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ORIGINAL PAPER

Feasibility and functional correlates of left atrial volume changes during stress echocardiography in chronic coronary syndromes

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Abstract

An enlarged left atrial volume index (LAVI) at rest mirrors increased LA pressure and/or impairment of LA function. A cardiovascular stress may acutely modify left atrial volume (LAV) within minutes. Aim of this study was to assess the feasibility and functional correlates of LAV-stress echocardiography (SE) Out of 514 subjects referred to 10 quality-controlled labs, LAV-SE was completed in 490 (359 male, age 67 ± 12 years) with suspected or known chronic coronary syndromes (n = 462) or asymptomatic controls (n = 28). The utilized stress was exercise in 177, vasodilator in 167, dobutamine in 146. LAV was measured with the biplane disk summation method. SE was performed with the ABCDE protocol. The intra-observer and inter-observer LAV variability were 5% and 8%, respectively. Δ-LAVI changes (stress-rest) were negatively correlated with resting LAVI ($r = -0.271$, $p < 0.001$) and heart rate reserve ($r = -.239$, $p < 0.001$). LAV-dilators were defined as those with stress-rest increase ≥ 6.8 ml/m^2, a cutoff derived from a calculated reference change value above the biological, analytical and observer variability of LAVI. LAV dilation occurred in 56 patients (11%), more frequently with exercise (16%) and dipyridamole (13%) compared to dobutamine (4%, $p < 0.01$). At multivariable logistic regression analysis, B-lines ≥ 2 (OR: 2.586, 95% CI = 1.1293–5.169, p = 0.007) and abnormal contractile reserve (OR: 2.207, 95% CI = 1.111–4.386, p = 0.024) were associated with LAV dilation. In conclusion, LAV-SE is feasible with high success rate and low variability in patients with chronic coronary syndromes. LAV dilation is more likely with reduced left ventricular contractile reserve and pulmonary congestion.

Keywords Echocardiography · Dipyridamole · Dobutamine · Exercise · Left atrial volume · Stress

Introduction

The left atrium (LA) is a highly dynamic chamber and plays an active part in the physiology of the entire cardiovascular system [1]. Measurement of left atrial volume index (LAVI) is an integral part of the standard assessment of left heart function, and its increase is considered a hallmark of diastolic dysfunction and chronically elevated left ventricular

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filling pressures [2, 3]. LA dilation at rest is associated with a higher risk of adverse events in many cardiovascular conditions, including coronary artery disease (CAD), heart failure with reduced ejection fraction, heart failure with preserved ejection fraction or hypertrophic cardiomyopathy [4].

Experimental studies demonstrate that left atrial volume (LAV) may change over seconds or minutes when the hemodynamic conditions are modified. It can acutely either decrease in presence of left ventricular unloading [5], or augment during stress for increased LA preload [6]. In fact, a Frank-Starling mechanism similar to left ventricle exists also for LA, with increased function for increasing volumes up to a point when increasing LAV leads to a fall in atrial performance [6]. In line of principle, experts agree that measurements of LA should be performed not only in resting state, but also during stress [4]. However, LAV dynamic assessment during stress echocardiography (SE) finds no place in current recommendations, both in CAD [7–9] and beyond CAD [10].

The present study hypotheses were that LAV can be assessed with satisfactory success rate in consecutive patients with known or suspected CAD referred to physical or pharmacological stress, and that patients with stress-induced LAV dilation may show greater pulmonary congestion and impairment in atrial and LV function. We therefore evaluated LAV at rest and during SE in 490 subjects referred for clinically driven SE in the prospective, multicenter, international SE2020 study [11].

Methods

Study population

In this prospective study, we initially evaluated 514 patients recruited by 10 laboratories of 9 countries (Argentina, Brazil, Bulgaria, Hungary, Italy, Poland, Russian Federation, Serbia, Spain). The inclusion criteria were: 1) Age > 18 years; 2) referral for known or suspected CAD, with any degree of resting left ventricular function (preserved or reduced); 3) no severe primary valvular disease, congenital heart disease, hypertrophic or restrictive cardiomyopathy; 4) wall motion imaging by transthoracic echocardiography of acceptable quality at rest; 5) willingness to give their written informed consent allowing scientific utilization of observational data, respectful of privacy rights.

All patients underwent SE testing as part of a clinically-driven work-up and according to the referring physician's indications. Written informed consent was obtained from all patients before testing. The study protocol was reviewed and approved by the institutional ethics committees as a part of the SE 2020 study (148-Comitato Etico Lazio-1, July 16, 2016; Clinical trials. Gov Identifier NCT 030.49995). The study was funded partly by travel grants of the Italian Society of Echocardiography and Cardiovascular Imaging with dedicated sessions during national meetings. No support from industry was received.

Transthoracic echocardiography

We used commercially available ultrasound machines. All patients underwent comprehensive transthoracic echocardiography at rest. All measurements were taken by certified cardiologists according to the recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging [12]. Patients underwent SE according to the recommended protocols [7, 8] with one of the following stresses: semi-supine cycle ergometry [25 watts increments every 2 min]; treadmill exercise; dobutamine (up to 40 mcg/kg/min with atropine co-administration up to 1 mg); or dipyridamole (0.84 mg/kg over 6 or 4 min). Electrocardiogram and blood pressure were monitored continuously. Criteria for terminating the test were severe chest pain, diagnostic ST-segment shift, excessive blood pressure increase (systolic blood pressure ≥ 240 mmHg, diastolic blood pressure ≥ 120 mmHg), symptomatic hypotension with sudden drop in blood pressure (> 40 mmHg), limiting dyspnea, maximal predicted heart rate, significant arrhythmias or limiting side effects [7, 8]. The quadruple imaging protocol of SE was used (ABCD protocol) when each laboratory had completed the upstream quality control process [13]. Echocardiographic imaging was performed from parasternal long axis view, short axis view, and apical 4-, 3- and 2-chamber view, using conventional 2-dimensional echocardiography. Step A included assessment of regional wall motion abnormalities (RWMA) and was performed in all patients at rest and peak stress. 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 left ventricle [14]. Step B of protocol included the assessment of B-lines with lung ultrasound and the 4-site simplified scan, from mid-axillary to anterior axillary and mid-clavicular lines on the third intercostal space [15]. Step C of protocol included the force-based assessment of left ventricular contractile reserve (LVCR) as the stress/rest ratio of force, calculated as systolic blood pressure/end-systolic volume from biplane Simpson's method [16]. Step D of protocol was available in 230 patients and included pulsed-Doppler assessment of coronary flow velocity reserve (CFVR), defined as the ratio between hyperemic peak and basal peak diastolic coronary flow velocities in mid-distal left anterior descending coronary artery [17]. The procedure for acquisition between centers was standardized through a web-based learning module before starting data collection. All readers (one for each center) underwent a quality

control as previously described for RWMA, B-lines, end-systolic volume and CFVR. Imaging-independent Step E of the ABCDE protocol included EKG-based assessment of heart rate reserve (HRR) as peak/rest ratio of heart rate as an index of cardiac autonomic dysfunction [18]. Mitral regurgitation severity was semi-quantitatively assessed in 96 patients with a 4-point score from 0 (absent) to 3 (severe).

SE positivity criteria

All positivity criteria were determined a priori. The A criterion was considered positive in presence of stress-induced RWMA (WMSI stress > rest), when at least two adjacent segments of the same vascular territory of the left ventricle showed an increment of at least one point of WMS during SE. The B criterion was considered positive in presence of stress or rest B-lines ≥ 2 units. The C criterion was considered positive in presence of force-based LVCR ≤ 2.0 for exercise and dobutamine (≤ 1.1 for vasodilators). The D criterion was considered positive in presence of CFVR ≤ 2.0. The E criterion was considered positive in presence of HRR < 1.80 for exercise and dobutamine (≤ 1.22 for dipyridamole) [14].

LAVI measurement

Echocardiographic measurements of the LA were obtained offline from the apical 4- and 2- chamber views with the biplane disk summation method [12]. Measurements were recorded at rest and at peak stress (Fig. 1). Left atrial size was measured at ventricular end-systole (when the LA chamber was at diastole) in the frame preceding mitral valve opening at the end of T wave on the ECG. The LA planimetry was traced and the volume was computed by the online software package and indexed to body surface area, according to current guidelines [12]. While tracing the endocardium, care was taken to exclude LA appendage and ostia of pulmonary veins. Each value represents the average of 3 measurements [5 in presence of atrial fibrillation]. To evaluate inter-observer and intra-observer variability, two independent observers measured LAV in 10 randomly selected patients without knowledge of the results obtained by the other observer; and the same observer (DM) measured LAV one month after the first measurement. LAVI was estimated as LAV divided by the body surface area.

Quality control

The quality control procedures of RWMA, B-lines, end-systolic volume, and CFVR have already been described in detail. In all cases, the readers had at least 90% agreement with the gold standard reading of the coordinating lab [14, 17]. A similar approach was adopted for LAV reading. The procedure for acquisition between centers was standardized through a web-based learning module before starting data collection. We selected 20 cases of 5 patients (with rest and stress images in 4- and 2-chamber view). The privacy

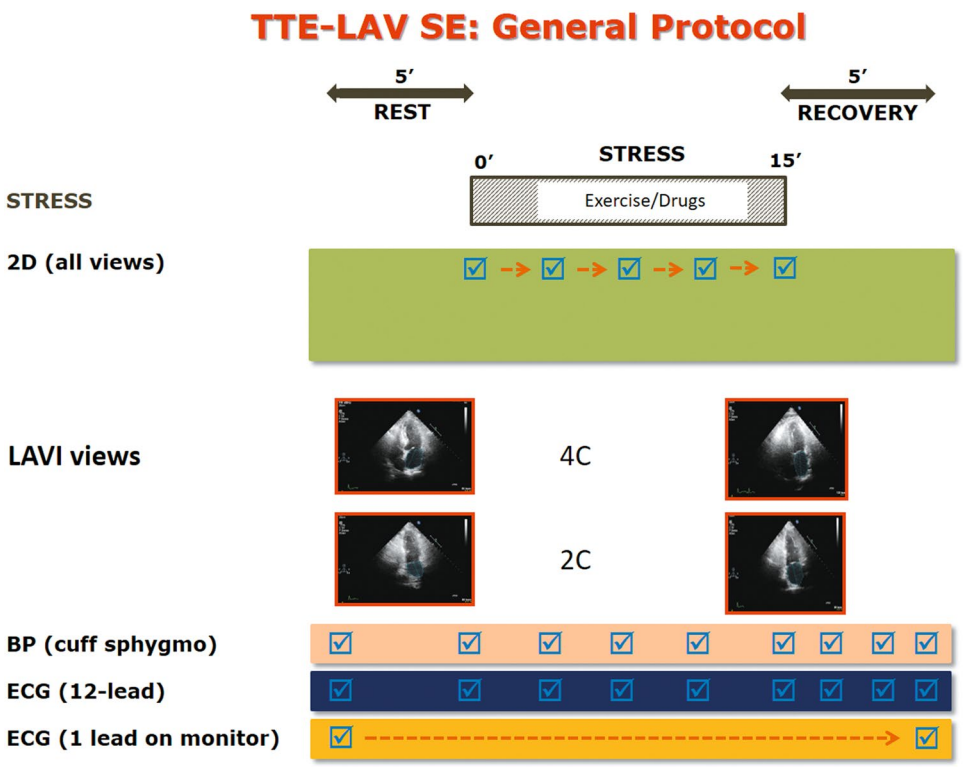

Fig. 1 LAV-Stress echo protocol. The LAV acquisition is performed at rest and peak stress with the apical 4-chamber (4C) and 2-chamber (2C) views

of patients during acquisition, storage, and transmission of the study was protected. All images were anonymized, and the identity of patients or the study condition (rest or stress) was not disclosed at any time to the readers. Each SE study was structured in a single video-clip of 10–15 s, with either resting or stress images. For each clip, the planimetric area was measured. The diagnostic gold standard was the average reading of two experienced readers (EP and QC). The answer of the reader was considered correct if concordant with reference standard reading ± 15%. The a priori determined pass threshold was 18/20 (≥ 90%) with R value of intra-class correlation coefficient > 0.90. The LA images were selected to represent the wide variety of stress testing modes, responses, results and image quality. They came from quality controlled laboratories in four countries (Bulgaria-Sofia, Italy Pisa-Cisanello, Poland-Lodz, Serbia-Belgrade). Four clips for each patient were selected: rest and stress, each with 4- and 2- chamber views. The stress employed was semi-supine exercise in 3, dobutamine in 1, and dipyridamole in 1 patient.

LA strain

A subset of 61 subjects (with technically excellent acoustic window) were prospectively recruited in a single center (Buenos Aires, Investigaciones Medica) for attempting simultaneous LAVI and LA strain assessment during exercise. 2D-Speckle tracking echocardiography (STE)-derived LA reservoir strain was assessed with Vivid E 95 (GE Healthcare), equipped with 5 MHz transducer. According to recommendations for the standardization of LA deformation imaging by STE [19], frame rate was 60–70 at rest and 80–90 during stress. LA deformation imaging was measured manually using the QRS as the reference point, tracing the LA endocardial borders in the apical 4- and 2-chamber views at rest and peak stress. Images were analyzed off-line (EchoPac Version 201). Global peak amplitude longitudinal strain (PALS) of LA reservoir function was assessed at rest and peak exercise stress and expressed in % values. LA reservoir function was estimated as the peak positive strain value corresponding to the period between the R wave and the T wave on the ECG. Global peak amplitude longitudinal strain (PALS) was achieved as the mean of the 12 atrial segments from 4- and 2-chamber values [19].

Data storage and analysis

The results for each test were entered in the data bank at the time of testing by each recruiting center and sent periodically to the coordinating center with the electronic case report form with clinical data. After checking for internal consistency by trained technical staff, and double-checking with the center for data verification on possibly inconsistent input, the data were added to the data bank and frozen. The data were analyzed by personnel unaware of the study hypothesis.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median [25th; 75th percentile] as appropriate. Categorical variables are described as numbers (percent). Continuous variables were compared by independent Student's t test or Mann–Whitney test according to variable distribution. Proportions were compared by chi-square statistics. Correlations between Δ-LAVI changes (stress-rest) and WMSI, B-lines, LVCR, CFVR, HRR and degree of mitral regurgitation were estimated using Spearman's coefficients.

Defining LAV-dilators

The definition of LAV dilation is based on a well validated statistic called reference change value (RCV). One of the main advantages of this statistic is that it includes biological, analytical, and observer variability. Mathematically, the reference change value is based on the total coefficient of variation (ratio of the standard deviation to the mean) and RCV is calculated according to the formula $k \times \sqrt{2} \times$ average total coefficient of variation obtained over several measurements where $k = 1.65$ for a one-tailed test and $k = 1.96$ for two-tailed test [20]. Interpretation of the numerical value of the reference change value in the context of the present study is that it represents an optimal cut-off value for LAVI change between rest and stress that would be representative of a real difference above the total variability of LAVI. Using a randomly chosen subset of patients (n = 46) for which serial measurements were available, the average total coefficient of variation in serial LAVI measurement was calculated to be 0.10 while RCV (%) was 22.4%. Given that the mean LAVI in this subset was 30.1 ml/m^2, the absolute RCV value was calculated at 6.7 ml/m^2. On this basis, a LAVI change of ≥ 6.8 ml/m^2 between rest and stress was considered a real change above background variation and was used as a cut-off to identify a LAV-"dilator" cohort. Independent predictors of LAVI increase were assessed by multivariable logistic regression analysis. Odds ratios with the corresponding 95% confidence interval were estimated. Selection of independent predictors was performed with a backward approach using a p value of 0.10 as threshold for inclusion in the model. A probability value of < 0.05 was considered statistically significant. All statistical calculations were performed using SPSS for Windows, release 18.0 (Chicago, Illinois) and StataCorp 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.

Results

Out of 514 pts initially referred for clinically-driven SE, LAVI-SE was successfully performed in 490 (feasibility = 95%) subjects (age 67 ± 12 years) presenting with known or suspected chronic CAD (n = 388), dyspnea (n = 74) as chief complaint, or young asymptomatic controls referred for screening (n = 28). The main reasons for exclusion due to technically inadequate imaging were insufficient depth of the field of view cutting atria to focus on left ventricular imaging (n = 6), or foreshortening of LA preventing accurate measurements in at least one of the two apical projections required for analysis (n = 18).

Most active recruiting centers were Lodz (n = 189), Pisa-Cisanello (n = 117), Benevento (n = 53), Buenos Aires (n = 51, also performed all 2D-STE studies), La Coruna (n = 35) and Szeged (n = 31), with the remaining 14 studies from 4 centers.

The main clinical characteristics of the 490 study patients are described in Table 1. Exercise mode (N = 177) was semi-supine (n = 142) or treadmill with peak stress imaging (n = 35). Twelve patients were in atrial fibrillation at the time of testing.

LAVI quality control and variability

The intra-observer and inter-observer variability of absolute LAVI measurements at baseline and during stress assessed by 2 independent observers in a set of 20 consecutive clip resulted in, respectively, 5% and 6% at rest and 5% and 8% at peak stress. The between-observer and within-observer correlation coefficients were R = 0.92 and R = 0.96 at rest, and R = 0.92 and R = 0.93 at peak stress, respectively. All the accredited readers achieved ≥ 90% concordance with core lab reading on LA assessment of planimetric area. The intra-class correlation coefficient of each of the readers with core lab reading was > 0.90.

Table 1 The clinical and echocardiographic characteristics of patients

	LAVI stress-rest decrease/no change (n = 434)	LAVI stress-rest increase (n = 56)	*p*
Age (years)	66 ± 12	68 ± 12	*0.356*
Male sex	278 (64%)	36 (64%)	*0.990*
Hypertension	316 (73%)	39 (70%)	*0.617*
Diabetes	106 (26%)	14 (27%)	*0.814*
Previous MI	68 (19%)	10 (22%)	*0.631*
Type of stress:			
Exercise	148 (34%)	29 (52%)	**< 0.001**
Vasodilator	145 (33%)	22 (39%)	
Dobutamine	141 (32%)	5 (9%)	
LV EF rest (%)	69 ± 10	62 ± 10	*0.156*
LAVI rest (ml/m^2)	29 ± 11	28 ± 11	*0.513*
LAVI stress (ml/m^2)	26 ± 10	42 ± 13	**< 0.001**
LAVI stress-rest change (*ml/m^2*)	− 2 [− 7;1]	11 [8;16]	**< 0.001**
Step A—WMSI at rest	1.05 ± 0.15	1.04 ± 0.17	*0.798*
Step A—WMSI at peak	1.07 ± 0.17	1.06 ± 0.20	*0.924*
Step A—RWMA (%)	47 (12%)	4 (8%)	*0.452*
Step B- B lines ≥ 2 rest or peak (%)	119 (28%)	29 (54%)	**< 0.001**
Step C- Force at rest (mmHg/ml)	4.7 ± 2.2	4.2 ± 1.8	*0.134*
Step C- Force at stress (mmHg/ml)	7.5 ± 4.6	5.6 ± 2.4	***0.003***
Step C- LVCR	1.63 ± 0.71	1.36 ± 0.45	***0.008***
Step D- CFVR (n = 230)	2.26 ± 0.59	2.10 ± 0.60	*0.386*
Step E- Heart rate at rest (b/m)	68 ± 13	67 ± 11	*0.666*
Step E—Heart rate at peak (b/m)	115 ± 30	106 ± 25	*0.044*
Step E—HRR	1.71 ± 0.45	1.60 ± 0.39	*0.105*
Step F—MR ≥ 2 rest or peak (%)	17 (4%)	5 (11%)	*0.065*

Bold character indicates statistical significance ($p < 0.05$)

Values are mean ± SD or n (%)

CFVR coronary flow velocity reserve, *EF* ejection fraction, *LAVI* left atrial volume index, *LVCR* left ventricular contractile reserve, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *MI* myocardial infarction, *MR* mitral regurgitation, *RWMA* regional wall motion abnormalities

LAVI stress responses

At cumulative analysis, LAVI was on average reduced during SE (rest = 29 ± 11 ml/m^2 vs stress = 27.5 ± 12 ml/m^2, p < 0.001). LAVI increase (≥ 6.8 ml/m^2) during stress occurred in 56 patients (11%). LAV dilation pattern was present with exercise (16%), dobutamine (4%) and dipyridamole (13%) stress (Table 1). An example of a patient with increase of LAVI is shown in Fig. 2. An example of a patient with decrease of LAVI is shown in Fig. 3.

The functional and coronary anatomic correlates of LAVI changes

Δ-LAVI was negatively correlated with resting LAVI (r = − 0.271, p < 0.001) and heart rate reserve (r = − 0.239,

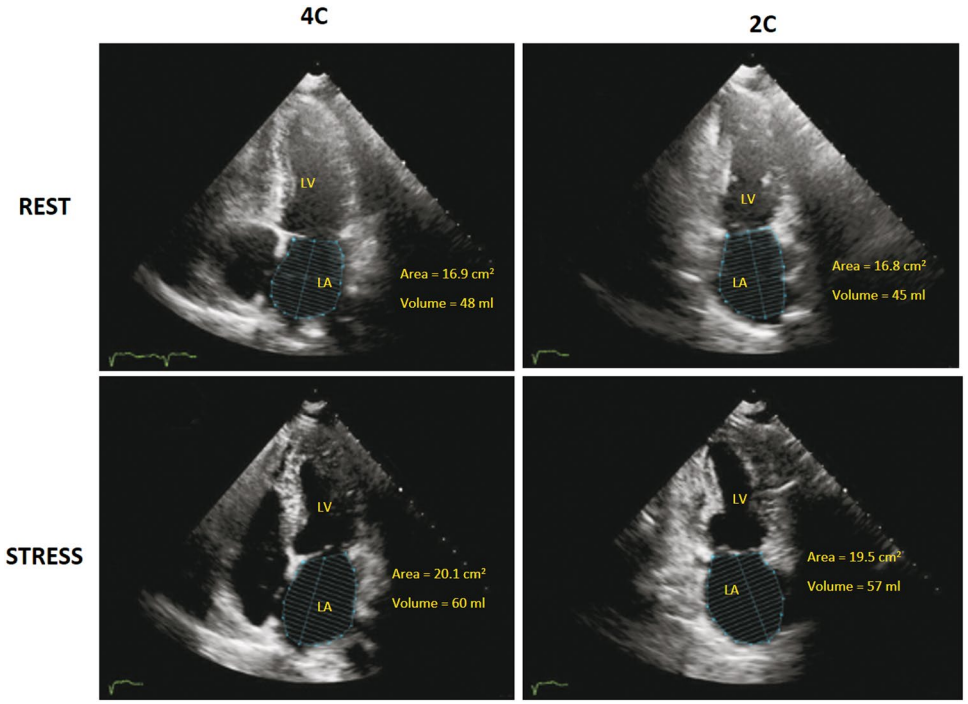

Fig. 2 An example of increased LAV during stress. Apical 4-chamber (left panels) and 2-chamber (right panels) views of a patient at rest (upper panels) and peak dipyridamole stress (lower panels). LAVI volume increases > 20% at peak stress. The end-systolic still frame in 2-chamber view shows akinesia of the basal inferior segment. *LA* left atrium, *LV* left ventricle

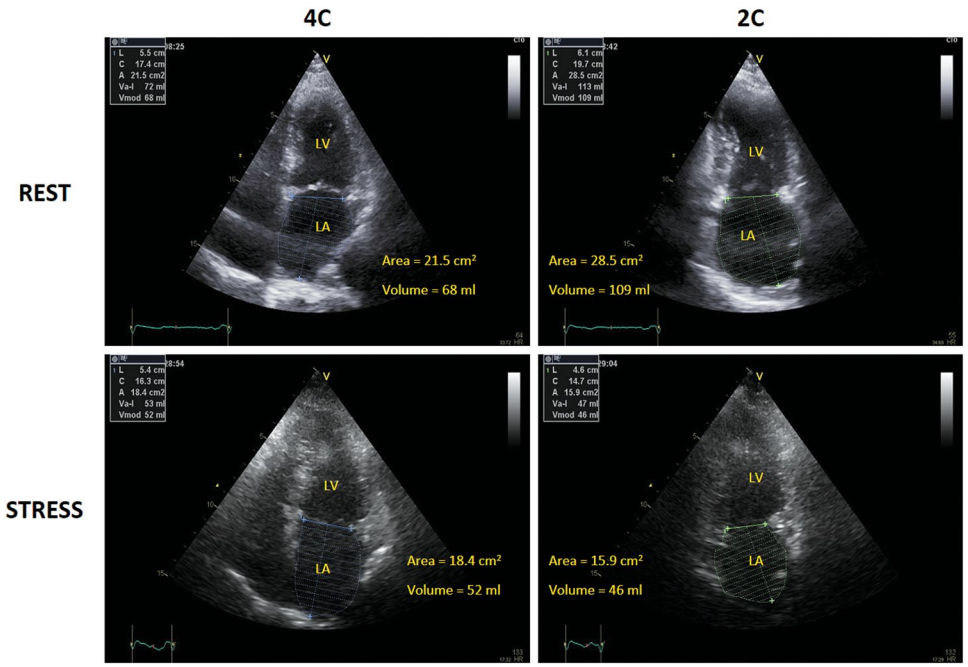

Fig. 3 An example of LAV reduction during stress. Apical 4-chamber (left panels) and 2-chamber (right panels) views of a patient at rest (upper panels) and peak dobutamine stress (lower panels). LAVI volume decreases > 20% at peak stress. *LA* left atrium, *LV* left ventricle

$p < 0.001$). At multivariable logistic regression analysis, B-lines ≥ 2 (OR: 2.586, 95% CI = 1.1293–5.169, p = 0.007) and abnormal LVCR (OR: 2.207, 95% CI = 1.111–4.386, p = 0.024) were associated with LAVI increase (≥ 6.8 ml/m^2) during stress (Table 2). There was no significant correlation between LAVI increase and peak WMSI. LAVI increase was less likely with dobutamine compared to exercise stress (OR: 0.246, 95% CI = 0.084–0.723, p = 0.011), and equally likely for exercise and dipyridamole.

When the 3 different types of stress were separately considered, the correlation between Δ-LAVI and LVCR was highest for vasodilators (r = − 0.210, p = 0.006), intermediate for dobutamine (r = − 0.208, p = 0.012), and lowest for exercise (r = − 0.093, p = 0.322). The correlation between Δ-LAVI and HRR was highest for dobutamine (r = − 0.228, p = 0.006), intermediate for exercise (r = − 0.125, p = 0.152), and lowest for dipyridamole (r = − 0.017, p = 0.834).

LA strain

Of the 61 subjects initially referred for combined LAVI and LA strain, LA-STE was attempted in 54 subjects (23 patients and 31 controls) with excellent quality images at rest and technically adequate LA strain at rest. Interpretable tracings were obtained in 50 subjects (22 patients and 28 controls) both at rest and peak exercise. Feasibility was 92.5% considering the 54 patients with interpretable LA-strain at rest, and 82% considering the population of 61 subjects initially referred for strain. Intra-observer variability (RA) of PALS at rest and during stress were 2.2 ± 1.6% and 2.3 ± 2.5% respectively. Inter-observer (RA and DLH) variability was 6 ± 7% at rest and 4.6 ± 4% during stress. Δ-LAVI was negatively correlated with Δ-PALS (n = 50, r = − 0.374, p = 0.007).

Discussion

LAVI measurement is highly feasible and reproducible during physical and pharmacological SE, with no additional imaging time and only minimal increase in off-line analysis time. Differently from other parameters such as B-lines or CFVR, LAV measurements do not increase the peak stress imaging time, since they are performed at the time of RWMA

Table 2 Univariate and multivariate predictors of LAVI increase during stress

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p value*	HR (95% CI)	*p value*
Age (years)	1.011 (0.987–1.041)	*0.355*		
Gender (male)	1.003 (0.561–1.794)	*0.990*		
Hypertension	0.857 (0.467–1.573)	*0.618*		
Diabetes	1.082 (0.563–2.079)	*0.814*		
Previous MI	1.202 (0.567–2.546)	*0.632*		
Vasodilator vs exercise	0.686 (0.372–1.264)	*0.227*	0.668 (0.308–1.450)	0.308
Dobutamine vs exercise	**0.160 (0.060–0.429)**	**< 0.001**	**0.246 (0.084–0.723)**	**0.011**
LAVI rest (ml/m^2)	0.990 (0.964–1.016)	*0.450*		
LV EF (%)	1.023 (0.991–1.056)	*0.160*		
WMSI at rest	0.766 (0.100–5.846)	*0.797*		
WMSI at peak	0.920 (0.167–5.067)	*0.923*		
RWMA (%)	0.666 (0.229–1.934)	*0.455*		
B-lines rest or peak	**3.051 (1.717–5.422)**	**< 0.001**	**2.586 (1.293–5.169)**	***0.007***
Force at rest (mmHg/ml)	0.894 (0.773–1.035)	*0.134*		
Force at stress (mmHg/ml)	**0.859 (0.779–0.947)**	***0.002***		
Abnormal LVCR	**2.252 (1.227–4.132)**	***0.009***	**2.207 (1.111–4.386)**	***0.024***
Abnormal CFVR	0.598 (0.188–1.905)	*0.384*		
Heart rate rest (b/m)	0.995 (0.971–1.019)	*0.666*		
Heart rate peak (b/m)	**0.989 (0.980–0.999)**	***0.045***		
Abnormal HRR	1.783 (0.883–3.597)	*0.107*		
MR ≥ 2 rest or peak (%)	3.077 (0.541–17.507)	*0.205*		

Bold character indicates statistical significance ($p < 0.05$)

OR for continuous variables are computed with reference to unit change in the explanatory variable

Abbreviations as in previous tables. Abnormal values of LVCR were considered ≤ 2.0 (≤ 1.1 for vasodilator); abnormal values of B-lines were considered with rest or stress ≥ 2 points; abnormal values of HRR were considered ≤ 1.8 (≤ 1.22 for vasodilator); abnormal values of CFVR were considered ≤ 2.0

assessment. We observed a heterogeneous behavior of LAV that ranges from reduction up to increase, with all the spectrum of responses in between. In analogy with what happens with left ventricular volume changes [8], LAV dilation during stress probably means LA dysfunction, with the rise in intra-cavitary distending pressure exceeding the possibility of LA to compensate for the increase in LA filling pressures by increasing LA function [6]. LAVI reduction during stress means a physiological response in LA with normal structure and function or with initial, reversible dysfunction [21]. Consistently with this interpretation, LAV dilation was more likely in presence of increased B-lines, which are a direct sign of increased extra-vascular lung water and are associated with higher left ventricular filling pressure and pulmonary artery wedge pressure acting as distending forces on LA [22]. LAV dilation was also more likely with a reduced LVCR, which is associated with higher LA distending pressures [23, 24]. LAV dilation occurred with all stresses and a similar rate with exercise and dipyridamole, but it was less likely with dobutamine, possibly for a more pronounced inotropic effect of high dose exogenous catecholamines on LA [25] compared to exercise or dipyridamole. In addition, at low doses dobutamine can increase venous capacitance and increase filling pressures, but dipyridamole and adenosine may increase filling pressures also in absence of inducible ischemia in presence of diastolic abnormalities due to the erectile properties of coronary arteriolar dilation [7, 8]. Also for LV, a stress-induced increase in end-systolic size is more commonly observed with exercise rather than with dobutamine [8].

Comparison with previous studies

From 2005 to 2019, only few studies addressed the changes in LAVI during exercise or dobutamine SE in < 400 subjects including 339 patients and 55 controls. Enrolled patients had heart failure and reduced ejection fraction [26, 27], CAD [28], hypertrophic cardiomyopathy [29], as well as healthy subjects and athletes [30]. No net changes were detectable at cumulative analysis in CAD or heart failure patients [26–28]. A reduction pattern was more often observed in young subjects (mean age 34 years) with small resting LAVI and trained athletes [30]. Consistently with our findings, all these studies showed an excellent success rate and low variability (< 5%) of LAV measurement at peak stress, and the possibility to detect acute dynamic changes occurring during a physical or pharmacological stress.

In expert hands of a single center, we also found a high feasibility of LA-STE with measurement of PALS at rest and during stress as an index of LA global reservoir function [31]. As previously reported by Sugimoto et al. in patients with mitral regurgitation, the normal LA strain pattern found in controls is an increase during exercise [32], and a LAV dilation in CAD patients is more often associated with an impaired LA strain reserve.

Clinical implications

LAV can be easily added to SE since it does not require extra-imaging time and only minimal (< 1 min) analysis time. When images are appropriately acquired, the analysis is simple and the success rate is excellent. The major feasibility limitation is that SE image acquisition is usually focused on zoomed LV and regional wall motion, with image depth too small to include LA boundaries and sometimes with foreshortening of LA precluding a correct data analysis. The apical views to optimize LA may not be the same to optimize LV. When LAVI is systematically measured, a wide spectrum of responses can be detected, from reduction to dilation. In theory, a stress-induced dilation can identify an early stage in the classic cascade of events of atrial disease based upon resting LAVI [27], with the possibility to identify incipient atrial failure when resting LAVI is still normal or near-normal. Reversible damage of LA may be more likely when resting LAVI is dilated but capable to decrease during stress.

In perspective, the acceptance and utilization of LAVI during stress can be made easier by several facilitating factors. Cardiologists already know that LAVI is an important biomarker of left ventricular diastolic dysfunction and know how to measure it at rest. The parameter is easy to measure in virtually all patients with an acceptable echocardiographic window. It can be obtained by all cardiologists with all machines. It requires very little extra-imaging and analysis time. It is simple to understand and to apply. No extra-cost, no top-level machines, and no additional software are required. LAV imaging is usually not degraded by stress, and success rate is very high. However, the incorporation of LAV into routine stress echo is not justified until data showing its added value for predicting outcome and future LAV dilation become available. In addition, LAV dilation during stress can be an ominous sign but it is certainly non-specific for a given disease, since it could be due to CAD, diastolic dysfunction, mitral valve disease, and so on.

Limitations

The technique of LAVI measurement from 2D is well standardized and shows limited variability at rest and during stress. In perspective, SE can benefit from advanced imaging with real-time three- dimensional echocardiography, offering a more accurate assessment of LAVI, independent of geometric assumptions although more dependent on image quality and patient cooperation [17].

LAV misses potentially important information on LA global, reservoir, conduit and contractile (booster) function, which requires an integration of LA volume fraction

by volumetric 2D echocardiography, spectral Doppler, tissue Doppler and deformation indices [11]. There is little doubt that a combined assessment of LAVI and LA strain at rest and during stress may allow a more comprehensive assessment of LA morphology and function [4].

Diastolic function was not systematically assessed with e′, E/e′, pulmonary artery systolic pressure with tricuspid regurgitant jet velocities, but B-lines which are associated to pulmonary congestion, diastolic dysfunction, hemodynamic congestion and worse outcome [15] predicted LAV dilation.

Different exercise protocols were used by different centers, and the most used semi-supine exercise is expected to be associated with lower exercise performance than treadmill exercise. Data on oxygen consumption and respiratory exchange ratio during exercise were not available.

In conclusion, LAVI can be easily measured during SE, with excellent success rate and good reproducibility. LAV dilation is more likely with reduced left ventricular contractile reserve and pulmonary congestion. Further studies are needed to justify its incorporation into routine SE.

Author contributions DM is the subproject leader; QC is the principal investigator of SE2020; VL is responsible for data analysis. CC is responsible for data quality control and reader' certification. MDN and MP helped to develop the web-based training. EP is the study chairman, designed the protocol, organized the content of web-based training, contributed to data analysis and drafted the manuscript. All authors contributed to the study design, undertook the quality control up to certification, are active recruiting members of SE 2020 consortium, critically revised the manuscript for an intellectually important contribution and approved the submitted version.

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Compliance with ethical standard

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