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ORIGINAL PAPER

Mechanical concordance between left atrium and left atrial appendage in nonvalvular atrial fibrillation: can it be exploited to avoid transesophageal echocardiography prior to electrical cardioversion during Covid-19 pandemic?

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Abstract

Transesophageal echocardiography (TEE) is the gold standard for assessing left atrial appendage (LAA) mechanic and thrombosis (LAAT); however, TEE is a high-risk procedure for viral transmission during coronavirus disease 2019 (COVID-19) pandemic. We investigated whether deformation indices of left atrium (LA) at transthoracic echocardiography (TTE) correlate with those of LAA assessed by TEE in nonvalvular atrial fibrillation (NVAF) patients undergoing electrical cardioversion (ECV). Consecutive patients with NVAF of ≥ 48 h or unknown duration, who underwent TEE and TTE at our Institution before ECV were retrospectively investigated. Standard echo-Doppler and LA and LAA myocardial strain and strain rate parameters were analyzed. A total of 115 NVAF patients (71.3 ± 8.1 yr/o, 59.1% men) were included: LAAT was diagnosed in 25 (21.7%) patients. Compared to patients without LAAT, those with LAAT had significantly higher CHA$_2$DS$_2$-VASc Risk score (4.5 ± 1.4 vs. 3.5 ± 1.1, $p < 0.001$), and lower ejection fraction (46.0 ± 14.8 vs. $57.6 \pm 8.6\%$, $p < 0.001$). In LAAT patients, global strain of LA (8.7 ± 2.6 vs. $16.3 \pm 4.5\%$, $p < 0.001$) and LAA (7.0 ± 1.7 vs. $11.7 \pm 2.0\%$, $p < 0.001$) was significantly reduced compared to non-LAAT patients. A close relationship between left atrial strain reservoir (LASr) and LAA-global strain was demonstrated ($r = 0.81$). By univariable analysis, CHA$_2$DS$_2$-VASc Risk Score (OR 2.01, 95%CI 1.34–3.00), NT-proBNP (OR 1.36, 95%CI 1.19–1.54), ejection fraction (OR 0.92, 95%CI 0.88–0.96), E/e' ratio (OR 2.07, 95%CI 1.51–2.85), and LASr (OR 0.39, 95%CI 0.25–0.62) were strongly associated with LAAT presence at TEE. By multivariable analysis, only LASr (OR 0.40, 95%CI 0.24–0.70) retained statistical significance. ROC curve analysis revealed that an LASr cut-off value $\leq 9.3\%$ had 98.9% sensibility and 100% specificity to identify LAAT by TEE ($AUC = 0.98$). In patients with NVAF of ≥ 48 h or unknown duration, scheduled to undergo ECV, LA deformation assessment by TTE might substitute invasive measurement of LAA function by TEE, simplifying diagnostic approach and possibly contributing to reduce COVID-19 infection diffusion.

Keywords COVID-19 · Nonvalvular atrial fibrillation · Transesophageal echocardiography · Left atrial appendage thrombosis · Left atrial myocardial strain analysis

Abbreviations

AF	Atrial fibrillation
BSA	Body surface area
COVID-19	Coronavirus disease 2019
CT	Computed tomography
ECV	Electrical cardioversion
eGFR	Estimated glomerular filtration rate
EV	Emptying velocity
FV	Filling velocity
GPS	Global peak strain
ICC	Intraclass correlation coefficient
LA	Left atrium/left atrial

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LAA	Left atrial appendage
LAAT	Left atrial appendage thrombosis
LASr	Left atrial strain reservoir
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
NT-proBNP	N-terminal pro-brain natriuretic peptide
NVAF	Nonvalvular atrial fibrillation
SEC	Spontaneous echo contrast
SPAP	Systolic pulmonary artery pressure
SR	Strain rate
STE	Speckle tracking echocardiography
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography

Introduction

Left atrial appendage (LAA) is the most common site for thrombus formation in the setting of nonvalvular atrial fibrillation (NVAF) [1]. Therefore, it is important to be able to identify, or rule out, presence of LAA thrombosis (LAAT) in NVAF patients prior to performing electrical cardioversion (ECV) [2].

Transesophageal echocardiography (TEE) is considered the gold standard imaging modality to evaluate LAA anatomy and morphology [3, 4]. However, TEE is rather invasive and contraindicated in patients with esophageal injury or diverticulum, or not feasible in case of dysphagia or inability to swallow the TEE probe [5].

Current coronavirus disease 2019 (COVID-19) pandemic is heavily affecting all countries worldwide [6]; as it is due to an airborne virus, TEE is considered a high-risk procedure for the possible transmission of this viral infection [7, 8]. Therefore, the American Society of Echocardiography recommends to avoid TEE testing and to use alternative diagnostic tools for LAA imaging whenever possible [8].

Previous studies demonstrated that speckle tracking echocardiography (STE), as an implementation of standard transthoracic echocardiography (TTE), may allow a more accurate analysis of the left atrium (LA), thus providing additional diagnostic and prognostic information on the pro-thrombotic state of the LA [9–16]. These studies demonstrated that impaired LA deformation could effectively predict LAAT in NVAF patients. On the other hand, only a few studies have employed TEE with STE methodology for the assessment of LAA myocardial strain and strain rate (SR) parameters in NVAF patients [17–19]; however, those, as well as previous studies [9–16], did not concomitantly investigate both LA and LAA deformation indices in the same patients. Accordingly, the present research was designed to investigate whether a correlation exists between LA and LAA myocardial strain parameters measured by both TTE and TEE in the same patients, and whether this could possibly be exploited to predict presence of LAA thrombi in a population of NVAF patients undergoing ECV, without the need for TEE.

Methods

Patient evaluation and clinical measures

This retrospective study included all consecutive patients with NVAF of $\geq$ 48 h or unknown duration referred to our Echo Laboratory for TEE examination to rule out LAAT prior to ECV, between April 2016 and February 2021.

As per local practice, echocardiographic screening for the presence of thrombus in the LA or LAA was the preferred approach instead of pre-anticoagulation in candidates for early elective cardioversion of atrial fibrillation (AF).

Main indications for early elective ECV were the following: symptomatic AF, rapid ventricular rates despite rate-control therapy, clinical signs of congestive heart failure, tendency to arterial hypotension.

NVAF was defined according to the 2016 and 2020 ESC Guidelines [3, 4]. Main exclusion criteria were: AF duration $<$ 48 h, patients already on oral anticoagulant treatment for $\geq$ 3 weeks, significant valvular heart disease (prosthetic valve, severe mitral valve regurgitation, or more than mild mitral valve stenosis), technical inability to perform either TEE or STE analysis (inappropriate endocardial border definition of both LA and LAA), patient's refusal to undergo TEE examination.

On admission, the following information were recorded: age, gender, body surface area (BSA), prevalence of cardiovascular risk factors (hypertension, smoking, type-2 diabetes, dyslipidemia), history of coronary artery disease, history of transient ischemic attack/stroke, and current medical treatment. Blood was drawn for routine blood chemistry, plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and estimated glomerular filtration rate (eGFR) [20].

Thromboembolic risk of each patient was assessed by CHA_2DS_2-VASc Risk Score [21].

Patients underwent medical history evaluation, physical examination, 12-lead ECG, and conventional TTE and TEE implemented with STE analysis of both LA and LAA, respectively. All examinations were performed in AF on the same day, before ECV.

Transthoracic echocardiography

Transthoracic echocardiographic examinations were performed by the same experienced cardiologist, using commercially available Philips Sparq ultrasound machine (Philips Healthcare, Andover, Massachusetts, USA) with a

2.5 mHz transducer. Five consecutive cardiac cycles were stored in cine-loop format for subsequent offline analysis.

Measurements were performed according to the criteria of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [22, 23]. The following conventional parameters were measured: left ventricular mass index (by Deveraux formula [24]); left ventricular end-diastolic volume index, left atrial volume index (LAVi), and left ventricular ejection fraction (LVEF) by modified biplane Simpson's rule [22]; left atrial emptying fraction calculated as (LAVi max−LAVi min)/LAVi max × 100 [25]; left ventricular diastolic function by E/A ratio and average E/e' ratio [23]; degree of concomitant mitral regurgitation [26]; tricuspid annular plane systolic excursion, and systolic pulmonary artery pressure (SPAP) calculated by Bernoulli equation, where $\text{SPAP} = 4 \times (\text{tricuspid regurgitation velocity})^2 + \text{estimated right atrial pressure}$ [27].

Transesophageal echocardiography

After TTE, transesophageal exams were performed by the same operator using Philips Sparq ultrasound machine (Philips Healthcare, Andover, Massachusetts, USA) with a 5 MHz multiplane transducer.

The LAA was visualized from the mid-esophageal position at 0°, 45°, 90° and 135°. The grayscale frame rate was set to 60 to 90 frames/second. On average, 5 cardiac cycles were acquired for both 2D and pulsed-wave Doppler recordings.

The maximum and minimum LAA areas were measured by planimetry. LAA area change (%) was calculated using the following formula: LAA area change = [(maximal LAA area−minimal LAA area)/maximal LAA area] × 100.

LAA flow measurements were obtained by placing the pulsed wave sample-volume in the proximal one-third segment of the LAA with suitable gain and filter adjustments [28]. LAA emptying (LAA-EV) and LAA filling velocities (LAA-FV) were recorded.

A thrombus in the LAA was defined as an echo-dense mass of more than 2 mm in diameter attached to the LAA wall that could be distinguished from the surrounding endocardium or pectinate muscles [29].

Spontaneous echo contrast (SEC) was diagnosed by the presence of characteristic dynamic smoke-like swirling echoes in the LA or the LAA, distinct from background white noise caused by excessive gain [30]. The intensity of SEC was graded according to the classification (1 to 4 +) proposed by Fatkin et al. [31]. Dense SEC was defined as grade 4 +. All images were recorded on a hard disk for subsequent offline analysis.

Speckle tracking echocardiography

Two-dimensional STE assessment was performed immediately after conventional echocardiography, during the same examination, by using the Philips QLAB 10.3.1 ultrasound software (Philips Healthcare, Andover, Massachusetts, USA).

To calculate LA strain, we employed the software used for the analysis of left ventricular function. The QRS onset was used as reference point [32]. First, we manually traced the atrial endocardium using three reference points, the first placed at the medial mitral annulus, the second at the lateral mitral annulus and the third at the atrial roof. The epicardial surface was automatically calculated, and after manually reducing the region of interest to the atrial thickness, to include only the atrial wall, the software automatically divided the atrial wall into seven segments. We repeated these steps from each of the two apical views: 4-chamber (seven segments) and 2-chamber (seven segments) using a "biplane method"; the apical 3-chamber view was excluded because the values of the antero-septal wall correspond to the ascending aorta.

Once the longitudinal atrial strain curves were obtained, the left atrial strain reservoir (LASr), was calculated by averaging the values of peak positive global atrial strain, measured at the end of the reservoir phase, observed in 4- and 2-chamber views.

From the atrial strain, strain rate (SR) curves were derived, which allowed the measurement of LA-SR in AF: peak positive LA-SR, plotted as a positive curve from baseline to the peak positive of longitudinal SR; peak negative LA-SR, plotted as a negative curve from baseline to the peak negative of longitudinal SR; peak-to-peak LA-SR as the sum of the two peaks.

To account for beat-to-beat variation in STE measurements we employed the index-beat method [33]. The STE results were estimated using the ratio of preceding (RR1) to pre-preceding (RR2) RR interval. We selected the beat with the smallest difference between RR1-RR2 intervals.

LAA longitudinal strain analysis was performed using two-dimensional images recorded during the TEE examination. After manual selection of the region of interest, the software marked the endocardial, mid-myocardial, and epicardial borders. The accuracy of the borders was checked by the operator and manually adjusted to cover the full thickness of the LAA wall. The software divided LAA images into seven segments (2 medial, 2 lateral, and 3 apical segments) and generated curves of strain for each segment. Longitudinal LAA wall deformation was assessed by measuring the peak negative longitudinal strain during the LAA contractile period. LAA global peak strain (GPS) was obtained by averaging all seven segmental strain curves if they were tracked adequately.

Statistical analysis

Patients were grouped according to the presence or absence of LAAT at TEE: patients with LAAT (Group 1), and patients without LAAT (Group 2). NVAF patients with grade 4 SEC were included in the LAAT group.

For each group of patients, continuous data were summarized as mean ± standard deviation, while categorical data were presented as frequency and percentage.

Each continuous variable was checked through the Shapiro–Wilk test and all data were determined to be normally distributed. An independent two-tailed t-test was used to estimate the difference between the means. Categorical variables were compared using the chi-square test or the Fisher's exact test.

The relationship of av. LASr with LAA-GPS and of av. peak-to-peak LA-SR with LAA flow velocities in the whole population was evaluated by Pearson's correlation coefficient.

Univariable logistic regression analysis was performed to evaluate the effect of the main demographic, clinical, laboratory, conventional and functional echocardiographic variables on the occurrence of LAAT at TEE. For each variable investigated, correspondent odds ratios with 95% confidence intervals were calculated. Variables with a p value < 0.05 were then entered into a multivariable model. To avoid multicollinearity, the variables with high degree of collinearity were not included in the multivariable analysis.

The receiver operating characteristics (ROC) curve analysis was performed to establish the sensitivity and the specificity of the main statistically significant continuous variable for predicting CV events. Area under curve (AUC) was estimated.

To evaluate intra- and interobserver variability in the assessment of main conventional and functional echocardiographic parameters, the key echocardiographic variables were re-measured in a sized subgroup of 15 patients (randomly selected) by the cardiologist who performed all echocardiographic examinations and by a second one. The analyses were performed in a blinded manner. Both raters chose the frame on which to perform each measurement. The intraclass correlation coefficient (ICC) was employed as statistical method for assessing intra- and inter-observer measurement variability. An ICC of 0.70 or more was considered to indicate acceptable reliability.

Values of $p < 0.05$ were considered statistically significant.

Statistical analysis was performed with SPSS version 25 (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 115 consecutive patients were analyzed (71.3 ± 8.1 yr/o, 59.1% men). Another 7 patients were excluded due to technical problems, refusal/inability to perform TEE.

A LAAT was detected in 25 patients (21.7%) (Group 1), while 90 patients without LAAT (78.3%) were classified as controls (Group 2). Among patients diagnosed with LAAT, a thrombus in the LAA was detected in 20 patients (80.0%), while 5 patients (20.0%) showed grade 4 SEC.

Among the NVAF patients enrolled in the present study during the COVID-19 pandemic (between February 2020 and February 2021), no patient was diagnosed with SARS-CoV-2 infection.

Demographic and clinical parameters

Table 1 shows the main clinical characteristics of the two groups. No significant differences were observed between groups regarding age, sex, BSA, and cardiovascular risk factors. Incidence of previous transient ischemic attack/stroke was significantly higher in patients with LAAT ($p = 0.01$), consistent with a significantly higher CHA_2DS_2-VASc Risk score (4.5 ± 1.4 vs. 3.5 ± 1.1, $p < 0.001$). In comparison to patients without LAAT, patients with LAAT had significantly higher values of plasma NT-proBNP (898.2 ± 330.9 vs. 295.7 ± 399.3 pg/ml, $p < 0.001$) and significantly lower values of eGFR (70.7 ± 24.9 vs. 80.1 ± 22.2 ml/min/m^2, $p = 0.04$). At the time of echocardiographic examination, both groups of NVAF patients were mostly treated with low molecular weight heparin (LMWH), whereas vitamin K antagonists (VKAs) and novel oral anticoagulants (NOACs) were administered in approximately one-fifth and one-third of NVAF patients respectively, without any statistically significant difference between the two groups. The mean period after anticoagulants beginning at the time of echocardiography was 1.2 ± 0.8 weeks.

Transthoracic echocardiographic parameters

Main conventional and functional TTE parameters measured in the two groups are reported in Table 2. LVEF was significantly lower in Group 1 than Group 2 patients (46.0 ± 14.8 vs. 57.6 ± 8.6%, $p < 0.001$), whereas LV filling pressures (as assessed by the average E/e' ratio) were significantly increased in patients with LAAT than those without (18.0 ± 5.1 vs. 10.5 ± 2.0, $p < 0.001$). A moderate mitral regurgitation was significantly more prevalent among patients without LAAT ($p = 0.01$). Conversely, Group 1 patients were more frequently diagnosed with mild mitral

Table 1 Main demographic and clinical characteristics of the two groups of NVAF patients, those with LAAT and those without

Demographic and clinical parameters	NVAF pts with LAAT (n = 25)	NVAF pts without LAAT (n = 90)	P value
Age (yrs)	72.7 ± 8.5	70.9 ± 7.4	0.25
Male sex (%)	13 (52.0)	55 (61.1)	0.49
BSA (m^2)	1.89 ± 0.22	1.95 ± 0.24	0.22
Hypertension (%)	19 (76.0)	63 (70.0)	0.62
Smokers (%)	7 (28.0)	29 (32.2)	0.81
Type 2 diabetes (%)	9 (36.0)	23 (25.5)	0.32
Dyslipidemia (%)	16 (64.0)	51 (56.6)	0.65
History of CAD (%)	4 (16.0)	25 (27.7)	0.30
Previous TIA/stroke (%)	9 (36.0)	11 (12.2)	**0.01**
CHA_2DS_2-VASc Risk Score	4.5 ± 1.4	3.5 ± 1.1	**< 0.001**
Heart rate (bpm)	82.9 ± 13.5	80.9 ± 13.3	0.46
eGFR (ml/min/m^2)	70.7 ± 24.9	80.1 ± 22.2	**0.04**
NT-proBNP (pg/ml)	898.2 ± 330.9	295.7 ± 399.3	**< 0.001**
LMWH (%)	14 (56.0)	45 (50.0)	0.65
VKAs (%)	4 (16.0)	16 (17.8)	0.84
NOACs (%)	7 (28.0)	29 (32.2)	0.81
Antiplatelets (%)	4 (16.0)	18 (20.0)	0.78
Antihypertensives (%)	20 (80.0)	68 (75.5)	0.79
Beta blockers (%)	17 (68.0)	46 (51.1)	0.17
Diuretics (%)	16 (64.0)	44 (48.8)	0.26
Antiarrhythmics (%)	11 (44.0)	44 (48.8)	0.82

Data are expressed as mean ± SD or as number (percentage). Significant p values are in bold. BSA, body surface area. CAD, coronary artery disease. CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age at least 75 years (doubled), Diabetes, Stroke/transient ischemic attack/thromboembolism (doubled), Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), Age 65–74 years, Sex category (female)

eGFR, estimated glomerular filtration rate, *LAAT* left atrial appendage thrombosis, *LMWH* low molecular weight heparin, *NOACs* novel oral anticoagulants, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *NVAF* non-valvular atrial fibrillation, *TIA* transient ischemic attack, *VKAs* vitamin K antagonists

regurgitation ($p = 0.01$). These findings confirmed the protective role of mitral regurgitation against the incidence of SEC and/or LAAT in AF patients: the high-velocity flow inside the left atrium may prevent clot formation [34].

LA myocardial strain and SR parameters were adequately measured in all patients; all LA functional parameters were significantly lower in Group 1 in comparison to Group 2 patients (all $p < 0.001$) and to the accepted reference values [35, 36].

Transesophageal echocardiographic parameters

Table 3 summarizes all conventional and functional TEE parameters detected in the two groups. “Cactus shape” was the prevalent LAA shape observed in Group 1 patients ($p < 0.001$), while “chicken wing” was the most common LAA shape diagnosed in Group 2 patients ($p = 0.002$). This finding supported the major role played by the LAA morphology on the hemodynamics in NVAF patients [37].

Moreover, patients with evidence of LAAT at TEE examination showed significantly lower LAA-FV and LAA-EV than Group 2 patients (both $p < 0.001$).

Finally, all LAA myocardial strain and SR parameters were significantly lower in Group 1 patients with LAAT than Group 2 patients without LAAT (all $p < 0.001$).

Figure 1 illustrates an example of av. LASr (Panel A) and av. LAA-GPS (Panel B) measured in a NVAF patient with LAAT detected by TEE examination enrolled in the present study.

A strong linear relationship between av. LASr and LAA-GPS was found ($r = 0.81$) (Fig. 2). Furthermore, av. peak-to-peak LA SR strongly correlated with both LAA-EV ($r = 0.84$) and LAA-FV ($r = 0.88$) (Fig. 3, panels A and B respectively).

By univariable logistic regression analysis (Table 4), CHA_2DS_2-VASc Risk Score (OR 2.01, 95%CI 1.34–3.00, $p = 0.001$), NT-proBNP (OR 1.36, 95%CI 1.19–1.54, $p < 0.001$), LVEF (OR 0.92, 95%CI 0.88–0.96, $p < 0.001$), E/e’ ratio (OR 2.07, 95%CI 1.51–2.85, $p < 0.001$) and LASr (OR

Table 2 Main conventional and functional echocardiographic parameters assessed by 2D-TTE implemented with 2D-STE analysis of left atrium in the two groups of NVAF patients, those with LAAT and those without

Conventional and functional TTE parameters	NVAF pts with LAAT (n = 25)	NVAF pts without LAAT (n = 90)	P value
LVEDVi (ml/m^2)	40.6 ± 13.9	43.3 ± 13.9	0.35
RWT	0.43 ± 0.07	0.41 ± 0.06	0.12
LVMi (g/m^2)	106.3 ± 29.5	102.6 ± 29.3	0.54
LVEF (%)	46.0 ± 14.8	57.6 ± 8.6	**< 0.001**
Average E/e’ ratio	18.0 ± 5.1	10.5 ± 2.0	**< 0.001**
LAVi (ml/m^2)	48.4 ± 8.2	45.8 ± 11.2	0.24
LA-EF (%)	21.7 ± 5.1	33.6 ± 6.6	**< 0.001**
4C LASr (%)	7.7 ± 2.4	14.0 ± 4.6	**< 0.001**
2C LASr (%)	9.7 ± 2.8	18.6 ± 4.4	**< 0.001**
Av. LASr (%)	8.7 ± 2.6	16.3 ± 4.5	**< 0.001**
Av. Peak positive LA SR (s^{-1})	1.36 ± 0.22	1.77 ± 0.51	**< 0.001**
Av. Peak negative LA SR (s^{-1})	0.73 ± 0.24	0.95 ± 0.19	**< 0.001**
Av. Peak to peak LA SR (s^{-1})	2.09 ± 0.32	2.71 ± 0.56	**< 0.001**
Mild MR (%)	22 (88.0)	56 (62.2)	**0.01**
Moderate MR (%)	3 (12.0)	34 (37.8)	**0.01**
RVIT (mm)	34.8 ± 5.2	33.5 ± 5.8	0.27
TAPSE (mm)	17.3 ± 4.0	18.6 ± 4.4	0.15
SPAP (mmHg)	39.6 ± 11.2	37.1 ± 12.2	0.31

Data are expressed as mean ± SD or as number (percentage). Significant p values are in bold. 2D, two-dimensional

Av average, *LA* left atrial, *LA-EF* left atrial-emptying fraction, *LASr* left atrial strain reservoir, *LAVi* left atrial volume index, *LAAT* left atrial appendage thrombosis, *LVEDVi* left ventricular end-diastolic volume index, *LVEF* left ventricular ejection fraction, *LVMi* left ventricular mass index, *MR* mitral regurgitation, *NVAF* non-valvular atrial fibrillation, *RVIT* right ventricular inflow tract, *RWT* relative wall thickness, *SPAP* systolic pulmonary artery pressure, *SR* strain rate, *STE* speckle tracking echocardiography, *TAPSE*, tricuspid annular plane systolic excursion, *TTE* transthoracic echocardiography

0.39, 95%CI 0.25–0.62, $p < 0.001$) were strongly associated with presence of LAAT at TEE examination. By multivariable logistic regression analysis only LASr (OR 0.40, 95%CI 0.24–0.70, $p = 0.001$) retained statistical significance.

ROC curve analysis revealed that an LASr cut-off value ≤ 9.3% had 98.9% sensibility and 100% specificity for the detection of LAAT at TEE (AUC = 0.98, $p < 0.001$) (Fig. 4).

Intra- and inter-observer variability

Detailed intra- and interobserver variability analysis of the main conventional and functional echocardiographic parameters, re-measured in a group of 15 randomly selected NVAF patients, is reported in the Supplemental Table. Intra- and interobserver agreement between the raters, expressed as ICCs with 95% confidence interval, ranged from 0.78 to 0.91 and from 0.76 to 0.87, respectively.

Discussion

Main findings of the study

The present study on a consecutive population of NVAF patients scheduled for early ECV demonstrated that:

(1) In comparison to controls, NVAF patients with LAAT had significantly lower LA and LAA deformation indices;
(2) LA myocardial strain was strongly correlated with both LAA myocardial strain and LAA flow velocities in the whole population;
(3) An LASr cut-off value ≤ 9.3%, as noninvasively detected by 2D-STE analysis, had significantly high

Table 3 Main conventional and functional echocardiographic parameters assessed by 2D-TEE implemented with 2D-STE analysis of LAA in the two groups of NVAF patients, those with LAAT and those without

Conventional and functional TEE parameters	NVAF pts with LAAT (n = 25)	NVAF pts without LAAT (n = 90)	P value
LAA CW shape (%)	2 (8.0)	38 (42.2)	**0.002**
LAA WS shape (%)	4 (16.0)	25 (27.8)	0.30
LAA CF shape (%)	6 (24.0)	18 (20.0)	0.78
LAA Cactus shape (%)	13 (52.0)	9 (10.0)	**< 0.001**
LAA ostial diameter (mm)	2.07 ± 0.34	1.95 ± 0.31	0.07
LAA 2D-area (cm^2)	6.6 ± 2.4	5.2 ± 1.5	**< 0.001**
LAA area change (%)	18.3 ± 2.2	30.9 ± 3.4	**< 0.001**
LAA-EV (cm/s)	24.0 ± 4.0	57.1 ± 16.3	**< 0.001**
LAA-FV (cm/s)	26.1 ± 5.6	54.1 ± 18.1	**< 0.001**
LAA lateral wall strain (%)	5.9 ± 2.1	10.3 ± 1.7	**< 0.001**
LAA medial wall strain (%)	8.0 ± 1.7	12.6 ± 2.5	**< 0.001**
LAA apical wall strain (%)	7.0 ± 1.6	12.1 ± 1.9	**< 0.001**
LAA global peak strain (%)	7.0 ± 1.7	11.7 ± 2.0	**< 0.001**
LAA global SR (s^{-1})	1.79 ± 0.44	2.64 ± 0.70	**< 0.001**

Data are expressed as mean ± SD or as number (percentage)

Significant p values are in bold. 2D, two-dimensional

CF cauliflower, *CW* chicken wing, *EV* emptying velocity, *FV* filling velocity, *LAA* left atrial appendage, *LAAT* left atrial appendage thrombosis, *NVAF* non-valvular atrial fibrillation, *SEC* spontaneous echo contrast, *SR* strain rate, *STE* speckle tracking echocardiography, *TEE* transesophageal echocardiography, *WS* windsock

sensibility (98.9%) and specificity (100%) for the prediction of LAAT at TEE examination.

These findings are particularly relevant during the current Covid-19 pandemic, as TEE carries a heightened risk for spread of coronavirus-2 because it may induce aerosolization of a large amount of virus due to coughing or gagging during the examination [7, 8]. Accordingly, the American Society of Echocardiography (ASE) guidelines recommend that TEEs should be avoided to minimize the risk of viral transmission, and suggest alternative imaging modalities, such as off-axis TTE, TTE with ultrasound-enhancing agents, contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), to rule out LAAT prior to ECV [8, 38]. However, those tests have limitations: long waiting lists, risk of moving a patient through the hospital to the CT or MRI suite, need to disinfect the CT or MRI room, iodinated contrast and radiation for CT and long scan times for MRI, and finally possible claustrophobia.

On the other hand, a TTE implemented with STE analysis of LA strain and SR indices may be easily performed at the bedside, and it has been proposed as a screening tool for the detection of LAA stasis in patients with persistent NVAF [9–16].

Comparison with findings of previous studies and interpretation of results

During the last decade, a variety of studies [9–16] found significant correlation between LA strain and LAA function as assessed by TTE implemented with STE, and concluded that LA strain assessment can noninvasively predict LAA stasis and presence of LAA thrombi. However, other studies [39, 40] indicate that, in patients with paroxysmal AF and sinus rhythm on ECG, the left atrium and the LAA may show mechanical discordance, and information obtained through LA examination with TTE may not directly reflect LAA functional or wall motion abnormalities.

Moreover, other Authors employed a STE analysis focused only on LAA myocardial strain and SR parameters in NVAF patients [17–19]. These studies all revealed a severe impairment in LAA deformation indices in NVAF patients with LAAT in comparison to those without.

Differently from previous studies which separately analyzed LA and LAA strain parameters by TTE [9–16] and TEE [17–19] respectively, the present study performed a concomitant analysis of both LA and LAA myocardial deformation indices in the same NVAF patients.

LA reservoir strain, as noninvasively assessed by TTE implemented by STE analysis, was confirmed to improve the echocardiographic prediction of LA stasis in NVAF patients.

LA reservoir strain measured by STE analysis is a marker of structural atrial remodeling that is intrinsic to the pathophysiology of the AF and represents the substrate for its maintenance [41, 42]. LA structural remodeling is characterized by replacement of healthy atrial tissue with fibrotic tissue. Previous studies demonstrated a negative correlation between LA strain and the extent of fibrosis on delayed-enhancement cardiac magnetic resonance in patients with persistent NVAF [43, 44]. The increased atrial stiffness results in atrial myopathy and dilatation [45, 46]. LA structural remodeling can also lead to reduced atrial contractility and blood stasis and can potentially be linked to the process of thrombus formation [42].

For these reasons, measurement of functional echocardiographic parameters might also provide additional insights into the major site of thromboembolism in AF patients [42, 47]. Notably, severely impaired LA strain, reflecting advanced atrial cardiomyopathy [48, 49] and decreased LAA flow velocities measured at TEE, is associated with a thromboembolic state [47].

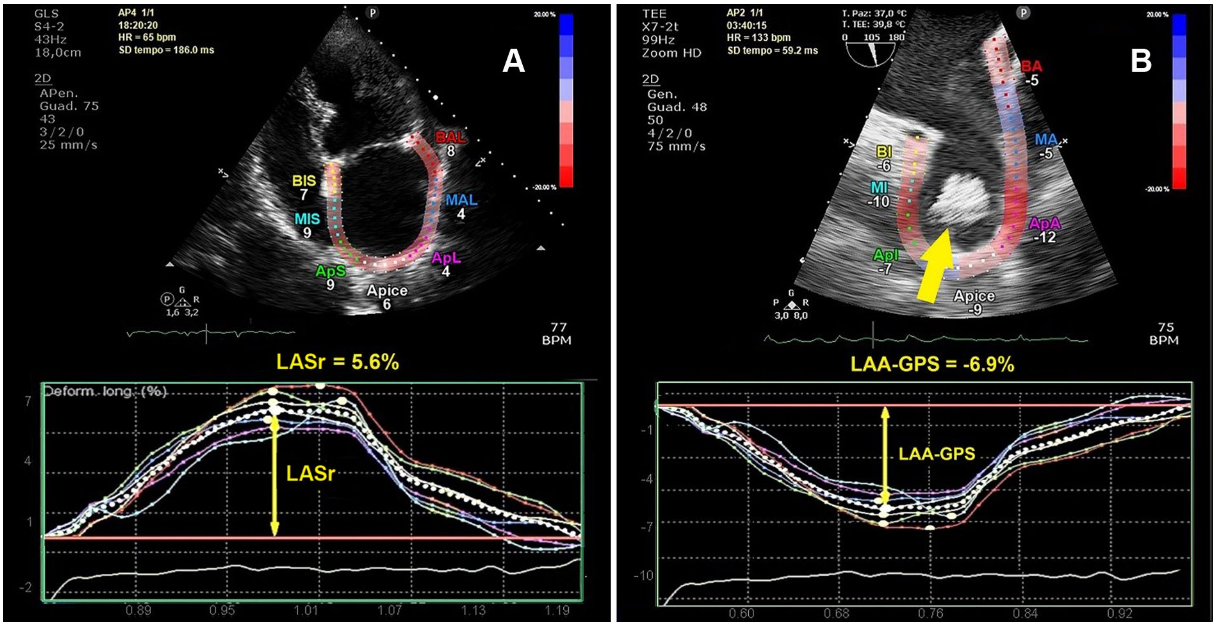

Fig. 1 Example of LASr (Panel **A**) and LAA global peak strain (Panel **B**), assessed by 2D-STE analysis, in a NVAF patient with LAAT enrolled in the study. Yellow arrow indicates the LAAT detected by TEE (Panel **B**). 2D, two-dimensional. *GPS* global peak strain, *LA* left atrial, *LAA* left atrial appendage, *LAAT* left atrial appendage thrombosis, *LASr* left atrial strain reservoir, *NVAF* non-valvular atrial fibrillation, *STE* speckle tracking echocardiography, *TEE* transesophageal echocardiography

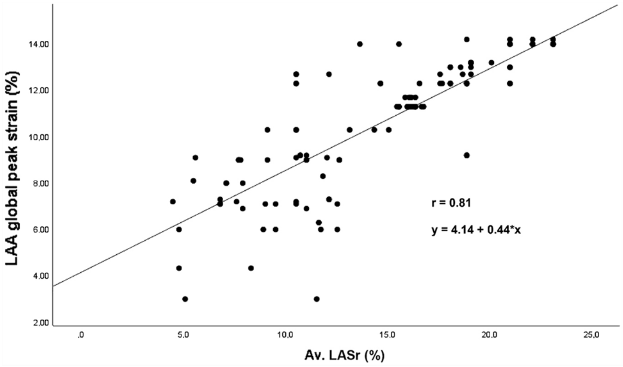

Fig. 2 The correlation between average LASr and LAA global peak strain in the whole study population, evaluated by using the Pearson's correlation coefficient. LA, left atrial. LAA, left atrial appendage. LASr, left atrial strain reservoir

On the other hand, a STE analysis focused only on LAA myocardial strain and SR parameters, even if validated in previous studies at the population level [17–19], appears to not improve the echocardiographic prediction of LA stasis in NVAF patients, mostly in the risk assessment for each individual patient. Furthermore, a STE analysis should be used for detecting a subclinical cardiac dysfunction [50–52] rather than confirming an overt cardiac dysfunction, such as a LAAT and/or dense SEC. A TEE examination immediately and directly reveals LAAT and/or dense SEC. Therefore, a STE analysis of LAA strain indices could be considered as unnecessary or futile in this clinical setting.

Implications for clinical practice

LA deformation assessment by TTE implemented with 2D-STE analysis might improve risk stratification of embolism in NVAF patients [9–16]. In fact, LA myocardial strain parameters may identify NVAF patients with a higher risk of LAAT and unsuccessful ECV [53].

In our study a significantly impaired LASr value was detected in NVAF patients with high CHA_2DS_2-VASc Risk Score, high NT-proBNP levels, and left ventricular systolic and diastolic dysfunction. In particular, an LASr cut-off value $\leq 9.3\%$ was independently associated with LAAT at TEE with extremely high sensibility and specificity. Therefore, noninvasive estimation of LA reservoir strain by TTE may reasonably suggest to avoid or postpone TEE examination in those NVAF patients who are diagnosed with a significantly depressed LASr value by 2D-STE analysis. These patients should be treated with rate-control therapy and oral anticoagulants, and reassessed.

On the other hand, NVAF patients who are diagnosed with normal LA deformation have a significantly lower probability to be diagnosed with LAAT at TEE. In those patients, the possibility to undergo ECV without the preliminary three to four weeks of anticoagulation could be considered in individual cases, particularly if there is no evidence of elevated

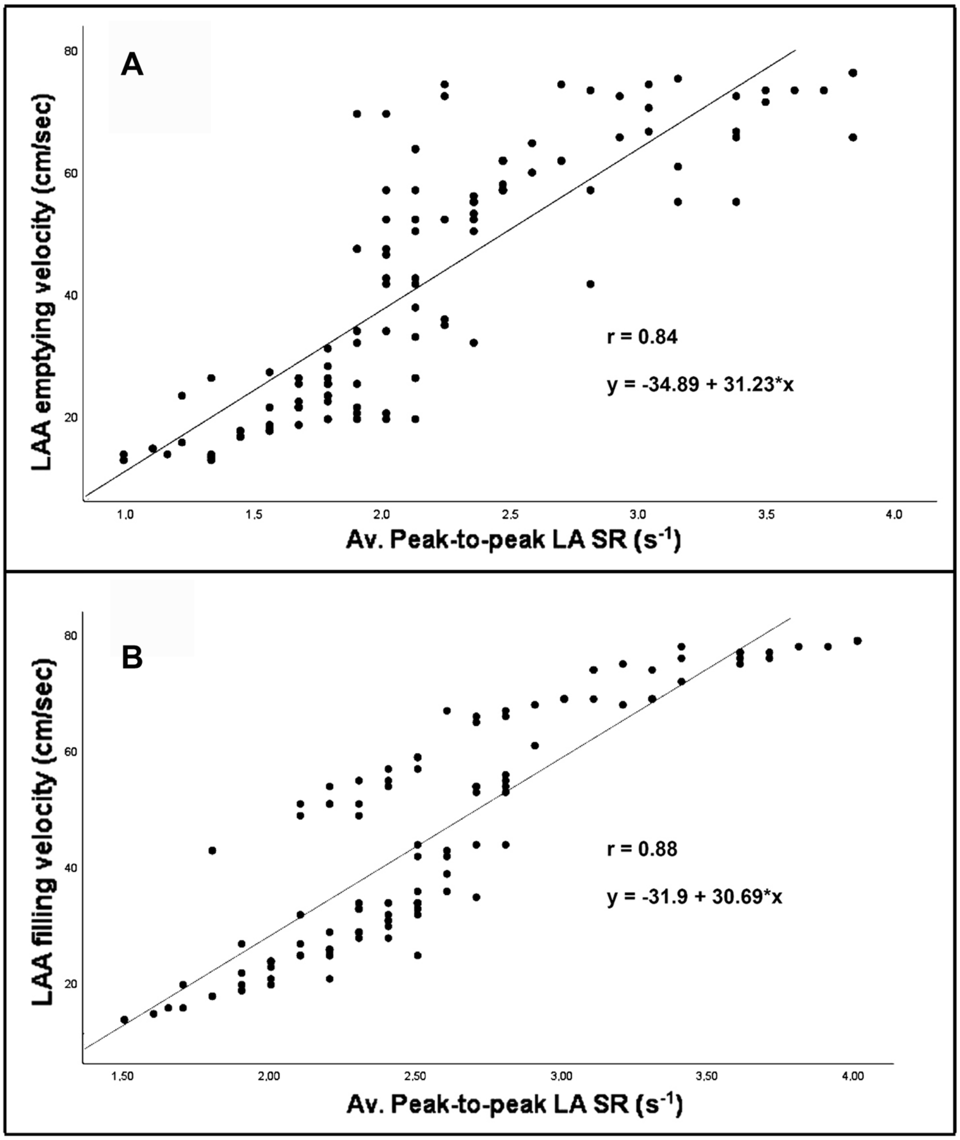

Fig. 3 The correlation of peak-to-peak LA SR with LAA-EV (Panel **A**) and LAA-FV (Panel **B**) in the whole study population, evaluated by using the Pearson's correlation coefficient. *EV* emptying velocity, *FV* filling velocity, *LA* Left atrial, *LAA* left atrial appendage, *SR* strain rate

thromboembolic risk score, increased natriuretic peptides, low ejection fraction and increased left ventricular filling pressures. However, larger prospective studies should confirm our results.

Strengths and limitations of the study

The present study demonstrates a strong mechanical concordance between LA and LAA in a consecutive population of NVAF patients planned for early ECV. Moreover, our results suggest that an appropriate cut-off of left atrial reservoir strain could help the clinician to clearly distinguish, among NVAF patients, those patients who have a significantly increased probability to be found with LAAT at TEE examination.

Consistent with previous studies [9–19, 54, 55], the present study demonstrated that STE methodology is an accurate, easily available, and relatively reproducible technique for the evaluation of regional LA and LAA mechanics in NVAF patients.

However, several limitations of the present study should be addressed. First, the study population was limited to patients with NVAF of ≥ 48 h or unknown duration, without a group of non-AF patients. Secondly, all conventional and functional echocardiographic parameters were acquired during AF, which could have affected some of the parameters considered, due to beat-to-beat variability. Nevertheless, all LA and LAA myocardial strain and SR parameters were adequately recorded in the whole study population by using the index-beat method [33]. Moreover, LA and LAA myocardial strain parameters were calculated by using a software developed for the evaluation of left ventricular strain, because a dedicated software for LA analysis was not available. In addition, in our series the prevalence of LAAT and/

Table 4 Univariable and multivariable logistic regression analysis for the identifying of main clinical, laboratory, conventional and functional echocardiographic parameters associated with LAAT at TEE examination

VARIABLES	UNIVARIATE LOGISTIC REGRESSION ANALYSIS			MULTIVARIATE LOGISTIC REGRESSION ANALYSIS		
	OR	95% CI	P value	OR	95% CI	P value
CHA_2DS_2-VASc Risk Score	2.01	1.34–3.00	**0.001**	1.47	0.61–3.56	0.39
eGFR (ml/min/m^2)	0.98	0.96–1.00	0.21			
NT-proBNP (× 100 pg/ml)	1.36	1.19–1.54	**< 0.001**	1.07	0.84–1.38	0.58
LVMi (g/m^2)	1.01	0.99–1.02	0.23			
LAVi (ml/m^2)	1.02	0.98–1.06	0.41			
LVEF (%)	0.92	0.88–0.96	**< 0.001**	0.89	0.77–1.02	0.11
Average E/e’ ratio	2.07	1.51–2.85	**< 0.001**			
Moderate MR	0.35	0.10–1.29	0.12			
Average LASr (%)	0.39	0.25–0.62	**< 0.001**	0.40	0.24–0.70	**0.001**
SPAP (mmHg)	1.02	0.98–1.05	0.37			

Significant p values are in bold

CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age at least 75 years (doubled), Diabetes, Stroke/transient ischemic attack/thromboembolism (doubled), Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), Age 65–74 years, Sex category (female)

eGFR estimated glomerular filtration rate, *LA* left atrial, *LAAT* left atrial appendage thrombosis, *LASr* left atrial strain reservoir, *LAVi* left atrial volume index, *LVEF* left ventricular ejection fraction, *LVMi* left ventricular mass indexed, *MR* mitral regurgitation, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *SPAP* systolic pulmonary artery pressure, *TEE* transesophageal echocardiography

or dense SEC was 21.7%, a higher value compared to what reported in the literature [56]. A possible explanation of this finding could be that NVAF patients who were on anticoagulant treatment for ≥ 3 weeks before TEE examination were not included. Finally, in the present study, the LAA morphology was evaluated by two-dimensional TEE views; three-dimensional computed tomography or fluoroscopy with contrast for assessing LAA morphology would have exposed the NVAF patients to unjustified ionizing radiation.

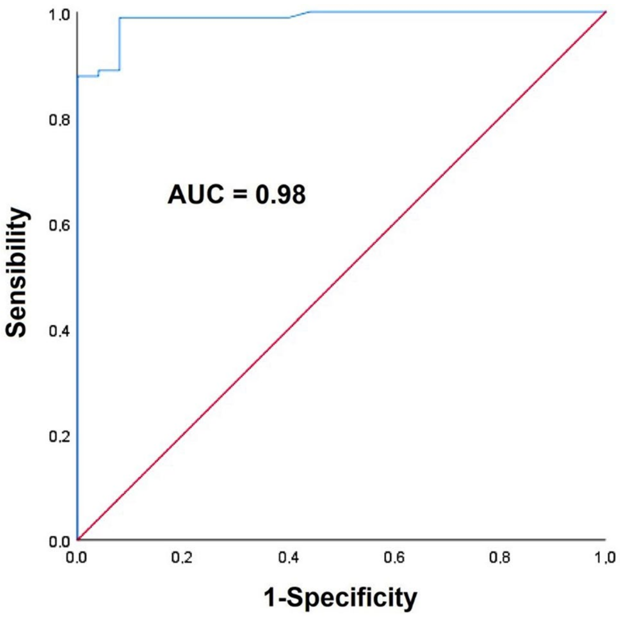

Fig. 4 ROC curve analysis to determine the best cut-off of LASr value for predicting LAAT. *AUC* area under the curve, *LAAT* left atrial appendage thrombosis, *LASr* left atrial strain reservoir, *ROC* Receiver operator characteristics

Conclusions

In a population of NVAF patients scheduled for early ECV, LA and LAA myocardial strain parameters are strongly correlated to each other. Impaired LA strain, as assessed by TTE, largely predicts LA thrombi by TEE in NVAF patients. During Covid-19 pandemic, TTE implemented with STE analysis of LA deformation properties might help the clinician to avoid or postpone TEE examination, contributing to reduce diffusion of virus. Large prospective studies are warranted to define the additive role of LA reservoir strain in thromboembolic risk assessment of NVAF patients in clinical practice.

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Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval The authors declare that this paper has not been orally presented at any professional meeting. There is no conflict of interest, including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence, the present manuscript.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

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