Assessment of the effects of frequent ventricular extrasystoles on the left ventricle using speckle tracking echocardiography in apparently normal hearts

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Abstract

Objective: Impairment in left ventricular (LV) function due to excessive ventricular extrasystoles (VESs) occurs during long-time follow-up. Speckle tracking echocardiography (STE) has been shown to be superior to conventional methods for evaluating cardiac functions. We aimed to use STE for early detection of LV dysfunction in patients with apparently normal hearts who have frequent VESs.

Methods: Fifty-five patients with frequent VESs were identified according to the Lown classification (Grade 2; unifocal more than 30 times in 1 h). Subjects aged 22-60 years with frequent VESs that had been detected for at least 1 year were included in the study according to the inclusion criteria. Forty-five subjects with similar demographic characteristics, but without VESs, were included as the control group. All participants were evaluated by STE.

Results: Fifty-five patients with frequent VESs (mean age 47 years, range 22-60 years; 42.2% male) and 45 control subjects (mean age 46 years, range 22–60 years; 37.8% male) were enrolled in the study. Global LV longitudinal strain (GLS) was decreased in patients with frequent VESs (-18.41±3.37 and -21.82±2.43; p<0.001). In addition, global LV circumferential strain was decreased in patients with frequent VESs (-16.83±6.06, -20.51±6.02; p<0.001). The frequency and exposure time of VESs were negatively correlated with GLS (r=-0.398, p<0.001; r=-0.191, p=0.001, respectively).

Conclusion: STE revealed that LV functions were decreased in patients with VESs. This deterioration increased with the frequency and exposure time of VESs. Impairment of LV function due to excessive VESs occurs during long-time follow-up. STE may be used for early detection of LV dysfunction. *(Anatol J Cardiol 2016; 16: 48-54)*

Keywords: ventricular extrasystole, speckle tracking echocardiography, cardiomyopathy

Introduction

The clinical significance of ventricular extrasystoles (VESs) in patients without structural cardiovascular disease is controversial. VESs have previously been considered a benign condition (1-3). Contrary to these previous findings, later studies showed a prognostic significance of frequent VESs. Recent clinical trials have reported that frequent VESs cause left atrial (LA) and left ventricular (LV) dysfunction (4-12). Conventional assessment of LV function, which is based on visual interpretation, is subjective and experience-dependent. Even slightly reduced LV ejection fraction (LVEF) and slightly increased LV size were still within normal limits in these studies (4-10). Thus, it can be difficult to decide the treatment time. Speckle tracking echocardiography (STE) is a new method that assesses LV function semi automatically, with a simplified operational procedure and high reproducibility; it has been shown to be superior to conventional methods to evaluate cardiac functions and predict cardiovascular outcomes (13, 14). We aimed to investigate the effects of VESs on LV function and to use STE for early detection of LV dysfunction in patients with apparently normal hearts who have frequent VESs. This is the first study to assess the effects of frequent VESs on LV function using STE.

Methods

Study population

The study was approved by the Çanakkale Onsekiz Mart University Ethics Committee and conformed to the principles outlined in the Declaration of Helsinki. All subjects participating in the study gave informed consent. In this prospective study, 55 consecutive patients with frequent VESs that had been detected for at least 1 year were included in the study. Patients with fre-

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quent VESs (Grade 2; unifocal more than 30 times in 1 h, according to the Lown classification) were identified, and individuals aged 18-60 years were enrolled in the study. Volunteers (22-60 years old) with similar demographic characteristics but without VESs were included as the control group. All participants were monitored with ambulatory Holter ECG in terms of VESs and the average daily number of VESs was determined. The subjects were evaluated to determine whether they met the inclusion criteria for the study in the outpatient clinic. All participants were initially evaluated by a standard echocardiographic examination. Exclusion criteria included patients with LV hypertrophy, LV ejection fraction <55% or right ventricular fractional area change <35%, and valvular heart disease. Additionally, patients with grade 2-3 hypertension (15), those with uncontrolled hypertension, those with diabetics using insulin, and those with a history of atrial fibrillation or cardiomyopathies were also excluded from this study. Patients with normal coronary arteries (n=12), as determined by coronary angiography, or with normal myocardial perfusion scintigraphy (n=8) within the past year were enrolled in the study. A treadmill exercise test was performed on other participants to rule out coronary artery disease. Patients with chronic systemic or inflammatory diseases and any form of malignancy were also excluded from this study. Beta-blockers and calcium channel blockers were stopped 48 h before enrollment into the study. Patients using amiodarone were excluded from the study because of the long duration of action.

Standard echocardiography

Echocardiographic studies were performed using a high-quality echocardiography device (Vivid 7, GE, USA). Standard echocardiographic examinations were performed by two cardiologists. Our echocardiography device was calibrated for use in international studies by independent organizations (certificate no: B14091148). Measurements of LV and LA dimensions were made in accordance with the current European Society of Echocardiography recommendations (16). LA volume index (LAVI) and LVEF were measured using the modified biplane Simpson's rule. The ratio between peak early (E) and late (A) diastolic LV filling velocities and E wave deceleration time was determined by standard Doppler imaging. The timings of mitral and aortic valve opening and closing were defined by a pulsed-wave Doppler tracing of the mitral inflow and LV outflow. Lateral wall and septum tissue Doppler parameters (E′ and A′) were measured. E/E′ was calculated manually. Particular attention was given to limiting myocardial tissue and extracardiac structures, providing sufficient reliable data to obtain a gray-scale image.

Speckle tracking

Apical four, apical long-axis, two-chamber, and parasternal short-axis images were acquired using conventional two-dimensional gray-scale echocardiography for speckle tracking evaluation; these were performed during a breath hold with a stable ECG recording. Speckle tracking evaluation was performed by the same cardiologist. Three consecutive heartbeats were recorded and averaged. If VESs were frequent, LV strain measurements were performed after two beats from the VES. The frame rate was adjusted to between 60 and 120 frames per second. We have used the automatic function imaging method. The regions of interest were manually outlined by marking the endocardial borders at the mitral annulus level and at the apex on each digital loop; the epicardial surface was generated by the software (EchoPac, version 7.0.1 GE, USA) so that the region of interest (ROI) was created (Fig. 1). The ROI was corrected manually, if necessary. After any manual adjustment, ROI was divided into six segments. Each segment was scored automatically by the software according to the image quality. Whether the tracking quality for each segment could be considered acceptable was determined by the software. The peak systolic strain values in a 17-segment LV model were used in the present study. End-systole was defined as aortic valve closure in the apical long-axis view. The results for all three planes were then combined in a single bulls-eye summary that provided the global longitudinal strain (GLS) (Fig. 2). Global circumferential strain (GCS) was measured in the parasternal short-axis view.

Ventricular ectopic beats

The origin of the VESs was analyzed according to the ECG criteria. VESs with left bundle branch block (LBBB) morphology, inferior axis, and V3 transversion were considered to be of right ventricular outflow tract (RVOT) origin. VESs with right bundle branch block morphology, inferior axis, and V3 transversion were considered to be of left ventricular outflow tract (LVOT) origin. VESs with LBBB morphology, superior axis, and V3 transversion were considered to be of right ventricular (RV) apex origin.

Statistical analysis

All analyses were performed using the statistical software SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA). Quantitative variables were expressed as a mean ± SD or median (minimum–maximum) and qualitative variables were expressed as a percent (%). All measurements were evaluated with the Kolmogorov-Smirnov test for normality. Comparison of parametric values between two groups was performed using the Mann-Whitney U test or Student *t*-test. Categorical variables were compared by the likelihood ratio χ^2 test or Fisher's exact test. Correlation analysis was performed with the Spearman test. A $p<0.05$ was considered statistically significant.

Results

There were 55 patients with frequent VESs and 45 controls in our study. The general characteristics were similar between the groups of the study population (Table 1). The daily average number of VESs was 2535 beats per day (range 706-8434), as determined by the 24-h ambulatory ECG recording. The average duration of VES exposure was 3.4 years. VES characteristics from the

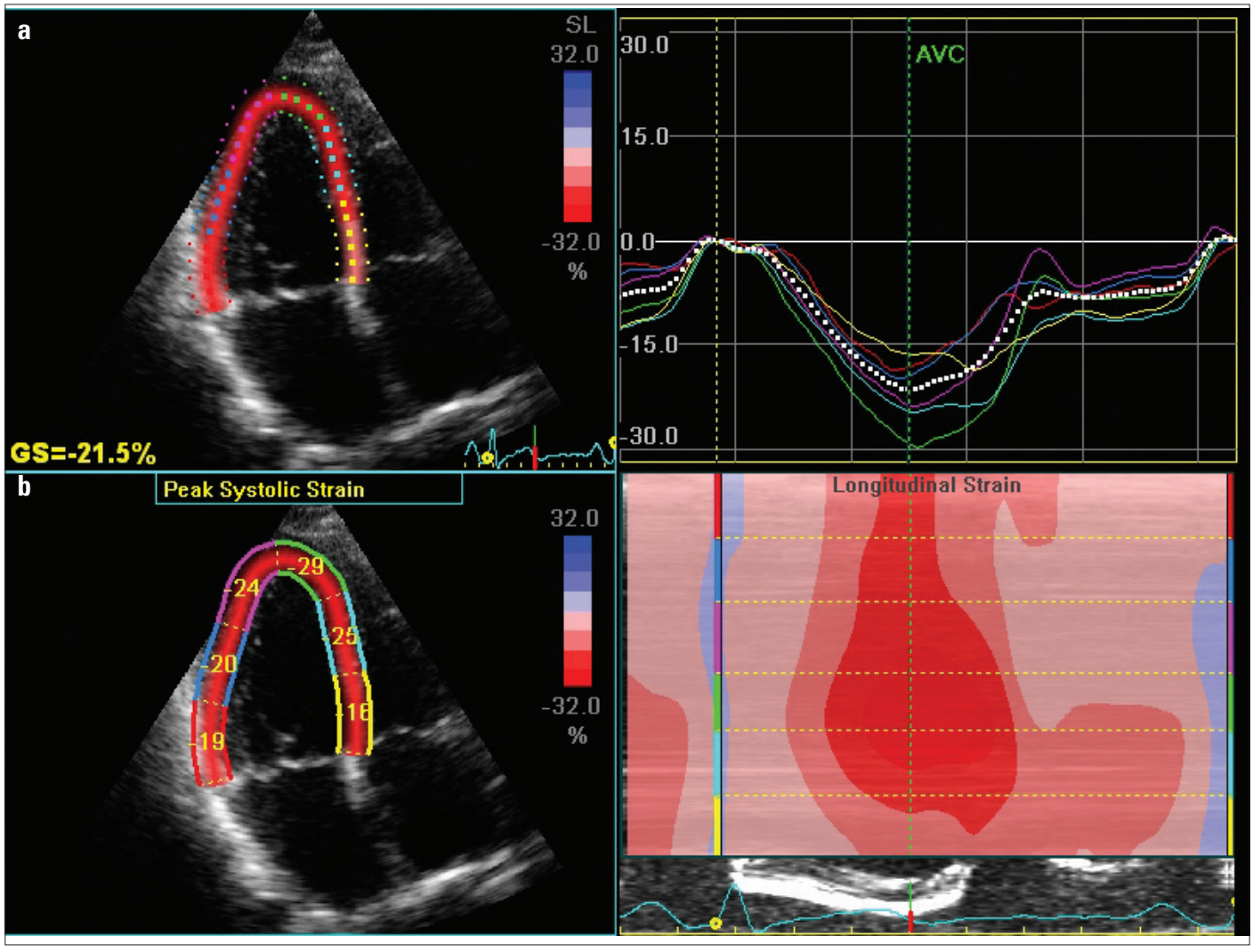

Figure 1. a, b. Assessment of LV function using STE

55 patients were analyzed according to the ECG criteria. The VESs were of RVOT origin in majority of our patients (84.4%). The VESs were of LVOT origin in 11.1% patients. The VESs were of RV apex origin in 4.4% patients. Echocardiography parameters were compared with the control group. In particular, LAVI, LV end-diastolic diameter (LVEDd), and LV end-systolic diameter (LVESd) were higher in the VESs group (p=0.001, p=0.022, and p<0.001 respectively). Other echocardiography and Doppler parameters were similar between both groups (Table 2). The average frame rate of both groups was 104 (80–120) in speckle tracking analysis. GLS and GCS were significantly lower in the VESs group (-18.41±3.37 and -21.82±2.43, p<0.001 vs. -16.83±6.06 and -20.51±6.02, p<0.001, respectively) as shown in Table 3. In the correlation analysis, GLS was negatively correlated with the number and exposure time of VESs (r=-0.398, p<0.001 and r=-0.191, p=0.001, respectively). Additionally, the frequency of VESs was positively correlated with LAVI and LVEDd (r=0.349, p=0.001 and r=+0.276, p=0.010, respectively) and inter- and intra-observer variability coefficients of measurements ranged between 2.8% and 3.4%.

Discussion

In this representative study, we demonstrated that GLS and GCS of the left ventricle were decreased in patients with frequent VESs and LV dysfunction was correlated with the frequency of VESs. Enlargement of the left ventricle due to frequent VESs has been shown on conventional echocardiography (9, 10). Furthermore, improvement in the left ventricle size after VES ablation has been shown in several follow-up studies (17, 18). Similar to previous studies conducted using conventional methods (11, 12), we found the LVEDd, LVESd, and LAVI were significantly increased in patients with frequent VESs compared with the controls. However, even a slightly increased LV size, it was still within normal limits in our study and in previous studies (11, 12), In addition to these findings, we showed decreases in LV function using STE. From this perspective, STE has shown altered LV contractility, whereas LVEF remains preserved (17-20). Recent studies reported that the frequency of VES was a predictor of LV dysfunction during long-term follow-up examina-

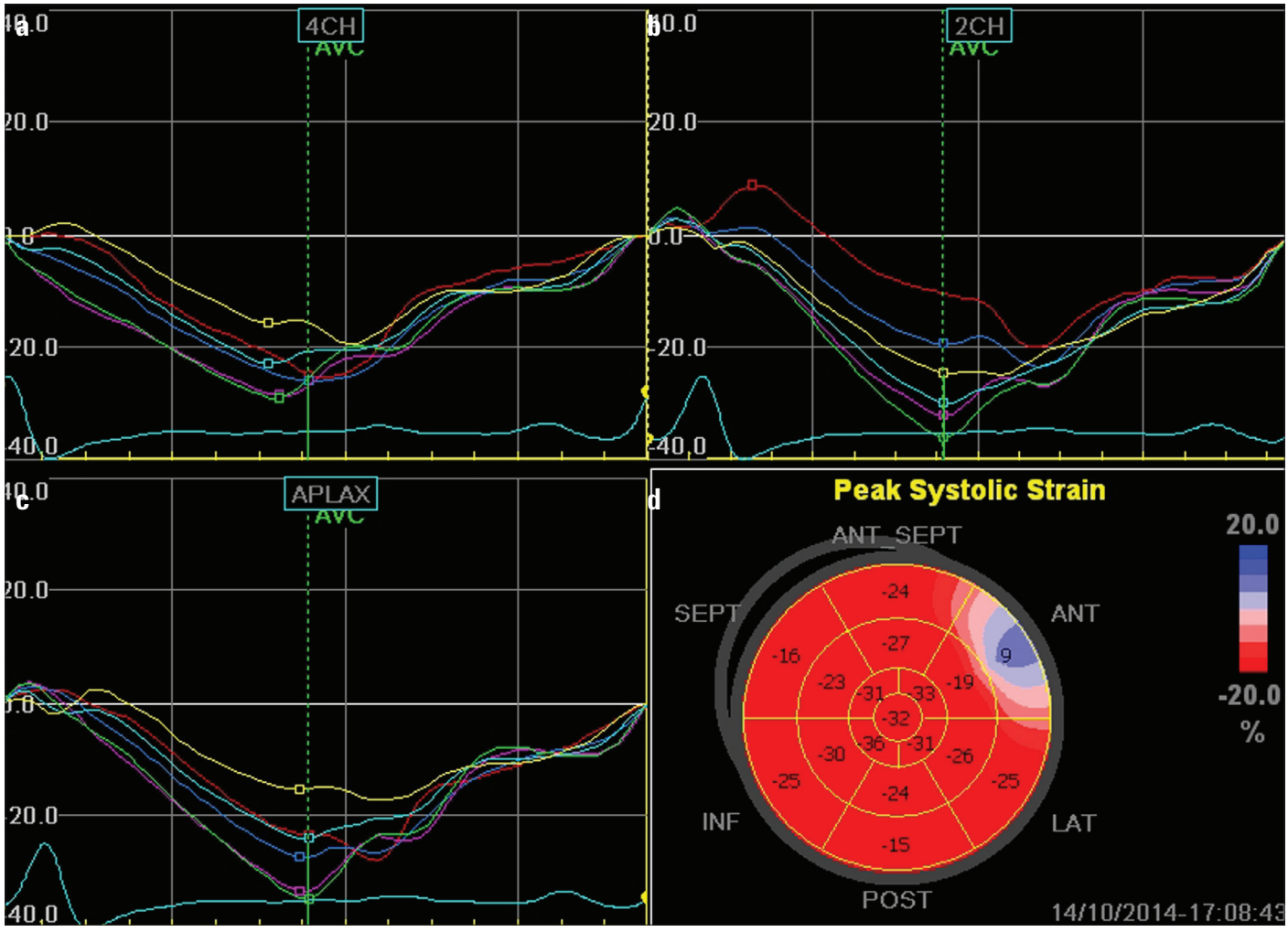

Figure 2. a-d. Measurement of GLS and bulls-eye image of LV

tions (11). Impairment of LVEF due to excessive VES occurs in long-time follow-up (11, 12). These findings suggest that STE detects the effects of VESs on LV function early.

Interventricular and intraventricular synchrony is impaired in the presence of VES because of their prematurity and altered ventricular activation, which may cause LV dysfunction. Thus, LV hemodynamics may be negatively influenced, causing impaired ventricular systolic performance (21). It is not clear which mechanisms cause LV dysfunction in patients with frequent VES; however, several mechanisms have been suggested to explain deterioration in LV systolic functions. A few studies have proposed that tachycardia-induced cardiomyopathy (4, 8, 22-24) may be involved, whereas others suggest that bradycardia-induced cardiomyopathy is involved because each VES could not produce an effective cardiac output (3, 6, 17). In addition to the systolic dysfunction, diastolic dysfunction may also occur because of impaired relaxation, which may further worsen LV functions (20). Some authors asserted that ventricular dyssynchrony and increased oxygen consumption may be possible pathogenic mechanisms (7). Alternatively, one theory suggests that an RVOT VES reverses the direction of LV contraction (25, 26). Also, adverse effects of VESs on LV function were showed with induced ectopic beats in animal experiments (27-32). Furthermore, in experimental studies with dogs, there were clear increases in pressure in both ventricular intracardiac pressure measurements performed with catheterization during VES (2, 3). Likewise, we found that LAVI was higher in the VESs group than in controls. A recent study showed that LA functions are affected by VESs adversely because of intraventricular dyssynchrony (9). We have also shown that GLS and GCS of LV were disrupted after each VES (Fig. 3) and that the degree of deterioration was related to the frequency of VESs. There are no obvious cut-off points about how much the number of VESs or how long the exposure of the VESs for development of cardiomyopathy (5, 9, 12, 33). Decresed LV function occurred for a long period in clinical trials on humans (11), whereas it was identified in a short time in experimental studies with canine (30, 31).

STE is tool used to support clinical decision-making by assessing LV function semiautomatically with a simplified operational procedure and high reproducibility (34). Additionally, STE has low intra- and inter-observer variability as well as the advantages that it is not angle dependent and it is not affected

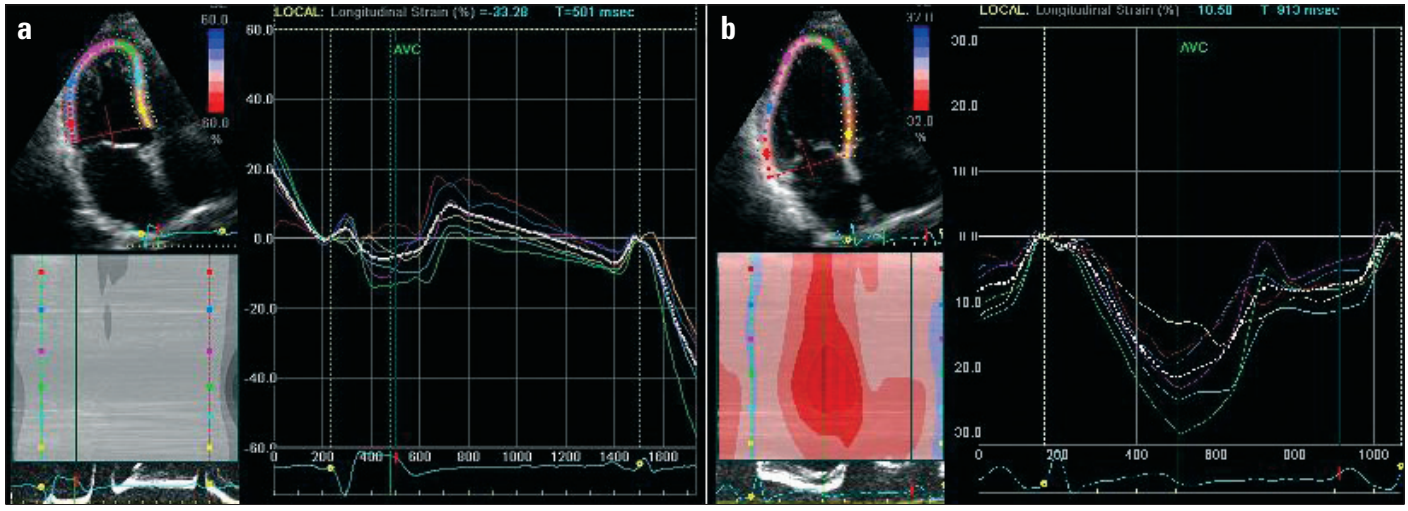

Figure 3. a, b. Deteriorated LV strain after VES (a), normal LV strain after normal beat in the same subject (b)

Table 1. General characteristics of the study population

Variables	VESs group (n=55)	Control group (n=45)	*P*
Mean age, years	47 (22-60)	46 (22-60)	0.880
Male gender, % n	42.2 (19)	37.8 (17)	0.667
BMI, kg/m^2	27.9 (16.8-43)	28.4±4.0	0.824
BSA, m^2	1.95 (1.4-2.5)	1.90 (1.5-2.3)	0.556
Hypertension, % n	18.1 (10)	16 (8)	0.598
Diabetes mellitus, % n	12.7 (7)	10 (5)	0.535
Smoking, % n	18.1 (10)	18 (9)	0.788
AHR, per minute, per minute	74 (50-90)	78 (51-90)	0.103
SBP, mm Hg	126±8.6	124±9.2	0.866
DBP, mm Hg pressure, mm Hg	78±7.5	77±8.3	0.756
AED of VES, years duration of VES, years	3.5	0	<0.001
Drugs (%)			
ACEI	17.2	17.89	0.898
ARB	4.4	6.1	0.438
CCB	15.6	8.9	0.334
BB	15.6	11.1	0.535
HTCZ	13.3	15.6	0.764
VEBs characteristics of the study population			
RVOT	84.4	0	<0.001
LVOT	4.4	0	<0.001
RV apex	11.1	0	<0.001

ACEI - angiotensin converting enzyme inhibitor; AED- averaged exposure duration; AHR- averaged heart rate; ARB - angiotensin receptor blocker; BMI - body mass index; BSA - body surface area; BB - beta-blockers; CCB - calcium channel blocker; DBP- diastolic blood pressure; HCTZ - hydrochlorothiazide; VESs - ventricular extrasystoles; RVOT - right ventricular outflow tract; LVOT - left ventricular outflow tract; RV - right ventricle. SBP- systolic blood pressure. Mann-Whitney U test or Student *t*-test.

Table 2. Echocardiographic and speckle tracking parameters of the study population

Variables	VESs group (n=55)	Control group (n=45)	*P*
LVEDd, mm	46.47±4.3	45.3±3.7	0.322
LVESd, mm	30.6 (22-40)	b28.02 (21-45)	0.021
LVEF, %	63 (55-68)	65 (60-72)	0.102
LVSWd, mm	7.4 (5-9)	7.5 (6-11)	0.650
LWPWd, mm	8 (5-10)	8 (5-11)	0.358
LVMI, g/m^2	79.9 (69-94)	79.6 (73-95)	0.353
LAVI, mL/m^2	29 (17-57)	24 (10.9-54)	0.001
Mitral E, cm/s	0.83±0.14	0.81±0.13	0.700
Mitral A, cm/s	0.76 (0.48-1.0)	0.77 (0.54-1.04)	0.320
EDT, ms	198.92±34.11	190.02±33.17	0.122
Mitral E/A ratio	1.13 (0.79-1.56)	1.12 (0.69-1.69)	0.459
Septal E′, cm/s	0.11 (0.07-0.19)	0.11 (0.05-0.18)	0.256
Septal A′, cm/s	0.10 (0.06-0.15)	0.10 (0.08-0.14)	0.507
Lateral E′, cm/s	0.13±0.03	0.12±0.02	0.493
Lateral A′, cm/s	0.11 (0.07-0.16)	0.12 (0.07-0.15)	0.471
E/E′ ratio	7.54±1.53	7.25±1.51	0.421
Strain parameters			
GLS, %	-18.41±3.37	-21.82±2.43	<0.001
GCS, %	-16.83±6.06	-20.51±6.02	<0.001

EDT - Mitral E deceleration time; GLS - global longitudinal strain; GCS - global circumferential strain; LAVI - left atrial volume index; LVEDd - left ventricular end-diastolic diameter; LVESd - left ventricular end-systolic diameter; LVEF - left ventricular ejection fraction; LVSWd - left ventricular septal wall diameter; LWPWd - left ventricular posterior wall diameter; LVMI - left ventricular mass index. Mann–Whitney U test or Student *t*-test.

by tethering and LV translation motion (35, 36). Moreover, a recent study with a 5-year follow-up test showed that GLS is a superior predictor of cardiovascular outcome compared with conventional methods, including LVEF or the wall motion score

Table 3. Correlations between frequency of VESs with strain and echocardiographic parameters

Variables	r	*P*
GLS	-0.398	<0.001
LAVI	0.349	0.001
LVEDd	0.276	0.010

GLS - global longitudinal strain; LAVI - left atrial volume index; LVEDd - left ventricular end-diastolic diameter. Spearman test

index, and it may become the optimal method for evaluating global LV systolic function (37). A cut-off value to predict cardiovascular outcomes or LV dysfunction is not clear yet (38). GLS was assessed by monitoring various cardiovascular conditions and different cut-off values were determined to predict cardiovascular outcomes. However, recent researches have reported that early measurements with STE in cardiovascular disease could be used as a risk stratification tool for added monitoring (39-41).

Study limitations

Our study population was limited in numbers because of the strict inclusion and exclusion criteria. This study was a cross-sectional study and the results illustrate the relationship. The trend of VESs can be quite variable. Simultaneous STE imaging with long-term ECG records may better determine the effects of VESs. In addition to other major limitations of our study is that the exact duration of exposure to VESs was not known, so we have specified the exposure time of VESs, at least, as 1 year. There is clearly a need for a prospective follow-up study.

Conclusion

We found that LV function was disrupted after each VES and the degree of deterioration was related to the frequency of VESs. Long-term follow-up studies are warranted to clarify the role of STE in predicting LV dysfunction and clinical implications of VESs in these patients. We suggest that patients with frequent VESs should be closely followed for determination of LV dysfunction and that STE provides useful information about LV function in patients with frequent VESs but otherwise normal hearts. STE is superior to the conventional method. Additionally, speckle tracking is more sensitive and more objective due to semi automatical method. Moreover, STE may be used for early detection LV dysfunction in these subjects. The duration of exposure time and cut-off values of VESs that may cause LV dysfunction should be investigated in a prospective manner.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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