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Original Article

Left atrial volume changes during exercise stress echocardiography in heart failure and hypertrophic cardiomyopathy☆

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Abbreviations: ESE, exercise stress echocardiography; HCM, hypertrophic cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrium; LAP, left atrial pressure; LAVI, left atrial volume index; LVCR, left ventricular contractile reserve; MR, mitral regurgitation; SPAP, systolic pulmonary artery pressure.

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ABSTRACT

Objective: We aimed to assess feasibility and functional correlates of left atrial volume index (LAVI) changes during exercise stress echocardiography (ESE).
Methods: ESE on a bike or treadmill was performed in 363 patients with heart failure with preserved ejection fraction (HFpEF, n = 173), reduced ejection fraction (HFrEF, n = 59), or hypertrophic cardiomyopathy (HCM, n = 131). The LAVI stress-rest increase ≥6.8 ml/m^2 was defined as dilation.
Results: LAVI measurements were feasible in 100%. LAVI did not change in HFrEF being at rest 32 (25-45) vs at stress 36 (24-54) ml/m^2, P = NS and in HCM at rest 35 (26-48) vs at stress 38 (28-48) ml/m^2, P = NS, whereas it decreased in HFpEF from 30 (24-40) to 29 (21-37) ml/m^2 at stress, P = 0.007. LA dilation occurred in 107 (30%) patients (27% with treadmill vs 33% with bike ESE, P = NS): 26 with HFpEF (15%), 26 with HFrEF (44%), and 55 with HCM (42%) with P < 0.001 for HFrEF and HCM vs HFpEF.
A multivariate analysis revealed as the predictors for LAVI dilation E/e' > 14 at rest with odds ratio (OR) 4.4, LVEF <50% with OR 2.9, and LAVI at rest <35 ml/m^2 with OR 2.7.
Conclusion: The LAVI assessment during ESE was highly feasible and dilation equally frequent with a treadmill or bike. LA dilation was three-fold more frequent in HCM and HFrEF and could be predicted by increased resting E/e' and impaired EF as well as smaller baseline LAVI.

1. Introduction

The left atrial volume index (LAVI) is a well-recognized parameter, used not only for the left atrium (LA) quantification but strongly recommended over the LA diameter for the left ventricular diastolic function stratification and used as a potent prognostic marker in a wide range of clinical conditions.[1–4] Its acute changes during stress echocardiography have been so far described in sparse studies with more focus given on long-term remodeling.[5–7] LAVI in the absence of significant mitral valve stenosis or regurgitation, atrial fibrillation, and frequent arrhythmia, especially related to atrioventricular dissociation, reflects in the proportional manner the chronically increased filling pressure of the left ventricle, the advancement of diastolic impairment, and the myocardial hypertrophy acting as a "barometer of the heart."

In the previous study from our stress echo 2020 network, Morrone et al. showed[8] that a subset of patients with suspected or diagnosed coronary artery disease undergoing pharmacological or exercise stress echocardiography (ESE) presents LAVI dilation. The pattern of stress-induced LAVI dilation correlated with an abnormal left ventricle contractile reserve (LVCR) as well as with the increase of B-lines, a direct sign of pulmonary congestion correlated with an increase in pulmonary capillary wedge pressure.

However, LAVI plays also an important role outside chronic coronary syndromes, and ESE is the recommended test modality for applications beyond coronary artery disease.

Our aim was to assess the feasibility and functional correlations of LAVI changes during ESE performed with a treadmill or semi-supine bike in patients with heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and hypertrophic cardiomyopathy (HCM).

2. Methods

The study was approved by the Ethical Committee as a part of the SE 2020 study (148-Comitato Etico Lazio-1, July 16,2016; Clinical trials.Gov Identifier NCT 030.49995). All patients gave their informed consent to enter the study.

2.1. Study group

We included 363 consecutive subjects undergoing clinically indicated ESE in 17 centers of 10 countries from Europa, Russian Federation, and America participating in SE 2020 study described in earlier articles.[9,10]

Three subgroups were analyzed: HFpEF, n = 173, HFrEF, n = 59, and HCM, n = 131. Detailed inclusion/exclusion criteria were formulated in the SE 2020 protocol in respective subprojects of the SE 2020 study. For this study, the following inclusion/exclusion criteria were accepted:

For all three groups:

- Patients aged >18 years;
- Good visualization for at least 14 LV segments as the condition for qualification to stress echocardiography; and
- Both sinus rhythm and atrial fibrillation at the baseline assessment were allowed.

As exclusion criteria served for all groups:

- Presence of prognosis-limiting comorbidities, such as advanced cancer and reducing life expectancy to <1 year;
- Pregnancy/lactation;
- Unwillingness to give informed consent and to enter a regular follow-up program.

Specifically, to the HFrEF group, the following were included:

- Patients with reported diminished exercise tolerance and proved or suspected heart failure with symptoms ranging from I to III NYHA class;
- LV ejection fraction <50% as assessed at baseline echocardiography (etiology of CAD and DCM of heart failure was allowed, significant mitral and aortic valve stenosis, and severe primary valve regurgitation excluded).

To the HFpEF group:

- Patients with known and suspected heart failure from I to III NYHA class;
- LV ejection fraction ≥50% at baseline echocardiography, significant mitral and aortic stenosis, as well as severe primary valve regurgitation (organic) excluded;
- Patients with no alternative causes of dyspnea such as anemia and/or chronic obstructive lung disease.

To HCM group:

- Patients with an LV myocardial thickness ≥15 mm in any segment in the absence of another cause of LV hypertrophy and

resting (or after Valsalva maneuver) left ventricular outflow tract gradient <50 mmHg
- Specific exclusion criteria for this group included phenocopies of HCM such as infiltrative/storage disease (eg, Fabry disease), ejection fraction <45%, and history of coronary artery disease.

2.2. Echocardiographic rest and stress assessment

Transthoracic echocardiography at rest and ESE was performed with high-end echocardiographic systems. An electrocardiogram (ECG) tracing was displayed on the monitor during the examination. The echocardiographic measurements were acquired following the recommendations.[11,12] All echocardiographers in Stress Echo 2020 had passed the quality control of reading examinations with interobserver reproducibility exceeding 90%.[13] An ESE modality was a semisupine bike in 178 and a treadmill in 185 patients. Criteria for interrupting the test were chest pain, induced wall motion abnormalities, significant rhythm disturbances, excessive blood pressure increase or hypotonia, limiting dyspnoea and fatigue, legs pain, or predicted heart rate.

The definition of LAVI dilation was based on a well-validated statistic called reference change value, taking into account a biological, analytical, and observer variability with the LAVI change of $\geq$6.8 ml/m^2 between rest and stress considered as a change above background variation and used as a cutoff to identify a LAVI—dilator cohort.[5,14,15]

2.3. Statistical analysis

The distribution of variables was assessed with the D'Agostino—Pearson test, and adequate parametric or nonparametric tests were used. Accordingly to distribution, data were expressed as mean ± standard deviation or median and interquartile range or frequency for categorical data. Multiple-samples comparison was performed with analysis of variance and the Newman—Keuls test or Kruskal—Wallis test, respectively. The frequency of categorical data was compared with the chi^2 test. One-sample comparisons were performed with paired t-test or Wilcoxon test. For correlation, Pearson's or Spearman coefficients were calculated. Statistical significance was set at $P < 0.05$. A multivariate stepwise logistic regression analysis was conducted on the variables significant in univariate analysis with P value set at < 0.05 for entering and >0.1 for removing variable. Analyses were conducted with MedCalc V. 12.1.4 (Frank Schoonjans, Belgium).

3. Results

3.1. Rest and stress characteristics of patients

Main characteristics of the study patients at rest and stress are summarized in Table 1 and Table 2. The LAVI reducer prevalence was around 30% and similar in all groups, whereas LAVI dilators were 3-times more frequent in HFrEF (44%) and HCM (42%) as compared to HFpEF patients (15%), Table 2.

As far as the comparison between the type of ESE is concerned in the group examined with ergometer LAVI profiles, the prevalence was as follow: 26% reducers, 41% with stable LAVI, and 33% dilators, whereas in the group examined with a treadmill, there were 32% reducers, 41% with stable parameter, and 27% dilators, and this proportions did not differ statistically.

3.2. Predictors of dilated LAVI during ESE

We analyzed patients with reduced (LAVI diminished during stress by > 6.8 ml/m^2), stable (stress-rest changes ± 6.8 ml/m^2), and dilated LAVI (rest-stress increase >6.8 ml/m^2). LAVI reducers displayed higher resting LAVI and less frequent advanced mitral regurgitation (Table 3). At peak, ESE dilators showed more frequent MR, lowest LVCR, and higher E/e', Table 4.

Abnormal (>34 ml/m^2) LAVI values measured at the peak of ESE better then resting LAVI separated patients with abnormal LVCR, increased E/e', greater then mild mitral regurgitation, and similarly with increased SPAP (Fig. 1).

At individual patient analysis based on rest LAVI values, 209 patients showed normal (<35 ml/m^2), 103 moderately abnormal (35-50 ml/m^2), and 51 severely abnormal (>50 ml/m^2) LAVI. During stress, 170 patients (47%) were reclassified with 88 (24%) increasing their LAVI of at least one grade (Fig. 2). Fig. 3 displays an example of a patient with a small reduction of LAVI during ESE.

3.3. Predictors of LAVI changes during ESE

Predictors of LAVI dilation detected in the univariate and multivariate logistic regression analysis are shown in Table 5. A multivariate stepwise analysis revealed as the predictors for LAVI exercise-related dilation 3 parameters: E/E' >14 at rest with OR 4.4, 95% CI (1.9-9.9), rest LVEF <50% with OR 2.9, 95% CI (1.2-6.9), and LAVI at rest <35 ml/m^2 with OR 2.7, 95% CI (1.2-6.2).

Finally, we analyzed exercise-related LAVI changes while going from normal filling pressure with E/e' < 12 at both rest and stress trough mild stage of diastolic dysfunction with E/e' normal at rest but elevated at stress, toward E/e' elevation $\geq$12 at both rest and stress, and the most advanced stage with E/e' > 15 at rest and stress. We found that "LAVI volumetric behavior during ESE" reflected consistently LAP pressure burden (revealed as the noninvasive proxy E/e' ratio) showing transition from reduction through stabilization toward a dilation pattern, see Table 6 and Fig. 4.

4. Discussion

LAVI is a highly dynamic variable and may change substantially during ESE in HFrEF, HFpEF, and HCM. In all these conditions, the LAVI assessment is feasible with a high success rate showing a heterogeneous response at an individual patient analysis. The LAVI-dilator pattern is threefold more frequent in HFrEF and HCM compared with HFpEF patients. Some functional variables are associated with the LAVI-dilator pattern. These variables are the increase in E/e' (a widely accepted proxy of increased left ventricular filling pressure), the reduction of LVEF, and more frequent and advanced mitral regurgitation. All these variables potentially concur in determining of the increased left atrial pressure through abnormalities of the LV diastolic, systolic, or mitral valve function. Although, to some extent, the LAVI dilatation during exercise may act as a physiological increase of an atrial reservoir function at a later stage, a decompensation occurs with signs of backward failure with a possible B-line appearance, as observed in the HFpEF subgroup.

Dilators showed the highest value of E/e' at rest as well as the higher percentage of moderate and severe MR as compared to reducers. Moreover, at peak stage of ESE, higher E/e' with more frequent MR (especially advanced grades) and lower LVCR and LVEF were observed consistently in the dilator group, see Fig. 5 (central figure).

Table 1
Demographic and clinical characteristic as well as resting echo data

Variable	Group 1 HFrEF, N = 59	Group 2 HFpEF, N = 173	Group 3 HCM, N = 131	P value HFrEF vs HFpEF	P value HFpEF vs HCM	P value HFrEF vs HCM
Age (years)	61 (51–71)	69 (63–75)	52 (42–61)	<0.05	<0.05	<0.05
Sex,	42/17	63/110	84/47	<0.001	<0.001	ns
M/F, (M %)	(71.2%)	(36.4%)	(64.1%)			
BSA (m^2)	1.91 (1.8–2.1)	1.93 (1.8–2.1)	1.89 (1.7–2.0)	ns	<0.05	ns
BMI (kg/m^2)	26.5 (24.2–30.1)	29.4 (26.1–32.6)	25.7 (23.3–28.1)	<0.05	<0.05	ns
NYHA class 1	10 (17.9%)	23 (13.5%)	81 (61.8%)	=0.03	<0.001	<0.001
2	37 (66.1%)	138 (80.7%)	44 (33.6%)			
3	9 (16.1%)	10 (5.8%)	6 (4.6%)			
HA	35 (59.3%)	153 (88.4%)	43 (32.8%)	<0.001	<0.001	=0.001
Diabetes	15 (25.4%)	55 (31.8%)	3 (2.3%)	ns	<0.001	=0.001
Dyslipidemia	35 (59.3%)	92 (53.2%)	32 (24.4%)	ns	<0.001	<0.001
Smoking	22 (40%)	23 (13.3%)	31 (23.8%)	<0.001	=0.03	ns
HR rest (bpm)	69 (60–81)	72 (64–80)	65 (60–73)	ns	<0.05	<0.05
DBP rest (mmHg)	75 ± 10	77 ± 10	76 ± 9	ns	ns	ns
SBP rest (mmHg	115 ± 19	129 ± 18	120 ± 16	<0.05	<0.05	<0.05
EF rest (%	38 (32–46)	62 (55–67)	67 (62–72)	<0.05	<0.05	<0.05
WMSI rest	2.0 (1.4–2.3)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	<0.05	<0.05	<0.05
E/e' rest	12.9 (9.7–16.3)	10.2 (8.3–12.6)	9.9 (7.6–12.9)	<0.05	ns	<0.05
SPAP rest	29 (21–39)	27 (23–36)	28 (25–33)	ns	ns	ns
TAPSE rest	20 (16–24)	24 (21–28)	24 (21–26)	<0.05	ns	<0.05
B lines rest (n)	0 (0–4)	1 (0–3)	0 (0–0)	ns	<0.05	<0.05
LAVI rest (ml/m^2)	32 (25–45)	30 (24–40)	35 (26–48)	ns	<0.05	ns
MR rest 0	17 (28.8%)	115 (66.9%)	61 (47.3%)	<0.001	= 0.001	= 0.006
1	25 (42.2%)	49 (28.5%)	51 (39.5%)			
2	12 (20.3%)	6 (3.5%)	16 (12.4%)			
3	5 (8.5%)	2 (1.2%)	1 (0.8%)			

HR—heart rate, DPB—diastolic blood pressure, SBP—systolic blood pressure, EF—ejection fraction, WMSI—wall motion score index, LAD—left anterior descending coronary artery, LAVI—left atrial volume index.

Table 2
Hemodynamic and echo data at peak

Variable	Group 1 HFrEF, N = 59	Group 2 HFpEF, N = 173	Group 3 HCM, N = 131	P value HFrEF vs HFpEF	P value HFpEF vs HCM	P value HFrEF vs HCM
HR peak (bpm)	120 ± 26	124 ± 23	132 ± 26	ns	<0.05	<0.05
SBP peak (mmHg)	144 ± 34	165 ± 27	164 ± 28	<0.05	ns	<0.05
DBP peak (mmHg)	82 ± 12	83 ± 16	85 ± 12	ns	ns	ns
EF peak (%)	37 (29–48)	70 (63–76)	73 (67–77)	<0.05	<0.05	<0.05
WMSI peak	2.0 (1.15–2.3)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	<0.05	ns	<0.05
E/e' peak	14 (10.2–20)	12 (9.7–15)	10 (7.6–13.4)	ns	<0.05	<0.05
SPAP peak	41 (25–59)	38 (30–55)	40 (31–50)	ns	ns	ns
TAPSE peak	26 (21–30)	27 (24–31)	30 (25–34)	ns	ns	ns
B-line peak	1 (0–10)	3 (1–5)	0 (0–1)	<0.05	<0.05	<0.05
LVCR	1.4 (1.1–1.8)	1.7 (1.3–2.2)	1.6 (1.3–2.1)	<0.05	ns	ns
LAVI peak (ml/m^2)	36 (24–54)	29 (21–37)	38 (28–48)	<0.05	<0.05	ns
Δ LAVI	4.8 (−6.5–15)	−2.3 (−7.7–3.4)	2.2 (−15.3–18.9)	<0.05	<0.05	ns
MR peak 0	14 (28.6%)	124 (77%)	51 (40.5%)	<0.001	<0.001	ns
1	16 (32.7%)	30 (18.6%)	50 (39.7%)			
2	12 (24.5%)	4 (2.5%)	19 (15.1%)			
3	6 (12,2%)	3 (1.9%)	4 (3.2%)			
4	1 (2%)	0 (0%)	2 (1.6%)			
Reducer LAVI	15 (25.4%)	48 (27.7%)	43 (32.8%)	<0.001	<0.001	ns
Stable LAVI	18 (30.5%)	99 (57.2%)	33 (25.2%)			
Dilator LAVI	26 (44.1%)	26 (15%)	55 (42%)			
Positive SE (visual)	16 (27.1%)	7 (7.5%)	5 (3.8%)	0.002	ns	<0.001

HR—heart rate, DPB—diastolic blood pressure, SBP—systolic blood pressure, EF—ejection fraction, WMSI—wall motion score index, LVCR—left ventricular contractile reserve (force at peak/force rest ratio; Force = SBP/LVESV, LVESV.

One of the most important findings is the relationship between E/e' values (at rest and peak ESE) and LAVI at rest and peak as well as its dynamics. Achieved results are displayed in Fig. 4 and reveal the reduction of LAVI in subjects with normal E/e' (and the lowest LAP pressure) stable LAVI behavior at early stages of diastolic dysfunction, followed by the small and large dilation of median LA (by circa 10 ml/m^2) in patients with moderately and severely elevated left atrial pressure. On the other hand, the pathologic dilation may be limited in most advanced stage by the increasing stiffness of severely remodeled LA. This seems to be supported by the relationship between basal LAVI and LAVI values at peak exercise in our group. According to Fig. 2, the typical reaction for exercise was the stabilization or increase of volume in the smallest LA group, whereas in the patients with the most enlarged atria, the typical reaction was more often the reduction of LAVI.

Finally, in the multivariable analysis to the predictors of a significant increase of LAVI during ESE belonged E/E' ratio >14 and LVEF lowered <50%, as well as LAVI <35 ml/m^2 at rest offering still greater potential or reserve for dilation, whereas atria with LAVI >50 ml/m^2 at rest tended to diminished at peak stage.

Table 3
Resting characteristic of groups with reduced, stable, and dilated LAVI

Variable	Group 1 Reduced LAVI N = 106	Group 2 Stable LAVI N = 150	Group 3 Dilated LAVI N = 107	P value reduced vs stable	P value stable vs dilated	P value reduced vs dilated
Age	62 (44–71)	66 (55–71)	61 (49–70)	ns	ns	ns
Sex M (%)	54 (50.9%)	70 (46.7%)	65 (60.7%)	ns	=0.04	ns
BMI	26.9 (24.2–30.9)	28.1 (25.1–30.8)	26.8 (24.4–30.4)	ns	ns	ns
BSA	1.9 (1.72–2.05)	1.9 (1.78–2.06)	1.92 (1.76–2.08)	ns	ns	ns
NYHA class				ns	ns	ns
1	38 (36.5%)	39 (26.5%)	37 (34.6%)			
2	61 (58.7%)	100 (68%)	58 (54.2%)			
3	5 (4.8%)	8 (5.4%)	12 (11.2%)			
Hypertension	58 (54.7%)	113 (75.3%)	60 (56.1%)	=0.0009	=0.002	ns
Diabetes	19 (17.9%)	36 (24.0%)	18 (16.8%)	ns	ns	ns
Dyslipidemia	42 (39.6%)	72 (48%)	45 (42.1%)	ns	ns	ns
Smoking	14 (13.2%)	32 (21.6%)	30 (28.8%)	ns	ns	=0.009
HR rest (bpm)	71 (63–80)	70 (62–77)	69 (60–78)	ns	ns	ns
SBP rest (mmHg)	124 ± 18	127 ± 19	119 ± 18	ns	<0.05	ns
DBP rest (mmHg)	80 (70–80)	80 (70–80)	74 (70–80)	ns	ns	ns
EF rest (%)	64 (57–69)	62 (54–68)	60 (45–69)	ns	ns	ns
WMSI rest	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.39)	ns	ns	ns
E/e' rest	10 (8–13.2)	10 (8–12)	11.3 (8–15.4)	ns	<0.05	<0.05
SPAP rest	26 (23–30)	28 (22–36)	30 (25–35)	ns	ns	ns
TAPSE rest	24 (20–26)	23 (21–27)	23 (20–26)	ns	ns	ns
B lines rest (n)	0 (0–1.0)	0 (0–2.5)	0 (0–2.0)	ns	ns	ns
LAVI rest (ml/m^2)	44 (36–55)	29 (22–38)	27 (23–34)	<0.05	ns	<0.05
MR rest				<0.001	0.048	<0.001
0	75 (70.8%)	69 (46.6%)	49 (46.2%)			
1	28 (26.4%)	61 (41.2%)	36 (34%)			
2	3 (2.8%)	17 (11.5%)	14 (13.2%)			
3	0 (0)	1 (0.7%)	7 (6.6%)			

Table 4
Peak stress characteristic of reduced, stable, and dilated LAVI during ESE

Variable	Group 1 Reduced LAVI N = 106	Group 2 Stable LAVI, N = 150	Group 3 Dilated LAVI N = 107	P value reduced vs stable	P value stable vs dilated	P value reduced vs dilated
HR peak (bpm)	130 (116–150)	121 (107–137)	125 (106–140)	<0.05	ns	<0.05
SBP peak (mmHg)	167 (150–180)	160 (145–180)	150 (135–171)	ns	<0.05	<0.05
DBP peak (mmHg)	80 (80–90)	80 (79–94)	80 (70–90)	ns	ns	ns
EF peak	71 (62–77)	68 (60–75)	67 (52–75)	ns	ns	<0.05
WMSI peak	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.13)	ns	ns	ns
E/e' peak	10.8 (8.1–14.2)	11.1 (8.5–14)	13 (9.9–16.6)	ns	<0.05	<0.05
SPAP peak*	37 (25–51)	39 (30–53)	42 (35–55)	ns	ns	ns
TAPSE peak	29 (25–33)	27 (23–31)	27 (22–31)	ns	ns	ns
B lines peak	0.5 (0–2.0)	3.0 (0–5.8)	1.0 (0–4.0)	ns	ns	ns
LVCR	1.71 (1.4–2.47)	1.63 (1.3–2.09)	1.4 (1.06–1.9)	ns	<0.05	<0.05
LAVI peak (ml/m^2)	27 (20–34)	29 (23–37)	47 (37–60)	<0.05	<0.05	<0.05
Δ LAVI	−14.6 (−25.05 −9.07)	0.0 (−3.05–3.11)	16.6 (10.4–29.7)	<0.05	<0.05	<0.05
MR peak				ns	ns	<0.001
0	70 (68.6%)	76 (58%)	43 (41.7%)			
1	25 (24.5%)	38 (29%)	33 (32%)			
2	6 (5.9%)	12 (9.2%)	17 (16.5%)			
3	1 (1.0%)	4 (3.1%)	8 (7.8%)			
4	0 (0%)	1 (0.8%)	2 (1.9%)			

• SPAP peak feasible: Reduced n = 40, stable n = 68, and dilated n = 58.

4.1. Comparison with previous studies

Our findings confirm and expand previous, limited experiences showing the high success rate of LAVI imaging during ESE already documented in chronic coronary syndromes, hypertrophic cardiomyopathy, valvular heart disease, and heart failure.[16]

The atrial volume and function during exercise were examined by Schnell F et al. in group of 45 subjects including normal individuals, endurance athletes, and patients with chronic thromboembolic pulmonary hypertension (CTEPH).[17] The authors observed larger LAVI at rest in athletes (56 ml/m^2) than in controls (40 ml/m^2) and CTEPH (31 ml/m^2), which decreased consistently during exercise. In contrary, the right atrial volume index (RAVI) increased during stress in patients with CTEPH (from 64 to 79 ml/m^2) while decreasing in controls and athletes. The authors hypothesized that an increase of the reservoir function of both atria provides adequate filling for ventricles and the maintenance of cardiac output. In their group reservoir, the function of the left atrium was enhanced mainly by diminishing of minimal LAVI (end-diastolic volume) without significant increasing of maximal LAVI (reflecting a maximal LA volume during the ventricular end systole); nevertheless, in more pathological states, this may require also the increase of maximal LAVI, what probably took place in our small and large dilators. The pathologic character of significant atrial dilation is suggested by Schnell observation concerning RAVI enlargement in patients with CTEPH.

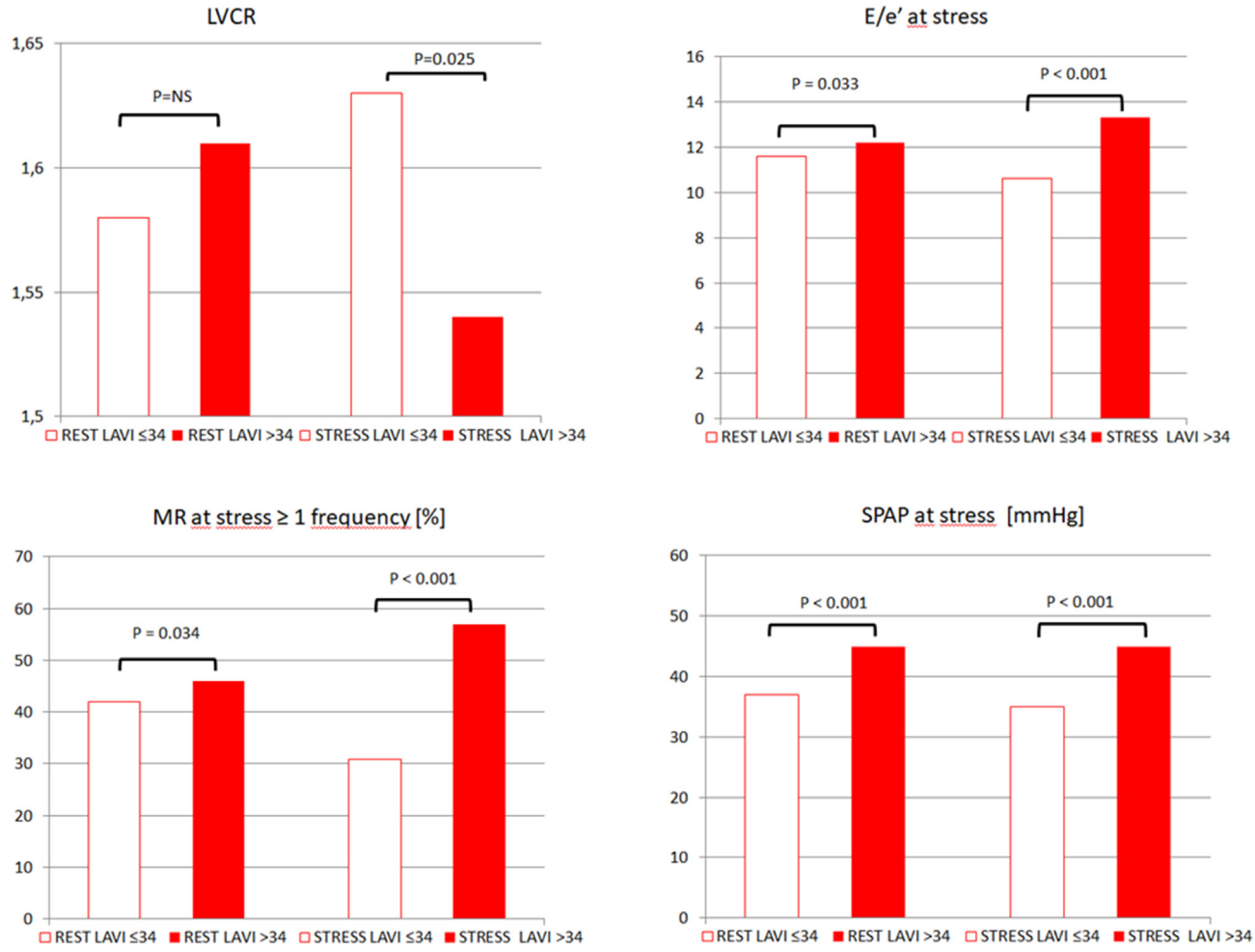

Figure 1. Functional correlates of LAVI at rest and peak ESE. The comparison of the global systolic left ventricular function parameter LVCR (left upper panel), frequency of mitral regurgitation (left lower panel), E/e' (right upper panel), and SPAP values (right lower panel) between groups with normal/mildly enlarged (white bars) and significantly enlarged LAVI (red bars) assessed at rest (left columns in each panel) and at peak stress (right columns). The patients with larger LAVI at stress displayed lower LVCR, higher E/e', SPAP, and MR frequency. Stress LAVI was more closely related to impaired hemodynamics. E/e'—the ratio of maximal velocity of an early wave of mitral inflow (E) to maximal velocity of mitral annulus motion early phase (e'), LAVI—left atrial volume index, LVCR—left ventricular contractility reserve, MR—mitral regurgitation, SPAP—systolic pulmonary artery pressure.

The valuable observation of the mechanism of exercise-related lung congestion in patients with HFpEF has been recently published by Reddy et al.[18] The authors noticed that patients with HFpEF who developed lung congestion during exercise test, confirmed with a B-line appearance, were characterized not only by increased pulmonary capillary wedge pressure but also by increased pulmonary artery and right atrial pressure as well as by indices of deranged right ventricle—pulmonary artery coupling, i.e., lower ratios of TAPSE, FAC (fractional area change), and RV S' to mean pulmonary artery pressure. Nevertheless, in our group, only a small subgroup developed pulmonary congestion during ESE, and we did not observe a significant and consistent impairment of pulmonary pressure and RV function in the LAVI dilators.

We pooled data from semisupine and treadmill ESE which have a different hemodynamic effect and could have influence on volume changes and stress LAV changes to some extent. According to the literature, the bicycle increases the blood pressure significantly but not so much the heart rate compared with the treadmill. However, the final double product is similar.[19] Semisupine exercise increases pulmonary capillary wedge pressure more than upright exercise, and the treadmill increases the end-diastolic volume of the left ventricle more than semisupine exercise in healthy subjects.[20,21] The observational study design did not interfere with the individual choice of the referring physician, which is a matter of personal experience, awareness of the individual patient indications, and local practice. However, the prevalence of LAV dilation, reduction, and stabilization was similar with the both tests used in our population, suggesting their comparable impact on the left atrium.

4.2. Study limitations

Each group had a moderate sample size limiting the statistical strength of subgroup analyses. However, the findings were consistent, suggesting that observed functional correlations act similarly across various cardiovascular conditions.

Concentration on volumetric data limited to LA in its reservoir phase neglected more comprehensive analysis of the LA function, which, however, is especially challenging in time-limited settings of ESE.

We used different exercise modalities, such as a treadmill and supine bike with some difference in type of hemodynamic stress

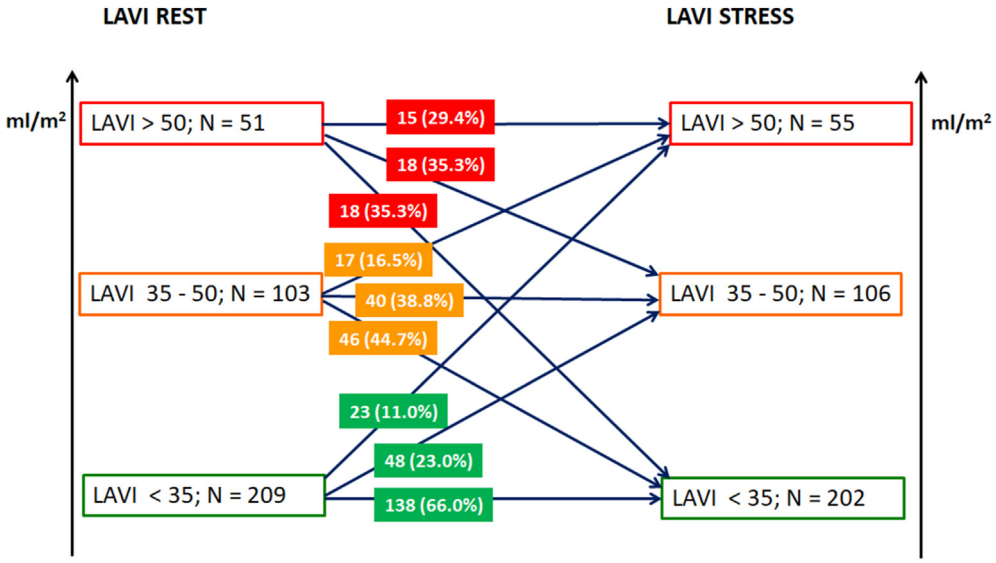

Figure 2. Changes of LAVI during ESE as a function of LAVI at rest. The central panel displays the numbers of patients transferred between categories of normal or mildly (<35 ml/m^2), moderately (35-50 ml/m^2), and severely enlarged (>50 ml/m^2) LAVI. During stress, 170 patients (47%) were reclassified with 88 (24%) increasing their LAVI of at least one grade. About 138 patients from the normal resting LAVI group (66%) did not dilate significantly during ESE. In the group comparison, the median of normal LAVI increased significantly from 25.8 to 28.9 ml/m^2, $P < 0.001$, whereas the largest LAVI decreased from 60.5 to 38.4 ml/m^2, $P < 0.0001$, and intermediate from 40.2 to 36.4 ml/m^2, $P = 0.002$.

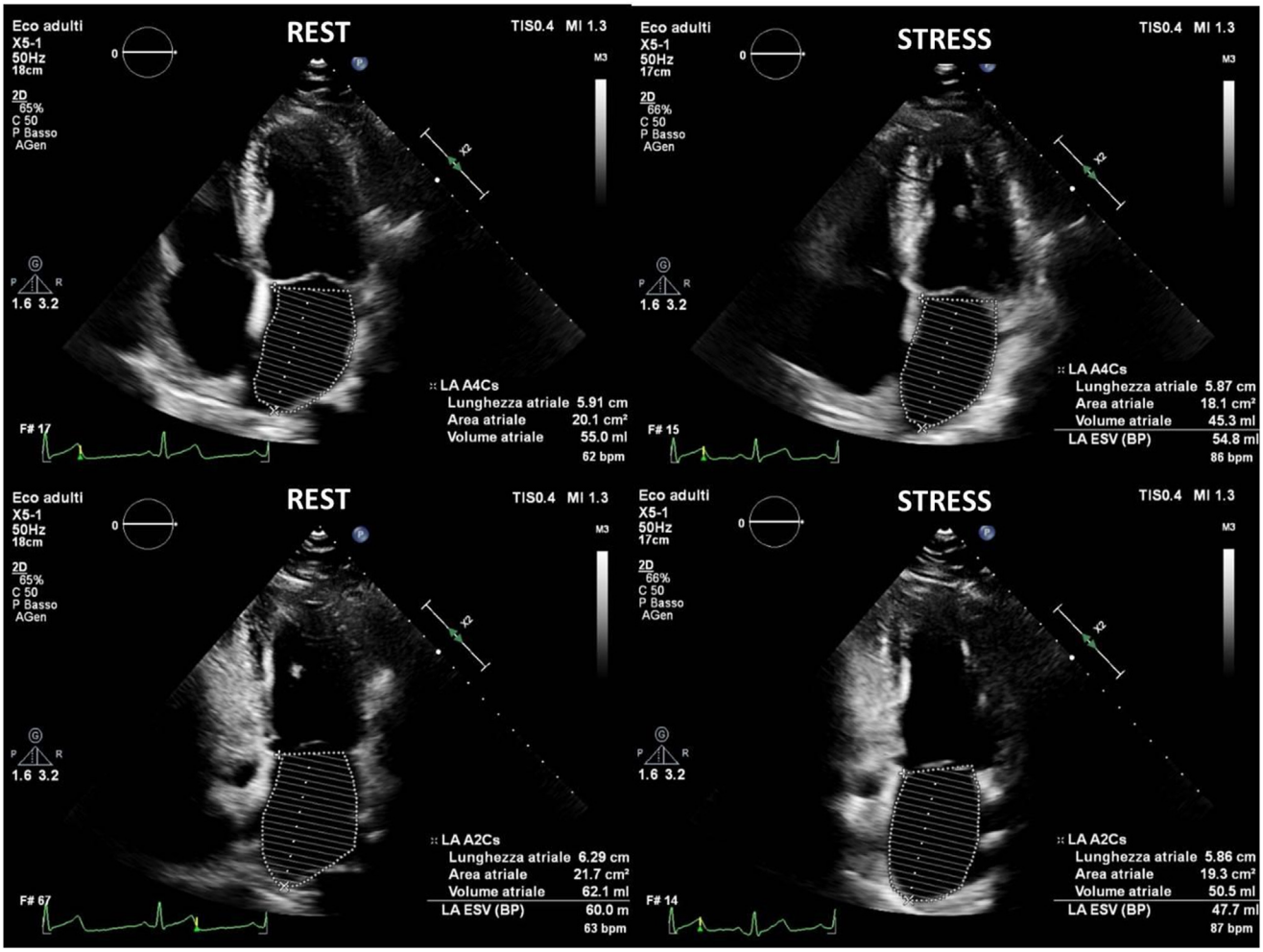

Figure 3. The examples of LAVI measured in 4-chamber and 2-chamber views in a patient showing LAVI reduction during ESE. A patient with BSA 2.2 m^2 and the slight reduction of LAVI (Δ 5 ml/m^2, which is < 6.8 ml/m^2 cutoff value) during ESE: from 27 ml/m^2 to 22 ml/m^2 as calculated for biplane LAVI (given in the Figure).

Table 5
Univariate and multivariate analysis of predictors for ESE-related LAVI dilation

Univariate analysis in whole group				Multivariate analysis in whole group		
Parameter	OR	95% CI	P	OR	95% CI	P
E/e rest >14	3.0	1.8–5.1	<0.001	4.4	1.9–9.9	<0.001
E/e stress >14	2.1	1.3–3.5	0.003			
MR rest > 2nd grade	17.9	2.2–147.3	0.007			
MR stress > 2nd grade	4.1	1.4–11.5	0.008			
LVEF < 50%	2.0	1.2–3.4	0.01	2.9	1.2–6.9	0.01
LVCR < 2	2.1	1.2–3.6	0.01			
B-lines rest >10	15.4	1.8–131	0.012			
B-lines stress >10	3.8	1.3–11.1	0.016			
LAVI rest < 35 ml/m^2	3.1	1.9-5.2	<0.001	2.7	1.2–6.2	0.02

Multivariate analysis in HFpEF				Multivariate analysis in HFrEF			Multivariate analysis in HCM		
Parameter	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
E/e rest >14	na	na	na	na	Na	Na	5.0	1.5-16.3	0.007
E/e stress >14	na	na	na	9.0	2.1–37.5	0.003	na	na	na
LAVI rest < 35 ml/m^2	5.2	1.5–18.2	0.01	na	na	na	9.6	3.9–23.2	<0.001

Table 6
Natural history of LA dysfunction. Comparison between LAVI in group I: normal or mildly increased E/e' both at rest and stress (<12), group II with substantial increase of E/e' during stress only (<12 at rest and ≥12 at peak EXE), and group III with E/e' elevated in rest and stress ≥12. Additionally, group IV with very high E/e' at rest and stress (>15 at both stages) was analyzed showing the extreme dilation of the left atrium during stress

Variable	Group I N = 157	Group II N = 57	Group III N = 98	Group IV N = 41	P value 1 vs 2	P value 2 vs 3	P value 1 vs 3	P value 1 vs 4	P value 2 vs 4	P value 3 vs 4
LAVI rest ml/m^2	31 (23–42)	31 (26–38)	39 (27–48)	40 (31–50)	ns	0.002	<0.001	0.003	0.002	ns
LAVI peak ml/m^2	29 (21–39)	32 (24–39)	39 (32–56)	51 (37–69)	ns	<0.001	<0.001	<0.001	<0.001	0.035
P value rest vs stress	0.034	ns	0.026	<0.001	NA	NA	NA	NA	NA	NA
ESE LAVI change	Reduction	Stabilization	Light dilatation	Large dilatation	NA	NA	NA	NA	NA	NA

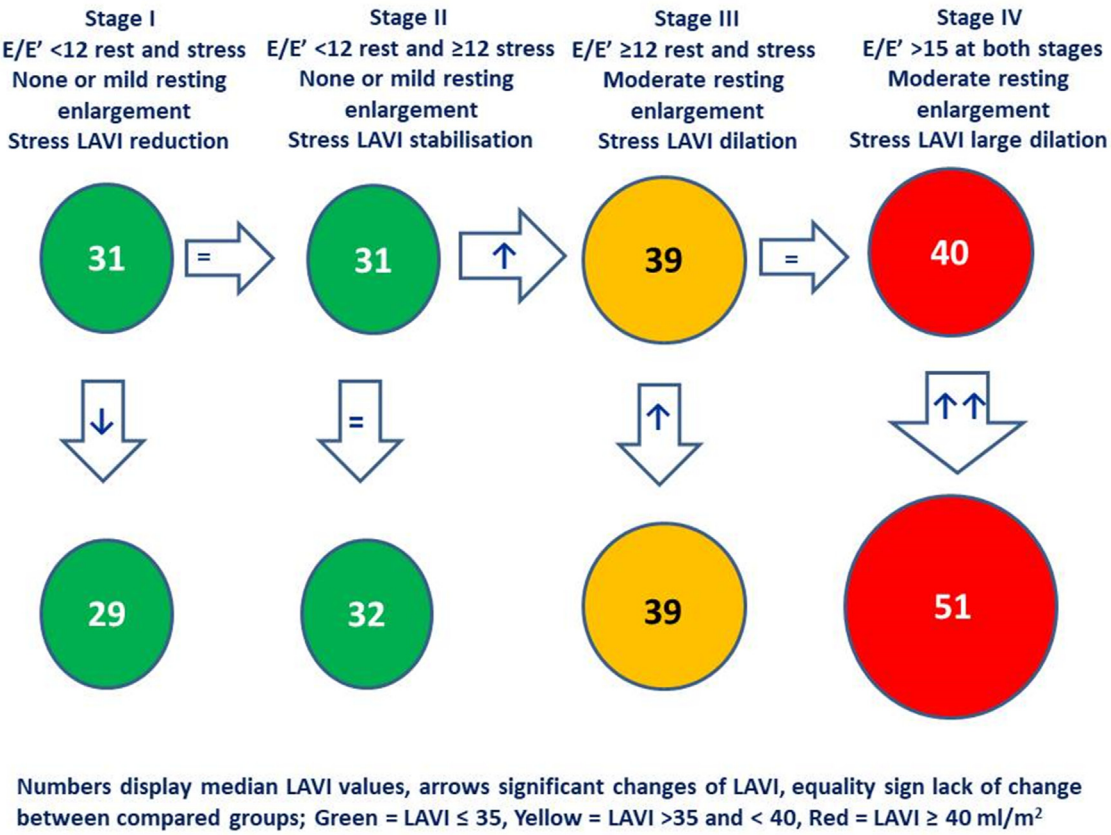

Figure 4. Evolution of LAVI ESE-induced changes in relations to E/e' values at rest and at stress. LAVI seems to compensate the short intervals of elevated E/e' related to exercise only but dilates significantly in more advanced stages, while E/e' is elevated also at rest. E/e'—the ratio of maximal velocity of early wave of mitral inflow (E) to maximal velocity of mitral annulus motion early phase (E'), LAVI—left atrial volume index.

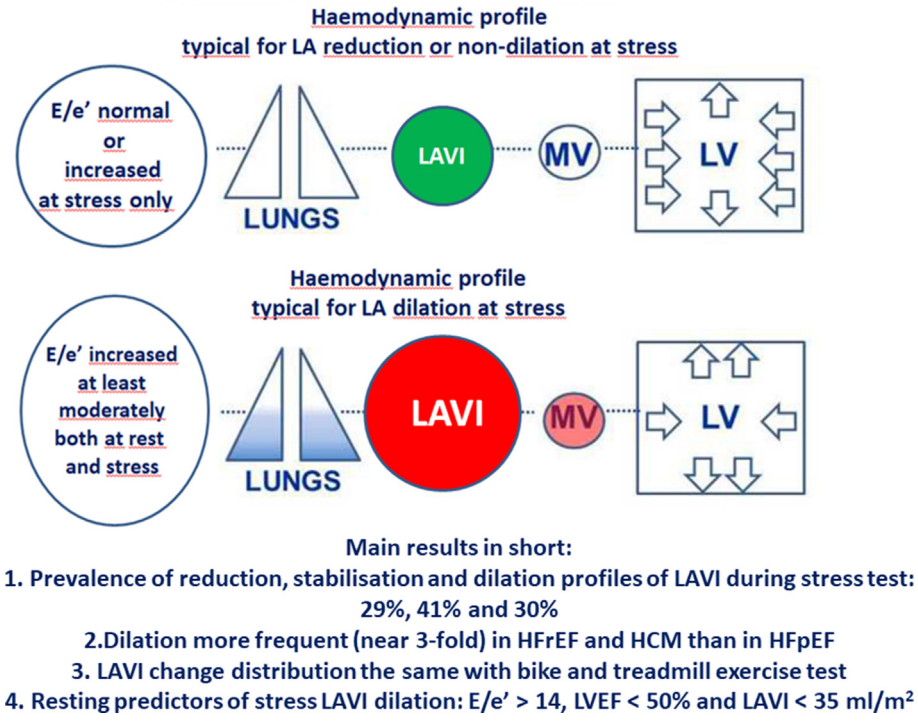

Figure 5. (Graphical abstract) Graphic presentation of pathophysiologic changes of the LV function and circulation's hemodynamics as typical for LAVI reductors or nondilators (upper panel) and dilators (lower panel). The upper panel displays a normal function of the left ventricle (good contractility represented by preserved LVEF or LVCR expressed as triple inward arrows inside the box) as well as nonelevated LV pressure (or its proxy E/e', illustrated with an outward single arrow), normal or elevated only at the stress E/e' ratio (regular circle) and absent B-lines in lungs and MR (clear lungs and mitral valve icons) in the presence of small LA at stress (green LAVI). The opposite situation related to the LAVI dilator pattern (red, increased LAVI) is rendered in the lower panel. E/e'—ratio of early mitral inflow velocity to early mitral annulus motion velocity, LAVI—left atrial volume index, LUNGS—white icon represents the absence of B-lines, partially blue-filled represents water congestion with present B-lines, LV—left ventricle, arrows directed inwardly represent left ventricular contractile reserve (LVCR) or left ventricular ejection fraction (LVEF). MV—mitral valve, white circle represents absent or mild MR, red one—the presence of MR above second grade, MR—mitral regurgitation.

induced, which are, however, both widely accepted for ESE beyond coronary artery diseases.

Despite observed in our study similar prevalence of the reduced, stable, and dilated LAVI pattern in both bicycle and treadmill tests, more detailed, quantitative comparisons of the LAVI reaction to various types of exercise loading in various groups of patients, as well as the dependence from the achieved workload is needed in the future.

Finally, the analysis of clinical outcomes should be advocated in a longitudinal study to understand better the prognostic significance of LAVI changes during ESE.

5. Conclusions

LAVI is a relatively simple parameter that can be obtained with a high success rate in various cardiovascular conditions from HFrEF to HFpEF and HCM and measured at peak stress reflects the functional status more closely than rest values.

The LAVI dilator pattern is associated with more frequent and severe mitral regurgitation, diastolic dysfunction, and pulmonary congestion, all known as adverse predictors of outcomes. With only a minimal increase on analysis time, LAVI can be a further useful adjunct to comprehensive SE also beyond coronary artery disease.

5.1. Competency in medical knowledge

The echocardiographic assessment of LAVI exercise changes and their classification to proposed patterns of reducers, stable LAVI, and dilators provides a novel and integral tool reflecting status and function of both circulations. High feasibility, simplicity, time efficiency, and noninvasiveness of the LAVI assessment supports its wider use in the settings of various ESE and clinical entities.

5.2. Translational outlook

Although widely appreciated in the resting assessment of the left ventricular function, LAVI still requires a further detailed diagnostic and prognostic evaluation as far as its dynamic changes are concerned. This study may be seen as the preliminary confirmation of high feasibility in both kinds of ESE, bike and treadmill based, wide diagnostic potential of the LAVI change assessment in patients with different types of heart failure, as well as the indicator of the underestimation of this patient and operator friendly parameter in the present clinical practice.

Conflict of interest

There is no conflict of interest.

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