Cardiovascular Ultrasound

RESEARCH

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Left atrial function during exercise stress echocardiography as a sign of paroxysmal/persistent atrial fibrillation

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Abstract

Objective Atrial cardiomyopathy is closely associated with atrial fibrillation (AF), and some patients exhibit no dysfunction at rest but demonstrate evident changes in left atrial (LA) function and LA volume during exercise. This study aimed to identify distinguishing signs during exercise stress echocardiography (ESE) among patients in sinus rhythm (SR), with and without history of paroxysmal/persistent AF (PAF).

Methods A prospective cohort of 1055 patients in SR was enrolled across 12 centers. The main study cohort was divided into two groups: the modeling group ($n=513$) and the verification group ($n=542$). All patients underwent ESE, which included B-lines, LA volume index (LAVi), and LA strain of the reservoir phase (LASr).

Results Age, resting and stress LAVi and LASr, and B-lines were identified as a combination of detectors for PAF in both groups. In the entire cohort, aside from resting and stress LAVi and LASr, additional parameters differentiating PAF and non-PAF patients were the presence of systemic hypertension, exercise E/e' > 7, worse right ventricle (RV) contraction during exercise (Δ tricuspid annular plane systolic excursion < 5 mm), a lower left ventricular contractile reserve (< 1.6), and a reduced chronotropic reserve (heart rate reserve < 1.64). The composite score, summing all 9 items, yielded a score of > 4 as the best sensitivity (79%) and specificity (65%).

Conclusion ESE can complement rest echocardiography in the identification of previous PAF in patients with SR through the evaluation of LA functional reservoir and volume reserve, LV chronotropic, diastolic, and systolic reserve, and RV contractile reserve.

Keywords Atrial fibrillation, B-lines, Left atrium, Reservoir strain, Exercise stress echo

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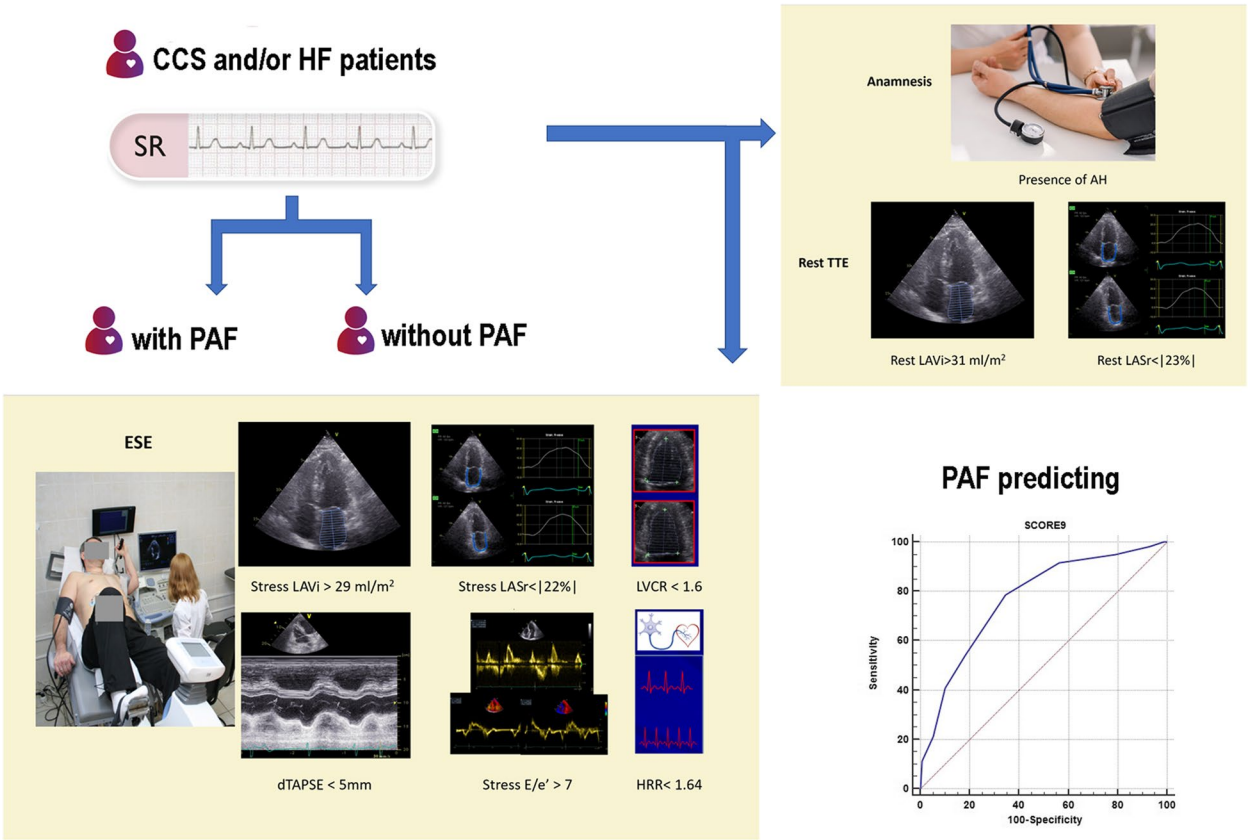
Graphical Abstract

A scoring system predicting the probability of PAF. The score was computed using the cutoff values as in the illustration. The score >4 demonstrated a sensitivity of 79% and a specificity of 65% of PAF.



Background

Atrial fibrillation (AF) is the most prevalent atrial tachyarrhythmia, affecting an estimated 2% to 4% of adults worldwide, excluding those with asymptomatic forms of the disease [1]. AF is a well-recognized and treatable risk factor for stroke, but it often remains asymptomatic or subclinical, leading to underdiagnosis. It is noteworthy that approximately 25% of cryptogenic strokes are attributed to asymptomatic AF, highlighting the substantial thromboembolic risk associated with this condition [2].

The pathogenesis of AF is believed to be closely linked to structural and functional changes in the atria, which fall under the newly proposed concept of "atrial cardiomyopathy" [3, 4]. Excessive tension in the wall of the left atrium (LA) is thought to be responsible for mechanical and structural remodeling, resulting in the replacement of muscle fibers with connective tissue. This increased tension and reduced muscle fibers ultimately lead to impaired LA functional reserve.

Two-dimensional (2D) strain imaging of the LA is an innovative echocardiographic parameter that holds the potential for early AF detection. In particular, the LA strain of the reservoir phase (LASr) is informative and highly reproducible, therefore suitable for a multicenter study [5, 6]. Our hypothesis is that patients with paroxysmal/persistent AF may not exhibit LA dysfunction at rest, yet they may display evidence of LA functional changes and LA volume alterations during exercise. Patients with permanent AF tend to have more pronounced LA impairment, but given their arrhythmia, they typically receive appropriate treatment for stroke prevention without additional diagnostic methods. These stress atrial markers can be useful in the early identification of atrial cardiomyopathy and incipient rhythm disturbances, showing persistent functional abnormalities in patients with previous AF history despite current SR.

The aim of this study was to identify distinguishing signs during exercise stress echo (ESE) between patients

in sinus rhythm (SR) with and without history of paroxysmal/persistent AF (PAF).

Methods

A prospective cohort of 1146 consecutive patients was initially considered from 12 cardiology institutions in 11 countries. These patients were referred for clinically-driven ESE as part of the Stress Echo 2020-2030 study network [7, 8]. Recruitment occurred between November 2020 and February 2024. The patients were referred for ESE due to conditions such as heart failure and/or chronic coronary syndromes (CCS).

Inclusion criteria encompassed patients aged over 18 years who underwent an analysis of LA function during ESE, including the assessment of LA volume index (LAVI) and LASr. Exclusion criteria comprised the presence of AF during the test, including permanent AF, as well as severe valvular or congenital heart disease or LA views of inadequate image quality.

The main study cohort was subdivided into two groups: the modeling group and the verification group. All consecutive patients in whom LASr assessment was feasible at rest from November 2020 until July 2022 were included in the modeling group. Subsequently, all consecutive patients with feasible LASr assessment from August 2022 until February 2024 were included in the verification group. Data from patients in the modeling group were utilized to develop a formula for detecting PAF. The verification group was established to assess the formula's significance for independent "all-comer" patients. The study protocol was reviewed and approved by the institutional ethics committees, as a part of the more comprehensive stress echo 2020 study (Clinical trials.Gov Identifier NCT 030.49995) and stress echo 2030 study (Clinical trials. Gov Identifier NCT 050.81115) [9].

Echocardiography

Transthoracic echocardiography (TTE) was performed using commercially available ultrasound machines equipped with multifrequency phased-array sector scan probes and second harmonic technology. All patients underwent comprehensive TTE at rest. All measurements were taken by certified cardiologists according to the current recommendations [10].

Stress echocardiography

All patients underwent comprehensive ESE with the ABCDE + protocol [11]. There were two types of exercise tests: semi-supine bike and post-treadmill. Loops for wall motion, contractile reserve, and LASr analysis were obtained immediately at peak stress and post-stress, as soon as possible, up to 1.5 min. The B-lines, diastolic function parameters were obtained till 3 min after exercise. Regional wall motion abnormalities (RWMA), B-lines, and when possible, coronary flow velocity reserve in the mid-distal left anterior descending artery were assessed. Wall motion score index (WMSI) was calculated in each patient at baseline and peak stress, in a four-point score ranging from 1 (normal) to 4 (dyskinetic) in a 17-segment model of the LV [12]. B-lines were evaluated with a simplified 4-site scan in the third intercostal space, between mid-axillary to anterior axillary and anterior axillary to mid-clavicular lines, each space scored from 0 (normal horizontal A-lines) to 10 (white lung), with a cumulative score per patient from 0 (normal) to 40 (severely abnormal). The stress-rest change in B-lines was Δ B-lines, with higher values indicating more pulmonary congestion during stress. Left ventricle (LV) contractile reserve was assessed as the stress/rest ratio of force, calculated as systolic blood pressure/end-systolic volume. Coronary flow velocity reserve was assessed during the standard SE examination using intermittent imaging of wall motion and left anterior descending artery. HRR was calculated as the peak/rest heart rate from a 12-lead electrocardiogram (ECG). The procedure of acquisition was standardized between centers through a web-based learning module before starting data collection. All readers (one for each center) underwent quality control as previously described [13, 14].

Additionally, we conducted assessments of several cardiac parameters at rest and peak or immediately post-ESE. These included LV ejection fraction (EF), LV end-diastolic volume, E/e', pulmonary artery systolic pressure estimation, and the so-called step L for LA: LAVi and LASr. Continuous ECG monitoring was used throughout the test, and blood pressure measurements were taken at each stage. The criteria for interrupting the test included the following conditions: severe chest pain, diagnostic ST-segment abnormalities, excessive blood pressure increase (systolic blood pressure $\geq$ 240 mmHg, diastolic blood pressure $\geq$ 120 mmHg), achievement of > 85% of target HR, muscular exhaustion, and significant arrhythmias [15].

LA assessment

LAVI was measured from apical 4- and 2-chamber views using the modified method of disks and indexed for the body surface area. LASr was measured by speckle-tracking echocardiography using frame rates from 40 to 80/s. The speckle tracking technique is a postprocessing algorithm that quantifies LA deformation by tracking the motion of speckles within the whole myocardium through the cardiac cycle. The LASr was calculated from either an apical 4-chamber view (average from 6 LA segments) or combined 4- and 2-chamber views (average value from 12 LA segments)

according to recommendations [16]. In each patient, the same approach (single apical or biplane views) was used at rest and peak ESE. LASr was calculated at LV-end diastole, with the QRS beginning as the zero-reference time point used as a surrogate of end-diastole. The first positive peak corresponds to the LA reservoir phase, and values are expressed as percentage points, algebraically positive (Fig. 1). Both LAVi and LASr were measured using offline echocardiography software from the rest and peak/near peak loops. All measurements were conducted by the sonographers without prior knowledge of the objective of this study.

Statistical analysis. In the presentation of data, we used the following formats as appropriate: mean ± standard deviation (SD) for normally distributed continuous variables; number (percentage) for categorical variables; median (interquartile range) for skewed continuous variables. To assess the distribution of the data, we conducted a Kolmogorov-Smirnov test. Group differences were analyzed depending on the type of data: Student's t-test for normally distributed continuous variables, ANOVA for normally distributed continuous variables with multiple groups, Kruskal-Wallis test for skewed continuous variables with multiple groups; Chi-square or Fisher exact tests for categorical variables. In the modeling group, logistic regression was employed to create a detecting formula. The "enter" method was used, with variables included if they had a significance level (p-value) of < 0.1. Receiver operating characteristic (ROC) analysis was conducted to determine the cut-off values of prognostic discriminators in the modeling group and to assess their accuracy in predicting outcomes in the verification group. A probability value < 0.05 was considered statistically significant in all analyses. The Statistica package version 10.0 (Stat Soft Inc., Tulsa, Oklahoma, USA) and MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium) were used for statistical analysis.

Results

Rest LAVI and LASr parameters were obtained in all patients, by selection. The study population consisted of 935 patients without a history of PAF, 120 with paroxysmal/persistent AF, and 91 with permanent AF. A total of 91 patients were excluded from the study due to the presence of AF during the test, including those with

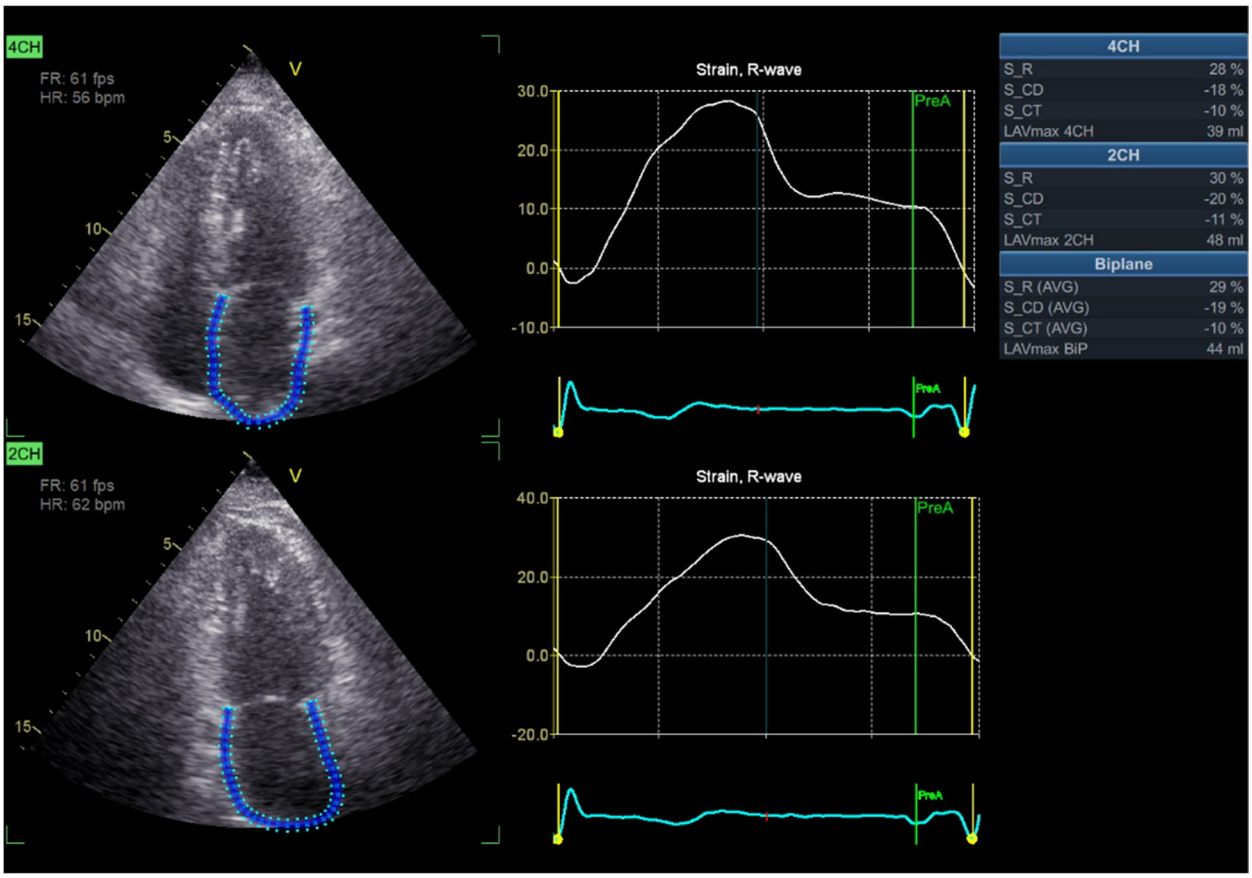


Fig. 1 Example of LAVI and LASr measurement

permanent AF. The bike tests were performed on 678 patients (64%), the treadmill tests were conducted in 377 patients (36%). Extrasystolic beats were recorded in 423 patients (40%), of whom 73 (7%) had bigeminy, and 47 patients (4.5%) experienced supraventricular tachycardia during exercise.

There were 44 patients (4%) with moderate mitral regurgitation, 368 patients (38%) with mild to trivial mitral regurgitation, and the majority of the remaining patients had no mitral regurgitation.

The modeling group comprised 513 patients, while the verification group consisted of 542 patients. The baseline clinical characteristics, echocardiography, and ESE data are summarized in Table 1.

Within the modeling group, patients were further divided into subgroups based on the presence or absence of PAF. The key differences between these subgroups are presented in Table 2. Patients with PAF showed more prevalent systemic hypertension compared to patients in SR without a history of AF. In patients with PAF, TTE showed a larger LAVI (at rest and during exercise), reduced LASr (limited/absence of functional reserve during exercise), higher E wave velocity, and lower HRR, indicative of a reduced cardiac sympathetic reserve and cardiac autonomic imbalance.

The differences in LA sizes and function during exercise for the entire study cohort are presented in Table 3.

LAVi during exercise did not significantly change in either group ($p=0.43$ for one group and $p=0.85$ for the other). LASr during exercise significantly increased in patients without a history of PAF ($p<0.000001$), whereas it did not change significantly in patients with a history of PAF ($p=0.06$).

There was no significant correlation between LASr at rest and B-lines at rest ($r=$-0.06, $p=0.06$). However, there were mild but significant correlations between LASr at rest and exercise B-lines ($r=$-0.15, $p<0.0001$), and between exercise LASr and exercise B-lines ($r=$-0.18, $p<0.0001$).

Logistic Regression analysis

Logistic regression analysis resulted in the creation of a predictive model for PAF that exhibited a high level of statistical significance (p-value <0.0001). The coefficients and constant for this formula are provided in Table 4.

The formula generated from logistic regression analysis achieved a classification accuracy of 91.6%, correctly identifying cases in the modeling group. The discriminator was > 0.0893. The ROC analysis showed an area under the curve (AUC) of 0.78, with a highly significant p-value of < 0.0001, as illustrated in Fig. 2.

In the verification group, this predictive formula also demonstrated significant discriminative capabilities for PAF, with a sensitivity of 49% and specificity of 79%. The AUC in the verification group was 0.67, indicating a meaningful discriminatory power (p-value < 0.0001).

ROC-analysis for PAF prediction

For easier clinical application, a simplified scoring system was created to predict the probability of PAF. This scoring system is constructed using the variables that better differentiate the two groups (those with and without PAF) in the overall patient population, combining the modeling and verification groups (as shown in Table 5). The score was computed using the cutoff values. This system enables clinicians to evaluate the likelihood of PAF in patients based on these defined criteria.

The ROC analysis of the scoring model using the entire cohort showed an AUC of 0.77, indicating a high ability to distinguish between patients with and without PAF (p-value < 0.0001). This scoring system demonstrated a sensitivity of 79% and a specificity of 65%. A higher score indicates a greater likelihood of PAF, as evidenced by a Chi-squared test for trend ($p<0.0001$). Notably, the use of this score proved significantly more accurate compared to relying solely on the known increase in LAVi at rest in the main cohort ($p<0.003$), as depicted in Fig. 3. Among the parameters, E/e' and stress-rest variation of tricuspid annular plane systolic excursion (ΔTAPSE) were less frequently obtained during SE, resulting in a patient group of 474. The model utilizing 7 parameters, excluding E/e' and ΔTAPSE, also yielded high accuracy in detecting PAF. If the score exceeded 3, the AUC of the ROC curve was 0.73 (p-value < 0.0001), with a sensitivity of 66% and a specificity of 69%.

Two hundred thirty-eight patients comprised two matched groups. The average age was 67.9 ± 9.6 years in one group and 67.9 ± 9.7 years in the other ($p=0.996$). There were no significant differences in the distribution of sex, diabetes mellitus, hypertension, or ischemia between the groups. Only LAVi and LASR at rest and during stress showed statistically significant differences among all the echocardiography and stress echocardiography parameters (Table 6). Additionally, Scores 9 and 7 differed significantly between the groups ($p<0.000005$ for both comparisons).

Discussion

We evaluated a cohort consisting of 1055 patients in SR during ESE aiming to find distinguishing signs of those having PAF. This evaluation covered the assessment of LA morphology (using LAVI) and function (using LASr), as well as B-lines and HRR. The results suggest that this comprehensive method is practical and informative.

Not surprisingly, a history of PAF was associated with advanced age and a high prevalence of systemic

Table 1 Clinical, echocardiographic and stress echo findings in the study population

	Modeling group ***N*** **= 513**	**Verification group** ***N*** **= 542**	***p***
Age	64.3 ± 11.1	62.3 ± 12.6	0.007
Male/female	315/198	291/251	0.014
Prior PAF	50 (9.7%)	70 (12.9%)	0.128
Body mass index, kg/m^2	28.4 (25.0-30.7)	27.3 (24.6-30.1)	0.003
Body surface area, m^2	1.94 ± 0.22	1.88 ± 0.21	0.001
Hypertension	75%	75%	0.939
Diabetes	19%	16%	0.252
Smoking	10%	10%	0.973
Obesity	33%	26%	0.014
Prior MI	21%	13%	0.0008
Prior PCI	26%	18%	0.006
Dyspnea NYHA Class	2 (1-2)	1 (1-2)	0.0006
HR rest, beats/min	70 (62-78)	70 (62-78)	0.906
SBP rest, mmHg	130 (118-145)	128 (120-138)	0.009
DBP rest, mmHg	80 (70-90)	80 (70-86)	0.026
IMM, g/m^2	90.1 (76.4-107.6)	89.6 (74.2-109.8)	0.599
RWT	0.42 (0.37-0.48)	0.43 (0.37-0.49)	0.098
E rest, cm/s	70 (58-84)	75 (63-89)	0.0001
e' rest, cm/s	8.9 (7.4-10.5)	9.5 (7.6-11.5)	0.002
E/e' rest	8.3 (6.5-10.4)	8.3 (6.5-10.2)	0.670
LVEDV rest, ml	94 (75-123)	85 (58-107)	0.0001
LVESV rest, ml	34 (26-50)	30 (24-40)	0.0001
LVEF at rest, %	61.6 (56.4-66.7)	63.7 (58.1-67.9)	0.002
WMSI rest	1.00 (1.00-1.06)	1.00 (1.00-1.00)	0.266
GLS LV rest, |%|	17.2 (14.0-20.0)	17.0 (14.5-19.2)	0.410
TAPSE rest, mm	23 (21-27)	22 (20-25)	0.0001
LASr rest, |%|	27.5 ± 9.2	27.6 ± 9.3	0.894
LAVi_rest, ml/m^2	28 (22-35)	28 (22-36)	0.890
LAD flow rest (n = 469), cm/s	25 (21-31)	25 (21-31)	0.791
B-lines at rest, number	0 (0-1)	0 (0-2)	0.025
HR stress, beats/min	130 (116-142)	130 (115-143)	0.610
SBP stress, mmHg	173 (155-195)	176 (158-194)	0.418
DBP stress, mmHg	85 (72-96)	90 (80-99)	0.0001
LVEDV stress, ml	85 (65-109)	80 (65-100)	0.026
LVESV stress, ml	26 (18-39)	25 (19-34)	0.247
E stress, cm/s	100 (82 -118)	105 (90 -120)	0.0001
e' stress, cm/s	11.5 (9.5-13.2)	11.5 (9.5-14.0)	0.060
E/e'stress	8.7 (6.9-10.7)	8.8 (7.3-11.0)	0.164
TAPSE stress, mm	28 (24-31)	25 (22-29)	0.0001
LASr stress, %	29.1 ± 10.7	29.9 ± 10.4	0.251
LAVi stress, ml/m^2	28.3 (21.1-38.0)	27.7 (22.4-36.0)	0.990
GLS LV stress, |%|	17.0 (14.0-20.0)	17.4 (12.6-20.6)	0.936
LVEF stress, %	68.0 (60.2-74.5)	68.4 (61.1-73.8)	0.964
WMSI stress, unit	1.0 (1.00-1.25)	1.0 (1.00-1.19)	0.132
LAD flow stress (n = 428), cm/s	50.0 (39.8-62.3)	54.0 (42.0-63.0)	0.287
B-lines stress, number	1 (0-3)	2 (0-4)	0.027
Ischemia	36%	41%	0.123
dWMSI	0 (0-0.17)	0 (0-0.18)	0.578
LV contractile reserve	1.78 (1.38-2.23)	1.69 (1.33-2.12)	0.063

Table 1 (continued)

	Modeling group *N* = 513	Verification group *N* = 542	*p*
CFVR	2.02 (1.60-2.38)	2.08 (1.71-2.36)	0.181
HRR	1.82 (1.59-2.11)	1.81 (1.57-2.07)	0.502
Δ B-lines	0 (0-2)	0 (0-2)	0.285

Abbreviations: *CFVR* coronary flow velocity reserve, *DBP* diastolic blood pressure, *GLS* global longitudinal strain, *HR* heart rate, *HRR* heart rate reserve, *IMM* index of myocardial mass is this LVMI, left ventricular mass index, *LAD* left anterior descending artery, *LAS* left atrial strain, *LAVi* left atrial volume index, *LV* left ventricle, *LVEF* left ventricle ejection fraction, *LVEDV* left ventricle end-diastolic volume, *LVESV* left ventricle end systolic volume, *LVMI* left ventricular mass index, *MI* myocardial infarction, *NS* non-significant, *PCI* percutaneous coronary intervention, *RWT* relative wall thickness, *SBP* systolic blood pressure, *TAPSE* tricuspid annular plane systolic excursion, *WMSI* wall motion score index

hypertension. Resting TTE revealed higher LAVI and lower LASr values in patients with a history of PAF. Additionally, ESE demonstrated a diminished chronotropic, contractile response with more pronounced diastolic dysfunction of the LV, reduced right ventricular contractile reserve, and a lower atrial functional reserve in these patients compared to individuals without a history of PAF.

In the modeling group, a logistic regression formula was developed and subsequently validated in the independent verification group. Logistic regression, though useful, cannot be directly applied during tests due to its complex formula. Instead, Score9/Score7 offer a simpler, more immediate alternative during multiparameter stress echocardiography. The simplified scores was settled for the whole cohort. The primary hypothesis driving the study was that changes in the size and function of the remodeled LA would manifest at rest but sometimes only during ESE. The study confirmed this hypothesis by revealing significant differences in LAVi and LASr at rest and during ESE between groups with and without PAF, even when other clinical and echocardiographic characteristics were similar. Score 9 demonstrated high sensitivity with moderate specificity. We believe that emphasizing sensitivity is crucial for identifying patients with PAF who may require further examination, such as multi-day EKG monitoring.

The findings demonstrated that LAVi and LASr during ESE have additive value in identifying atrial dysfunction in PAF. Moreover, the inclusion of rest and stress parameters collectively provides a more informative approach to detecting atrial myopathy. Indeed, the simple score, which incorporates known parameters of LA size at rest along with age and contractile parameters of the LA during exercise, exhibited greater predictive power compared to relying solely on resting LAVI.

The main clinical implication is to offer a potential means to identify patients with PAF within the SR population, including those with asymptomatic/subclinical undiagnosed forms. Such identification could be instrumental in devising preventive strategies for strokes, especially considering that nearly 65% of patients with cryptogenic stroke are found to have atrial myopathy, with 25% of these cases attributed to asymptomatic AF, which carries a substantial risk of thromboembolism [17, 18]. Potentially, the study findings could provide valuable information on changes in atrial function, which may be useful for further examination and close follow-up of patients who do not experience noticeable arrhythmias.

Numerous previous studies have consistently demonstrated a connection between LA enlargement, decreased LASr at rest, and the presence of AF or stroke [3, 4, 18–20]. In patients with SR, these studies have also revealed an association between progressive LA remodeling, as assessed through serial TTE, and the progression of AF over extended follow-up periods. Patients who eventually developed persistent AF were found to have higher LAVi, and lower LASr compared to those in the PAF group [19].

Recent pilot and multicenter studies have further expanded our understanding by demonstrating that patients with AF exhibit LA dilation along with reduced LASr at rest and during stress. Importantly, LASr fails to increase during ESE, and patients with PAF display higher values of E/e' during stress (Table 4), resembling those seen in individuals with heart failure, CCS, and symptomatic AF [21–23]. These studies have indicated that LA dysfunction progresses from SR to PAF and eventually to permanent AF, and it is associated with more significant LV systolic dysfunction, increased LV filling pressure, and pulmonary congestion. In contrast, the normal healthy cohort showed a significant increase in deformation without changes in atrial stiffness during maximum ESE [24].

While previous studies on the function of the LA during exercise, using LASr, have been conducted in relatively small groups of 177 and 252 patients [5, 22], the current study was designed to comprehensively assess signs of LA dysfunction in a large cohort of patients, excluding those with AF during the test. The current study was planned to compose signs of LA dysfunction in

Table 2 Differences in clinic, echocardiography, and ESE parameters in patients with and without PAF among the modeling group

	Patients without PAF ***N*** **= 463**	**Patients with PAF** ***N*** **= 50**	***p***
Age, years	64.0 ± 11.4	66.0 ± 7.5	0.008
Body mass index, kg/m^2	27.9 (25.2-31.0)	28.3 (25.4-32.4)	0.445
Body surface area, m^2	1.93 ± 0.21	2.0 ± 0.25	0.04
Hypertension	73%	88%	0.033
Diabetes	19%	13%	0.331
Smoking	10%	12%	0.571
Obesity	33%	36%	0.769
Prior MI	22%	18%	0.667
Prior PCI	26%	20%	0.400
Dyspnea NYHA Class	2 (1-2)	2 (1-2)	0.601
HR rest, beats/min	70 (62-78)	71 (63-77)	0.874
SBP rest, mmHg	130 (118-145)	129 (120-140)	0.719
DBP rest, mmHg	80 (70-90)	80 (68-87)	0.726
IMM, g/m^2	83.3 (75.9-107.2)	95.2 (84.9-109.9)	0.114
RWT	0.42 (0.37-0.48)	0.41 (0.37-0.46)	0.591
E rest, cm/s	70 (58-84)	70 (58-99)	0.448
e' rest, cm/s	9.0 (7.4-10.5)	8.7 (7.5-9.9)	0.645
E/e' rest	8.3 (6.6-10.3)	7.7 (6.4-13.7)	0.499
GLS LV rest, |%|	17.0 ± 3.9	17.0 ± 3.6	0.948
TAPSE rest, mm	23 (21-27)	23 (19-27)	0.513
LASr rest, |%|	27.9 ± 8.9	23.5 ± 10.8	0.001
LAVi_rest, ml/m^2	27.2 (21.3-34.7)	35.0 (31-44.7)	0.0001
LAD flow rest, cm/s	25 (21-31)	28 (22-31)	0.483
LVEDV rest, ml	93 (75-122)	98 (80-135)	0.187
LVESV rest, ml	34 (26-49)	36 (27-58)	0.342
LVEF at rest, %	61.6 (56.4-66.5)	62.1 (57.4-67.6)	0.723
WMSI rest	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.277
B-lines at rest, number 4-region scan	0 (0-1)	1 (0-1)	0.210
HR stress, beats/min	130 (117-144)	125 (108-133)	0.003
SBP stress, mmHg	174 (155-195)	169(150 -190)	0.227
DBP stress, mmHg	84 (72-96)	87 (68-96)	0.842
LVEDV stress, ml	85 (65-108)	92 (65-124)	0.112
LVESV stress, ml	26 (18-39)	27 (18-44)	0.517
E stress, cm/s	100 (90-120)	112 (90-120)	0.02
e' stress, cm/s	11.5 (9.5-13.1)	11.4 (9.2-13.5)	0.775
E/e'stress	8.6 (6.8-10.7)	9.8 (8.1-11.1)	0.125
TAPSE stress, mm	28 (25-31)	26 (23-31)	0.261
LASr stress, |%|	29.6 ± 10.6	23.3 ± 10.0	0.002
LAVi stress, ml/m^2	27.6 (20.5-36.1)	35.1 (30.0-46.4)	0.0001
GLS LV stress, |%|, (*n* = 222)	16.8 ± 4.6	18.6 ± 4.2	0.078
LVEF stress, %	67.7 (60.3-74.2)	69.8 (59.9-74.9)	0.835
WMSI stress, unit	1.00 (1.00-1.25)	1.00 (1.00-1.19)	0.326
LAD flow stress, cm/s	51 (40-63)	48 (35-54)	0.224
B-lines stress (number) 4-region scan	1 (0-3)	1 (0-3)	0.401
Ischemia	37%	27%	0.235
LV contractile reserve	1.79 (1.38-2.23)	1.79 (1.38-2.19)	0.665
CFVR (*n* = 153)	2.04 (1.60-2.42)	1.64 (1.42-1.94)	0.101
HRR	1.83 (1.61-2.12)	1.67 (1.50-1.93)	0.023
Δ B-lines	0 (0-2)	0 (0-1)	0.054

Abbreviations: *CFVR* coronary flow velocity reserve, *DBP* diastolic blood pressure, *GLS* global longitudinal strain, *HR* heart rate, *HRR* heart rate reserve, *IMM* index of myocardial mass is this LVMI, left ventricular mass index, *LAD* left anterior descending artery, *LAS* left atrial strain, *LAVi* left atrial volume index, *LV* left ventricle, *LVEF* left ventricle ejection fraction, *LVEDV* left ventricle end-diastolic volume, *LVESV* left ventricle end systolic volume, *LVMI* left ventricular mass index, *MI* myocardial infarction, *NS* non-significant, *PCI* percutaneous coronary intervention, *RWT* relative wall thickness, *SBP* systolic blood pressure, *TAPSE* tricuspid annular plane systolic excursion, *WMSI* wall motion score index

Table 3 Differences in left atrium parameters in patients with and without PAF history

Variables	SR, no PAF history *N* = 935	SR, PAF history *N* = 120	*P*- values
Rest LAVI	27.1 (21.7-34.7)	34.3 (26.0-43.0)	< 0.0001
Rest LASr	28.0 ± 9.0	23.9 ± 10.5	< 0.001
Stress LAVI	27.0 (21.0-35.9)	33.9 (28.0-43.9)	< 0.0001
Stress LASr	30.3 ± 10.3	24.0 ± 10.2	< 0.001

Abbreviations: *LAVi* left atrial volume index, *LASr* left atrial reservoir strain

Table 4 Coefficients and Standard Errors in logistic regression analysis

Variable	Coefficient	Std. Error
Age	0.017290	0.02278
Rest LAVi	0.0066306	0.02054
Rest LASr	-0.072410	0.03444
Stress LAVi	0.047206	0.02543
Stress LASr	-0.0043906	0.02631
Δ B-lines during exercise	-0.16605	0.09263
Constant	-3.3053	

Table 5 Cut-off values of the parameters for calculating the score

Variables	ROC-analysis cut-off value	SCORE
History of hypertension	yes	1
Rest LAVI	> 31	1
Rest LASr	< 23	1
Stress LAVI	> 29	1
Stress LASr	< 22	1
E/e' stress (*n* = 609)	> 7	1
ΔTAPSE (*n* = 820)	< 5	1
HRR	< 1.64	1
LVCR	< 1.6	1
SCORE	**> 4**	

Abbreviations: *LAVi* left atrial volume index, *LASr* left atrial reservoir strain, *Δ-TAPSE* difference between stress and rest tricuspid annular plane systolic excursion, *HRR* heart rate reserve, *LVCR* left ventricle contractile reserve

a large group, excluding patients with AF during the test, and further verification in the independent multicenter group in patients with heart failure and/or CCS.

In our study, we also noticed an increased E/e' value during ESE in the PAF group, consistent with higher LV filling pressures during ESE, a well-known consequence and cause of LA dysfunction when LA dilation exceeds the range of LA Starling curve. This phenomenon is explained by atrial dysfunction, which can lead to exercise intolerance, as has been observed in previous studies [25, 26]. Additionally, the PAF group exhibited a reduced ability to achieve a higher heart rate during exercise, resulting in a smaller HRR, which is consistent with a reduced cardiac sympathetic reserve. Cardiac autonomic dysfunction is known to be a key player in the vulnerability to atrial arrhythmias, especially in the presence of LA dilation and reduced LA functional reserve.

Recognizing that some differences in echocardiographic parameters might be explained by age, the groups were matched by age. The main finding regarding differences

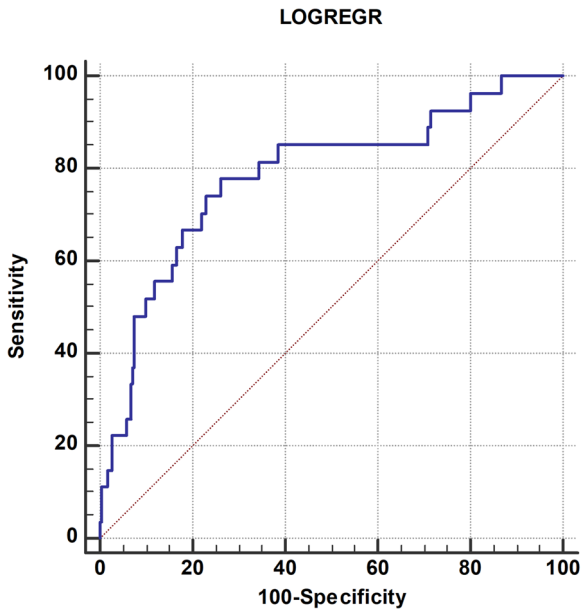


Fig. 2 Logistic regression analysis formula predictive value by ROC-analysis

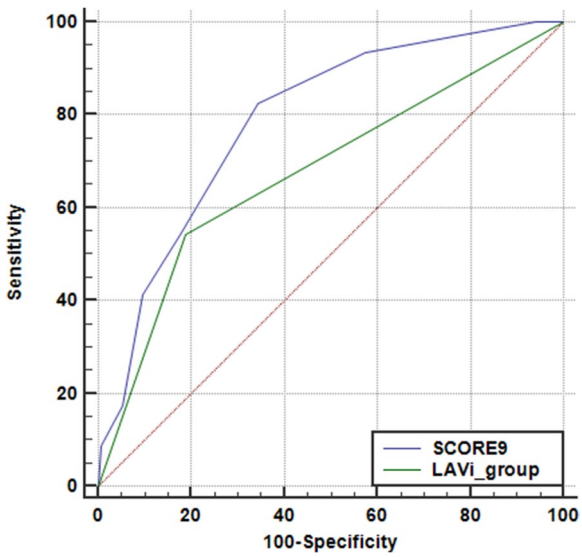


Fig. 3 Comparison of predictive values of LAVi at rest (in blue) and a composite score (in green) inclusive of age, rest LAVI, and stress LASr

Table 6 Differences in left atrium parameters in patients with and without PAF history in the matched groups

Variables	SR, no PAF history *N* = 119	SR, PAF history *N* = 119	*P*- values
Rest LAVI	27.9 (22.2-36.0)	34.3 (26.2-43.3)	< 0.001
Rest LASr	27.9 ± 9.8	23.8 ± 10.5	< 0.01
Stress LAVI	30.0 (23.8-39.7)	34.0 (28.0-43.9)	< 0.006
Stress LASr	29.0 ± 9.8	23.8 ± 10.2	< 0.001

Abbreviations: *LAVi* left atrial volume index, *LASr* left atrial reservoir strain

in LA sizes and function at rest and during stress tests between patients with and without PAF remained consistent. However, due to the relatively small sample sizes, some echocardiographic and stress echocardiography parameters might not have reached statistical significance.

Further studies are needed to explore the value of stress and rest indicators of LA dysfunction in groups without a known history of PAF. This could prove invaluable for the active diagnosis of possible asymptomatic AF, which is an essential step in identifying and managing this condition, especially considering its association with stroke risk [27, 28]. In addition, ongoing outcome studies will clarify whether patients with high vulnerability scores for AF but in SR at the time of study will develop episodes of PAF in the follow-up.

Study limitations

We did not divide patients with persistent and paroxysmal AF. The multicenter nature of the study allowed a multi-vendor assessment of LA function, but LASr may show some inter-vendor variability, although the adopted cutoff values for abnormality have been validated across different vendors and the inter-vendor variability does not apply to stress-rest variation, evaluated in the same patient with the same vendor.

Among LA strain parameters, only LASr was measured to simplify the method. We did not separately analyze the conduit and contractile phases, as LASr is more reproducible, easier to measure, and provides a better representation of the overall function of the LA. We focused on LASr, but right atrial strain can be even more important for detecting AF.

We only considered ESE, but similar patterns of normal responses of LAVI (with a slight increase or decrease during stress) and LASr (with an increase during stress) were observed during dobutamine and vasodilator stress echo [5, 29].

The study is among the largest with ESE in AF. A larger data set analyzed with artificial-intelligence using ECG [30] may be needed to optimize the prognostic potential of a combined anatomic and functional approach based on ESE.

Conclusion

ESE evaluation can be a valuable adjunct to rest LAVI and rest LASr for identifying patients in SR with history of PAF. Six different measures applied during ESE in patients with SR may help to identify those with prior PAF: LA contractile reserve with LASr, LA volume reserve with LAVI, LV contractile reserve with force, chronotropic reserve with HRR, right ventricular contractile reserve with Δ-TAPSE, and LV diastolic reserve with E/e'. This multifaceted approach identifies new spectrum of abnormal physiological responses to exercise detectable during ESE which can support understanding of symptoms and clinical management of individuals in SR, e.g. proactive monitoring programs to identify recurrences of AF and subsequent increase of cardiovascular risk.

Abbreviations

AF	Atrial fibrillation
CCS	Chronic coronary syndromes
ECG	Electrocardiogram
EF	Ejection fraction
ESE	Exercise stress echocardiography
HR	Hazard ratio
HRR	Heart rate reserve
LA	Left atrial
LASr	Left atrial strain of the reservoir phase
LAVi	Left atrial volume index
LV	Left ventricle
PAF	Paroxysmal-persistent atrial fibrillation
RWMA	Regional wall motion abnormality
SR	Sinus rhythm
TAPSE	Tricuspid annular plane systolic excursion
TTE	Transthoracic echocardiography
2DE	Two-dimensional echocardiography
WMSI	Wall motion score index

Appendix: Stress echo 2030 study group

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Authors' contributions
A.Z. originated idea, collected patients, prepared images and loops, and drafted the manuscript, Q.C. is the principal investigator of SE2030, collected patients, and drafted the manuscript, made the data quality control and contributed to data analysis, J.V.P. collected patients, E. K. collected patients, and drafted the manuscript, I. B. collected patients, prepared images and loops, and drafted the manuscript, R. P. collected patients, A. B. collected patients, E. M. collected patients, M. L. collected patients, H. R.-Z., S. K. collected patients, G.A. collected patients, A. V. collected patients, K. W.-D. collected patients, J. D. K. collected patients, R.A. collected patients, O. Z. collected patients, J. C. collected patients, J. L. collected patients, N. C. R. collected patients, P.A.P. served as the study co-chair, critically reviewed the protocol, helped to orient the data analysis, and critically revised the manuscript; E.P. served as the study chairman, designed the protocol, helped to orient the data analysis, and critically reviewed the manuscript; P. C., M.P. and S.C. are the Presidents and President-elect of the SIECVI, the scientific society that endorsed, organized, and funded the study. All authors contributed to the study design, undertook the quality control up to certification, critically revised the manuscript for an intellectually important contribution, and approved the submitted version.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
The study was managed and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients before inclusion. The study protocol was reviewed and approved by the institutional ethics committees, as a part of the more comprehensive stress echo 2020 study (148-Comitato Etico Lazio-1, July 16, 2016; Clinical trials.Gov Identifier NCT 030.49995) and stress echo 2030 study (291/294/295 Comitato Etico Lazio-1, March 8, 2021; Clinical trials.Gov Identifier NCT 050.81115).

Competing interests
The authors declare no competing interests.

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