European Heart Journal – Cardiovascular Imaging (2015) **16**, 364–372
doi:10.1093/ehjci/jeu219

# Normal values and clinical relevance of left atrial myocardial function analysed by speckle-tracking echocardiography: multicentre study

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*Received 6 July 2014; accepted after revision 15 September 2014; online publish-ahead-of-print 3 November 2014*

**Aims** The aim of this multicentre study was to determine the normal range and the clinical relevance of the myocardial function of the left atrium (LA) analysed by 2D speckle-tracking echocardiography (2DSTE).

**Methods and results** We analysed 329 healthy adult subjects prospectively included in 10 centres and a validation group of 377 patients with left ventricular diastolic dysfunction (LVDD). LA myocardial function was analysed by LA strain rate peak during LA contraction (LA-SRa) and LA strain peak during LA relaxation (LA-Strain). The range of values of LA myocardial function in healthy subjects was LA-SRa $-2.11 \pm 0.61$ $s^{-1}$ and LA-Strain $45.5 \pm 11.4\%$, and the lowest expected values of these LA analyses (calculated as $-1.96$ SD from the mean of healthy subjects) were LA-SRa $-0.91$ $s^{-1}$ and LA-Strain 23.1%. Concerning the clinical relevance of these LA myocardial analyses, LA-SRa and LA-Strain detected subtle LA dysfunction in patients with LVDD, even though LA volumetric measurements were normal. In addition, in these patients we found that the functional class (dyspnoea–NYHA classification) was inversely related to both LA-Strain and LA-SRa.

**Conclusion** In the present multicentre study analysing a large cohort of healthy subjects and patients with LVDD, the normal range and the clinical relevance of the myocardial function of the LA using 2DSTE have been determined.

**Keywords** Speckle tracking • Echocardiography • Left atrial • Strain

## Introduction

The functional echocardiographic analysis of the left atrium (LA) is known since more than 30 years.[1,2] The first studies validating the echocardiographic assessment of LA function were carried out using volumetric analyses such as LA ejection fraction (LAEF).[1,2] In the last years, thanks to the contribution of new myocardial techniques such as 2D speckle-tracking echocardiography (2DSTE), the myocardial function of the LA in diverse heart diseases could be comprehensively analysed.[3–20] Nonetheless, despite these progresses in LA myocardial measurements, the incremental clinical value of LA myocardial analyses using 2DSTE over conventional LA volumetric measurements remains poorly understood. In addition, the definition of a normal LA myocardial function is lacking. Some studies analysing healthy subjects with 2DSTE have reported the values of the myocardial function of the LA in this population.[21–26] However, these studies were limited to determine the normal range of the myocardial function of the LA because of the small number of patients analysed (<80 women or men).[21–26]

Therefore, on the basis of the weak evidence regarding the normal values and the clinical significance of LA myocardial analyses using 2DSTE, the aim of the present multicentre study was to analyse a

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large cohort of healthy subjects and patients with a common condition such as left ventricular (LV) diastolic dysfunction (LVDD) with the purpose of determining the normal range and the clinical relevance of the myocardial function of the LA using 2DSTE.

# Methods

## Study population

We enrolled healthy subjects ≥18 years of age prospectively included in nine centres in Japan and in one centre in Germany. These subjects were part of the Japanese Ultrasound Speckle Tracking of the Left Ventricle Research Project,[27,28] which enrolled consecutively healthy volunteer subjects in different university hospitals and was endorsed by the Japanese Society of Echocardiography.[27,28] Healthy subjects were defined as all those individuals with the absence of any disease and cardiovascular risk factors such as obesity, diabetes, hypertension, and hypercholesterolaemia; no medication; and normal findings in transthoracic echocardiography according to the diagnostic criteria of the European Association of Cardiovascular Imaging (EACI).[29–31] The ethics committees from each of the hospitals approved this research project, and informed consent was obtained from all of the subjects.[27,28]

## Validation group

To determine the clinical relevance of LA myocardial measurements using 2DSTE in a common condition, we analysed a group of patients with LVDD included in previous studies of our research group.[11,28,32,33] LVDD was defined according to the diagnostic criteria of the EACI: septal or lateral mitral annular early-diastolic (e′) peak velocity <8 or <10 cm/s using tissue Doppler imaging (TDI), respectively, or maximal LA volume index (LAVI) ≥34 mL/m$^2$.[30] In this group of patients with the purpose of excluding non-cardiac causes of dyspnoea, we excluded patients with the following characteristics: (i) severe pulmonary disease defined as pulmonary pathology with requirement of supplemental oxygen or need of treatment with corticoids; (ii) severe kidney disease defined as estimated glomerular filtration rate (GFR) <30 mL/min/1.73 m$^2$ for at least 3 months or severe acute renal failure with dialysis requirement; and (iii) severe chronic liver disease. In addition, patients with LV systolic dysfunction (i.e. LVEF <50%) and severe valvular heart disease were excluded. Furthermore, to avoid underestimations of LA myocardial analyses, patients with poor 2D imaging quality in ≥1 myocardial segments of the LA or atrial arrhythmias at the moment of the study or in the last 90 days were also excluded.

## Volumetric analyses of the LA using conventional 2D echocardiography

All patients were examined at rest in the left lateral decubitus position using one of the following ultrasound systems: Vivid 7 or Vivid E9 from GE Healthcare. LV diameters, LV volumes, LV mass, LVEF (Simpson's method), LV diastolic function, grade of LVDD, and LA volumetric measurements were assessed as recommended by the EACI.[29,30] LA volumetric analyses were performed using the Simpson's method.[1,2,11,20,29,34] LA

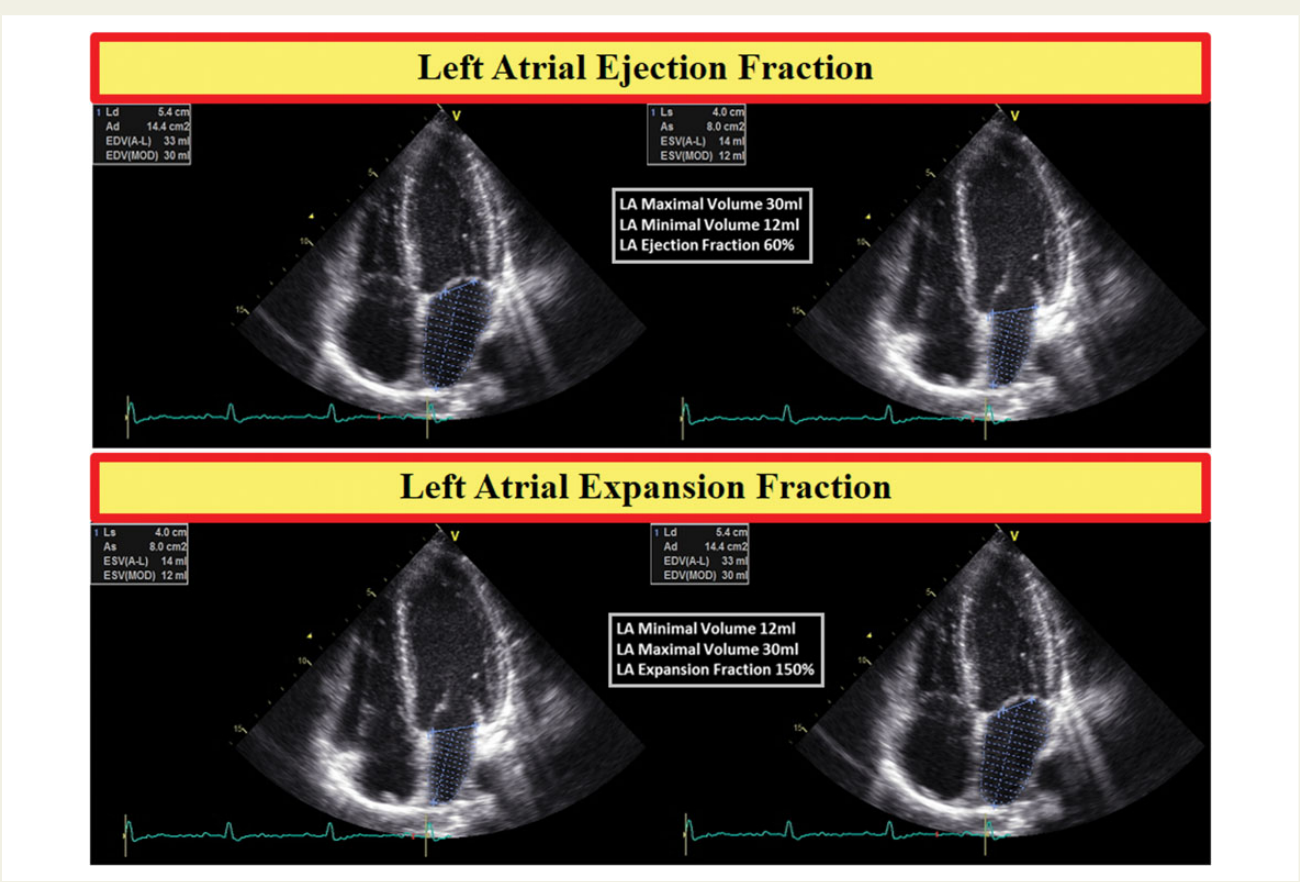


**Figure 1** Volumetric function of the LA using conventional 2D echocardiography. The volumetric LA reservoir and pump function was evaluated by LAExF and LAEF using the Simpson's method, respectively.

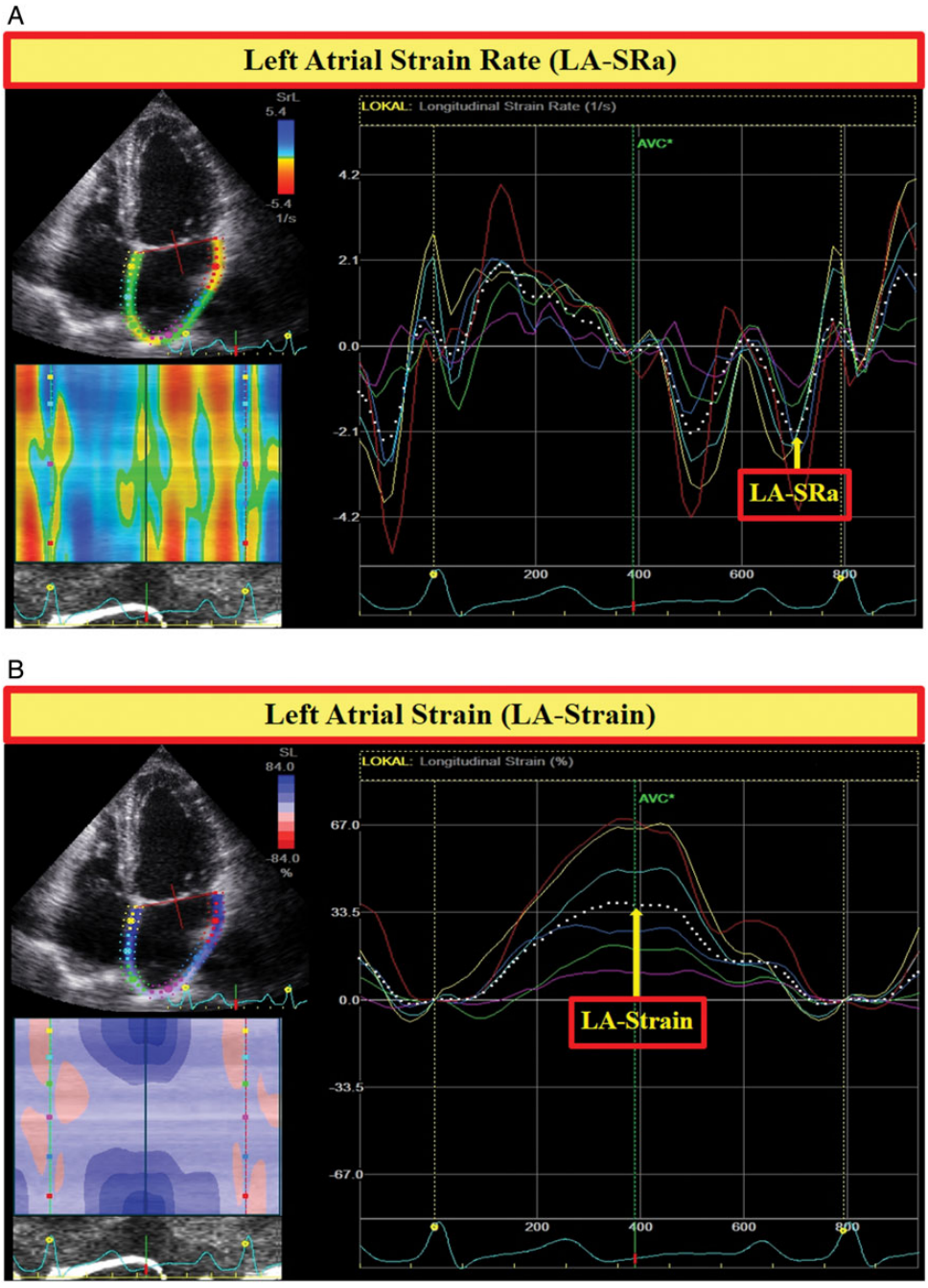


**Figure 2** Myocardial function of the LA using 2DSTE. (*A*) The myocardial pump function of the LA was analysed by LA-SRa (i.e. LA strain rate peak in longitudinal direction during LA contraction at the time of the late diastole of the LV). (*B*) The myocardial reservoir function of the LA was evaluated by LA-Strain (i.e. LA strain peak in longitudinal direction during LA relaxation at the time of the systole of the LV). The fragmented white curve indicates the average of LA strain and LA strain rate from all segments of the LA.

volumetric pump function was evaluated by means of LAEF ([maximal volume − minimal volume]/maximal volume) and LA volumetric reservoir function was analysed by LA expansion fraction (LAExF) ([maximal volume − minimal volume]/minimal volume); *Figure 1*.[1,2,11,20,29,34] In addition, according to the guidelines on chamber quantification of the EACI, LA enlargement was defined as LAVI >28 mL/m$^2$.[2,29] These measurements were derived from the volumetric analyses of the LA in the apical four-chamber and two-chamber views.

## Myocardial analyses of the LA using 2DSTE

The myocardial analyses of the LA were performed offline and blinded to the clinical characteristics of the subjects using 2DSTE with the following ultrasound software package: Echo-Pac version 113.0 from GE.[11,20] On the basis of previous validated studies and the guidelines on myocardial mechanisms of the EACI,[11–20,35] the myocardial function of the LA was evaluated by LA strain and LA strain rate. The myocardial pump function

**Table 1 Clinical and LV characteristics of the healthy population and of the cohort with LVDD**

| | Healthy subjects ($n = 329$) | Patients with LVDD ($n = 377$) |
|---|---|---|
| Clinical characteristics | | |
| Age, years | 36.1 ± 12.7 | 69.9 ± 9.2 |
| Women, % | 46.5 | 44.4 |
| Body mass index, kg/m$^2$ | 22.4 ± 2.5 | 28.6 ± 5.1 |
| Systolic blood pressure, mmHg | 119.1 ± 10.0 | 137.5 ± 18.0 |
| Diastolic blood pressure, mmHg | 70.8 ± 8.7 | 79.8 ± 12.2 |
| Left ventricular characteristics | | |
| LV ejection fraction, % | 63.6 ± 5.7 | 62.7 ± 6.7 |
| LV mass, g/m$^2$ | 74.7 ± 15.4 | 102.1 ± 29.3 |
| Septal early-diastolic mitral annular velocity (e′) by TDI, cm/s | 11.4 ± 2.2 | 5.4 ± 1.3 |
| Lateral early-diastolic mitral annular velocity (e′) by TDI, cm/s | 13.9 ± 2.8 | 7.3 ± 1.7 |
| Mitral early-diastolic inflow velocity (*E*-wave), cm/s | 77.9 ± 15.8 | 72.6 ± 22.3 |
| Mitral *E*/e′ septal–lateral ratio | 6.4 ± 1.4 | 12.0 ± 4.7 |
| Mitral late-diastolic inflow velocity (*A*-wave), cm/s | 51.9 ± 14.2 | 76.4 ± 22.4 |
| LV global longitudinal systolic strain, % | −21.1 ± 2.1 | −19.0 ± 2.9 |
| LV global longitudinal early-diastolic strain rate, s$^{-1}$ | 1.56 ± 0.28 | 1.04 ± 0.30 |

Data are expressed as mean ± SD or percentages. In the cohort of patients with LVDD, the rates of comorbidities were: hypertension 87.3%, diabetes 28.4%, obesity 40.6%, history of coronary artery disease 48.8%, anaemia (haemoglobin < 12 g/dL) 20.1%, kidney disease (GFR <60 mL/min/1.73 m$^2$) 30.6%.
SD, standard deviation; TDI, tissue Doppler imaging; LVDD, left ventricular diastolic dysfunction.

**Table 2 Volumetric and myocardial function of the LA in healthy subjects and in patients with LVDD**

| | Healthy subjects ($n = 329$) | Patients with LVDD ($n = 377$) |
|---|---|---|
| LA volumetric function | | |
| LA pump function, % | | |
| LA ejection fraction (LAEF) | 65.8 ± 7.5 | 63.9 ± 11.8 |
| Lowest expected value[a] | 51.1 | 40.7 |
| LA reservoir function, % | | |
| LA expansion fraction (LAExF) | 207.1 ± 68.4 | 208.8 ± 102.7 |
| Lowest expected value[a] | 73.0 | 7.5 |
| LA remodelling, mL/m$^2$ | | |
| LA maximal volume index (LAVI) | 18.4 ± 5.7 | 25.8 ± 9.9 |
| Highest expected value[a] | 29.5 | 45.2 |
| LA myocardial function | | |
| LA pump function, s$^{-1}$ | | |
| LA strain rate (LA-SRa) | −2.11 ± 0.61 | −1.68 ± 0.64 |
| Lowest expected value[a] | −0.91 | −0.42 |
| LA reservoir function, % | | |
| LA strain (LA-Strain) | 45.5 ± 11.4 | 27.8 ± 10.6 |
| Lowest expected value[a] | 23.1 | 7.0 |

Data are expressed as mean ± SD. LA volumetric function was analysed by conventional 2D echocardiography using the Simpson's method. LA myocardial function was analysed using 2DSTE.
LVDD, LV diastolic dysfunction.
[a]The lowest expected value was calculated as −1.96 SD from the mean and the highest expected value was calculated as 1.96 SD from the mean. There were significant differences in LA myocardial function between healthy subjects and patients with LVDD ($P < 0.001$). Regarding LA volumetric function, the differences between healthy subjects and patients with LVDD had a *P*-value of >0.01.

of the LA was analysed by means of LA strain rate peak during LA contraction (LA-SRa) (namely, at the time of the late diastole of the LV; *Figure 2A*).[11,20] The myocardial reservoir function of the LA was evaluated by LA strain peak during LA relaxation (LA-Strain) (namely, at the time of the systole of the LV; *Figure 2B*).[11–20] These measurements were derived from the myocardial analyses of the LA in longitudinal direction in the apical

**Table 3 Distribution of the myocardial and volumetric function of the LA according to age and gender in healthy subjects and in patients with LVDD**

| | LA myocardial function | | LA volumetric function | |
|---|---|---|---|---|
| | LA-SRa, $s^{-1}$ | LA-Strain, % | LAEF, % | LAExF, % |
| Healthy subjects | | | | |
| Age distribution | | | | |
| 18–50 years of age | −2.09 ± 0.59 | 46.1 ± 11.2 | 66.7 ± 6.7 | 214.2 ± 66.0 |
| ≥51 years of age | −2.20 ± 0.70 | 42.2 ± 11.9 | 60.8 ± 9.0 | 170.2 ± 69.0 |
| *P*-value | 0.259 | 0.022 | <0.001 | <0.001 |
| Gender distribution | | | | |
| Women | −2.15 ± 0.68 | 46.1 ± 11.3 | 65.9 ± 7.3 | 208.1 ± 68.5 |
| Men | −2.07 ± 0.55 | 44.9 ± 11.5 | 65.6 ± 7.6 | 206.2 ± 68.4 |
| *P*-value | 0.249 | 0.382 | 0.726 | 0.794 |
| Patients with LVDD | | | | |
| Age distribution | | | | |
| 18–50 years of age | −1.75 ± 0.58 | 28.1 ± 3.1 | 63.6 ± 5.1 | 180.6 ± 42.6 |
| ≥51 years of age | −1.67 ± 0.64 | 27.7 ± 10.7 | 63.9 ± 11.9 | 209.5 ± 103.7 |
| *P*-value | 0.707 | 0.924 | 0.937 | 0.380 |
| Gender distribution | | | | |
| Women | −1.62 ± 0.63 | 27.1 ± 10.8 | 63.5 ± 11.5 | 204.0 ± 101.8 |
| Men | −1.72 ± 0.65 | 28.3 ± 10.5 | 64.3 ± 12.0 | 212.7 ± 103.4 |
| *P*-value | 0.160 | 0.268 | 0.504 | 0.415 |

Data are expressed as mean ± SD. There were significant differences in LA myocardial function between healthy subjects and patients with LVDD ($P < 0.001$). Regarding LA volumetric function, the differences between healthy subjects and patients with LVDD had a *P*-value of >0.01.
LVDD, LV diastolic dysfunction; LA-SRa, LA strain rate; LAEF, LA ejection fraction; LAExF, LA expansion fraction.

four-chamber and two-chamber views (i.e. 12 LA segments) and using QRS onset as the reference point.[11,20,35] Furthermore, we evaluated the myocardial systolic and diastolic function of the LV by means of the global longitudinal systolic strain and early-diastolic strain rate, which were derived from the analysis of the LV in the apical four-chamber, two-chamber, and long-axis views.[11,20,35] All echocardiographic measurements using 2DSTE, Doppler, and conventional 2D echocardiography were calculated as the average of three measurements.

## Statistical analysis

Continuous data were presented as mean ± standard deviation (SD) and dichotomous data in percentage. Differences in continuous variables between two groups were analysed using Student's *t*-test. Categorical variables were compared by the $\chi^2$ test and Fisher exact test as appropriate. Comparisons between three or more groups were analysed using a one-way analysis of variance (ANOVA). The relationship of volumetric and myocardial LA measurements with continuous variables was analysed using a simple regression analysis. In addition, in order to identify the variables with the strongest association with LA measurements, we performed a multivariate stepwise forward linear regression analysis. Following the recommendations on chamber quantification of the EACI,[29] the lowest expected value of both volumetric and myocardial LA measurements was calculated as −1.96 SD from the mean. With the purpose of determining the reproducibility of LA measurements, we analysed the intra- and inter-observer variability on 20 randomly selected subjects. All statistical analyses were performed with Statview 5.0 (SAS Institute) and SPSS 22.0 (IBM). Differences were considered statistically significant when $P < 0.05$.

# Results

## Clinical characteristics of the cohort of healthy subjects and patients with LVDD

A total of 346 healthy subjects met the eligibility criteria during the study period. However, in this group of individuals, LA measurements could not be analysed in 17 subjects because of an inadequate 2D imaging quality for an analysis by 2DSTE in ≥1 segments of the LA (feasibility 95.1%). Thus, 329 healthy adult subjects (181 Asians and 148 Europeans) with adequate imaging quality for an analysis by 2DSTE were finally studied and analysed. Clinical characteristics and conventional LV measurements of these subjects are shown in *Table 1*. Concerning the validation group, a total of 402 patients with LVDD were initially included. Nevertheless, 25 patients had inadequate 2D imaging quality for an analysis by 2DSTE (feasibility 93.8%). Accordingly, 377 patients with LVDD were finally analysed. Clinical and LV characteristics of these patients are shown in *Table 1*.

## Range of values of the myocardial and volumetric function of the LA in healthy subjects

The range of values of the volumetric and myocardial function of the LA using conventional 2D echocardiography and 2DSTE in healthy subjects is provided in *Table 2*. Moreover, we determined

**Table 4 Interrelations of the myocardial and volumetric function of the LA with different clinical variables in the healthy population and in patients with LVDD**

| Variables | LA myocardial function | | | | LA volumetric function | | | |
|---|---|---|---|---|---|---|---|---|
| | LA-SRa | | LA-Strain | | LAEF | | LAExF | |
| | *r* | *P* | *r* | *P* | *r* | *P* | *r* | *P* |
| Healthy subjects | | | | | | | | |
| Age, years | 0.12 | 0.024 | −0.13 | 0.014 | −0.27[a] | <0.001 | −0.22[a] | <0.001 |
| LV longitudinal strain, % | 0.03 | 0.501 | 0.29[a] | <0.001 | 0.02 | 0.662 | 0.05 | 0.315 |
| LV longitudinal SRe, $s^{-1}$ | 0.07 | 0.199 | 0.36 | <0.001 | 0.13 | 0.014 | 0.12 | 0.025 |
| Septal mitral e′ velocity, cm/s | −0.01 | 0.822 | 0.21 | <0.001 | 0.13 | 0.013 | 0.10 | 0.050 |
| Lateral mitral e′ velocity, cm/s | −0.12 | 0.044 | 0.13 | 0.024 | 0.16 | 0.006 | 0.14 | 0.013 |
| Mitral *E*/e′ septal–lateral ratio | −0.04 | 0.413 | 0.04 | 0.424 | −0.01 | 0.890 | −0.01 | 0.923 |
| LAVI, $mL/m^2$ | −0.29[a] | <0.001 | −0.32[a] | <0.001 | −0.10 | 0.056 | −0.06 | 0.266 |
| LVEF, % | 0.14 | 0.007 | 0.07 | 0.172 | −0.08 | 0.130 | −0.08 | 0.133 |
| LV mass, $g/m^2$ | −0.22[a] | <0.001 | −0.11 | 0.042 | −0.07 | 0.166 | −0.05 | 0.355 |
| Systolic blood pressure, mmHg | 0.06 | 0.255 | −0.10 | 0.066 | −0.10 | 0.064 | −0.11 | 0.031 |
| Body surface area, $m^2$ | 0.01 | 0.912 | −0.26 | <0.001 | 0.10 | 0.063 | 0.09 | 0.080 |
| Patients with LVDD | | | | | | | | |
| Age, years | −0.09 | 0.057 | −0.15 | 0.002 | −0.14 | 0.004 | −0.08 | 0.086 |
| LV longitudinal strain, % | 0.02 | 0.665 | 0.06 | 0.225 | 0.01 | 0.974 | 0.01 | 0.720 |
| LV longitudinal SRe, $s^{-1}$ | 0.10 | 0.035 | 0.13 | 0.007 | 0.13 | 0.009 | 0.09 | 0.056 |
| Septal mitral e′ velocity, cm/s | 0.21 | <0.001 | 0.21 | <0.001 | 0.21 | <0.001 | 0.17 | <0.001 |
| Lateral mitral e′ velocity, cm/s | 0.17 | <0.001 | 0.21 | <0.001 | 0.21 | <0.001 | 0.15 | 0.002 |
| Mitral *E*/e′ septal–lateral ratio | −0.33[a] | <0.001 | −0.30[a] | <0.001 | −0.33[a] | <0.001 | −0.26[a] | <0.001 |
| LAVI, $mL/m^2$ | −0.40[a] | <0.001 | −0.38[a] | <0.001 | −0.49[a] | <0.001 | −0.40[a] | <0.001 |
| LVEF, % | 0.09 | 0.054 | 0.13 | 0.009 | 0.18 | <0.001 | 0.15 | 0.002 |
| LV mass, $g/m^2$ | −0.21 | <0.001 | −0.20 | <0.001 | −0.23 | <0.001 | −0.17 | <0.001 |
| Systolic blood pressure, mmHg | 0.01 | 0.751 | −0.08 | 0.096 | −0.08 | 0.083 | −0.04 | 0.339 |
| Body surface area, $m^2$ | −0.03 | 0.548 | 0.04 | 0.386 | 0.07 | 0.131 | 0.07 | 0.123 |
| Haemoglobin, g/dL | 0.09 | 0.064 | 0.10 | 0.037 | 0.07 | 0.131 | 0.10 | 0.043 |
| GFR, mL/min/1.73 $m^2$ | 0.12 | 0.027 | 0.13 | 0.019 | 0.12 | 0.037 | 0.08 | 0.166 |

LA-SRa, LA strain rate; LAEF, LA ejection fraction; LAExF, LA expansion fraction; LVDD, LV diastolic dysfunction; LV longitudinal strain, LV global longitudinal systolic strain; LV longitudinal SRe, LV global longitudinal early-diastolic strain rate; e′, early-diastolic annular mitral peak velocity by TDI; GFR, glomerular filtration rate.
[a]Variable with the strongest association in a forward stepwise multivariable regression analysis.

the lowest expected value of these measurements in this population (calculated as −1.96 SD from the mean), which is displayed in *Table 2*.

## Distribution of the myocardial and volumetric function of the LA according to age and gender in the healthy population

Regarding the volumetric LA function, both LAEF and LAExF were significantly different between young and older healthy subjects (*Table 3*). On the other hand, there were no differences in the myocardial pump function (LA-SRa) between the different groups of age, but there were some differences between older and young healthy subjects in the myocardial LA reservoir function (i.e. LA-Strain; *Table 3*). Concerning the gender, the differences between healthy women and men in the volumetric and myocardial function of the LA were not significant (*Table 3*).

## Interrelations of the myocardial and volumetric function of the LA in healthy subjects

In the analysis of the factors that could influence on the function of the LA in the healthy population, we found that both volumetric and myocardial LA measurements were inversely linked to the size of the LA and the age of the healthy subjects (*Table 4*). Nonetheless, the association of age and LAVI with LA functional analyses, while was statistically significant, was slight with an *r*-value of <0.35 (*Table 4*). Furthermore, in order to evaluate a possible race variation in the function of the LA, we analysed a subgroup of Asian ($n = 115$; age 39 ± 12 years) and European ($n = 115$; age 34 ± 12 years) healthy subjects of similar age. In this regard, there were no significant differences in the myocardial function of the LA (Asians: LA-Strain 44.7 ± 8.0% and LA-SRa −2.01 ± 0.40 $s^{-1}$; Europeans: LA-Strain 42.8 ± 9.3% and LA-SRa −2.11 ± 0.48 $s^{-1}$; *P*-values: 0.107 and

0.104, respectively), but there were some differences in the volumetric LA function between Asian and European healthy subjects (Asians: LAEF 64.5 ± 7.6% and LAExF 195.2 ± 63.6%; Europeans: LAEF 67.2 ± 6.5% and LAExF 218.3 ± 67.0%; *P*-values: 0.004 and 0.007, respectively).

## Clinical relevance of LA myocardial analyses using 2DSTE

To determine the clinical relevance of LA myocardial measurements using 2DSTE, we analysed a group of 377 patients with LVDD (*Table 1*). LA myocardial analyses using 2DSTE indicated the presence of subtle LA dysfunction, even though LA volumetric measurements were normal (*Figure 3*). Moreover, we found that the symptomatic status was significantly linked to the myocardial function of the LA. In this regard, both LA-Strain and LA-SRa were significantly lower in patients with NYHA class ≥II than in those with NYHA class I (*Table 5*). In line, the functional class (dyspnoea–NYHA classification) was inversely related to LA-Strain and LA-SRa (*Table 5*).

## Interrelations of the myocardial and volumetric function of the LA in patients with LVDD

In the analysis of the factors that could influence on the function of the LA in patients with LVDD, we found that both the volumetric and the myocardial LA function were principally related to the diastolic

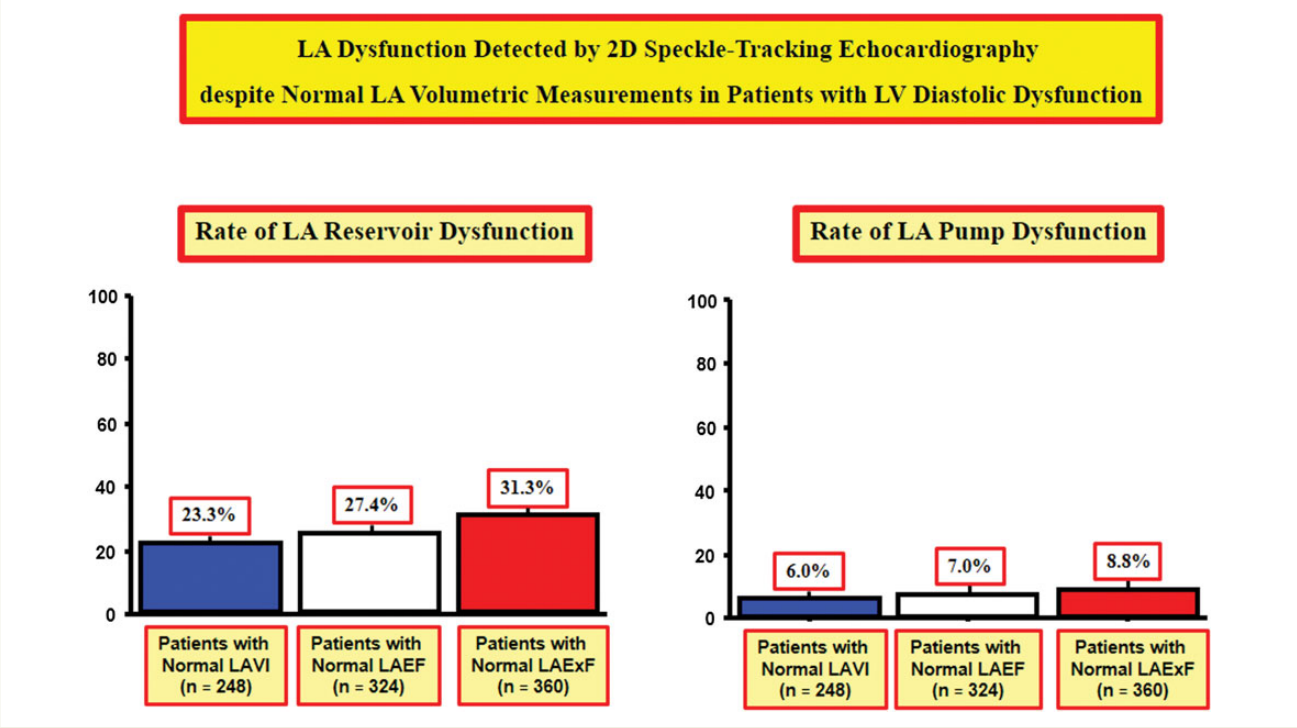


**Figure 3** LA dysfunction detected by 2DSTE despite normal LA volumetric measurements in patients with LVDD. Normal LA volumetric measurements using LAEF and LAExF were defined according to the normal range of these measurements in the healthy population (namely, LAEF ≥51.1% and LAExF ≥73%). Normal LA volume was defined as LAVI ≤28 mL/m$^2$ according to the recommendations on chamber quantification of the EACI.[29] To define LA reservoir and pump dysfunction using 2DSTE, the lowest expected values of LA-Strain and LA-SRa in the healthy population were used as cut-offs (namely, LA-Strain <23.1% and LA-SRa > −0.91 s$^{-1}$, respectively).

**Table 5 Worsening of symptomatic status linked to deterioration of LA myocardial function in patients with LVDD**

| | NYHA functional class | | | |
|---|---|---|---|---|
| | Class I (*n* = 186) | Class II (*n* = 119) | Class III–IV (*n* = 72) | *P*-ANOVA |
| LA reservoir function (LA-Strain), % | 30.3 ± 11.1 | 26.7 ± 8.9[a] | 22.9 ± 10.0[b] | <0.001 |
| LA pump function (LA-SRa), s$^{-1}$ | −1.79 ± 0.63 | −1.64 ± 0.62[a] | −1.45 ± 0.66[b] | <0.001 |

Data are expressed as mean ± SD.
LVDD, LV diastolic dysfunction; ANOVA, analysis of variance; LA-SRa, LA strain rate.
[a]$P < 0.05$, NYHA class II vs. class I.
[b]$P < 0.05$, NYHA class III–IV vs. class I.

**Table 6 Reproducibility of the myocardial and volumetric function of the LA**

| | LA myocardial function | | LA volumetric function | |
|---|---|---|---|---|
| | LA-SRa, $s^{-1}$ ($n = 20$) | LA-Strain, % ($n = 20$) | LAEF, % ($n = 20$) | LAExF, % ($n = 20$) |
| Intra-observer variability | | | | |
| Absolute mean difference (± SD) | 0.06 ± 0.05 | 0.90 ± 0.74 | 0.98 ± 0.71 | 9.39 ± 11.8 |
| Inter-observer variability | | | | |
| Absolute mean difference (± SD) | 0.10 ± 0.05 | 1.10 ± 0.62 | 1.22 ± 0.97 | 8.82 ± 8.83 |

Data are expressed as mean ± SD.
SD, standard deviation; LA-SRa, LA strain rate; LAEF, LA ejection fraction; LAExF, LA expansion fraction.

function of the LV (*Table 4*). In agreement, we evidenced that the volumetric and myocardial function of the LA were inversely related to LA remodelling (determined by LAVI) and to LV filling pressures (determined by mitral *E*/*e*′ ratio; *Table 4*), and in consequence, to the grade of LVDD (Grade I: LA-SRa −1.88 ± 0.60 $s^{-1}$, LA-Strain 30.3 ± 9.1%, and LAEF 67.3 ± 9.0%; Grade II: LA-SRa −1.78 ± 0.66 $s^{-1}$, LA-Strain 29.8 ± 11.4%, and LAEF 65.6 ± 10.9%; Grade III: LA-SRa −1.39 ± 0.55 $s^{-1}$, LA-Strain 23.4 ± 9.6%, and LAEF 59.2 ± 13.2%; all $P < 0.001$).

## Reproducibility of the myocardial and volumetric function of the LA using 2DSTE and conventional 2D echocardiography

The reproducibility of the volumetric and myocardial function of the LA was adequate (*Table 6*). In effect, both the myocardial and the volumetric LA function using 2DSTE and conventional 2D echocardiography had a low inter-observer and intra-observer variability (*Table 6*).

# Discussion

In the present multicentre study analysing a large cohort of healthy subjects and patients with LVDD, we have determined the normal range and the clinical relevance of LA myocardial measurements using 2DSTE.

## Definition of normal LA myocardial function

Some studies analysing healthy subjects with 2DSTE have reported the values of the myocardial function of the LA in this population.[21–26] However, these studies were limited to determine the normal range or to define a normal LA myocardial function because of the small number of patients analysed (<80 women or men).[21–26] For these reasons, one of the objectives of the present study was to establish the normal range of the myocardial function of the LA analysing a large cohort of healthy subjects. In this regard, in a cohort of 329 healthy subjects, we determined the range of values of both the myocardial and the volumetric function of the LA, which were analysed using 2DSTE and conventional 2D echocardiography with adequate feasibility and reproducibility. Thus, we consider that these findings could be of great usefulness to define a normal function of the LA.

## Volumetric vs. myocardial analyses of the LA

LA maximal volume index (LAVI) remains the main echocardiographic parameter to assess the remodelling and indirectly the function of the LA.[29] In addition, derived volumetric indices of LA reservoir and pump function such as LAExF and LAEF have also been proposed.[1,2,34] However, it has been demonstrated that these volumetric measurements have some limitations, such as low sensitivity to detect subtle LA dysfunction.[12,20] In this regard, recent studies using 2DSTE showed the low sensitivity of LAVI and LAEF to identify an early alteration of the LA in different clinical settings.[12,20] In agreement with these reports, we demonstrated that LA myocardial analyses using 2DSTE identified LA dysfunction despite normal LAEF and normal LAVI in patients with LVDD. Furthermore, we found that the functional class (dyspnoea–NYHA classification) was significantly related to both LA-Strain and LA-SRa. Therefore, we consider that myocardial LA analyses using 2DSTE have several advantages over volumetric LA measurements, which make these myocardial parameters necessary methods to assess both the reservoir and the pump function of the LA.

## Limitations

Some considerations should be taken into account when analysing the myocardial function of the LA. Recent studies evidenced that 2DSTE values of the LV vary between different software packages such as GE, Philips, and Toshiba.[27,36] Thus, while there are no data showing a variability between different ultrasound software packages regarding LA analyses, we consider that the normal range of LA myocardial analyses showed in this study should be considered according to the ultrasound software package utilized (namely, Echo-Pac from GE), which so far is the most extensively validated software to analyse the LA with 2DSTE.[3–25] It is also important to note that we did not evaluate the repeatability of LA measurements. Nonetheless, the reproducibility of both volumetric and myocardial LA analyses was adequate, with low inter-observer and intra-observer variability. Furthermore, it should be noted that, in agreement with previous studies,[37–40] we found that the diastolic function of the LV was significantly linked to the myocardial function of the LA. Hence, we believe that both LV and LA myocardial parameters should be assessed in the setting of a possible LV or LA dysfunction.

## Conclusions

In the present multicentre study analysing a large cohort of healthy subjects and patients with LVDD, we have determined the normal range and the clinical relevance of the myocardial function of the LA analysed by 2DSTE. Therefore, we consider that these findings provide important evidence to introduce LA myocardial analyses using 2DSTE into the clinical practice.

## Acknowledgements

The authors thank all the co-investigators from the different centres in Japan and Germany for their participation in this study.

**Conflict of interest:** none declared.

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