the pathophysiology of LVDD.(3) In line, LA volumetric changes over the currently proposed cut-off (i.e. LAVI>34 ml/m²) can be seen only at the advanced LVDD, after the chronically elevated LV filling pressures impact the LA anatomy, leading to LA enlargement.(3) Thus, LAVI is not a sensitive parameter for detecting the early LV diastolic alterations.(3) In our study, adding LAS to the currently proposed diagnostic algorithm for LVDD increased significantly the rate of LVDD detection.(13) Therefore, adding LA strain to LAVI could be considered as a diagnostic step in order to reduce the number of patients with indeterminate LV diastolic function.(13)

In line, in patients with already established heart failure LA strain was found to be reduced even when LAVI was normal and an abnormal LAS strain was linked to elevated filling pressures irrespective of the LVEF.(15) According to our study results, a higher impairment of LA strain was linked to a higher grade of DD and the percentage of abnormal LA strain was correlated to the grade of DD in HFpEF patients, in HFrEF patients and in all HF patients.(15) These findings come to confirm the findings of previous studies on LA strain in HF entity.(6, 24) Moreover, in contrary to the so far published data, our study included patients of the whole HF spectrum, implying to LA dysfunction assessed by LA strain is an important pathophysiological mechanism for LVDD not only in HFpEF, where it's mostly studied, but also in HFrEF, where LAVI is often not affected.(15) In all our studies LA strain was well correlated to the other conventional parameters, validating the role of this software-dependent parameter.(13, 15)

Concerning the LA filling index (i.e. E mitral/LA strain), this newly introduced parameter by our team combines the LV and LA diastolic parameters with the purpose for better estimation of LV filling pressures.(14) Our hypothesis was based on the simple fact that the LA is exposed to the LV filling pressures during the diastolic phase of the cardiac circle, when the mitral valve is open. Given the many factors that lead to diastolic dysfunction, one parameter such as LA strain cannot detect all cases of elevated LV filling pressures, despite the good results of previous studies so far. Therefore, we introduced the E mitral/LA strain ratio and validated it in a small cohort of patients with invasive measurements. LA filling index performed well in detecting elevated LV filling pressures in patients with cardiovascular risk factors and preserved LVEF.(14)

Although LA strain is not included in the routine echocardiography in patients with cardiovascular risk factors, in our study almost 20% of patients with normal LV systolic and diastolic function had an abnormal LA strain.(12) Moreover, none of the patients without cardiovascular risk factors had an LA strain <23%, a finding that underlines the higher specificity of LA strain.(12) Our findings suggest that LA strain could be a useful parameter for detecting early LA alterations in patients in risk for cardiac abnormalities. Moreover, LA strain was well related to exertional dyspnea, NYHA functional class and elevated PCWP, even with a normal LAVI, and furthermore, a LA strain<23% was correlated to the risk of hospitalization due to HF within two years.(12, 13) These findings are in agreement with the results of previous studies and indicate the clinical relevance of this parameter.(25-28) Similar results were shown also for the LA filling index, which was linked to worse functional capacity and hospitalization within 2 years.(14)

5. Limitations

The main limitation of our studies was that LA strain is a relatively new parameter, that requires an offline analysis, which is not well established widely in comparison to the commonly used echocardiographic parameters. In this regard, pitfalls during the LA strain analysis are more common. Moreover, LA strain is a software-dependent parameter and our results should be interpreted based on the different software that were used. Furthermore, our analyses were performed retrospectively and thus the link between LA strain or LA filling index with clinical parameters should be interpreted as association and not as a causal analysis. Finally, our studies excluded patients with severe arrhythmias and bad imaging quality and therefore our findings cannot be generalized in those patients.

6. Conclusion:

The findings of these studies suggest that the use of new sensitive LA parameter such as LA strain could be useful and of clinical relevance in the evaluation of patients with CV risk factors and in those with established HF. Moreover, these studies suggest that LA strain or the new LA filling index (namely, the mitral E / LA strain ratio) could play an important role in detecting early LV diastolic alterations in patients with normal LVEF and cardiovascular risk factors and that additionally, LA strain could predict the presence of elevated filling pressures in patients with HF, regardless of the LVEF.

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Eidesstattliche Versicherung

„Ich, Athanasios Frydas, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Die Bedeutung des linksatrialen Strain bei Herzinsuffizinez selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst."

06.10.2020	Athanasios Frydas
Datum	Unterschrift

Anteilserklärung an den erfolgten Publikationen

Athanasios Frydas (A.F.) hatte folgenden Anteil an den Publikationen:

Publikation 1: Frydas A, Morris DA, Belyavskiy E, Radhakrishnan AK, Kropf M, Tadic M, Roessig L, Lam CSP, Shah SJ, Solomon SD, Pieske B, Pieske-Kraigher E. Left atrial strain as sensitive marker of left ventricular diastolic dysfunction in heart failure. ESC Heart Fail. 2020 Aug;7(4):1956-1965. doi: 10.1002/ehf2.12820. Epub 2020 Jul 2. PMID: 32613770; PMCID: PMC7373910. Impact factor: 3.902

Beiträge im Einzelnen:

Primär erfolgte die Durchführung der echokardiografischen Untersuchungen in verschiedenen, zertifizierten Studienzentren im Rahmen der SOCRATES-Studie. A.F. kontrollierte anschließend im akademischen Echo-Core-Lab der Charité (Campus-Virchow Klinikum) die Bild-Qualität der vorhandenen echokardiografischen Daten. Darüber hinaus führte A.F. alle die im Protokoll der SOCRATES-Studie beschriebenen echokardiographischen Messungen des primären Datensatzes durch. Zudem erfolgte durch A.F. die volumetrischen Messungen und die Strain-Analyse des linken Vorhofs. Die Ergebnisse und die gespeicherten Clips und Bilder mit den Messungen wurden durch Dr. med. Daniel-Armando Morris und Dr. med. univ. Elisabeth Pieske-Kraigher überprüft. Alle erhobenen Daten, die nicht durch die verwendete Software automatisch in einer Excel-Tabelle exportiert werden konnten, wurden vom A.F. manuell in die elektronische Datenbank übertragen. Die statistische Analyse erfolgte durch A.F. mit Supervision von Dr. med. Daniel-Armando Morris. Das Manuskript der Publikation inklusiver aller Abbildungen und Tabellen hat A.F. selbst erstellt. Eine Korrektur des Manuskripts erfolgte durch Univ-Prof. Dr. med. Burkert Pieske, Dr. med. Daniel-Armando Morris und genannte Co-Autoren. Das Einreichen des Manuskriptes, die Antwort auf die Kommentare der Gutachter, die finalen Korrekturen und die Veröffentlichung erfolgten selbständig durch A.F.

Publikation 2: Braunauer K, Düngen HD, Belyavskiy E, Aravind-Kumar R, Frydas A, Kropf M, Huang F, Marquez E, Tadic M, Osmanoglou E, Edelmann F, Tschöpe C, Boldt LH, Pieske B, Pieske-Kraigher E, Morris DA. Potential usefulness and clinical relevance of a novel left atrial filling index to estimate left ventricular filling pressures in patients with preserved left ventricular ejection fraction. Eur Heart J Cardiovasc Imaging. 2020 Mar 1;21(3):260-269. doi: 10.1093/ehjci/jez272. PMID: 31740950. Impact factor: 4.841

Beiträge im Einzelnen:

Für diese Studie war A.F. bei einem Teil der Datenerhebung beteiligt. Ferner führte A.F. ein Teil der echokardiographischen Analyse selbst durch. Zuletzt war A.F. bei der Erstellung der Diskussion und abschließenden Begutachtung beteiligt.

Publikation 3: Braunauer K, Pieske-Kraigher E, Belyavskiy E, Aravind-Kumar R, Kropf M, Kraft R, Frydas A, Marquez E, Osmanoglou E, Tschöpe C, Edelmann F, Pieske B, Düngen HD, Morris DA. Early detection of cardiac alterations by left atrial strain in patients with risk for cardiac abnormalities with preserved left ventricular systolic and diastolic function. Int J Cardiovasc Imaging. 2018 May;34(5):701-711. doi: 10.1007/s10554-017-1280-2. Epub 2017 Nov 23. PMID: 29170840. Impact factor: 1.969

Beiträge im Einzelnen:

Für diese Studie verwendeten wir die gleiche Patientenkohorte wie bei der Studie von Braunauer K et al. (Eur Heart J Cardiovasc Imaging. 2020). A.F. hat ein Teil der Datenerhebung und der echokardiographischen Analyse selbst durchgeführt. Ferner war A.F. bei der Fertigstellung des Manuskripts beteiligt.

Publikation 4: Morris DA, Belyavskiy E, Aravind-Kumar R, Kropf M, Frydas A, Braunauer K, Marquez E, Krisper M, Lindhorst R, Osmanoglou E, Boldt LH, Blaschke F, Haverkamp W, Tschöpe C, Edelmann F, Pieske B, Pieske-Kraigher E. Potential Usefulness and Clinical Relevance of Adding Left Atrial Strain to Left Atrial Volume Index in the Detection of Left Ventricular Diastolic Dysfunction. JACC Cardiovasc Imaging. 2018 Oct;11(10):1405-1415. doi: 10.1016/j.jcmg.2017.07.029. Epub 2017 Nov 15. PMID: 29153567. Impact factor: 12.740

Beiträge im Einzelnen:

Für diese Studie wurde ebenfalls die gleiche Patientenkohorte wie bei der Studie von Braunauer K et al. (Eur Heart J Cardiovasc Imaging, 2020) und Braunauer K et al. (Int J Cardiovasc Imaging, 2018). A.F. hat ein Teil der Datenerhebung und der echokardiographischen Analyse selbst durchgeführt. Zuletzt war A.F. bei der Erstellung der Diskussion und abschließenden Begutachtung beteiligt.

Univ.- Prof. Dr. med. Burkert Pieske

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Unterschrift, Datum und Stempel des erstbetreuenden Hochschullehrers

Athanasios Frydas

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ORIGINAL RESEARCH ARTICLE

Left atrial strain as sensitive marker of left ventricular diastolic dysfunction in heart failure

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Abstract

Aims The purpose of this retrospective analysis was to examine the association of left atrial (LA) strain (i.e. LA reservoir function) with left ventricular diastolic dysfunction (DD) in patients with heart failure with reduced and preserved left ventricular ejection fraction (LVEF).

Methods and results We analysed the baseline echocardiographic recordings of 300 patients in sinus rhythm from the SOCRATES-PRESERVED and SOCRATES-REDUCED studies. LA volume index was normal in 89 (29.7%), of whom 60.6% had an abnormal LA reservoir strain (i.e. ≤23%). In addition, the extent of LA strain impairment was significantly associated with the severity of DD according to the 2016 American Society of Echocardiography recommendations (DD grade I: LA strain 22.2 ± 6.6, rate of abnormal LA strain 62.9%; DD grade II: LA strain 16.6 ± 7.4, rate of abnormal LA strain 88.6%; DD grade III: LA strain 11.1 ± 5.4%, rate of abnormal LA strain 95.7%; all $P < 0.01$). In line with these findings, LA strain had a good diagnostic performance to determine severe DD [area under the curve 0.83 (95% CI 0.77–0.88), cut-off 14.1%, sensitivity 80%, specificity 77.8%], which was significantly better than for LA volume index, LA total emptying fraction, and the mitral E/e′ ratio.

Conclusions The findings of this analysis suggest that LA strain could be a useful parameter in the evaluation of DD in patients with heart failure and sinus rhythm, irrespective of LVEF.

Keywords Echocardiography; Left atrium; Speckle-tracking; Strain

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Introduction

The left atrium (LA) plays a fundamental role in the function of the heart, receiving the blood from the lung veins (reservoir function) at the systolic phase of the cardiac cycle, letting the blood flow passively to the left ventricle at the early diastole (conduit function) and pushing the blood actively towards the left ventricle during the late diastole (booster pump function).[1,2] The main parameter that is most commonly used to assess the left atrial structure is the left atrial volume index (LAVI).[3] Nevertheless, even a left atrium with a normal size can be dysfunctional, and LAVI has been shown to have low sensitivity in the early detection of left atrial dysfunction in the setting of LV diastolic dysfunction (DD).[4–7] A relatively novel method that is not yet used in clinical practice but has been shown to be able to assess the reservoir function of the left atrium is the LA longitudinal strain, an angle-independent parameter derived from speckle-tracking echocardiography. Particularly in HFpEF entity, a recent study suggested that LA strain has an important clinical and prognostic relevance, underlying the active role of the LA in the pathophysiology of the disease.[7] In addition, recent studies have suggested that LA strain could be of significant utility in the assessment of DD because this new LA parameter is significantly linked to the severity of DD.[4,8–10] Therefore, the purpose of this analysis was to examine the potential utility and association of LA strain with the severity of DD in patients with HF.

Methods

Study population

SOCRATES-REDUCED and SOCRATES-PRESERVED were two multicentre, randomized, double-blind, placebo-controlled, Phase 2 dose-finding trials conducted in parallel that tested the effects of the novel sGC stimulator vericiguat on surrogate imaging parameters and NTproBNP in patients from Europe, Northern America, Asia and Australia after stabilization from a worsening chronic HF episode. The study design with the inclusion and exclusion criteria and the study results for both studies, including other echocardiographic data have been already published.[11–14]

SOCRATES-REDUCED included patients ≥18 years old, with NYHA class II–IV symptoms, and LVEF <45%, who were clinically stable prior to randomization (no intravenous vasodilator therapy for at least 24 h and no intravenous diuretic therapy for at least 12 h; systolic blood pressure 110 mmHg or greater and less than 160 mm Hg, and heart rate 50/min or greater and less than 100/min) and had a recent episode of worsening chronic HF defined by three components: worsening HF symptoms requiring either hospitalization or outpatient administration of intravenous diuretics; signs of congestion (clinical or chest radiograph findings); and elevated natriuretic peptide level [N-terminal pro-B-type natriuretic peptide (NT-proBNP)] ≥ 1000 pg/mL or B-type natriuretic peptide (BNP) ≥ 300 pg/mL if in sinus rhythm, or NT-proBNP ≥1600 pg/mL or BNP ≥ 500 pg/mL if in atrial fibrillation. All patients had a history of chronic HF, defined as New York Heart Association (NYHA) class II–IV symptoms and treatment with guideline-directed medical HF therapy for 30 days or longer before hospitalization or intravenous diuretic administration without hospitalization. In total, 456 patients were included (age: 68 ± 12 years, women: 19.7%, BMI: 28 ± 5 kg/m^2, systolic blood pressure: 125.6 ± 13.5 mmHg, heart rate: 71.7 ± 12.4 b.p.m., diabetes mellitus: 48%, atrial fibrillation in baseline ECG: 33.8%) (*Table 1*).[12] Eligible patients for the SOCRATES-PRESERVED trial were ≥18 years old, had NYHA class II–IV symptom, LVEF ≥45%, elevated natriuretic peptide level, and LA enlargement by echocardiography at randomization defined as LAVI ≥28 mL/m^2, or LAV >58 mL (male)/ >52 mL (female) or LA area >20 cm^2, or LA diameter >40 mm (male)/>38 mm (female), according to the American Society of Echocardiography (ASE) guidelines of 2005 that were active at the time of the SOCRATES trial design.[13,15] Four hundred seventy-seven patients were finally included in the study (age: 73 ± 10 years, women: 47.6%, BMI: 30.2 ± 6 kg/m^2, systolic blood pressure: 133 ± 14 mmHg, heart rate: 70 ± 12 b.p.m., diabetes mellitus: 48.6%, atrial fibrillation in baseline ECG: 39.8%) (*Table 1*).

Considering the aforementioned clinical and biomarker HF diagnostic criteria, according to the 2016 recommendations for DD of the ASE, for the purpose of this echocardiographic *post hoc* analysis of the baseline echocardiograms of the SOCRATES-PRESERVED and SOCRATES-REDUCED studies, the LVEF used to define HF patients with preserved LVEF was LVEF ≥50% and to define patients with reduced LVEF was LVEF <50%. Institutional review board or ethics committee approval was obtained at each study site. All patients provided written informed consent.

Table 1 Clinical and echocardiographic characteristics of the study population

	SOCRATES-PRESERVED (*n* = 477)	SOCRATES-REDUCED (*n* = 456)
Age, years	73 ± 10	68 ± 12
Women	47.6%	19.7%
BMI, kg/m^2	30.2 ± 6	28 ± 5
Systolic BP, mmHg	133 ± 14	125.6 ± 13.5
Heart rate, b.p.m.	70 ± 12	71.7 ± 12.4
Diabetes mellitus	48.6%	48%
Parameters	**Echocardiography analysis (*n* = 300)**	
LVEF, %	42.4 ± 16.6	
LV mass index, g/m^2	141.1 ± 41.9	
LAVI, mL/m^2	43.1 ± 13.5	
TR velocity, m/s	2.82 ± 0.54	
Mitral E-wave, cm/s	86.8 ± 28.3	
Mitral E/A ratio	1.48 ± 0.87	
Mitral septal e', cm/s	5.1 ± 2.1	
Mitral lateral e', cm/s	7.5 ± 3.0	
Mitral E/e' average ratio	15.0 ± 6.5	
LA strain, %	17.5 ± 7.9	
LA total emptying fraction, %	41.3 ± 14.0	

Data are expressed as mean ± SD or percentages. E, mitral early-diastolic inflow peak velocity by pulsed-wave Doppler; e', septal or lateral mitral annular early-diastolic peak velocity by tissue Doppler imaging. TR, tricuspid regurgitation (in 27 patients, TR measurements were not possible).

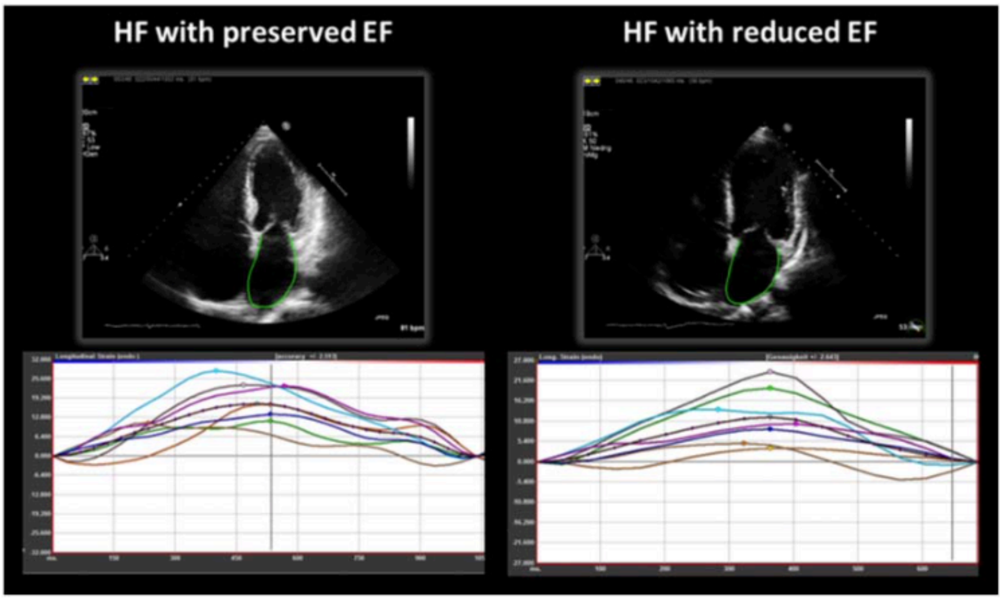
Echocardiographic analysis

The Academic Echo Core Lab (AECL) Charité was responsible for the quality of image acquisition and analysis in SOCRATES trials. The echocardiographic data from the participating sites were delivered to the AECL in DICOM format and saved on a central server. The analysis was conducted by means of the TomTec 2D Cardiac Performance Analysis Software (Version 4.6). All measurements and analyses were conducted by one experienced cardiologist, whose focus was echocardiography. All measurements were performed in triplicate on three consecutive cardiac cycles, and the average was calculated. Images and/or clips were saved for each measurement and analysis accordingly. Subsequently, all performed measurements underwent an over-reading process. For this purpose, one single experienced cardiologist, whose focus was also echocardiography, checked each single measurement. In case of an error, the over-reader re-performed the corresponding tracing. In order to test the reproducibility of the measurements, a set of 20 random cases were selected and evaluated by our data manager for intra-observer and inter-observer variability. The reader and the over-reader were certified by the European Association of Cardiovascular Imaging (EACVI) for adult transthoracic echocardiography. The reader and the over-reader were blinded to all other data. Patients with arrhythmia (i.e. atrial fibrillation, atrial tachycardia, bigeminus, trigeminus, and junctional rhythm) or pacemaker rhythm during the image acquisition, patients with indeterminate grading of DD according to the 2016 ASE/EACVI criteria and echocardiographic recordings with bad imaging quality, defined as dropout of 1 or more LA segments or foreshortening of the LA were excluded from the analysis. All measurements were conducted according to the ASE and the EACVI recommendations.[16]

For the 2D speckle-tracking (2DSTE) analysis of the LA, the cardiac cycle was defined from the onset of the QRS wave to the onset of the next QRS wave. Recording frame rate was set at 50–80 frames/s. LA diastolic functional properties were evaluated by means of LA peak longitudinal strain in the LA filling phase during LV contraction (i.e. LA strain and reflecting LA reservoir function). Measurements were performed in the apical four-chamber and two-chamber views, as shown in *Figure 1*. An abnormal LA strain was defined as $\leq$23%, based on published data regarding the lower limit of normality.[5,17–19] . LA maximal volume was measured at the end-systole when the left atrium had its maximum volume and LA minimal volume was measured at the end-diastole, when the left atrium had its minimum volume. LA total emptying fraction (LAEF) was defined as [(maximal volume − minimal volume)/maximal volume].

The severity of LV diastolic dysfunction was defined according to the current criteria of ASE and EACVI for HF patients with reduced LVEF and HF patients with preserved LVEF.[3] Accordingly, a mitral E/A ratio $\leq$0.8 and mitral E velocity $\leq$50 cm/s defined Grade I DD; in case of a mitral E/A ratio $\leq$0.8 and a mitral E velocity $>$50 cm/s or E/A ratio $>$0.8 to <2, three additional criteria were included: (i) Average (septal + lateral) E/e′ $>$ 14; (ii) TR Vmax $>$2.8 m/s; (iii) LAVI $>$34 mL/m^2. Patients of this category with no positive or only one additional positive criterion were still classified with

Figure 1 LA strain assessed by 2D speckle-tracking echocardiography. The average of LA strain from all LA segments indicated by the fragmented line.



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Grade I DD, and with two or three positive criteria as Grade II DD. In cases where only two additional parameters could be read and one of the remaining criteria was negative, patients were not classifiable and were excluded from the analysis (iii). Finally, patients with a mitral E/A ratio ≥2 were defined as Grade III or Severe DD [3].

Statistical analysis

Continuous data were presented as mean ± standard deviation and dichotomous data in percentages. Categorical variables were compared by χ^2 test and Fisher's exact test. Differences in continuous variables between two groups were analysed using Student's *t*-test, whereas comparisons between three or more groups were analysed using a one-way analysis of variance. The correlation of LA strain with LV diastolic parameters was analysed using a Pearson correlation analysis (with *R* correlation coefficient as the main analysis). Based on the results of the NORRE study on the echocardiographic reference ranges for normal left atrial function parameters in a cohort of 371 healthy people (mean of lower limit of normality for LAS in the whole study population 26.1 ± 0.7%; 27.7 ± 1.5% for age 40–60 years old; 22.7 ± 2.0% for age ≥60 years old), and after calculating the mean of the lower limit of normality for the 95% confidential interval, we conducted an additional analysis dividing our study patients in three groups by using a LA strain cut-off of 20% and 28%.[19] We assumed a LA strain <20% to be pathological, LA strain 20–28% to be a grey zone, and LA strain >28% to be normal. The diagnostic performance of LA strain to determine a severe DD (defined as mitral E/A ratio ≥2 according to the 2016 ASE/EACVI criteria) was analysed by means of the area under the curve (AUC) of receiver operating characteristic curve analysis. The optimal cut-off value of LA strain was determined by the Youden Index (Youden Index = sensitivity + specificity − 1) and receiver operating characteristic curves of LA strain versus LA volumetric parameters such as LAVI and LAEF were compared by the DeLong's method. The reproducibility of LA strain was analysed on 20 randomly selected patients of the SOCRATES-PRESERVED and SOCRATES-REDUCED trials in order to determine the intra-observer and inter-observer variability by means of coefficient of variation and interclass correlation coefficient. All statistical analyses were performed with SPSS version 23.0 (IBM) and MedCalc version 18.11 (MedCalc Software bvba). Differences were considered statistically significant when $P < 0.05$.

Results

Baseline echocardiographic data of 933 patients were evaluated for the purpose of our analysis. However, patients with arrhythmia (i.e. atrial fibrillation, atrial tachycardia, bigeminus, trigeminus, and junctional rhythm) or pacemaker rhythm during the image acquisition (*n* = 529), patients with poor 2D imaging quality of the LA (*n* = 84), and patients with indeterminate grading of DD according to the 2016 ASE/EACVI criteria (*n* = 20) were excluded from this *post hoc* analysis (*Figure 2*). Thus, a total of 300 patients [172 (57%) with LVEF <50% and 128 (43%) with HFpEF] were finally included. The clinical and echocardiographic characteristics of the patients are shown in *Table 1*.

Association of left atrial strain with the severity of left ventricular diastolic dysfunction

Using the current ASE/EACVI criteria for the severity of DD, LA strain was significantly associated with the severity of DD (Grade I: LA strain 22.2 ± 6.6%; Grade II: LA strain 16.6 ± 7.4%; Grade III: LA strain 11.1 ± 5.4%; $P < 0.01$). In line with these findings, the prevalence of any abnormal LA strain value was significantly linked to the severity of DD (Grade I: 62.9%; Grade II: 88.6%; Grade III: 95.7%; $P < 0.01$). Likewise,

Figure 2 Diagram showing the total number of analysed echocardiographic recordings after the exclusion of patients with arrhythmia (i.e. atrial fibrillation, atrial tachycardia, bigeminus, trigeminus, junctional rhythm), pacemaker rhythm, bad 2D imaging quality of the LA or intermediate grade of DD.

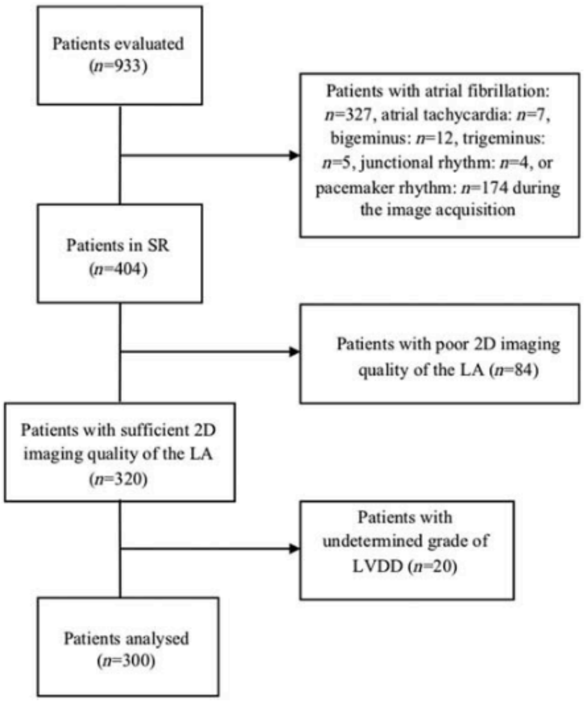

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Table 2 Association of LA strain with the severity of LV diastolic dysfunction

Severity of LV diastolic dysfunction				
All patients	Grade I (n = 116)	Grade II (n = 114)	Grade III (n = 70)	P value
LA strain, %	22.2 ± 6.6	16.6 ± 7.4	11.1 ± 5.4	<0.01
Abnormal LA strain	62.9%	88.6%	95.7%	<0.01
HF with LVEF <50%	Grade I (n = 51)	Grade II (n = 66)	Grade III (n = 55)	P value
LA strain	18.6 ± 5.5	13.2 ± 7.3	9.2 ± 3.4	<0.01
Abnormal LA strain	86.2%	95.4%	100%	<0.01
HF with LVEF ≥50%	Grade I (n = 65)	Grade II (n = 48)	Grade III (n = 15)	P value
LA strain	25.0 ± 6.1	21.1 ± 4.8	18.0 ± 5.7	<0.01
Abnormal LA strain	44.6%	79.1%	80%	<0.01

Data are expressed as mean ± SD or percentages. Abnormal LA strain, LA strain ≤23%.

Table 3 Correlation of LA strain with LV diastolic parameters

	Correlation with LA strain	
All patients	Pearson R coefficient	P value
Mitral E/A ratio	−0.52	<0.01
LAVI (mL/m^2)	−0.45	<0.01
E/e′ (average)	−0.28	<0.01
TR velocity, m/s	−0,28	<0.01
HF with LVEF <50%	Pearson R coefficient	P value
Mitral E/A ratio	−0.53	<0.01
LAVI, mL/m^2	−0.40	<0.01
E/e′ (average)	−0.16	<0.03
TR velocity, m/s	−0.36	<0.01
HF with LVEF ≥50%	Pearson R coefficient	P value
Mitral E/A ratio	−0.42	<0.01
LAVI, mL/m^2	−0.36	<0.01
E/e′ (average)	−0.42	<0.01
TR velocity, m/s	−0,208	<0.02

both in patients with HF with preserved LVEF (LVEF ≥50%) and with HF with reduced LVEF (LVEF <50%), the association of LA strain with the severity of DD was significant (*Table 2*).

Correlation of left atrial strain with left ventricular diastolic parameters

Left atrial strain was significantly correlated with LV diastolic parameters as shown at *Table 3*. In effect, the Pearson correlation of LA strain with conventional parameters of DD such as mitral E/e′, LAVI, mitral E/A ratio, and TR velocity was statistically significant both in HF patients with preserved and reduced LVEF (*Table 3*). Consistent with these findings, a greater impairment of LV diastolic parameters was significantly associated with a lower LA strain in the subgroups of patients with preserved or reduced LVEF. Nevertheless, in the HFpEF group, a greater impairment of LA strain was not associated with a more depressed LV GLS (*Table 4*).

Table 4 Association of the severity of LA strain with LV diastolic parameters

HF with LVEF <50%	LA strain >28% (n = 6)	LA strain 28–20% (n = 21)	LA strain <20% (n = 145)	P value
Mitral E/A ratio	0.88 ± 0.24	0.85 ± 0.42	1.80 ± 0.99	<0.01
Mitral E/A ratio ≥2	0%	0%	41%	<0.01
LAVI, mL/m^2	34.1 ± 5.7	37.1 ± 9.1	47.7 ± 14.6	<0.01
LAVI >34 mL/m^2	50%	60%	80%	<0.01
Mitral E/e′ (average)	14.0 ± 2.8	13.2 ± 4.2	16.2 ± 7.0	0.14
Mitral E/e′ (average) ≥14	33.3%	30%	50.7%	0.17
TR velocity, m/s	2.69 ± 0.41	2.56 ± 0.60	2.90 ± 0.49	0.02
TR velocity >2.8 m/s	n/a	22.2%	55.8%	0.02
LV GLS, %	15.3 ± 3.9	13.3 ± 4.4	8.8 ± 3.1	<0.01
HF with LVEF ≥50%	LA strain >28% (n = 25)	LA strain 28–20% (n = 64)	LA strain <20% (n = 39)	P value
Mitral E/A ratio	0.91 ± 0.29	1.21 ± 0.64	1.55 ± 0.70	<0.01
Mitral E/A ratio ≥2	0%	9.6%	24.3%	<0.01
LAVI, mL/m^2	34.6 ± 9.8	38.1 ± 9.5	44.4 ± 12.8	<0.01
LAVI >34 mL/m^2	40%	59.3%	79.4%	<0.01
Mitral E/e′ (average)	10.3 ± 4.3	13.9 ± 4.9	16.8 ± 7.4	<0.01
Mitral E/e′ (average) ≥14	16%	45.9%	51.2%	0.01
TR velocity, m/s	2.62 ± 0.59	2.75 ± 0.58	2.90 ± 0.54	0.19
TR velocity >2.8 m/s	26%	43.6%	61.1%	0.02
LV GLS, %	20.8 ± 4.0	19.4 ± 4.2	19.3 ± 3.5	0.30
GLS <16%	4.5%	17.9%	25%	0.14

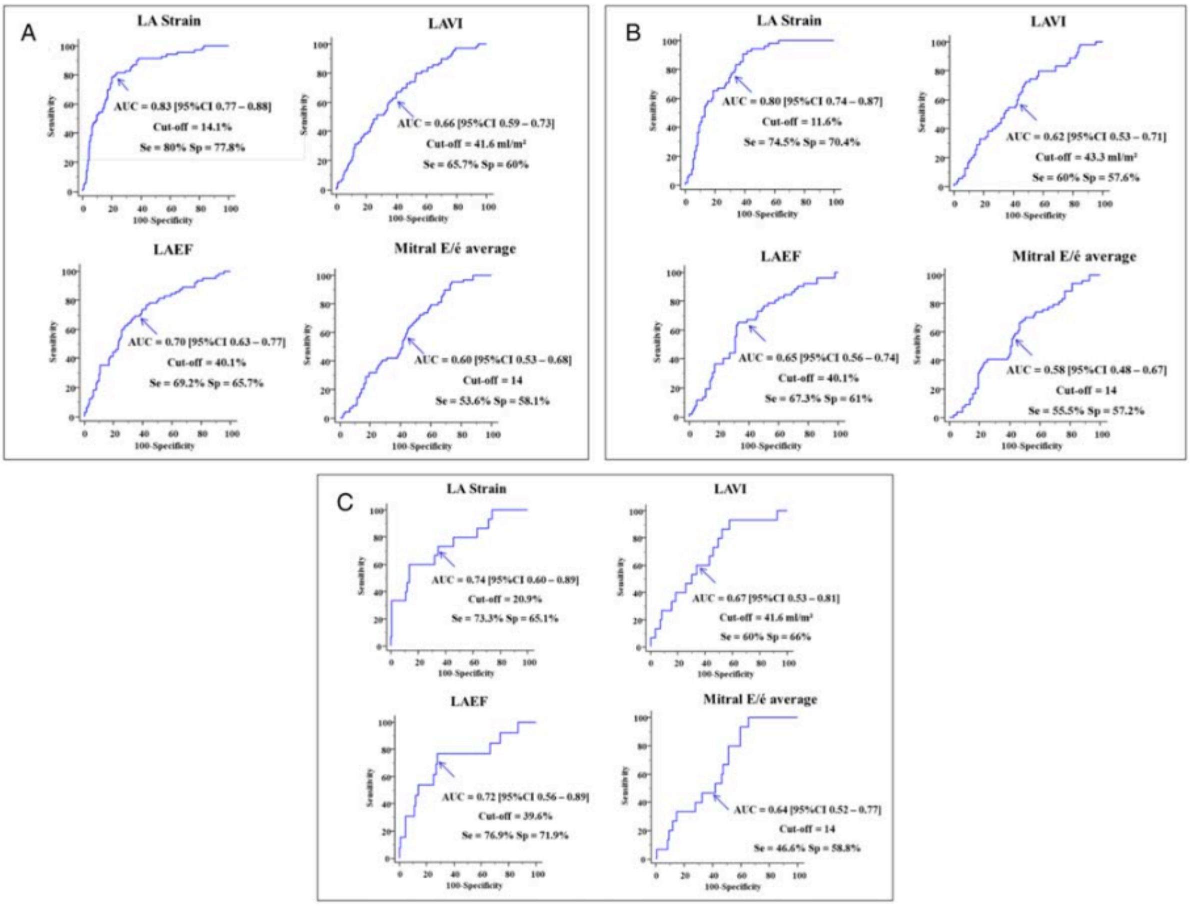
Data are expressed as mean ± SD. GLS was measured in the apical four-chamber view and is indicated in absolute values.

Diagnostic performance of left atrial strain versus left atrial volume index, left atrial total emptying fraction, and mitral E/e′ ratio to determine severe left ventricular diastolic dysfunction

Left atrial strain provided an appropriate diagnostic performance to determine a severe DD (AUC 0.83 [95% CI 0.77–0.88], cut-off 14.1%, sensitivity 80%, specificity 77.8%), which was significantly better than LA volumetric parameters such as LAVI and LAEF, and the mitral E/e′ ratio (LAVI = AUC 0.66 [95%CI 0.59–0.73], cut-off 41.6 mL/m^2, sensitivity 65.7%, specificity 60%; LAEF = AUC 0.70 [95%CI 0.63–0.77], cut-off 40.1%, sensitivity 69.2%, specificity 65.7%; E/e′ average = AUC 0.60 [95%CI 0.53–0.68], cut-off = 14, sensitivity = 53.6%, specificity = 58.1%; AUC comparison by DeLong's method: LA strain versus LAVI = *P* value <0.01, LA strain versus LAEF = *P* value <0.01; LA strain versus E/e′ average = *P* value <0.01; *Figure 3*). In line with these findings, the diagnostic performance of LA strain to determine severe DD was also appropriate and significantly better than that of LAVI, LAEF, and mitral E/e′ both in patients with preserved and reduced LVEF (*Figure 3*). Nonetheless, the diagnostic superiority of LA strain to detect severe DD over LAVI, LAEF, and the mitral E/e′ ratio was higher in patients with reduced LVEF than in patients with preserved LVEF (*Figure 3*).

Furthermore, a high proportion of patients had an abnormal LA strain despite a normal LAVI (HF patients with normal LAVI: rate of abnormal LA strain 60.6%; patients with LVEF <50% and normal LAVI: rate of abnormal LA strain 85%;

Figure 3 (A) Diagnostic performance of LA strain versus LAVI, LAEF, and the mitral E/e′ ratio to determine the severity of LV diastolic dysfunction in patients with heart failure, (B) diagnostic performance of LA strain versus LAVI, LAEF, and the mitral E/e′ ratio to determine the severity of LV diastolic dysfunction in patients with heart failure with reduced ejection fraction, (C) diagnostic performance of LA strain versus LAVI, LAEF, and the mitral E/e′ ratio to determine the severity of LV diastolic dysfunction in patients with heart failure with preserved ejection fraction. Severe LV diastolic dysfunction was defined according to the 2016 criteria of the ASE/EACVI. AUC, area under the curve; Se, sensitivity; Sp, specificity.



patients with preserved LVEF and normal LAVI: rate of abnormal LA strain 40.8%) (*Figure 4*).

Reproducibility of left atrial strain

In order to determine the reproducibility of LA strain in the setting of this *post hoc* analysis, 20 randomly selected patients of the SOCRATES-PRESERVED and SOCRATES-REDUCED trials were analysed twice by the reader and the over-reader. The reader and the over-reader were blinded to the results. By means of coefficient of variation as well as intraclass correlation coefficient intra-observer variability for LA strain was 9.1% and 0.983 [95% CI 0.956–0.993] accordingly; the inter-observer variability of the reader and the over-reader were 6.7% and 0.984 [95% CI 0.959–0.994] and 9.5% and 0.99 [95% CI 0.976–0.996] accordingly.

Discussion

This echocardiographic analysis using the baseline imaging data from the SOCRATES trial to assess the association of LA strain with conventional markers of LA size/function and LV diastolic function highlights that (i) LA strain is more sensitive than LAVI in detecting LA impairment in HF; (ii) LA strain inversely correlates with the severity of LV diastolic dysfunction; (iii) LA strain is superior to LAEF, LAVI, or E/e′ in predicting the presence of severe LV diastolic dysfunction and consequently of elevated LV filling pressures; and (iv) the diagnostic value of LA strain was independent from LVEF below or above the cut point of 50%.

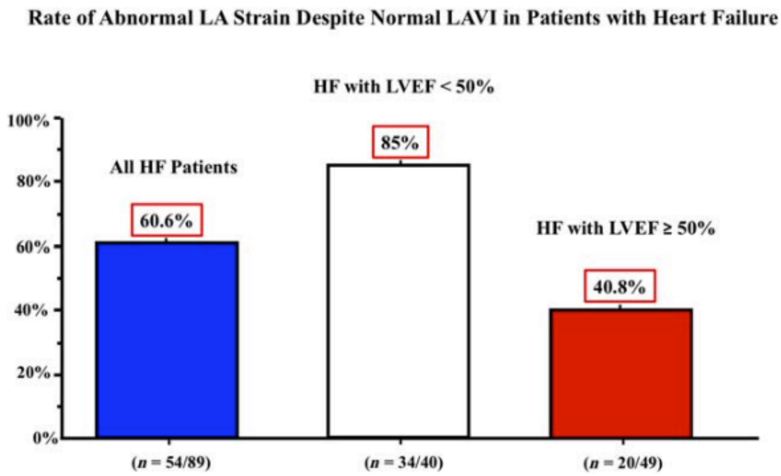
Correlation between left ventricular diastolic dysfunction and left atrial strain in patients with heart failure

In patients with HF (both with preserved and reduced LVEF), enlargement of the LA may be the result of increased resistance to LA emptying into a stiff left ventricle.[9,20–23] Although LA volume is related to LA dysfunction, its ability to detect LA dysfunction in its early stages was shown to be lower than LA strain.[5,10,24,25] Furthermore, studies in HF imply that LA function measured by LA strain can be abnormal even with a normal LA volume.[6,7,26–28] In line with these findings, our analysis demonstrates superior performance of LA strain for predicting severe diastolic dysfunction when compared with volumetric measurements, and this correlation was independent from LVEF measures. Interestingly, an important proportion of HF patients with reduced LA strain had a normal LAVI, a finding that confirms the higher sensitivity of LA strain versus LAVI to detect LA abnormalities in the setting of LV diastolic dysfunction.

Left atrial strain as a marker of left ventricular diastolic dysfunction in heart failure

Several invasive studies have demonstrated the significant association of LA strain with LV filling pressures.[29–31] In addition, several studies have shown a strong correlation of LA strain with DD.[4,25,26,28] However, it remains uncertain if LA strain is a more sensitive parameter than conventional LA parameters such as LAVI to detect LA abnormalities in patients with HF. In the present analysis, a high proportion of patients with normal LAVI had an abnormal LA strain, and LA strain had an adequate diagnostic performance to determine severe DD

Figure 4 Rate of abnormal LA strain in patients with heart failure and normal LAVI.



(Stage III) both in patients with preserved and reduced LVEF. Hence, based on these findings, we showed that LA strain could be considered a sensitive parameter of DD with potential usefulness to determine the severity of DD in patients with HF.

Interestingly, although in the HFrEF group a greater impairment in LA strain was significantly associated with more depressed LV GLS, this association was not found in the HFpEF group. This finding indicates that in our analysis, LV diastolic dysfunction was independent of GLS in the HFpEF subgroup.

While the role of LA strain has mostly been studied in HFpEF patients, in HFrEF, only two studies so far have examined the prognostic value of LA strain.[32,33] In line, Carluccio *et al*. found a significant correlation between an adverse outcome and the worsening of LA stain. In the same study, lower values of LA strain were linked to a worsening in HF.[33] In another study including 286 patients with HFrEF, LA strain was shown to be an independent prognostic marker.[32] These findings suggest that LV diastolic dysfunction, and not only systolic dysfunction, could be a marker of disease worsening in patients with HFrEF. Our analysis showed a significantly better performance of LA strain in the detection of severe LV diastolic dysfunction in comparison with LAEF, LAVI, or E/e′ in HFrEF. Hence, it seems that LA dysfunction as measured by LA strain by means of echocardiography is an important diagnostic parameter also in the HFrEF entity. Moreover, although the so far published studies on LA strain were conducted either in HFpEF or in HFrEF patients, our analysis included the whole spectrum of LVEF in HF, showing a good diagnostic performance of LA strain irrespective of the LVEF. Given the superiority of LA strain over traditional imaging parameters in prediction of severe diastolic dysfunction, further studies with invasive diagnostic methods are warranted in order to validate our results.

Limitations

Several limitations of our analysis should be taken into consideration when interpreting our results. First of all, LA strain values can be software-dependent, and thus, the cut-off values used in the present analysis should be taken into account according to the software that was used (i.e. TomTec 2D Cardiac Performance Analysis). Furthermore, our 2DSTE analysis was conducted in patients with good imaging quality and in sinus rhythm. Therefore, the results should not be generalized to patients with bad imaging quality and atrial arrhythmias. The severity of DD was defined according to echocardiographic criteria, and no invasive methods were used. All patients enrolled in the SOCRATES trial had worsening HF, defined by very recent hospitalization for HF; thus, our findings may not generalize to stable chronic HF. Finally, our analysis included a relatively small group of patients with HF, and it represents a *post hoc* analysis of the SOCRATES-REDUCED and SOCRATES-PRESERVED trials. Hence, further and larger studies are warranted with purpose of validating the findings from this analysis.

Conclusions

The findings of our study suggest that LA strain could be useful parameter in the evaluation of DD in patients with HF and sinus rhythm, irrespective of LVEF. Given the superiority of LA strain over traditional imaging parameters in prediction of severe diastolic dysfunction, bigger studies with invasive diagnostic methods are needed in order to validate our results.

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Conflict of interest

None declared.

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Potential usefulness and clinical relevance of a novel left atrial filling index to estimate left ventricular filling pressures in patients with preserved left ventricular ejection fraction

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Aims The aim of this study was to examine the potential usefulness and clinical relevance of a novel left atrial (LA) filling index using 2D speckle-tracking transthoracic echocardiography to estimate left ventricular (LV) filling pressures in patients with preserved LV ejection fraction (LVEF).

Methods and results The LA filling index was calculated as the ratio of the mitral early-diastolic inflow peak velocity (*E*) over LA reservoir strain (i.e. *E*/LA strain ratio). This index showed a good diagnostic performance to determine elevated LV filling pressures in a test-cohort ($n = 31$) using invasive measurements of LV end-diastolic pressure (area under the curve 0.82, cut-off > 3.27 = sensitivity 83.3%, specificity 78.9%), which was confirmed in a validation-cohort (patients with cardiovascular risk factors; $n = 486$) using the 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging criteria (cut-off > 3.27 = sensitivity 88.1%, specificity 77.6%) and in a specificity-validation cohort (patients free of cardiovascular risk factors, $n = 120$; cut-off > 3.27 = specificity 98.3%). Regarding the clinical relevance of the LA filling index, an elevated *E*/LA strain ratio (>3.27) was significantly associated with the risk of heart failure hospitalization at 2 years (odds ratio 4.3, 95% confidence interval 1.8–10.5), even adjusting this analysis by age, sex, renal failure, LV hypertrophy, or abnormal LV global longitudinal systolic strain.

Conclusion The findings from this study suggest that a novel LA filling index using 2D speckle-tracking echocardiography could be of potential usefulness and clinical relevance in estimating LV filling pressures in patients with preserved LVEF.

Keywords speckle-tracking • echocardiography • left atrium • strain

Introduction

Left atrial (LA) function and more precisely LA reservoir strain using 2D speckle-tracking transthoracic echocardiography has been associated with left ventricular (LV) diastolic dysfunction and elevated LV filling pressures.[1–8] The pathomechanism of impaired LA reservoir function in patients with elevated LV filling pressures involves elevated LA pressures, increased LA wall tension, reduced pulmonary venous emptying, and consequently reduced LA filling (i.e. reduced LA reservoir strain).[9–12] Nonetheless, in some patients a single

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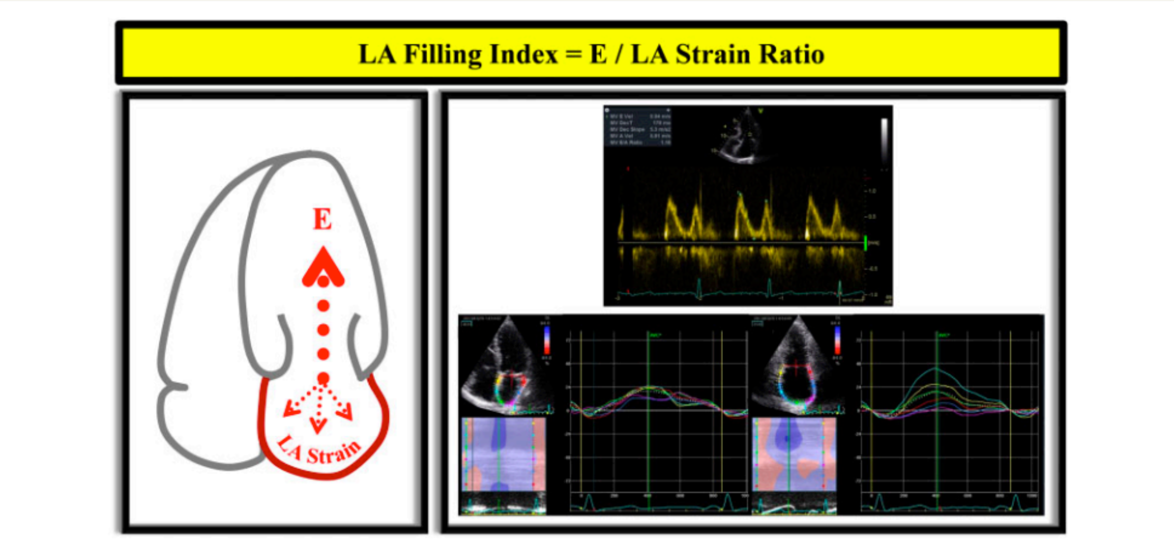

Figure 1 Assessment of the LA filling index. The LA filling index is calculated as the ratio of the mitral early-diastolic inflow peak velocity (*E*, cm/s) using pulsed-wave Doppler over LA strain using 2D speckle-tracking echocardiography (i.e. *E*/LA strain ratio). LA strain is determined as the average value of the longitudinal positive strain peak during LA relaxation or reservoir function from all segments of the LA in the apical four- and two-chamber views and using the onset of QRS as the referent point. In this patient with elevated LV filling pressures, the *E*/LA strain ratio was 5.2 (i.e. mitral *E* velocity 94 cm/s and LA strain 18%).

parameter could not be adequate to determine elevated LV filling pressures given the multifactorial pathophysiology of elevated LV filling pressures in patients with cardiovascular risk factors or cardiovascular diseases such as arterial hypertension, diabetes mellitus, or a history of coronary artery disease and preserved LV ejection fraction (LVEF).[13–16] Alternatively, an index that combines LV and LA diastolic measurements could more precisely describe the multifactorial changes of LV diastolic pressures in those patients. In this regard, we hypothesized that a novel LA filling index that combines LA functional changes (i.e. LA reservoir strain) and the current status of LV diastolic pressures [i.e. mitral early-diastolic inflow peak velocity (*E*)] could be a useful indicator or index of LV filling pressures (*Figure 1*). Therefore, the purpose of this study was to examine the potential diagnostic usefulness and the clinical relevance of a novel LA filling index (the *E*/LA strain ratio) to estimate LV filling pressures in patients with cardiovascular risk factors or cardiovascular diseases such as arterial hypertension, diabetes mellitus, or history of coronary artery disease and preserved LVEF.

Methods

Study population

This cross-sectional and retrospective study included 517 patients with cardiovascular risk factors or cardiovascular diseases such as arterial hypertension, diabetes mellitus, or a history of coronary artery disease and preserved LVEF, who were referred to the Laboratory of Echocardiography at the Charité University Hospital between 2009 and 2015 for a conventional evaluation of LV diastolic function and were included in a previous study conducted by this research group on LA strain imaging.[4] In this population, at first we retrospectively identified patients with invasive measurements of LV filling pressures within 72 h of the echocardiographic examination ($n = 31$), who served as a test-cohort. Afterwards, we analysed the remaining patients ($n = 486$) in order to validate the findings of the test-cohort and to evaluate the clinical relevance of the LA filling index (validation-cohort). The study's inclusion criteria were: (i) presence of sinus rhythm; (ii) no atrial fibrillation in the last 3 months; (iii) preserved LVEF; and (iv) no significant valvular heart disease. Regarding the exclusion criteria of the study population, in accordance with the 2016 recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) for evaluation of LV diastolic dysfunction,[14] patients were excluded if they had significant valvular heart disease [at least mild valvular heart stenosis, moderate or severe aortic or mitral regurgitation, and severe pulmonary or tricuspid regurgitation (TR)], significant mitral annular calcification (≥5 mm), ventricular paced rhythm, or if they had undergone valvular heart surgery or interventions. In addition, patients were also excluded if imaging quality was inadequate for analysis with 2D speckle-tracking echocardiography in ≥1 LA segments. Moreover, in order to exclude non-cardiac causes of dyspnoea, patients with severe pulmonary disease (such as those with a requirement for supplemental oxygen or treatment with corticoids), patients with severe kidney disease (such as those requiring dialysis or with an indication for renal transplant), and patients with severe liver disease (such as those with Child-Pugh Class B and C or with an indication for liver transplantation) were also excluded from this study.

Furthermore, with the aim of validating the specificity of the cut-off of the LA filling index to determine elevated LV filling pressures (specificity-validation cohort), we retrospectively included a group of patients ($n = 120$) free of cardiovascular risk factors or cardiovascular diseases (i.e. no arterial hypertension, no diabetes mellitus, no obesity, and no evidence of coronary artery disease), who were referred to the Laboratory of Echocardiography at the Charité University Hospital between 2009 and 2015 for a cardiovascular or structural heart disease check-up and were part of the screening of a previous study conducted by this research group on LA strain imaging.[17]

The ethics committee of Charité University Hospital approved this research project and informed consent was obtained from all subjects.

Transthoracic echocardiography

Patients were examined at rest using a Vivid 7 or E9 (GE Healthcare) ultrasound system. All measurements were calculated as the average of three measurements and performed in conditions of respiratory (<20 breaths/min), haemodynamic (90–160 mmHg of systolic blood pressure), and electrical (51–99 beats/min) stability. 2D and Doppler measurements were performed as recommended by the ASE and the EACVI[14,18] and preserved LV systolic function was defined as LVEF $\geq$ 52% in men or $\geq$54% in women using the Simpson's biplane method.[18] LA reservoir strain was analysed at frame rates of 50–80 frames/s, an average of three measurements was made, and the onset of QRS was used as the referent point. These analyses were performed offline, using the Echo-Pac ultrasound software package from GE (version 113.0), and researchers were blinded to the clinical characteristics of the patients.

LA filling index

The LA filling index was determined as the ratio of the mitral *E* velocity over LA reservoir strain (i.e. *E*/LA strain ratio).[19] LA reservoir strain was measured as the average value of LA strain longitudinal positive peak from all LA segments in the apical 4- and 2-chamber views (i.e. 12 segments). Mitral *E* velocity was measured using pulsed-wave Doppler between mitral leaflet tips. *Figure 1* shows an example of how this parameter was obtained. The reproducibility of the LA filling index was analysed in 20 randomly selected patients and it proved to be adequate [intra- and interobserver variability = absolute mean difference 0.13 ± 0.12 and 0.42 ± 0.34; coefficient of variation 2.3% (95% confidence interval, 95% CI 1.0–3.0) and 6.7% (95% CI 4.5–8.4); intraclass correlation coefficient 0.998 (95% CI 0.995–0.999) and 0.983 (95% CI 0.957–0.993), respectively; Supplementary data online, *Figure S1* shows the Bland–Altman plot analysis of the *E*/LA strain ratio].

Definition of elevated LV filling pressures

According to the 2016 recommendations of the ASE and EACVI for estimation of LV filling pressures (i.e. Algorithm B),[14] elevated LV filling pressures were defined as: mitral *E*/*A* ratio $\geq$2 or $\geq$2 positive criteria [maximal LA volume index (LAVI) > 34 mL/m^2, mitral average *E*/*e*′ ratio > 14, or TR velocity > 2.8 m/s] when mitral *E*/*A* ratio $\leq$ 0.8 and mitral *E* inflow > 50 cm/s or mitral *E*/*A* ratio >0.8 to <2; and normal LV filling pressures were defined as: mitral *E*/*A* ratio $\leq$ 0.8 and mitral *E* inflow $\leq$ 50 cm/s or $\geq$ 2 negative criteria (LAVI > 34 mL/m^2, av. *E*/*e*′ > 14, or TR > 2.8 m/s) when mitral E/A ratio $\leq$ 0.8 and mitral E inflow > 50 cm/s or mitral *E*/*A* ratio >0.8 to <2. Furthermore, analysing retrospectively patients with invasive measurements of LV filling pressures within 72 h of the echocardiographic examination (n = 31, test-cohort), elevated LV filling pressures were defined as: LV end-diastolic pressure (LVEDP) > 16 mmHg.[13,20]

Statistical analysis

Continuous values were presented as mean ± standard deviation (SD) and dichotomous values in percentage. Differences in continuous variables between two groups were analysed using the Student's *t*-test and between three groups using the analysis of variance. Categorical variables were compared by the χ^2 test, the Fisher exact test, and the McNemar test as appropriate. The association of the LA filling index with continuous variables was analysed using a simple linear regression analysis (with β coefficient as the main analysis), and with dichotomous variables using a logistic regression analysis [with the odds ratio (OR) as the main analysis]. The diagnostic performance of the LA filling index to determine elevated LV filling pressures [using invasive measurements (LVEDP > 16 mmHg), test-cohort] was analysed by means of the area under the curve (AUC) of receiver operating characteristic curve analysis. The optimal cut-off value of the LA filling index was determined by the Youden Index. In addition, we tested the diagnostic performance of the cut-off of the LA filling index obtained from invasive measurements (test-cohort) to determine elevated LV filling pressures in the validation-cohort using the 2016 ASE/EACVI criteria and in the group of patients free of cardiovascular risk factors or cardiovascular diseases (i.e. specificity-validation cohort). Furthermore, a retrospective analysis was performed in order to analyse the association of an elevated LA filling index with the risk of heart failure (HF) hospitalization at 2 years by means of a logistic regression analysis (with the OR as the main analysis). In this regard, between 2016 and 2017, patients' digital medical records were retrospectively analysed to identify the percentage of HF hospitalization (defined as HF requiring hospitalization for compensation and treatment) within 2 years after inclusion in the study. All statistical analyses were performed with SPSS 23.0 (IBM) and MedCalc 19.1 (MedCalc Software bvba). Differences with a *P*-value of < 0.05 were considered statistically significant.

Results

Characteristics of the study population

A total of 558 patients with cardiovascular risk factors or cardiovascular diseases and preserved LVEF met the eligibility criteria during the study period (i.e. test-cohort and validation-cohort). However, it was not possible to perform LA strain analyses in 41 of these patients because of an inadequate 2D imaging quality of the LA (feasibility 92.7%). Thus, 517 of these patients with adequate imaging quality for an analysis of the *E*/LA strain ratio were finally included, namely 31 patients in the test-cohort and 486 patients in the validation-cohort. In addition, we included 120 patients free of cardiovascular risk factors or cardiovascular diseases (i.e. specificity-validation cohort) and, as it was expected, all of these patients had adequate imaging quality for an analysis of the *E*/LA strain ratio. Clinical and cardiac characteristics of the study population are shown in *Table 1*.

Diagnostic performance of the LA filling index to estimate LV filling pressures

In the test-cohort (patients with invasive measurements of LVEDP, n = 31), the LA filling index showed a good diagnostic performance to determine elevated LV filling pressures (AUC 0.82, cut-off *E*/LA strain ratio > 3.27 = sensitivity 83.3%, specificity 78.9%; *Figure 2* and *Table 2*), which was significantly better than the performance of conventional diastolic parameters such as the mitral *E*/*e*′ and *E*/*A* ratio, LAVI, and TR velocity (*Table 2*) and LA strain alone [AUC 0.77 (0.60–0.94), cut-off $\leq$ 23.0%, sensitivity 66.7%, specificity 68.4%].

In agreement with these findings, an elevated LA filling index (i.e. *E*/LA strain ratio > 3.27) showed a good diagnostic performance to determine elevated LV filling pressures in the validation cohort (n = 486) using the 2016 ASE/EACVI criteria (Algorithm B) (sensitivity 88.1%, specificity 77.6%; *Figure 2* and *Table 3*). A similar diagnostic

Table 1 Clinical and cardiac characteristics of the study population

	Test-cohort ($n = 31$)	Validation-cohort ($n = 486$)	Specificity-validation cohort ($n = 120$)
Clinical characteristics			
Age (years)	71.2 ± 8.9	67.7 ± 13.2	37.9 ± 14.1
Women	41.9%	46.3%	57.5%
Body mass index (kg/m^2)	28.4 ± 3.9	27.4 ± 4.8	23.9 ± 2.5
Systolic blood pressure (mmHg)	136.6 ± 19.5	135.9 ± 14.9	119.7 ± 8.6
Diastolic blood pressure (mmHg)	76.7 ± 11.4	80.5 ± 11.2	71.5 ± 7.9
Heart rate (b.p.m.)	70.8 ± 10.7	71.2 ± 9.2	71.7 ± 7.8
Creatinine (mg/dL)	1.0 ± 0.2	1.0 ± 0.4	0.8 ± 0.2
Estimated GFR (CKD-EPI) (mL/min/1.73 m^2)	69.6 ± 21.5	74.8 ± 34.5	118.5 ± 52.9
Arterial hypertension	100%	94.7%	0%
Diabetes mellitus	54.8%	29%	0%
History of coronary artery disease	74.2%	31.3%	0%
Symptomatic status (dyspnoea)	64.5%	45.1%	0%
Cardiac characteristics			
LV ejection fraction (%)	63.4 ± 7.6	62.0 ± 5.6	62.4 ± 5.4
LV global longitudinal strain (GLS) (%)	19.3 ± 2.9	18.7 ± 2.8	20.2 ± 2.3
LV mass index (g/m^2)	105.5 ± 24.0	100.0 ± 25.2	70.9 ± 17.7
LV mass index ≥ 96/116 g/m^2 in women/men	45.2%	35.2%	3.3%
Septal e' mitral annular velocity by TDI (cm/s)	5.6 ± 1.4	5.4 ± 1.9	10.5 ± 2.2
Lateral e' mitral annular velocity by TDI (cm/s)	7.3 ± 1.8	7.6 ± 2.4	13.2 ± 2.5
Mitral early-diastolic inflow velocity (*E*) (cm/s)	81.1 ± 27.4	70.6 ± 21.4	72.5 ± 15.6
Mitral E/e' septal-lateral average ratio (Av. E/e')	12.9 ± 4.2	11.8 ± 5.3	6.2 ± 1.4
Av. E/e' >14	25.8%	24.5%	0%
LA volume index (LAVI) (mL/m^2)	27.7 ± 9.0	27.1 ± 10.1	19.1 ± 5.4
LAVI >34 mL/m^2	16.1%	18.7%	0.8%
LA strain (%)	25.5 ± 9.2	26.7 ± 9.7	40.6 ± 12.1
LA filling index (*E*/LA strain ratio)	3.83 ± 2.86	3.02 ± 1.65	1.91 ± 0.62
TR jet peak velocity (m/s)	2.36 ± 0.54	2.23 ± 0.49	1.84 ± 0.23
Invasively measured LVEDP (mmHg)	15.6 ± 6.9	n/a	n/a

Values are expressed as mean ± SD or percentages.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate (GFR was available in 30 patients in the test-cohort, in 457 patients in the validation-cohort and in 87 patients in the specificity-validation-cohort); LVEDP, LV end-diastolic pressure; n/a, not applicable; TDI, pulsed tissue Doppler imaging; TR, tricuspid regurgitation (TR was available in 26 patients in the test-cohort, in 428 patients in the validation-cohort, and in all patients in the specificity-validation cohort).

performance of the LA filling index could be obtained when applying the 2016 ASE/EACVI criteria only to patients with structural cardiac disease [i.e. LA enlargement, LV hypertrophy, or abnormal LV global longitudinal systolic strain (GLS)] (sensitivity 86.8%, specificity 70.1%, *Table 3*), or when applying the two-steps approach of the 2016 ASE/EACVI criteria [i.e. at first applying the criteria to detect LV diastolic dysfunction (i.e. Algorithm A) and then, in case of positive criteria for LV diastolic dysfunction, applying the criteria to estimate LV filling pressures (i.e. Algorithm B)] (sensitivity 86.8%, specificity 100%; *Table 3*). In addition, an elevated *E*/LA strain ratio was significantly linked to the severity of LV diastolic dysfunction (*Table 4*) as well as to conventional parameters of LV diastolic function and LV filling pressures (Supplementary data online, *Table S1*).

In accordance with these findings, incorporating the *E*/LA strain ratio into the current echocardiographic approach to estimate LV filling pressures (i.e. incorporating the *E*/LA strain ratio within Algorithm B of the 2016 ASE/EACVI criteria), led to an adequate diagnostic performance of this approach to determine elevated LV filling pressures [analysis in the test-cohort with invasive measurements of LVEDP ($n = 31$); sensitivity 83.3%, specificity 79%, accuracy 80.7%; Supplementary data online, *Figures S2* and *S3*].

Furthermore, analysing the group of patients free of cardiovascular risk factors or cardiovascular diseases ($n = 120$) with the purpose of validating the specificity of the cut-off of an elevated LA filling index (specificity-validation cohort), only 1.7% of these patients had values of the LA filling index > 3.27 (i.e. specificity 98.3%).

Clinical relevance of the LA filling index

Analysing the validation-cohort, an *E*/LA strain ratio > 3.27 was significantly associated with a symptomatic status (dyspnoea), worse New York Heart Association (NYHA) functional class and HF hospitalization at 2 years, even adjusting these analyses by clinical variables, like age, sex and renal failure, by LV variables, like LV hypertrophy and abnormal GLS, as well as by diastolic variables

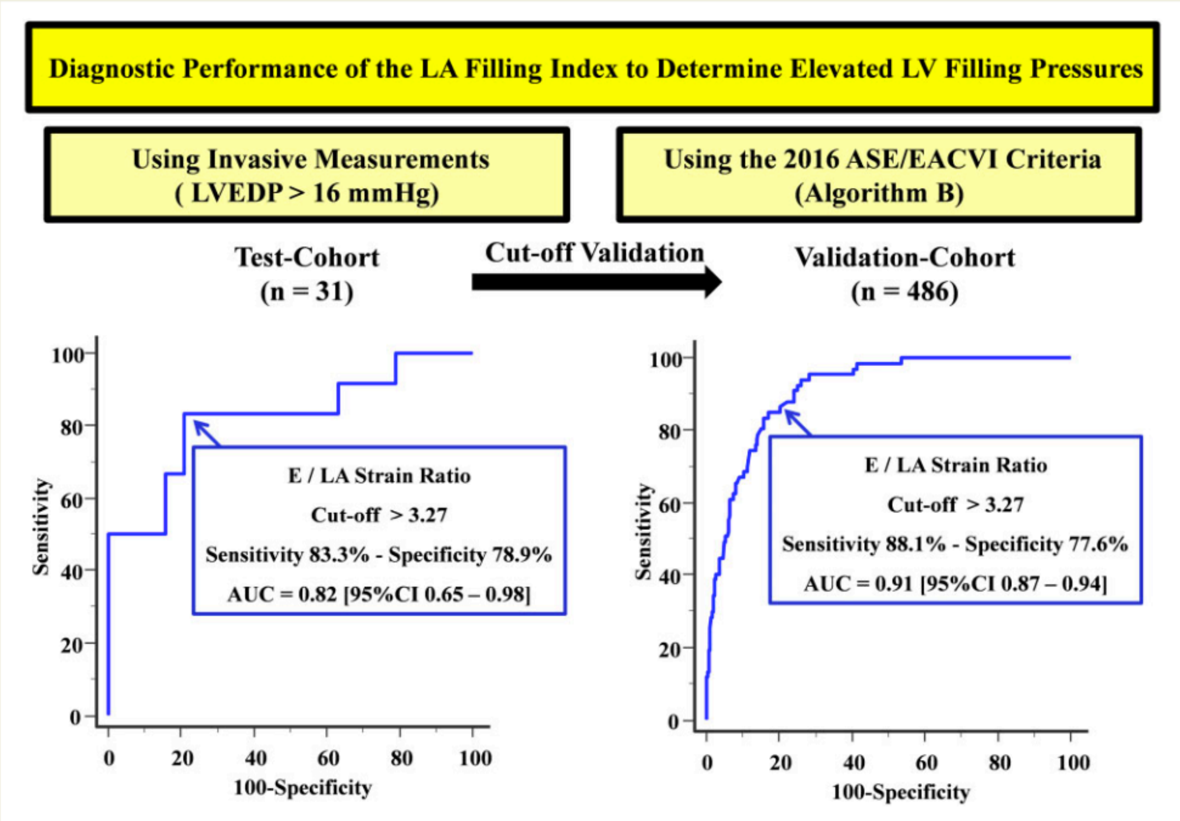

Figure 2 Diagnostic performance of the LA filling index to determine elevated LV filling pressures. AUC, area under the curve; CI, confidence interval; LVEDP, LV end-diastolic pressure.

Table 2 Diagnostic performance of the LA filling index vs. conventional parameters to determine elevated LV filling pressures (invasive measurements of LV end-diastolic pressure)

	Invasively measured LVEDP > 16 mmHg (*n* = 31)				
Parameter	**AUC**	**Cut-off**	**Sensitivity (%)**	**Specificity (%)**	**Accuracy (%)**
E/LA strain	0.82 (95% CI 0.65–0.98)	>3.27	83.3	78.9	80.6
Mitral *E/e′*	0.67 (95% CI 0.44–0.90)	>14	41.6	84.2	67.7
Mitral E/A	0.78 (95% CI 0.61–0.95)	≥2	16.6	100	67.7
LAVI	0.63 (95% CI 0.41–0.86)	>34 mL/m^2	25	89.4	64.5
TR velocity	0.55 (95% CI 0.31–0.79)	>2.8 m/s	27.2	86.6	61.5

Invasive measurements of LV end-diastolic pressure (LVEDP) were analysed in 31 patients (test-cohort).
AUC, area under the curve; CI, confidence interval; *E/e′*, mitral average septal-lateral mitral *E/e′* ratio; LAVI, maximal LA volume index; TR, tricuspid regurgitation.

like mitral *E/e′* ratio, mitral *e′* velocities, LAVI, and TR velocities (*Table 5*) or by adding this index to the 2016 ASE/EACVI criteria (Supplementary data online, *Figure S3*).

Furthermore, analysing the potential incremental clinical relevance of the LA filling index, we found that this LA index was more closely associated with LV filling pressures and HF hospitalization than the echocardiographic LV filling index (i.e. the mitral *E/e′* ratio) (*Figure 3*). In agreement with these findings, all LA diastolic parameters were more closely associated with HF hospitalization than LV diastolic parameters (*Figure 4*).

Table 3 Validation of the diagnostic performance of the LA filling index to determine elevated LV filling pressures (2016 criteria of the ASE and EACVI)

	All patients (n = 486)		
	Sensitivity	**Specificity**	**Accuracy**
E/LA strain ratio > 3.27	88.1%	77.6%	79.1%
	Patients with structural cardiac disease (n = 247)		
	Sensitivity	**Specificity**	**Accuracy**
E/LA strain ratio > 3.27	86.8%	70.1%	74.2%
	Applying the two-steps approach (Algorithm A + B) (n = 486)		
	Sensitivity	**Specificity**	**Accuracy**
E/LA strain ratio > 3.27	86.8%	100%	87.5%

The analysis was performed in the validation cohort (n = 486). Patients with structural cardiac disease (n = 247) were defined as: LA enlargement (LAVI >34 mL/m^2), LV hypertrophy (LV mass index >115/95 g/m^2 men/women), or abnormal LV global longitudinal systolic strain (GLS <16% in absolute values). The two-steps approach of the 2016 ASE/EACVI criteria was performed applying at first the approach to detect LV diastolic dysfunction (LVDD) (i.e. Algorithm A) and then in case of positive criteria for LVDD, applying the approach to estimate LV filling pressures (i.e. Algorithm B). Using the Algorithm A, LVDD was determined when >50% of the following criteria were positive: (I) septal or lateral mitral annular e'<7 cm/s or <10 cm/s, respectively; (II) mitral average septal-lateral E/e' ratio > 14; (III) LAVI > 34 mL/m^2; and (IV) TR jet peak velocity >2.8 m/s. Normal LV diastolic function was determined when <50% of these criteria were positive and indeterminate LV diastolic function was defined when only 50% of the criteria were positive. Using Algorithm A, 103 patients had indeterminate LV diastolic function and using Algorithm A + B, 2 patients had indeterminate grading of LVDD. Using Algorithm B, 3 out of 486 patients in the whole population and 2 out of 247 patients in the subgroup with structural cardiac disease had indeterminate grading of LV filling pressures and these patients were not included in the analysis.

Table 4 Association of the LA filling index with elevated LV filling pressures and the severity of LV diastolic dysfunction according to the 2016 ASE/EACVI criteria

	All patients						
	LV filling pressures			**Severity of LVDD**			
	Normal (n = 416)	**Elevated (n = 67)**	**P-value**	**Grade I (n = 416)**	**Grade II (n = 52)**	**Grade III (n = 15)**	**P-value**
E/LA strain	2.64 ± 1.15	5.34 ± 2.28	<0.01	2.64 ± 1.15	4.93 ± 1.59	6.79 ± 3.53	<0.01
E/LA strain > 3.27	22.4%	88.1%	<0.01	22.4%	86.5%	93.3%	<0.01
	Patients with structural cardiac disease						
	LV filling pressures			**Severity of LVDD**			
	Normal (n = 184)	**Elevated (n = 61)**	**P-value**	**Grade I (n = 184)**	**Grade II (n = 49)**	**Grade III (n = 12)**	**P-value**
E/LA strain	2.89 ± 1.29	5.34 ± 2.35	<0.01	2.89 ± 1.29	4.99 ± 1.62	6.79 ± 3.97	<0.01
E/LA strain > 3.27	29.9%	86.8%	<0.01	29.9%	85.7%	91.6%	<0.01
	Applying the two-steps approach (first Algorithm A and then Algorithm B)						
	LVDD (Algorithm A)			**Severity of LVDD (Algorithm B)**			
	Normal (n = 317)	**LVDD (n = 66)**	**P-value**	**Grade I (n = 3)**	**Grade II (n = 51)**	**Grade III (n = 10)**	**P-value**
E/LA strain	2.43 ± 0.97	5.20 ± 2.35	<0.01	2.54 ± 0.81	4.94 ± 1.60	7.30 ± 4.21	<0.01
E/LA strain > 3.27	16.7%	83.3%	<0.01	0%	86.2%	90%	<0.01

Values are expressed as mean ± SD or percentages. The analysis was performed in the validation cohort (n = 486). Groups and definitions as in *Table 3*.

Table 5 Association of the LA filling index with dyspnoea, worse functional capacity, and heart failure hospitalization

	E/LA strain ratio > 3.27					
	Symptomatic status (dyspnoea)		**NYHA functional class III–IV**		**HF hospitalization at 2 years**	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Unadjusted	4.4 (2.9–6.7)	<0.01	4.5 (2.5–8.0)	<0.01	4.3 (1.8–10.5)	<0.01
Adjusted by age and sex	4.2 (2.7–6.4)	<0.01	4.2 (2.3–7.5)	<0.01	4.1 (1.7–10.2)	<0.01
Adjusted by estimated GFR (<60 mL/min/1.73 m^2)	4.3 (2.8–6.6)	<0.01	3.4 (1.9–6.3)	<0.01	4.1 (1.6–10.6)	<0.01
Adjusted by LV mass index (>95/115 g/m^2 w/m)	4.4 (2.9–6.6)	<0.01	4.2 (2.3–7.6)	<0.01	3.7 (1.5–9.2)	<0.01
Adjusted by GLS (<16%)	4.0 (2.6–6.1)	<0.01	3.4 (1.9–6.2)	<0.01	4.2 (1.7–10.5)	<0.01
Adjusted by mitral *E*/*e′* (>14)	2.5 (1.5–3.9)	<0.01	3.0 (1.6–5.8)	<0.01	3.1 (1.2–8.4)	0.02
Adjusted by mitral *E*/*A* (≥2)	4.5 (3.0–6.7)	<0.01	4.5 (2.5–8.1)	<0.01	4.4 (1.8–10.5)	<0.01
Adjusted by LAVI (>34 mL/m^2)	4.1 (2.7–6.3)	<0.01	4.0 (2.2–7.4)	<0.01	2.5 (0.99–6.5)	0.05
Adjusted by *e′* septal (<7 cm/s) or lateral (<10 cm/s)	4.2 (2.7–6.6)	<0.01	4.0 (2.2–7.1)	<0.01	3.8 (1.6–9.2)	<0.01
Adjusted by TR velocity (>2.8 m/s)	3.5 (2.2–5.6)	<0.01	3.1 (1.6–5.8)	<0.01	2.6 (0.98–6.9)	0.06

The analyses were performed in the validation-cohort (*n* = 486). Adjusted by age and sex, adjusted by >65 years and women.
CI, confidence interval; *E*/*e′*, mitral average septal-lateral mitral *E*/*e′* ratio; GFR, glomerular filtration rate; GLS, left ventricular global longitudinal strain (in absolute values); LAVI, maximal LA volume index; TR, tricuspid regurgitation OR, odds ratio; w/m, women/men.

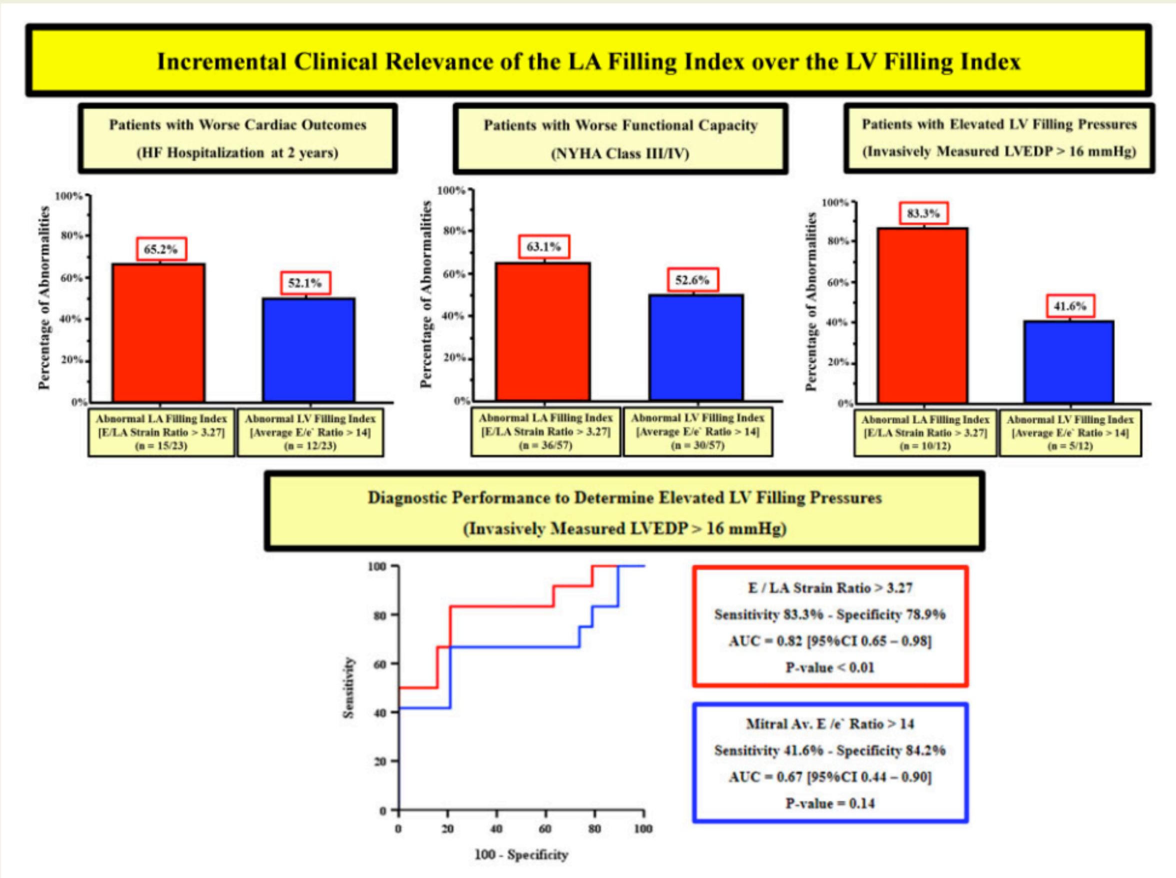

Figure 3 Incremental clinical relevance of the LA filling index over the LV filling index. Analyses referring to worse cardiac outcomes or worse functional capacity were performed in the validation-cohort (*n* = 486), analyses referring to invasively measured LV end-diastolic pressure (LVEDP) were performed in the test-cohort (*n* = 31). AUC, area under the curve; CI, confidence interval; LVEDP, LV end-diastolic pressure.

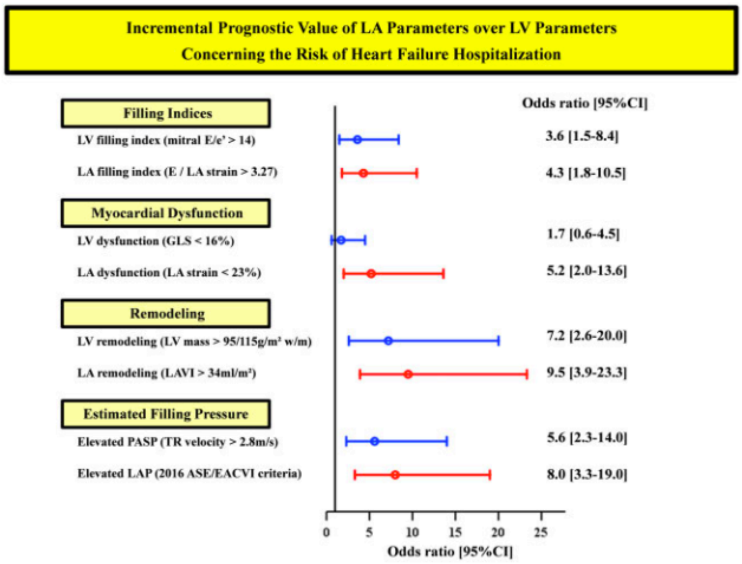

Figure 4 Incremental prognostic value of LA parameters over LV parameters concerning the risk of heart failure hospitalization. The analysis was performed in the validation-cohort (n = 486). CI, confidence interval; *E/e′*, mitral average septal-lateral mitral *E/e′* ratio; GLS, left ventricular global longitudinal strain (in absolute values); LAP, left atrial pressure (2016 ASE/EACVI criteria); LAVI, maximal LA volume index; PASP, pulmonary artery systolic pressure; TR, tricuspid regurgitation OR, odds ratio; w/m, women/men.

Discussion

This study evaluated the potential usefulness and clinical relevance of a novel LA filling index (the *E*/LA strain ratio) to estimate LV filling pressures in patients with cardiovascular risk factors and preserved LVEF. In effect, an elevated *E*/LA strain ratio was found to have an appropriate and potentially useful diagnostic performance to determine elevated LV filling pressures in these patients, with a very low rate of false positives when analysing a validation group of patients free of cardiovascular risk factors or cardiovascular diseases. In addition, regarding the clinical relevance of this new LA filling index, an elevated *E*/LA strain ratio was significantly associated with worse functional capacity and HF hospitalization at 2 years, even adjusting the analyses by age, sex, renal failure, LV hypertrophy, or abnormal GLS.

Elevated LA filling index as a potential parameter of elevated LV filling pressures

The LA cavity, being in direct continuum with the LV cavity during mitral valve opening in the diastole phase, is exposed to LV pressures during every diastole.[9–12] Accordingly, in patients with elevated LV filling pressures, LV diastolic pressures are transmitted back to the LA, resulting in elevated LA pressure, increased LA wall tension, reduced pulmonary venous emptying, and consequently reduced LA filling (i.e. reduced LA reservoir strain).[9–12] Recently, LA strain has proved to be a sensitive parameter to detect LA alterations in patients with LV diastolic dysfunction[1–4] and it has shown a significant correlation with invasive LV filling pressures.[5–8] Nonetheless, in some patients a single parameter could not be adequate to determine elevated LV filling pressures given the multifactorial pathophysiology of elevated LV filling pressures in patients with multiple cardiovascular risk factors or cardiovascular diseases and preserved LVEF.[13–16] Alternatively, an index that combines LV and LA diastolic measurements could potentially come closer to the multifactorial changes of LV diastolic pressures in those patients.

The LA filling index was defined as the ratio of the mitral *E* velocity over LA strain. Thus, this index would represent the patients' current LV filling status (i.e. mitral *E* velocity) and their LA functional changes (i.e. LA reservoir strain) which would be affected not only by elevated LV filling pressures but also by underlying myocardial alterations commonly caused by cardiovascular risk factors or cardiovascular diseases such as arterial hypertension, diabetes mellitus, or coronary artery disease.[4,17,21] In agreement with these pathophysiological considerations, in the present study an elevated *E*/LA strain ratio had a useful diagnostic performance to determine elevated LV filling pressures in these patients, with a very low rate of false positives when analysing a validation group of patients free of cardiovascular risk factors or cardiovascular diseases. Therefore, we consider that the LA filling index, by taking LA changes and increases in LV diastolic pressures into account, could potentially be a useful parameter to estimate LV filling pressures in patients with cardiovascular risk factors or cardiovascular diseases and preserved LVEF.

Potential clinical relevance of the LA filling index

Regarding the potential clinical relevance of the LA filling index, in the present study, an elevated *E*/LA strain ratio was significantly associated with worse functional capacity and HF hospitalization at 2 years, even adjusting these analyses by clinical variables, like age, sex and renal failure, by LV variables, like LV hypertrophy and abnormal GLS, as well as by diastolic variables. In accordance with these findings, the LA filling index was more closely associated with LV filling pressures and HF hospitalization than the LV filling index (i.e. the mitral *E*/*e*′ ratio), which was in agreement with the finding that all LA diastolic parameters had a stronger association with HF hospitalization than LV diastolic parameters. These results are consistent with a recent study in patients with atrial fibrillation, which has also found a significant association of an elevated E/LA strain ratio with HF hospitalization or worse cardiovascular outcomes.[19] Hence, further larger and prospective studies with the purpose of validating these findings are warranted, since the present study indicates that the potential usefulness of the *E*/LA strain ratio in the evaluation of LV filling pressures not only holds diagnostic importance but also significant clinical relevance.

Limitations

This study has some limitations that should be considered. Firstly, the link between the LA filling index and the risk of HF hospitalization should be considered as an association rather than a causal relationship, since the percentage of patients with HF hospitalization was determined using a retrospective analysis of the patients' digital medical records. Hence, further prospective studies are needed to confirm the prognostic value of the *E*/LA strain ratio in this setting. Secondly, data on invasive LV filling pressures were analysed retrospectively and available only in a limited number of patients. Therefore, further larger studies should validate the results of invasive measurements. Thirdly, it is important to note that in comparison to conventional LV diastolic parameters (such as the mitral *E*/*e*′ and *E*/*A* ratio, LAVI, and TR velocity), whose analyses are widely known in echocardiography-laboratories and can be directly performed on ultrasound systems, LA strain is lesser known and requires an additional offline analysis. Likewise, a common pitfall in speckle-tracking analyses is the possible influence of the vendor's software package.[22] Therefore, the findings of this study should be considered in the context of the ultrasound software package that was used, namely Echo-Pac from GE.

Conclusion

The findings from this study suggest that a novel LA filling index (the *E*/LA strain ratio) could be of potential usefulness and clinical relevance in estimating LV filling pressures in patients with cardiovascular risk factors or cardiovascular diseases and preserved LVEF. Hence, further larger and prospective studies with the aim of validating these results are warranted.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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IMAGE FOCUS

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Topsy-turvy heart: a case of congenital absence of the pericardium

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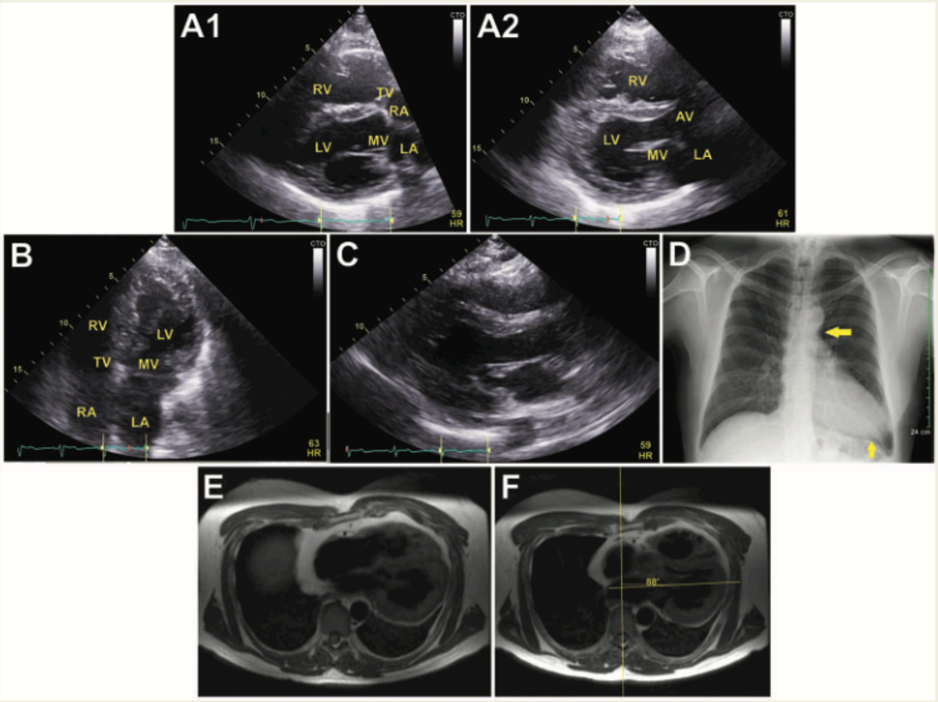

A 55-year-old man presented to the cardiology clinic with a history of palpitations. Blood pressure and cardiac auscultation were normal. A 48-h Holter monitor showed mild premature ventricular contraction burden. Echocardiography utilizing the standard parasternal windows for the long-axis view (LAX) resulted in an unusual foreshortened four-chamber view (*Panel A1*). To obtain the standard LAX, the transducer had to be placed in the left axilla (*Panel A2*). Accordingly, the four-chamber view was obtained with the probe location in the left posterior chest (*Panel B*). Unrestrained swinging motion of the heart was seen in real-time (Supplementary data online, *Video S1*). With the patient turned in the right lateral decubitus position and the transducer placed in the third left intercostal space, the expected LAX was obtained (*Panel C*). Chest X-ray depicted levoposition of the heart, a flattened and elongated left ventricle (LV), known as the 'Snoopy Nose Sign', and interposition of lung tissue resulting in a prominent notch between the aorta and pulmonary artery, as well as lung tissue between the diaphragm and heart (*Panel D*, arrows). Magnetic resonance imaging confirmed the suspected diagnosis of congenital absent pericardium (CAP) (*Panel E*). Note the clockwise-rotation of the heart with an angle of 88°; in a healthy individual it should be 40 ± 10.5° (*Panel F*). The incidence of CAP is <1 in 10 000. The unusual transducer positions required to obtain the expected LAX/four-chamber views and the ability to markedly shift the cardiac position by turning the patient supports the diagnosis of CAP. LA, left atrium; MV, mitral valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve.

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Potential Usefulness and Clinical Relevance of Adding Left Atrial Strain to Left Atrial Volume Index in the Detection of Left Ventricular Diastolic Dysfunction

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ABSTRACT

OBJECTIVES The purpose of this study was to analyze the potential usefulness and clinical relevance of adding left atrial (LA) strain to left atrial volume index (LAVI) in the detection of left ventricular diastolic dysfunction (LVDD) in patients with preserved left ventricular ejection fraction (LVEF).

BACKGROUND Recent studies have suggested that LA strain could be of use in the evaluation of LVDD. However, the potential utility and clinical significance of adding LA strain to LAVI in the detection of LVDD remains uncertain.

METHODS Using 2-dimensional speckle-tracking echocardiography, we analyzed a population of 517 patients in sinus rhythm at risk for LVDD such as those with arterial hypertension, diabetes mellitus, or history of coronary artery disease and preserved LVEF.

RESULTS In patients with LV diastolic alterations and estimated elevated LV filling pressures, the rate of abnormal LA strain was significantly higher than an abnormal LAVI (62.4% vs. 33.6%, $p < 0.01$). In line with this, in patients with normal LAVI, high rates of LV diastolic alterations and abnormal LA strain were present (rates 80% and 29.4%, respectively). In agreement with these findings, adding LA strain to LAVI in the current evaluation of LVDD increased significantly the rate of detection of LVDD (relative and absolute increase 73.3% and 9.9%; rate of detection of LVDD: from 13.5% to 23.4%; $p < 0.01$). Regarding the clinical relevance of these findings, an abnormal LA strain (i.e., <23%) was significantly associated with worse New York Heart Association functional class, even when LAVI was normal. Moreover, in a retrospective post hoc analysis an abnormal LA strain had a significant association with the risk of heart failure hospitalization at 2 years (odds ratio: 6.6 [95% confidence interval: 2.6 to 16.6]) even adjusting this analysis for age and sex and in patients with normal LAVI.

CONCLUSIONS The findings from this study provide important insights regarding the potential usefulness and clinical relevance of adding LA strain to LAVI in the detection of LVDD in patients with preserved LVEF. (J Am Coll Cardiol Img 2018;11:1405–15) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ASE = American Society of Echocardiography

av. E/e′ = ratio of mitral early diastolic inflow velocity (E) using pulsed wave Doppler to average of septal and lateral mitral annular early-diastolic peak velocity (e′) using tissue Doppler imaging

E/A = ratio of mitral early diastolic inflow velocity (E) to mitral late diastolic inflow velocity (A) using pulsed wave Doppler

LA = left atrial or left atrium

LAVI = maximal left atrial volume index

LV = left ventricular or left ventricle

LVDD = left ventricular diastolic dysfunction

PCWP = pulmonary capillary wedge pressure

Septal or lateral e′ = septal or lateral mitral annular early-diastolic peak velocity using tissue Doppler imaging

TR = tricuspid regurgitation jet peak velocity

The volumetric analysis of the left atrium (LA) using the maximal LA volume index (LAVI) is an adequate analysis to estimate the cumulative effect of increased left ventricular (LV) filling pressures over time (1,2). However, LAVI has limitations to detect early LV diastolic alterations because this volumetric parameter reflects mainly the chronic effect of increased LV filling pressures (1,2). Despite these limitations, in the clinical practice LAVI remains the unique recommended LA parameter to analyze changes caused by LV diastolic alterations on the LA (1,2). Notwithstanding, recent findings have found that a new LA functional parameter, LA strain, has a strong correlation to invasive gold standard diastolic measurements and LV filling pressures, even better than LAVI (3-6). In addition, recent studies have found that LA strain is significantly correlated to the severity of LV diastolic dysfunction (LVDD) and that this parameter could reflect earlier changes on the LA than LAVI in patients with LVDD (7-10). Nonetheless, despite these interesting and promising studies (Online Table 1), whether LA strain could help to detect higher rates of LVDD than using only LAVI or help to detect LV diastolic alterations when LAVI is normal remains uncertain.

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Therefore, the aim of the present study was to analyze a large cohort of patients at risk for LVDD and preserved left ventricular ejection fraction (LVEF) to determine the potential usefulness and clinical relevance of adding LA strain to LAVI in the detection of LVDD.

METHODS

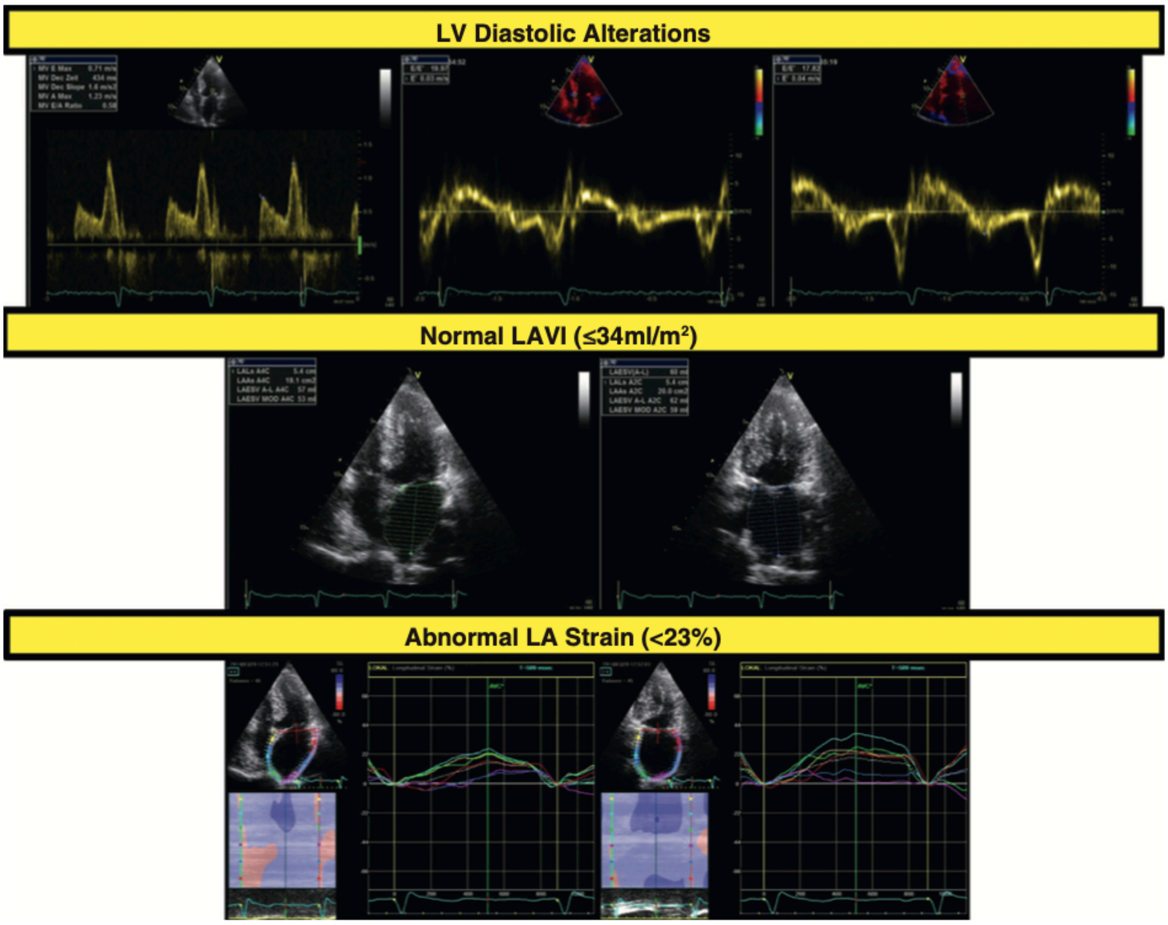
STUDY POPULATION. We included patients in sinus rhythm with some risk factor for LVDD such as those with arterial hypertension (systolic and diastolic blood pressure ≥140/90 mm Hg), diabetes mellitus (fasting plasma glucose ≥126 mg/dl), or history of coronary artery disease (history of acute coronary syndrome, stable angina, or coronary revascularization) and preserved LVEF (LVEF >50%) referred to the Laboratory of Echocardiography of the Charité University Hospital for detection of LVDD between May 2009 and October 2014 (some of these patients were enrolled in previous studies of our research group) (11-13).

Regarding the exclusion criteria of the study population, in line with the recommendations for LV diastolic measurements of the American Society of Echocardiography (ASE) (2), patients with at least mild valvular heart stenosis, moderate or severe aortic or mitral regurgitation, severe pulmonary or tricuspid regurgitation (TR), valvular heart surgery or intervention, significant mitral annular calcification (≥5 mm), ventricular paced rhythm, left bundle branch block, or LV assist devices were excluded. In addition, to avoid underestimations of LA strain values, patients with poor 2-dimensional imaging quality in ≥1 LA segments, history or presence of atrial fibrillation, supraventricular arrhythmias, or unavailable electrocardiogram in the past 90 days as well as those with hypermobile interatrial septum or interatrial septal aneurysm, were excluded from this study. Furthermore, with the purpose of excluding noncardiac causes of dyspnea, patients with severe pulmonary disease such as those with requirement of supplemental oxygen or need of treatment with corticoids, patients with severe kidney disease such as those with dialysis requirement or indication for renal transplantation, and patients with severe liver disease such as those with Child-Pugh class B and C or indication for liver transplantation were also excluded from this study.

The ethic committee from the Charité University Hospital approved this research project, and informed consent was obtained from all subjects.

MEASUREMENTS USING CONVENTIONAL TRANSTHORACIC ECHOCARDIOGRAPHY. All patients were examined at rest using a Vivid 7 or E9 (GE Healthcare, Horton, Norway) ultrasound system. Two-dimensional (2D) and Doppler measurements were performed as recommended by the ASE (1,2,14). Abnormal values of conventional LV diastolic parameters were determined according to the recent 2016 ASE criteria for LVDD (2): 1) septal or lateral mitral annular early-diastolic peak velocity (e′) <7 cm/s or <10 cm/s using tissue Doppler imaging, respectively; 2) mitral average septal-lateral (av.) E/e′ ratio >14; 3) LAVI >34 ml/m^2 (using the biplane Simpson method); and 4) TR jet peak velocity >2.8 m/s. In line with these criteria of the ASE, LVDD was determined when >50% of the aforementioned criteria were positive and normal LV diastolic function when <50% of these criteria were positive (Online Figure 1). In addition, indeterminate LV diastolic function was defined when only 50% of the criteria were positive (Online Figure 1). Likewise, the severity of LVDD was determined according to the 2016 ASE criteria for the grading of LVDD (Online Figure 1). Furthermore,

FIGURE 1 Usefulness of Adding Left Atrial Strain to Maximal Left Atrial Volume Index in the Detection of Left Ventricular Diastolic Alterations



This figure shows a patient with LV diastolic alterations and abnormal LA strain despite normal LAVI. LA strain was determined as the average value of the longitudinal positive strain peak during LA relaxation from all segments of the LA in the apical 4-chamber and 2-chamber views and using the onset of the QRS as the referent point (i.e., analyzing the cardiac cycle between 2 QRS of the ECG). The white curve (with white points) represents the average value of LA strain from all LA segments analyzed in the apical 4-chamber or 2-chamber view. ECG = electrocardiogram; LA = left arterial; LAVI = maximal left arterial volume index; LV = left ventricular.

we analyzed patients with LV diastolic alterations without including LAVI as diagnostic criteria to compare head-to-head LA strain versus LAVI in the detection of LVDD. In this regard, we defined patients with LV diastolic alterations as those with septal e′ <7 cm/s or lateral e′ <10 cm/s and the severity of LV diastolic alterations as mild (abnormal septal or lateral e′ + av. E/e′ <10), moderate (abnormal septal or lateral e′ + av. E/e′ 10 to 14), and severe or elevated LV filling pressures (abnormal septal or lateral e′ + av. E/e′ >14). Moreover, we analyzed the link of LA strain with pulmonary capillary wedge pressure (PCWP) using Nagueh's formula for the estimation of PCWP (i.e., estimated PCWP = 2 + 1.3 × mitral E/lateral e′ ratio) (15). All these measurements were calculated as the average of 3 measurements and performed at conditions of respiratory (<20 breaths/min), hemodynamic (90 to 160 mm Hg of systolic blood pressure), and electrical (51 to 99 beats/min) stability.

MEASUREMENTS USING 2D SPECKLE-TRACKING ECHOCARDIOGRAPHY. The analysis of LA strain using 2D speckle-tracing echocardiography was performed offline blinded to the clinical characteristics

TABLE 1 Clinical and Cardiac Characteristics of the Study Population (n = 517)

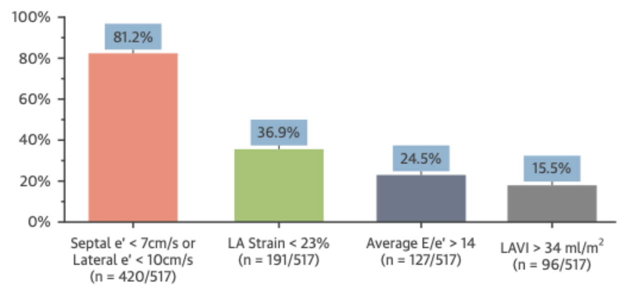
Clinical characteristics	
Age, yrs	68.0 ± 13.0
Women	46.0
Body mass index, kg/m^2	27.5 ± 4.8
Systolic blood pressure, mm Hg	135.9 ± 15.2
Diastolic blood pressure, mm Hg	80.3 ± 11.2
Heart rate, beats/min	71.2 ± 9.3
Arterial hypertension	95.0
Diabetes mellitus	30.6
History of coronary artery disease	33.8
Cardiac characteristics	
LV ejection fraction, %	62.1 ± 5.7
LV mass, g/m^2	100.3 ± 25.1
Septal e' mitral annular velocity by TDI, cm/s	5.5 ± 1.9
Lateral e' mitral annular velocity by TDI, cm/s	7.6 ± 2.4
Mitral early diastolic inflow velocity (E), cm/s	71.3 ± 21.9
Mitral E/e' septal-lateral average ratio (Av. E/e')	11.9 ± 5.2
LAVI, ml/m^2	27.1 ± 10.0
LA strain, %	26.6 ± 9.7
TR jet peak velocity, m/s	2.24 ± 0.49

Values are mean ± SD or %. TR was available in 454 patients.

E = mitral early diastolic inflow peak velocity by pulsed Doppler; e' = septal or lateral mitral annular early diastolic peak velocity by TDI; LA = left atrial; LAVI = maximal left atrial volume index; LV = left ventricular; LVDD = left ventricular diastolic dysfunction; TDI = pulsed tissue Doppler imaging; TR = tricuspid regurgitation.

of the patients and using the following ultrasound software package: Echo-Pac version 113.0 from GE Healthcare. LA strain was determined as the average value of the longitudinal positive strain peak during LA relaxation from all segments of the LA in the apical 4-chamber and 2-chamber views. Figure 1 shows an example regarding how the LA strain was analyzed. LA strain measurements were performed at frame rates of 50 to 80 frames/s, averaging 3 measurements, and using the onset of the QRS as the referent point (i.e., analyzing the cardiac cycle between 2 QRS complexes of the electrocardiogram). In addition, according to large studies in healthy subjects showing that the lower limit of normality of LA strain is at 23% (12,16,17), an abnormal LA strain was defined as LA strain <23% (12,16,17).

FIGURE 2 Rate of Abnormal LA Strain and Abnormal LAVI in Patients at Risk for LVDD and Preserved LVEF



Septal and lateral e' and average E/e' were measured by means of mitral annular and inflow Doppler analyses. Abbreviations as in Figure 1.

STATISTICAL ANALYSIS. Continuous data were presented as mean ± SD and dichotomous data in percentage. Differences in continuous variables between 2 groups were analyzed using the Student's *t* test. Categorical variables were compared by chi-square test, Fisher exact test, and McNemar test as appropriate. Comparisons between 3 or more groups were analyzed by 1-way analysis of variance. The association of LA strain with continuous variables was analyzed using a simple linear regression analysis (with β coefficient as main analysis) and with dichotomous variables using a logistic regression analysis (with odds ratio [OR] as main analysis). Moreover, we analyzed the association and diagnostic performance of LA strain with LVDD by means of the area under the curve of receiver-operating characteristic curve analysis. Furthermore, with the purpose of analyzing the association of an abnormal LA strain with symptomatic status (dyspnea), worse New York Heart Association functional class (NYHA), and elevated estimated PCWP, unadjusted and adjusted logistic regression analyses were performed. Moreover, we performed a retrospective post hoc analysis to analyze the association of an abnormal LA strain with the risk for heart failure (HF) hospitalization at 2 years by means of a logistic regression analysis (with OR and C-statistic as main analysis). In this regard, between November 2016 and January 2017, we analyzed retrospectively the digital medical records of the patients with the purpose of analyzing the rate of HF hospitalization (defined as HF requiring hospitalization for compensation and treatment) within 2 years after the inclusion in the study. In addition, we further analyzed in this retrospective post hoc analysis the association of LA strain with invasive LV filling pressures by analyzing those patients who had invasive measurements of LV end-diastolic pressure within 7 days of the echocardiography.

The adequate reproducibility of LA strain has been previously confirmed in several studies from our own and other laboratories (7–10,12,18,19). In effect, analyzing 20 randomly selected patients from the present study, the intraobserver and interobserver variability of LA strain was low (Online Table 2, Online Figure 2). All statistical analyses were performed with Statview 5.0 (SAS Institute Inc., Cary, North Carolina), SPSS 22.0 (IBM Inc., Armonk, New York), and MedCalc 17.6 (MedCalc Software bvba, Ostend, Belgium). Differences were considered statistically significant when $p < 0.05$.

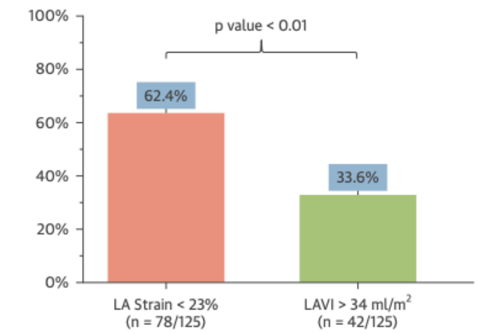
RESULTS

CHARACTERISTICS OF THE STUDY POPULATION. A total of 558 patients met the eligibility criteria during the study period. However, it was not possible to perform LA strain analyses and LAVI measurements in 41 patients because of inadequate 2D imaging quality of the LA (feasibility 92.7%). Thus, 517 patients with adequate 2D imaging quality for an analysis by LA strain and LAVI measurements were included. Clinical and cardiac characteristics of the study population are shown in Table 1. In this respect, 95% of the patients had arterial hypertension and, to a lesser extent, diabetes mellitus and history of coronary artery disease (30.6% and 33.8%, respectively). In addition, 46% of the population was female, and the mean age was 68 ± 13 years.

LA STRAIN IN COMPARISON WITH LAVI TO DETECT LV DIASTOLIC ALTERATIONS. Analyzing the whole cohort of 517 patients at risk for LVDD, 36.9% of these patients had an abnormal LA strain, whereas the rate of an abnormal LAVI was only 15.5% ($p < 0.01$) (Figure 2). In addition, in patients with LV diastolic alterations and estimated elevated LV filling pressures, the rate of abnormal LA strain was 62.4%, whereas the rate of abnormal LAVI was only 33.6% ($p < 0.01$) (Figure 3, Online Figure 3). In line with this, in patients with normal LAVI, high rates of LV diastolic alterations and abnormal LA strain were present (80.0% and 29.4%, respectively) (Figure 4). Moreover, LA strain was significantly more linked to the severity of LV diastolic alterations than LAVI (Tables 2 and 3). In agreement with these findings, in a retrospective post hoc analysis on 36 patients with invasive LV filling pressure measurements, an abnormal LA strain had significantly better diagnostic performance to determine elevated LV end-diastolic pressure (i.e., >16 mm Hg) than an abnormal LAVI (sensitivity 62.5% vs. 25% and specificity 75% vs. 85%) (Online Figure 4). Furthermore, in a simple linear regression analysis (with β coefficient as the main analysis), each estimated change in septal and lateral e′ per 1 cm/s was linked to a significant estimated absolute change in LA strain of 2.05% and 1.44%, respectively, which was more significant than with LAVI (Table 3).

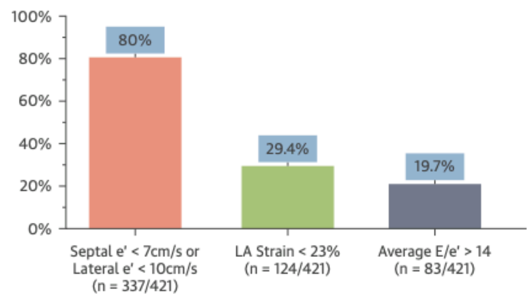
USEFULNESS OF ADDING LA STRAIN TO LAVI IN THE DETECTION OF LVDD. Regarding the diagnostic performance of LA strain to detect LVDD, analyzing patients with normal LV diastolic function and those with LVDD according to the 2016 diagnostic criteria of the ASE, an abnormal LA strain (i.e., <23%) had adequate sensitivity and accuracy to detect patients with LVDD (sensitivity 72.8%, accuracy 75.6%, specificity 76.2%, area under the curve 0.804) (Online Figure 5). In line with these findings, adding LA strain to LAVI in the current evaluation of LVDD increased significantly the rate of detection of LVDD (relative and absolute increase 73.3% and 9.9%, respectively; rate of detection of LVDD: from 13.5% to 23.4%; $p < 0.01$) (Figure 5).

FIGURE 3 Rate of Abnormal LA Strain and Abnormal LAVI in Patients With LV Diastolic Alterations and Estimated Elevated LV Filling Pressures



Patients with LV diastolic alterations and estimated elevated LV filling pressures were determined as those with abnormal septal or lateral e′ velocity and mitral E/e′ average >14. The p value was <0.01 in both the chi-square and the McNemar tests. Abbreviations as in Figure 1.

FIGURE 4 Rate of LV Diastolic Alterations and Abnormal LA Strain in Patients With Normal LAVI



Septal and lateral e′ and average E/e′ were measured by means of mitral annular and inflow Doppler analyses. Abbreviations as in Figure 1.

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TABLE 2 Association of LA Strain With the Severity of LV Diastolic Dysfunction

		LVDD (According to Septal-Lateral e' and av. E/e')			
	Normal (n = 97)	Mild (n = 134)	Moderate (n = 161)	Severe (n = 125)	p Value ANOVA
LA strain, %	32.2 ± 10.3	27.8 ± 9.1	25.7 ± 9.2	22.2 ± 8.1	<0.01
LAVI, ml/m²	24.5 ± 8.4	24.6 ± 8.4	26.4 ± 9.0	32.7 ± 11.8	<0.01
Abnormal LA strain	11.3	26.1	41.6	62.4	n/a
Abnormal LAVI	13.4	10.4	16.8	33.6	n/a
p value	0.82	<0.01	<0.01	<0.01	
		LVDD (According to 2016 ASE Criteria for LVDD)			
	Normal (n = 337)	**Mild or Indeterminate* (n = 113)**	**Moderate (n = 56)**	**Severe (n = 11)**	**p Value ANOVA**
LA strain, %	28.8 ± 9.8	24.0 ± 8.3	20.3 ± 6.4	17.7 ± 7.2	<0.01
Abnormal LA strain	23.7	55.8	69.6	81.8	n/a

Values are mean ± SD or %. Abnormal LA strain was defined as LA strain <23% and abnormal LAVI as >34 ml/m². The severity of LV diastolic dysfunction using only LV Doppler parameters was defined as: I) normal LVDD = normal septal and lateral e'; II) mild LVDD = abnormal septal or lateral e' + av. E/e' < 10; III) moderate LVDD = abnormal septal or lateral e' + av. E/e' 10 to 14; and IV) severe LVDD = abnormal septal or lateral e' + av. E/e' > 14. The definition of the severity of LVDD using the whole 2016 criteria of the ASE (namely, including LAVI among the criteria) is shown in Online Figure 1. *Patients with indeterminate LV diastolic function were also included in this subgroup because only 3 patients met the criteria for mild LVDD.

ANOVA = analysis of variance; ASE = American Society of Echocardiography; n/a = not applicable; other abbreviations as in Table 1.

Furthermore, regarding another potential usefulness of LA strain in the evaluation of LVDD, in the present study adding LA strain to the current 2016 ASE diagnostic algorithm for LVDD helped to further stratify patients with indeterminate LV diastolic function because a high proportion of these patients had normal LAVI but with LA strain alterations (Figure 6).

CLINICAL RELEVANCE OF USING LA STRAIN IN THE EVALUATION OF LVDD. Concerning the clinical relevance of LA strain, an abnormal LA strain (i.e., <23%) was significantly associated with symptomatic status (dyspnea) and higher estimated PCWP (Table 4, Figure 7). In line with these findings, an abnormal LA strain was also significantly linked to worse NYHA functional class and elevated estimated PCWP, even when LAVI was normal (Table 4, Figure 7). In addition, in a retrospective post hoc analysis, an abnormal LA strain had a significant association with the risk of HF hospitalization at 2 years (OR: 6.6 [95% confidence interval (CI): 2.6 to 16.6]) even when adjusting this analysis for age and sex and in patients with normal LAVI (Table 5). Moreover,

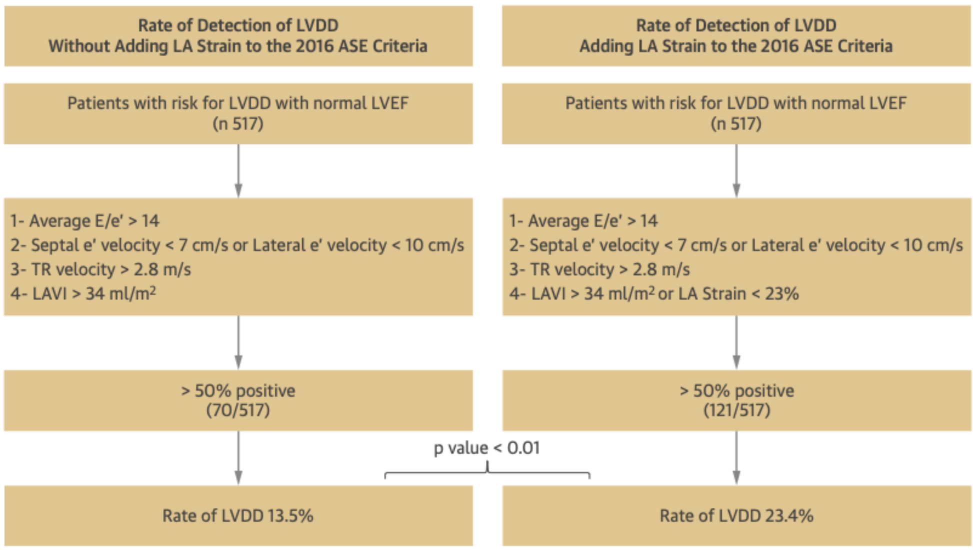
TABLE 3 Association of LV Diastolic Parameters With LA Strain and LAVI

	LA Strain, %		LAVI, ml/m²	
Continuous Analysis	β (95% CI)	p Value	β (95% CI)	p Value
Septal e' velocity, per 1 cm/s	2.05 (1.65 to 2.44)	<0.01	−1.25 (−0.81 to −1.69)	<0.01
Lateral e' velocity, per 1 cm/s	1.44 (1.12 to 1.76)	<0.01	−0.67 (−0.32 to −1.02)	<0.01
Mitral E/e' average, per 1 unit	−0.60 (−0.45 to −0.75)	<0.01	0.68 (0.53 to 0.84)	<0.01
LAVI, per 1 ml/m²	−0.37 (−0.29 to −0.44)	<0.01	n/a	n/a
TR velocity, per 0.1 m/s	−0.24 (−0.06 to −0.41)	<0.01	0.65 (0.47 to 0.83)	<0.01
	Abnormal LA Strain		**Abnormal LAVI**	
Dichotomous Analysis	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
Abnormal septal e' velocity (<7 cm/s)	6.2 (3.6 to 10.8)	<0.01	2.3 (1.2 to 4.1)	<0.01
Abnormal lateral e' velocity (<10 cm/s)	3.7 (2.2 to 6.3)	<0.01	1.1 (0.6 to 1.8)	0.74
Abnormal mitral E/e' average (>14)	4.2 (2.8 to 6.5)	<0.01	3.4 (2.1 to 5.5)	<0.01
Abnormal LAVI (>34 ml/m²)	5.5 (3.4 to 8.9)	<0.01	n/a	n/a
Abnormal TR velocity (>2.8 m/s)	2.0 (1.1 to 3.5)	0.01	5.6 (3.1 to 10.1)	<0.01

The β coefficient was used as an estimated change in LA strain for every estimated change in the continuous variable. See also Online Figure 6, which displays the correlation of LA strain with LAVI. Abnormal LA strain was defined as LA strain <23% and abnormal LAVI as >34 ml/m².

β = beta coefficient; CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 2.

FIGURE 5 Potential Usefulness of Adding LA Strain to LAVI in the Detection of LV Diastolic Dysfunction



Adding LA strain to LAVI in the evaluation of LVDD could help to increase significantly the detection of LVDD. The p value was <0.01 in both the chi-square and the McNemar tests. ASE = American Society of Echocardiography; LVDD = left ventricular diastolic dysfunction; LVEF = left ventricular ejection fraction; TR = tricuspid regurgitation jet peak velocity; other abbreviations as in Figure 1.

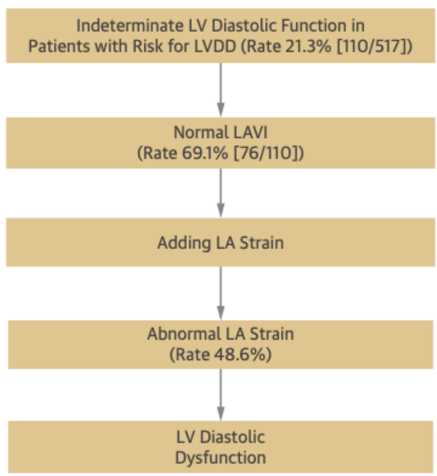
adding LA strain to LAVI for the estimation of the risk of HF hospitalization at 2 years increased and improved the performance of LAVI to estimate the risk of HF hospitalization (increase of the OR and C-statistic from 8.8 [95% CI: 3.9 to 20] to 18.9 [95% CI: 4.4 to 80.7] and from 0.734 to 0.764, respectively).

DISCUSSION

Analyzing a large cohort of patients at risk for LVDD and preserved LVEF, the findings from this study provide important data regarding the potential utility and clinical relevance of adding LA strain to LAVI in the detection of LVDD.

USEFULNESS OF ADDING LA STRAIN TO LAVI IN THE DETECTION OF LVDD. The volumetric analysis of the LA using LAVI is an adequate analysis to estimate the cumulative effect of increased LV filling pressures over time (1,2). However, LAVI has limitations to detect early LV diastolic alterations because this volumetric parameter reflects mainly the chronic effect of increased LV filling pressures (1,2). Despite these limitations, in the clinical practice LAVI remains the unique recommended LA parameter to analyze changes caused by LV diastolic alterations on the LA (1,2). In the present study analyzing a cohort of

FIGURE 6 Potential Usefulness of LA Strain in the Setting of Indeterminate LV Diastolic Function in Patients With Normal LAVI



Indeterminate LV diastolic function was defined according to the recent recommendations of the ASE for LVDD. Abbreviations as in Figures 1 and 5.

TABLE 4 Association of Abnormal LA Strain With Symptomatic Status (Dyspnea), Worse NYHA Functional Class, and Elevated Estimated PCWP

	All Patients		
	Normal LA Strain (n = 326)	Abnormal LA Strain (n = 191)	p Value
Symptomatic status (dyspnea)	34	67	<0.01
NYHA functional class III/IV	5.8	22.5	<0.01
Estimated PCWP, mm Hg	13.8 ± 4.9	18.1 ± 6.6	<0.01
Estimated PCWP >15 mm Hg	28.8	57.1	<0.01
HF hospitalization at 2 yrs	1.8	11	<0.01
	Patients With Normal LAVI		
	Normal LA Strain (n = 297)	Abnormal LA Strain (n = 124)	p Value
Symptomatic status (dyspnea)	33.3	64.5	<0.01
NYHA functional class III/IV	5.4	20.2	<0.01
Estimated PCWP, mm Hg	13.7 ± 5.1	17.1 ± 5.8	<0.01
Estimated PCWP >15 mm Hg	28.6	51.6	<0.01
HF hospitalization at 2 yrs	0.7	6.5	<0.01

Values are % or mean ± SD. PCWP was estimated in mm Hg using the Nagueh's formula: 2 + 1.3 x mitral E/lateral e' ratio. Abnormal LA strain was defined as LA strain <23%. Normal LAVI was defined as LAVI ≤34 ml/m^2.

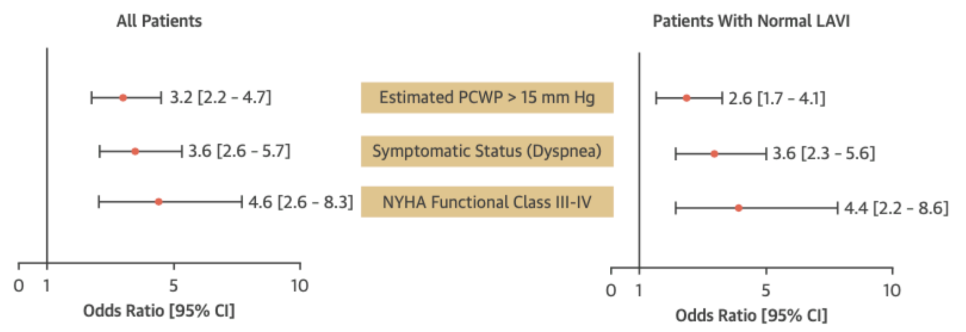
NYHA = New York Heart Association functional class; PCWP = indicates pulmonary capillary wedge pressure; other abbreviations as in Table 1.

517 patients at risk for LVDD and preserved LVEF, we found that a high proportion of patients with normal LAVI had LV diastolic alterations and abnormal LA strain. In agreement, patients with LV diastolic alterations had significantly higher rates of abnormal LA strain than abnormal LAVI. Thus, on the basis of these findings, we consider that LA strain could be a more useful parameter to detect earlier LV diastolic alterations than LAVI in patients preserved LVEF.

Furthermore, regarding another potential use for LA strain in the evaluation of LVDD, in the present study we found that adding LA strain to LAVI increased significantly the rate of detection of LVDD (relative and absolute increase 73.3% and 9.9%, respectively). Hence, we consider that adding LA strain to the current evaluation of LVDD could help to increase the detection of LVDD. In addition, adding LA strain to the current diagnostic algorithm of the ASE for LVDD could help to further stratify patients with indeterminate LV diastolic function because a high proportion of these patients have normal LAVI but with LA strain alterations.

CLINICAL RELEVANCE OF USING LA STRAIN IN THE EVALUATION OF LVDD. Although the use of LA strain could have benefits in comparison with LAVI concerning the earlier detection of LV diastolic changes, the clinical relevance of LAVI in patients at risk for LVDD and preserved LVEF has been widely studied and demonstrated (20-25), which was confirmed in this study. On the other hand, there is weak evidence on the clinical relevance of LA strain in this setting. In the present study, we found that abnormal LA strain was significantly associated with worse NYHA functional class and elevated estimated PCWP, even when LAVI was normal. In line with this, in retrospective post hoc analysis, an abnormal LA strain was significantly linked to the risk of HF hospitalization at 2 years, even adjusting this analysis for age and sex and in patients with normal LAVI. These findings are in agreement with recent studies in

FIGURE 7 Association of Abnormal LA Strain With Symptomatic Status, Worse NYHA Functional, and Elevated Estimated PCWP in All Patients and in Patients With Normal LAVI



The **bars** indicate the odds ratio (with 95% CI) of an abnormal LA strain linked to symptomatic status (dyspnea), elevated estimated PCWP, and worse NYHA functional class in all patients and in patients with normal LAVI. CI = confidence interval; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; other abbreviations as in Figure 1.

TABLE 5 Association of Abnormal LA Strain With Heart Failure Hospitalization at 2 Years

	Risk of Heart Failure Hospitalization at 2 Yrs Post Hoc Analysis in All Patients					
	Unadjusted			Adjusted by Age and Sex		
	OR	95% CI	p Value	OR	95% CI	p Value
Abnormal LA strain (<23%)	6.6	2.6-16.6	<0.01	5.7	2.2-14.7	<0.01
Abnormal LAVI (>34 ml/m^2)	8.8	3.9-20.0	<0.01	7.4	3.2-16.9	<0.01
Abnormal mitral E/e' average (>14)	3.5	1.6-7.8	<0.01	3.1	1.3-6.8	<0.01
Abnormal septal e' velocity (<7 cm/s)	4.9	1.1-21.1	0.03	3.4	0.7-15.2	0.10
Abnormal lateral e' velocity (<10 cm/s)	8.8	1.1-65.6	0.03	5.4	0.7-41.9	0.10
Abnormal TR velocity (>2.8 m/s)	4.9	2.1-11.5	<0.01	3.7	1.5-8.8	<0.01

	Risk of Heart Failure Hospitalization at 2 Yrs Post Hoc Analysis in Patients With Normal LAVI					
	Unadjusted			Adjusted by Age and Sex		
	OR	95% CI	p Value	OR	95% CI	p Value
Abnormal LA strain (<23%)	10.1	2.1-48.6	<0.01	9.5	1.9-46.4	<0.01
Abnormal LAVI (>34 ml/m^2)	n/a	n/a	n/a	n/a	n/a	n/a
Abnormal mitral E/e' average (>14)	0.4	0.1-3.5	0.44	0.3	0.1-2.9	0.33
Abnormal septal e' velocity (<7 cm/s)	1.7	0.3-8.2	0.49	1.3	0.2-7.1	0.73
Abnormal lateral e' velocity (<10 cm/s)	>10.0	0.01->10.0	0.96	>10	0.01->10.0	0.96
Abnormal TR velocity (>2.8 m/s)	1.5	0.1-12.4	0.70	1.2	0.1-10.3	0.86

Adjusted by age and sex indicates adjusted by >65 yrs and female. Normal LAVI was defined as LAVI ≤34 ml/m^2.
Abbreviations as in Tables 1 and 3.

patients with diastolic HF that have also found a significant association of an abnormal LA strain with the risk of HF hospitalization (26,27). Hence, we consider that further studies with the purpose of validating these findings are warranted because the present study indicates that the usefulness of LA strain in the evaluation of LVDD could be not only of diagnostic importance but also of significant clinical relevance.

STUDY LIMITATIONS. In comparison with conventional LV diastolic parameters (such as LAVI), whose analyses are widely known in laboratories of echocardiography and can be directly performed on ultrasound systems, LA strain is lesser known and requires an additional offline analysis. Furthermore, the possible influence of the vendor's software package on LA strain is another possible limitation. Recent studies have shown that LV longitudinal systolic strain values could vary between different software packages such as GE, Philips, and Toshiba (28-30). Thus, while there are no data showing variability between different ultrasound software packages regarding LA strain, we consider that the cutoff to define an abnormal LA strain reported in this study should be considered according to the ultrasound software package used (i.e., Echo-Pac from GE), which so far is the most extensively validated software to analyze the LA with speckle-tracking echocardiography (3-6,9,12,16,17). Nonetheless, a recent study analyzing a large cohort of healthy subjects with the Philips software (i.e., QLab) found a similar lower limit of normality for LA strain (i.e., at 23%) (31). Moreover, in the present study, we did not analyze the relationship of invasive LV diastolic measurements to LA strain in all patients. Thus, the main analyses of this study were based on the association of LA strain with echocardiographic markers of LV diastolic function rather than invasively confirmed LVDD. Nonetheless, several studies have previously shown a strong correlation of LA strain with invasive gold standard diastolic measurements and invasively confirmed LVDD (3-6), as has been shown in a small subgroup in this study. In addition, in the present study, echocardiographic 3D diastolic measurements were not performed, which have recently shown that by means of the minimal LA volume, it is possible to analyze the diastolic function of the LV (32). Furthermore, the findings regarding an abnormal LA strain and the risk for HF hospitalization should be considered merely as an association rather than a causal analysis because the rate of HF hospitalization was estimated merely analyzing retrospectively the digital medical records of the patients. Hence, further studies should confirm the link or causal association between an abnormal LA strain and the risk for HF hospitalization in patients at risk for LVDD and preserved LVEF. Moreover, patients with atrial fibrillation were excluded from this study. Hence, we consider

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that the findings from this study could be only extrapolated to a population with sinus rhythm with intermediate to high probability of LVDD, such as those with arterial hypertension, diabetes mellitus, or history of coronary artery disease and preserved LVEF.

CONCLUSIONS

Analyzing a large cohort of patients at risk for LVDD and preserved LVEF, the findings from this study provide important insights regarding the potential usefulness and clinical relevance of adding LA strain to LAVI in the detection of LVDD in patients with preserved LVEF.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Although LAVI is an adequate analysis to estimate the cumulative chronic effect of increased LV filling pressures, this volumetric parameter has limitations to detect earlier LV diastolic alterations. In this regard in the present study, LA strain detected significantly high rates of LV diastolic alterations despite normal LAVI. In line with this, we showed that adding LA strain to LAVI in the evaluation of LVDD increased significantly the rate of detection of LVDD.

TRANSLATIONAL OUTLOOK: Further studies to validate the clinical relevance of these findings are warranted because the present study suggests that abnormal LA strain is significantly linked to worse NYHA functional class and higher risk of HF hospitalization at 2 years, even adjusting these analyses for age and sex and in patients with normal LAVI.

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KEY WORDS echocardiography, left atrial, speckle-tracking, strain

APPENDIX For additional tables, references, and figures, please see the online version of this paper.

Lebenslauf

"Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht."

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1. Frydas A, Morris DA, Belyavskiy E, Radhakrishnan AK, Kropf M, Tadic M, Roessig L, Lam CSP, Shah SJ, Solomon SD, Pieske B, Pieske-Kraigher E. Left atrial strain as sensitive marker of left ventricular diastolic dysfunction in heart failure. ESC Heart Fail. 2020. Impact factor: 3.902

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