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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).

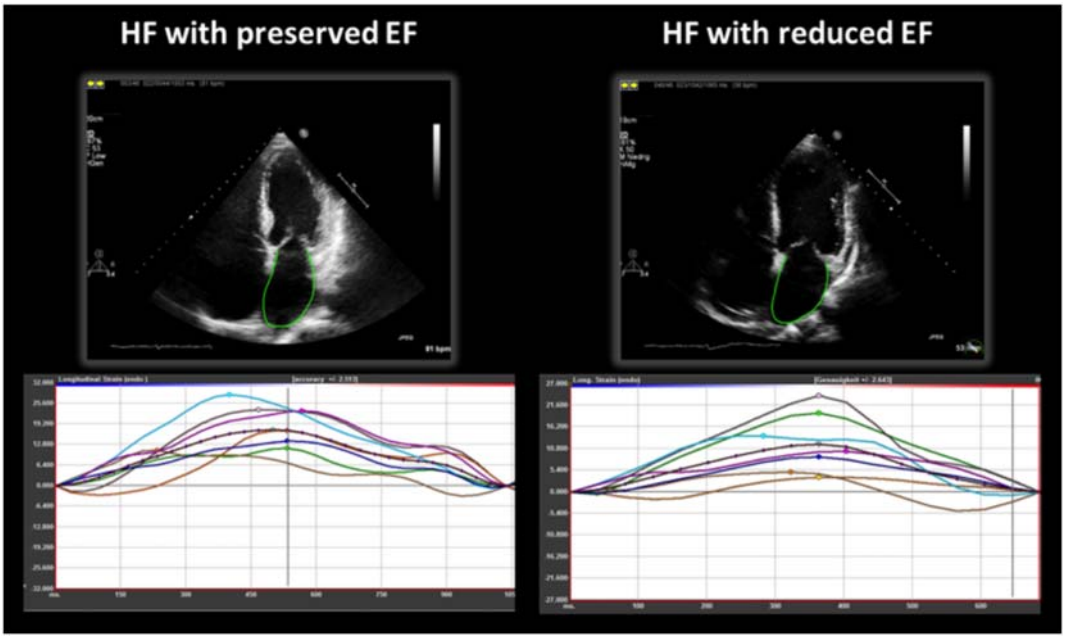
Echocardiographic analysis

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.



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.

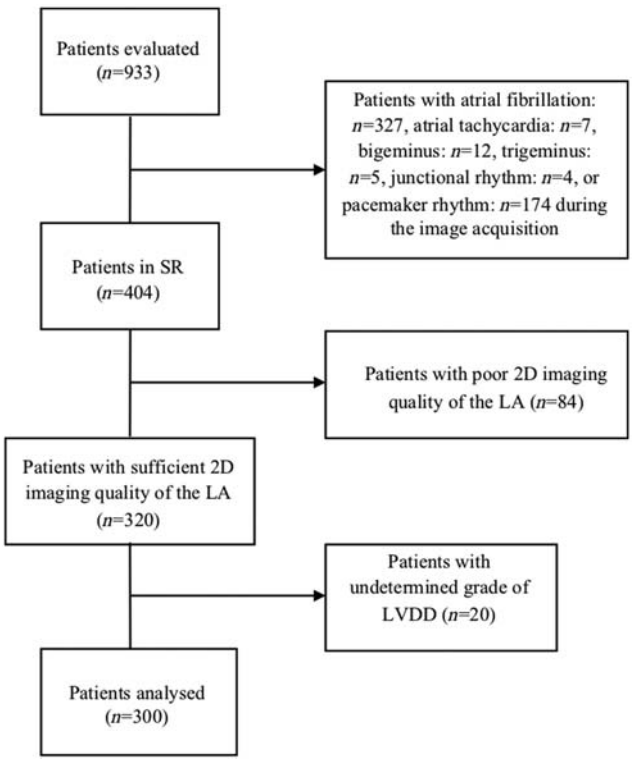


Table 2 Association of LA strain with the severity of LV diastolic dysfunction

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.

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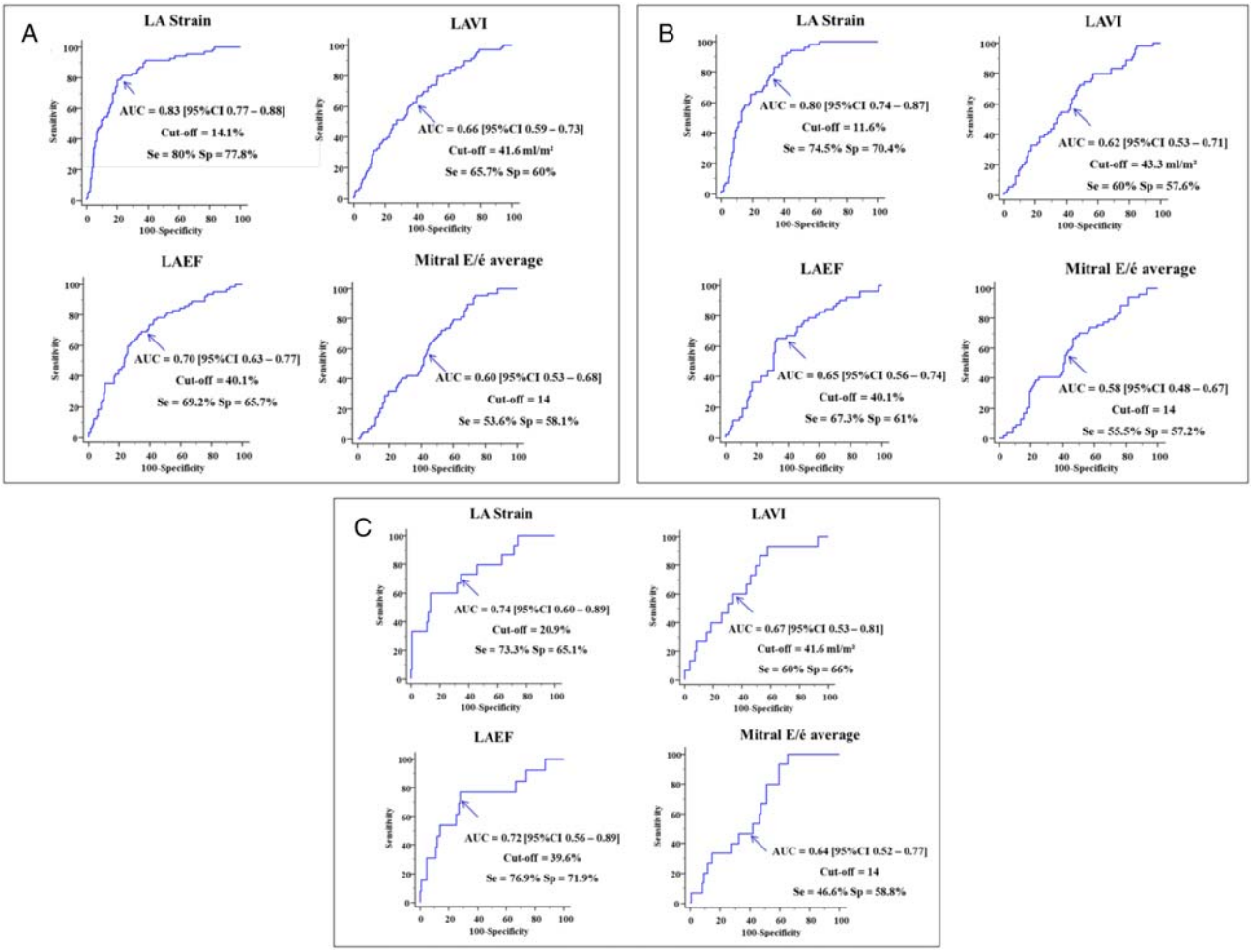
Diagnostic performance of left atrial strain versus left atrial volume index, left atrial total emptying fraction, and mitral E/e′ ratio to determine severe left ventricular diastolic dysfunction

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%.

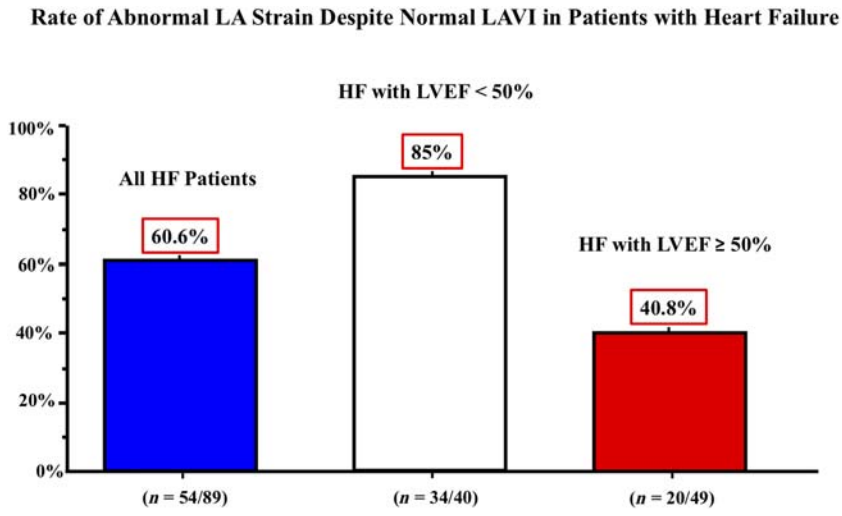
Correlation between left ventricular diastolic dysfunction and left atrial strain in patients with heart failure

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.



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(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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