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ASSOCIATIONS OF THE LEFT VENTRICLE MYOCARDIAL DEFORMATION PARAMETRS WITH CARDIOVASCULAR RISK IN PATIENTS WITH AN IMPLANTED CARDIOVERTER-DEFIBRILLATOR

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Aim. To study the impact of left ventricle (LV) deformation parameters by the two-dimensional strain method to assess the intended use of cardioverter defibrillator implantation for primary prevention of sudden cardiac death.

Methods. The study included 133 patients with congestive heart failure NYHA 3-4 functional class with a LV ejection fraction ≤35%, taking optimal drug therapy. The speckle-tracking echocardiography with the estimation of LV deformation indicators (segmental strains, global longitudinal and circular strain [GLS and GCS, respectively]) was carried out, after which the implantation of defibrillator for the purpose of primary prevention of sudden death was performed. The patients enrolled in the study were observed prospectively for two years after the operation (visits to the clinic after 3, 6, 12, 18, 24 months) for the registration of first-time ventricular tachyarrhythmias (VT) paroxysms and assessment of one-year cardiovascular mortality.

Results. The arrhythmic endpoint appeared in 27 patients (20%), 19 patients (14%) died due to acute decompensation of heart failure. Comparative analysis of the studied parameters of LV deformation did not reveal statistically significant differences in the groups of survivors and deceased patients. Patients with VT had the worst deformation characteristics. It was found that at absolute values of GLS<6% the risk of the first VT manifestation during the observation period increased almost threefold (odds ratio (OR)=2.59; 95% confidence interval (CI): 1.07-6.26; p=0.031). The second independent predictor of the arrhythmic point was the longitudinal strain of the anterior wall (OR=1.28; 95%CI: 1.14-1.45; p=0.0001 for univariate analysis and OR=1.55; 95%CI: 1.18-2.04; p=0.002 for multivariate analysis). Based on the multifactor analysis, which included indicators of myocardial deformation, age, sex, and ischemic heart disease, predictive model was obtained to predict VT with 71% sensitivity and 97% specificity. The area under the curve was 0.916 (95%CI: 0.850-0.981; p=0.0001).

Conclusion. LV deformation parameters do not help to predict cardiovascular mortality, but may be useful in stratification of VT risk. To achieve this GLS value as well as the segmental map of regional strains can be used.

Key words: chronic heart failure; myocardial deformation; left ventricle; cardioverter defibrillator; ventricular tachyarrhythmias.

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There is a considerable interest in the investigation of chronic heart failure (CHF) due to its high morbidity, which is linked to a substantial percentage of disability and mortality [1]. Undoubtedly, there have been significant advances in recent years in the diagnosis and treatment of the syndrome, attributed to the discovery of new classes of drugs [2] and the advent of breakthrough interventional technologies [3]. For instance, the widespread implantation of cardioverter-defibrillators (ICDs) has markedly decreased the occurrence of sudden cardiac death (SCD), which represents one of the terminal outcomes in the unfavorable progression of CHF [4]. However, according to expert consensus, the existing system for selecting candidates for ICD implantation for primary prevention of SCD is deemed ineffective [5]. Left ventricular ejection fraction (LVEF) ≤35% has been identified as a factor associated with patients at high risk for ventricular tachyarrhythmias (VTs), as well as patients with minimal likelihood of such events [6]. The system for determining contraindications to ICD implantation, which necessitates the clinician to make a prognostic decision about the probable life expectancy of a candidate for the procedure, appears to be imperfect [7]. Therefore, the current situation necessitates the development and implementation of new prognostic systems capable of simultaneously addressing two tasks: stratifying the risk of VT and determining the probability of cardiovascular death.

The initiation of these endpoints represents a manifestation of a complex interplay of local and systemic reactions in response to chronic heart failure triggers, leading to profound remodeling of the extracellular matrix of the heart [8]. It is reasonable to assume that the evaluation of this remodeling process could be valuable in the risk stratification of chronic heart failure. Therefore, M.H. Nikoo and colleagues concluded that myocardial deformation indices obtained through speckle-tracking echocardiography (echocardiography) can serve as predictors of ventricular tachycardia (VT) in patients with CHF with reduced LVEF [9]. Strain indices have been shown to correlate with electroanatomical mapping findings indicating the presence of scar fields responsible for the initiation and maintenance of VT [10]. J.J.Park et al., having measured global longitudinal strain (GLS) in 4172 patients with acute heart failure, demonstrated that an increase in the absolute value of this parameter for every 1% reduces the probability of death due to acute decompensated heart failure (ADHF) by 5% ($p<0.001$) [11]. The relative small number and clinical heterogeneity of participants in most such studies emphasize the demand for this area of scientific research.

The aim of the present study was to investigate LV myocardial deformation indices, as determined by the two-dimensional Strain method, to assess the perceived benefit of ICD implantation for primary prevention of SCD.

METHODS

Patient selection

This study was performed in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. The study design was approved by the local ethical committee (Minutes No. 3 of the Local Ethic Committee meeting dated 30.12.2021g), submitted to the public register clinicaltrials.gov (NCT05539898). All patients undergoing observation signed informed consent to participate in the study.

Patient recruitment was conducted between 2018 and 2021. The study included patients with CHF NYHA 3-4 functional class with LVEF ≤35% and optimal drug therapy (relevant at the time of inclusion in the study) for at least the last three months, who were planned to undergo implantation of a cardioverter-defibrillator for primary prevention of SCD.

Patients with hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, valvular heart disease and verified hereditary canalopathies were excluded from the study. The exclusion criterion also included indications for cardiac surgery (revascularization, correction of valve insufficiency) and the presence of severe heart rhythm disorders manifesting during hospitalization.

After screening for inclusion/exclusion criteria, 133 patients who underwent ICD implantation as a means of primary prevention of SCD were included in the study. In the presence of complete left bundle branch blockade or QRS complex duration ≥150 ms on ECG, ICD with cardiac resynchronization therapy (CRT-D) function was implanted in 78 patients (59%), the rest of patients were implanted with dual-chamber ICD.

Analyzing an echocardiogram

Speckle-tracking echocardiography (Echo) was performed in all patients before ICD implantation under normosystolic conditions using an expert-class EPIQ 5 ultrasound device (Philips, the Netherlands). The mandatory condition was the presence of sinus rhythm at the time of the study. Synchronized recording with electrocardiogram was used to determine the phases of the cardiac cycle. During the examination of patients, a recording was made on the hard disk of the ultrasound machine for subsequent viewing and frame-by-frame analysis of various parameters of the patient's working heart in real time (performed by two experts). To analyze LV mechanics, kinopleths of 3 cardiac cycles were recorded at a frame rate of at least 60 frames per second from the parasternal position on the short axis at the level of the mitral valve and apex. LV mechanics was then assessed with speckle tracking imaging ultrasound technology using an analysis program (EchoPAC, GE Healthcare, USA). Two-dimensional LV images recorded from the parasternal position along the short axis

Table 1.

Clinical and demographic characteristics of the patients included in the study

Clinical indicator	All patients (n=133)
Age, years	55 (50; 61)
Male gender, n (%)	78 (59)
Postinfarction cardiosclerosis, n (%)	55 (41)
Arterial hypertension, n (%)	54 (41)
Diabetes mellitus, n (%)	15 (11)
Obesity, n (%)	36 (27)
Stroke, n (%)	6 (5)
Chronic kidney disease, n (%)	48 (36)
Anaemia, n (%)	6 (5)
AF (paroxysmal/persistent form), n (%)	25 (19)
Left ventricular ejection fraction (Simpson), %	29 (25; 33)
Beta-adrenoblockers, n (%)	133 (100)
iACE/ARA II, n (%)	90 (68)
ARNI, n (%)	43 (32)
Mineralocorticoid antagonists, n (%)	119 (89)
Loop diuretics, n (%)	129 (97)
Sotalol, n (%)	21 (16)
Amiodarone, n (%)	43 (32)
Surgical revascularization in the history, n (%)	67 (50)

Notes: AF - atrial fibrillation; ACEi - angiotensin-converting enzyme inhibitors, ARA II - angiotensin II receptor antagonists, ARNI - angiotensin receptor and neprilysin inhibitors. Drug therapy relevant at the time of inclusion in the study is presented. Sotalol was prescribed for antiarrhythmic purpose in the presence of contraindications to amiodarone.

of the LV at the level of the mitral valve and at the level of the apex were automatically «frozen» at the end of systole, and the endocardial borders were delineated.

Postoperative follow-up

The patients included in the study received optimal drug therapy for CHF and were followed for 2 years by cardiologists of the center where implantation was performed (clinic visits after 3, 6, 12, 18, 24 months). Clinical status was assessed and ICD testing was performed during the clinic visits. The ICD programming protocol was described by the authors previously [12]. In case of decompensation of cardiac activity, the patient was unscheduled contact with the research physician, correction of therapy and assessment of clinical status was carried out jointly with cardiologists at the place of residence. Information on the occurrence of the endpoint was obtained from medical records and interviews with relatives, and data from remote ICD monitoring systems were used.

The arrhythmic end point was recorded: a sustained VT paroxysm (duration ≥30 s) detected in the «monitor» zone of VT or a VT paroxysm that required the use of electrotherapy (antitachycardic stimulation or shock therapy) for the first time during the two-year follow-up. The second endpoint of the study was one-year cardiovascular mortality, the primary cause of which was the development of ODSN.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 26 program. Accumulation, correction, systematization of the initial information and visualization of the obtained results were carried out in Microsoft Office Excel 2010 spreadsheets. The study materials were subjected to statistical processing using parametric and nonparametric analysis methods. Description and comparison of quantitative indicators was performed taking into account the distribution, the conformity of which to normal was assessed using the Kolmogorov-Smirnov criterion. When normal distribution was confirmed, data were described using arithmetic mean (M) and standard deviation (SD). Comparison was performed using Student's t-criterion. If the distribution was not normal, the median (Me), lower and upper quartiles (Q1; Q3) were indicated, and the values were compared using the Mann-Whitney test. Comparisons of indicators measured in nominal scale were made using Pearson's χ^2 criterion. We used the odds ratio (OR) as a quantitative measure of effect when comparing relative performance. Significance of a factor was proved if the confidence interval was found outside the no-effect boundary, taken as 1. The critical level of significance for testing statistical hypotheses was taken as 0.05. Multivariate prognostic models for determining the two-year probability of VT occurrence in patients with HFrEF on the basis of the studied Echo parameters were built using the binary logistic regression method. Independent variables were selected by stepwise backward selection method using the Waldowski statistic as an exclusion criterion. The statistical significance of the obtained model was determined using the χ^2 criterion. A measure of certainty indicating the portion of the variance that could be explained by logistic regression served as Nagelkerk's R^2. To assess the prognostic significance of the model and to find the threshold value of the obtained function at the cut-off point, ROC analysis with calculation of the area under the curve (AUC) was performed.

Table 2.

Indices of regional longitudinal and global longitudinal and circular myocardial deformation (%)

LV area	Reference values [24, 25]	All patients (n=133)
anterior wall	-16.8 (4.3)	-8.0 (-10; -5.3)
posterior wall	-17.0 (4.0)	-8.4 (-10.6; -4.7)
septal wall	-16.0 (4.1)	-6.9 (-8.5; -4.9)
side wall	-16.5 (4.1)	-5.5 (-9.5; -4.2)
Basal segments:		
front	-17.7 (4.1)	-7.7 (-11.5; -4.6)
anteroseptal	-13.9 (4.5)	-9.2 (-11.5; -6.2)
posterior septal	-14.6 (3.9)	-7.5 (-9.6; -3.3)
lower	-15.9 (3.9)	-9.6 (-10.7; -5.1)
lower lateral	-17.0 (4.0)	-5.8 (-10.6; -2.8)
anterolateral	-19.2 (3.7)	-4.9 (-8.6; -3.7)
all segments	-16.2 (4.3)	-6.7 (-10.3; -3.6)
Middle segments:		
front	-17.4 (3.6)	-5.8 (-11.0; -4.8)
anteroseptal	-17.1 (3.5)	-4.2 (-7.9; -2.8)
posterior septal	-17.9 (3.5)	-5.8 (-6.9; -4.3)
lower	-17.3 (3.7)	-5.8 (-9.1; -4.3)
lower lateral	-17.0 (3.8)	-5.4 (-7.8; -3.3)
anterolateral	-16.4 (3.5)	-5.5 (-8.5; -3.7)
all segments	-17.3 (3.6)	-5.8 (-7.4; -3.7)
Apical segments:		
front	-14.3 (4.7)	-9.3 (-13.1; -4.8)
anteroseptal	-16.1 (3.9)	-6.7 (-10.6; -4.7)
posterior septal	-17.8 (3.9)	-7.3 (-10.8; -4.5)
lower	-17.6 (4.3)	-7.3 (-9.6; -4.4)
lower lateral	-15.5 (4.3)	-9.1 (-11.8; -4.9)
anterolateral	-14.6 (4.0)	-8.1 (-9.5; -6.4)
all segments	-16.4 (4.3)	-8.3 (-9.7; -5.5)
GLS, Me (Q1;Q3)	-19.7 (-20.4; -18.9)	-7.3 (-8.9; -5.9)
GCS, Me (Q1;Q3)	-23.3 (-24.6; -22.1)	-9.6 (-11.9; -6.4)

Notes: hereafter GLS, global longitudinal strain; GCS, global circular strain.

RESULTS

A total of 133 patients underwent a complete protocol for follow-up and recording of endpoints (Table 1). All patients included in the study showed significant shifts of longitudinal deformation parameters in the majority of LV myocardial segments (Table 2). An arrhythmic endpoint occurred in 27 patients (20%) after 12 (6; 15) months. According to the prospective

follow-up data, 19 patients (14%) died in the first year after ICD implantation due to ADHF.

When comparing the values of maximum systolic longitudinal strain, the worst deformation characteristics in patients with VT were found in the segments corresponding to the posterior and anterior LV walls (p=0.001) - Fig. 1. Registration of arrhythmic endpoint had a direct correlation with the GLS value: patients with VT had lower absolute GLS values corresponding to worse LV longitudinal deformation. ROC analysis was additionally performed to determine the critical value of this indicator. The area under the ROC curve was 0.664±0.061 with 95% CI: 0.544-0.783. A cutoff GLS value of -6% was predictive of first manifestation of VT with a sensitivity of 44% and specificity of 76%. It was found that absolute GLS values <6% increased the risk of first manifestation of VT during the follow-up period by almost 3-fold (odds ratio (OR)=2.59; 95% confidence interval (CI): 1.07-6.26; p=0.031) - Figure 2. Differences in GLS were close to critical (p=0.055) - Table 3.

Using the same cut-off value (less than 6% in absolute values) for regional strains, it was found that worsening longitudinal strain in the anterior segments increased the risk of VT by 3.5-fold (OR=3.57; 95% CI: 1.40-9.09; p=0.006) and in the posterior segments by almost 8-fold (OR=7.67; 95% CI: 2.75-21.38; p=0.0001).

Comparative analysis of the studied parameters of LV deformation did not reveal statistically significant differences in the groups of survivors and patients who died due to ADHF (Table 4).

The studied strain indices along with sex, age, and presence of coronary heart disease were subjected to multivariate analysis (Table 5). The metrics of a better predictive model indicating the likelihood of VT occurrence were: sensitivity 71%, specificity 97%, AUC=0.916 (95% CI: 0.850-0.981), p=0.0001. According to Nagelkerk's R^2 value, the model accounted for 60.4% of the traits.

DISCUSSION

The introduction of the current clinical guidelines [6] has put the cardiac ultrasound specialist in a difficult situation when the accuracy of LVEF measurements determines the tactics of interventional prophylaxis of ЬICB [13]. In addition, there appeared a «gray zone» of values of this index (36-40%), when being in this zone, according to the recommendations for the management of patients with CHF, the patient is in the group of CHF with reduced LVEF, but has a risk of CHF, which does not imply ICD implantation [14]. The ambiguity of the clinical situations encountered forces the clinician to make clinically unjustified decisions or to go beyond the regulatory consensus. The most likely solution to this problem is to add new predictors of VT and cardiovascular death to the current single-factor system for risk stratification of CHF [5].

One of the disappointing results of this study was the lack of associations between the state of longitudinal deformation properties of LV myocardium and the cardiovascular mortality studied. It is worth noting that the study we presented examined patients with severe LV contractile dysfunction (the best GLS value was -11.7%). There are few works that have conducted a study on a similar cohort of patients. The authors of a subanalysis of the MADIT-CRT study, after obtaining similar data, concluded that longitudinal stretch parameters may only help in arrhythmic risk stratification [15].

The performed statistical analysis allowed to assume that the information on the state of regional and global LV contractility, based on the assessment of myocardial deformation, has great specificity in detecting the risk of VT in patients with CHF. According to a large meta-analysis (3198 patients from 12 previously conducted studies), an increase in LV mechanical variance, as determined by speckle-tracking Echo, for every 10 ms statistically signifi-

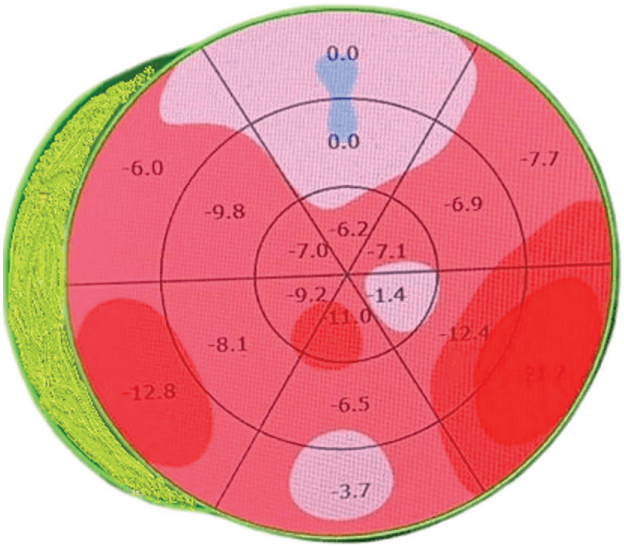

Fig. 1. Pattern of regional longitudinal strain distribution on an 18-segment left ventricular model («bull's eye») of a patient with registered ventricular tachycardia. Against the background of diffuse reduction of longitudinal strains, the worst indices of longitudinal deformation of the left ventricular myocardium were revealed in the anterior and posterior segments.

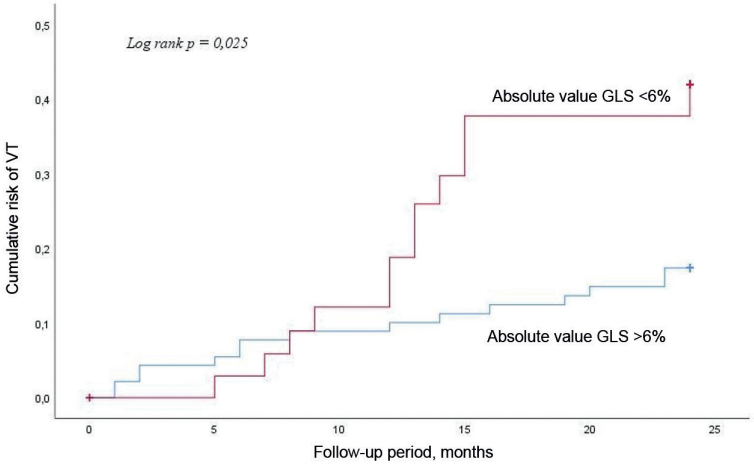

Fig. 2. Kaplan-Meier curve showing the relationship between GLS value and accumulated risk of ventricular tachyarrhythmias in the study cohort of patients.

cantly increased the risk of VT (OR=1.19; 95% CI: 1.09-1.29; p < 0.01) [16].

A team of authors led by F.Guerra investigated the ability to predict VT on the basis of GLS value and LV mechanical dispersion. The arrhythmic endpoint, as in our study, was recorded not only based on face-to-face clinic visits but also using data from remote ICD monitoring systems. It has been demonstrated that worse GLS scores correlate with a greater likelihood of VT; no such associations were found for mechanical variance, which agrees with the opinion of other authors [17]. It was emphasized that GLS showed prognostic potential only for the first manifestation of VT; no associations were found with recurrent episodes of VT.

Table 3.

Rates of regional longitudinal and global longitudinal and circular myocardial strain (%) as a function of reaching the arrhythmic end point

LV area	Patients without VT (n=106)	Patients with VT (n=27)	P
anterior wall	-9.3 (-10.3; -7.0)	-5.5 (-7.9; 2.6)	0.0001
posterior wall	-8.5 (-10.6; -5.1)	-5.5 (-6.0; -1.5)	0.0001
septal wall	-6.8 (-8.3; -4.3)	-6.9 (-8.8; -5.8)	0.189
side wall	-5.5 (-9.7; -4.2)	-6.7 (-8.5; -2.8)	0.942
all basal segments	-6.7 (-11.2; -3.4)	-7.0 (-9.4; -4.2)	0.961
all mid segments	-6.1 (-7.9; -3.7)	-5.4 (-6.6; -3.8)	0.061
all apical segments	-8.3 (-10.0; -5.6)	-6.4 (-8.0; -5.5)	0.105
GLS, Me (Q1;Q3)	-7.5 (-9.1; -6.1)	-5.9 (-7.4; -3.4)	0.009
GCS, Me (Q1;Q3)	-9.9 (-11.9; -7.3)	-8.5 (-10.6; -5.2)	0.055

Note: VT - ventricular tachyarrhythmias

A known limitation of the use of myocardial deformation indices for arrhythmic risk stratification is the lack of unified cutoff values. For example, T.Biering-Sørensen et al. expressed an opinion according to which the prognostic value was worse or equal to -7% [15]. M.H.Nikoo et al. suggested using a GLS value of -10% (specificity 90%; sensitivity 72.2%; AUC=0.84; p<0.001) to predict the probability of VT [9]. At the same time, the findings indicated that no episodes of VT were reported at a GLS better than or equal to -17%.

An additional result of our work, which is of interest for further research and discussion, is the description of the association between worsening regional longitudinal stretch in certain regions of the LV and risk of VT. Subanalysis of the MADIT-CRT study also showed that a decrease in regional longitudinal deformation of the posterior and, to a lesser extent, anterior wall myocardium can be considered as a risk factor for VT in patients with CHF with reduced LVEF of both ischemic and non-ischemic genesis [15, 18]. It was found that when LV posterior wall longitudinal stretch worsened worse than -7%, the risk of VT increased more than 2-fold (OR = 2.10; 95% CI: 1.63-2.69; p < 0.001). Such data were explained by the peculiarity of the anatomy of different LV walls, according to which the posterior LV wall is the flattest structure with a large angle of fiber inclination. This probably predisposes the cardiomyocytes of this region to greater myocardial stress and probably to greater susceptibility to arrhythmogenic remodeling [19]. The revealed abnormalities of local contractility can be explained by the peculiarities of coronary blood supply, since it is the posterior and anterior LV walls that most often suffer ischemic damage when the right and left coro-

Table 4.

Rates of regional longitudinal and global longitudinal and circular myocardial deformation (%) according to the achievement of the mortality end point

LV area	Surviving patients (n=114)	Deceased patients (n=19)	P
anterior wall	-8.0 (-10.0; -5.1)	-7.5 (-9.9; -7.0)	0.880
posterior wall	-8.4 (-10.6; -5.0)	-8.4 (-10.1; -5.4)	0.620
septal wall	-6.9 (-8.7; -4.9)	-6.8 (-8.1; -2.9)	0.342
side wall	-5.5 (-8.8; -4.2)	-6.2 (-9.9; -5.3)	0.158
all basal segments	-6.7 (-9.7; -3.4)	-7.2 (-10.8; -5.0)	0.318
all mid segments	-5.8 (-8.5; -3.6)	-5.1 (-8.2; -4.9)	0.518
all apical segments	-7.8 (-9.7; -5.5)	-8.9 (-9.5; -5.5)	0.847
GLS, Me (Q1;Q3)	-7.3 (-8.3; -5.9)	-7.3 (-9.2; -6.1)	0.354
GCS, Me (Q1;Q3)	-9.6 (-11.9; -6.4)	-10.2 (-13.8; -8.1)	0.457

Table 5.

Prognostic factors associated with the occurrence of ventricular tachyarrhythmias

Factor	Single-factor analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age	1.017	0.993-1.041	0.174	-	-	-
Male gender	1.537	0.850-2.782	0.155	-	-	-
Presence of CHD	1.928	1.258-2.954	0.003	-	-	-
GLS	1.405	1.115-1.771	0.004	3.259	1.694-6.271	0.0001
GCS	-	-	-	-	-	-
anterior wall LS	1.284	1.140-1.446	0.0001	1.553	1.181-2.042	0.002
posterior wall LS	1.229	1.097-1.377	0.0001	-	-	-
septal wall LS	0.862	0.717-1.037	0.114	0.391	0.227-0.674	0.001
side wall LS	1.000	0.884-1.131	0.999	0.648	0.484-0.868	0.004

Note: CHD, coronary heart disease; LS, longitudinal strain

nary arteries are affected, respectively [20, 21]. There are indications that the anterior wall of LV is actively innervated by fibers of stellate ganglion [22], and in the region of the posterior wall there are many parasympathetic nerve endings [21]. It is assumed that myocardial remodeling in these areas can also cause damage to the receptor part of the autonomous nervous system, manifesting a proarrhythmogenic effect [15].

Limitations of the study

Limitations of the study include the relatively small number of participants and its single-center nature, as well as the fact that speckle-tracking Echo was performed only in the absence of rhythm disturbances during the study. The present work did not analyze the relationship between the risk of VT and clinical factors, including regional features of atherosclerotic coronary lesions, presence, and nature of intraventricular conduction disorders.

CONCLUSION

The deformation indices of LV myocardium determined by the two-dimensional Strain method were studied in this study. The potential usefulness of preoperative screening of these parameters for arrhythmic risk assessment in patients referred for ICD implantation for primary prevention of SCD has been demonstrated. According to the results obtained, GLS and longitudinal LV anterior wall stretch values are independent predictors of the first manifestation of VT in CHF patients with LVEF ≤35%.

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