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Mechanical dyssynchrony for prediction of the cardiac resynchronization therapy response in patients with dilated cardiomyopathy

Aim — To evaluate the predictive value of indexes of left ventricular mechanical dyssynchrony (MD) as determined by data of electrocardiogram (ECG) – gated myocardial perfusion scintigraphy (ECG-MPS) for prediction of the efficacy of resynchronization therapy (RT) in patients with chronic heart failure (CHF).

Material and methods — This prospective study included 32 patients with nonischemic CHF and standard indications for RT. All patients underwent complete clinical an instrumental examination, including 24-h ECG monitoring and echocardiography (EchoCG). In order to evaluate the left ventricular (LV) myocardial perfusion, contractile function, and MD, myocardial perfusion scintigraphy was performed for all patients at rest prior to RT. In addition to the perfusion defect size at rest and hemodynamic parameters, LV MD was determined. The following indexes were used for analysis of dyssynchronization: phase standard deviation (PSD), phase histogram bandwidth (HBW), and phase histogram asymmetry and steepness. The treatment efficacy was evaluated by the clinical status of patients (clinical condition evaluation scale for CHF patient) and EchoCG at 6 months following RT. The criteria for a positive response to RT were an increase in LV ejection fraction (EF) by 5% and/or a decrease in the LV end-diastolic volume by 15% compared to preoperative values.

Results — According to ECG-MPS findings, all patients had scintigraphic signs of severe CHF with dilated LV cavity (end-diastolic volume, EDV 246 [217; 269] ml) and also of pronounced mechanical and electrical dyssynchrony. The values of mechanical dyssynchrony were PSD 53 [41; 61], HBW 176 [136; 202], asymmetry 1.62 [1.21; 1.89], and steepness 2.81 [1.21; 3.49]. The QRS duration was 165 [155; 175] msec. Furthermore, the LV perfusion was moderately impaired (perfusion defect size 4 [3; 10] %). Mean follow-up duration after implantation of the resynchronizing device was 6±1.7 mos. According to the selected criteria, 20 (63%) patients were considered as responders and 12 (37%) patients as non-responders. Before implantation of the cardiac synchronizing device, responders and non-responders differed only in LV MD (PSD 44 [35; 54] vs. 63 [58; 72]; p=0.0001); HBW 158 [118; 179] vs. 205 [199; 249]; p=0.0001; asymmetry 1.77 [1.62; 2.02] vs. 1.21 [0.93; 1.31]; p=0.0001; steepness 3.03 [2.60; 3.58] vs. 1.21 [0.19; 1.46]; p=0.0001), respectively. A one-factor logistic regression analysis showed that MD values were statistically significant predictors of a positive response to RT. A multi-factor logistic analysis of phase histogram steepness (odds ratio, OR 1.196; 95% confidence interval, CI 1.04–1.37) and PSD (OR 0.67; 95% CI 0.47–0.97) were identified as independent predictors for the response to RT. According to results of the ROC analysis, a PSD <55 and a phase histogram steepness >1.54 may predict the effectiveness of RT (AUC= 0.92; p=0.0001).

Conclusion — LV MD parameters determined with ECG-MPS allow predicting the effectiveness of RT in patients with nonischemic CHF. In this patient group, high values of standard deviation and low values of phase histogram steepness were independent predictors for the absence of response to RT after 6 mos. of follow-up.

Keywords — Chronic heart failure; myocardial perfusion scintigraphy; resynchronization therapy; mechanical dyssynchrony; prognosis

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Chronic heart failure (CHF) is one of the main problems of modern cardiology. According to J.G. F. Cleland [1], the late 20th and the early 21st century have marked the beginning of the CHF epidemic, which is predicted to affect almost all countries. A relatively large number of patients with heart failure are old to very old people [2, 3]. In Russia,

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with more than 30 million people of retirement age, the prevalence of CHF is 10.2% [4]. The origin, clinical course, and treatment of CHF are best studied in patients with left ventricular (LV) systolic dysfunction [5–7]. Drug therapy in these patients is not always successful, and surgical methods (cardiomyoplasty, LV prosthesis implantation, heart transplantation, etc.) have not been widely used due to insufficient efficacy, possible complications, and age-related restrictions for such severe surgical interventions. Cardiac resynchronization therapy (CRT) is one of the most promising methods for treating CHF, the efficacy of which in patients with severe CHF has been proven in multicenter randomized clinical trials [8–12]. CRT has changed significantly the treatment outcome of patients with drug-refractory CHF combined with cardiac dyssynchrony. Pooled data from seven randomized trials state a positive effect of CRT on mortality associated with CHF progression [13]. However, 30% of patients do not achieve improvements in cardiac contractile function and clinical status [14, 15]. This means that the existing selection criteria for CRT are not always effective. Thus, additional criteria for the selection of CHF patients for CRT are required.

Mechanical dyssynchrony (MD) is often detected in patients with CHF. Several studies have shown that MD assessment can play a key role in predicting the response to CRT [16–19]. Echocardiography is the most widely accessible method for assessing the contractile function of the heart. However, the multicenter trial PROSPECT showed that none of the standard echocardiographic parameters of dyssynchrony were reliable predictors of response to CRT [10]. Later trials demonstrated that tissue Doppler imaging of the myocardium, using strain rate imaging with 2D and 3D speckle tracking, shows promising results in predicting the response to CRT [20].

Several trials have shown that radionuclide methods estimate left ventricular mechanical dyssynchrony (LVMD) more accurately, thus playing an essential role in predicting the results of CRT [21–23]. Scintigraphic assessment of MD is based on equilibrium radionuclide ventriculography [24] and electrocardiogram synchronized myocardial perfusion scintigraphy (ECG-MPS) [25].

It should be noted that the results of most trials performed using this technique are based on mixed samples, including patients with CHF of various origins. Only a few works selectively analyzed patients with CHF of ischemic and non-ischemic origin [18, 19, 26]. Moreover, these works provide different threshold values of LVMD indicators for patients responding and not responding to CRT.

Aim

To evaluate the prognostic significance of LVMD indicators determined by ECG-MPS in predicting the efficacy of CRT in patients with CHF of non-ischemic origin.

Material and methods

Patients and study design

The prospective study included 32 patients with CHF of non-ischemic origin (with 20 male patients, mean age of 54 ± 12 years). The inclusion criteria were the following indications for CRT: functional class (FC) of heart failure II–III (n=10/22), QRS duration>150 ms, decreased left ventricular ejection fraction (EF)≤35%, and complete left bundle branch block (CLBBB) [27]. All patients underwent coronary angiography to exclude the ischemic origin of CHF, which did not reveal hemodynamically significant coronary stenosis. Cardiac resynchronization devices were implanted using the standard technique for biventricular pacing. Patients with permanent atrial fibrillation were subjected to a complete artificial atrioventricular block.

All patients underwent comprehensive clinical and laboratory examination, including history taking, complete blood count, biochemical blood tests, 12-lead ECG, 24-hour ECG monitoring, and echocardiography.

To assess perfusion, LV contractile function, and LVMD, all patients underwent resting ECG-MPS before CRT. Six months after CRT, patients underwent clinical examination (SHOCS [5]) and echocardiography. An increase in LVEF by 5% or more and/or a decrease in the left ventricular end-systolic volume (LVESV) by 15% or more, compared to preoperative values, were the criterion for a positive response to CRT [21, 25, 28–30].

The study was implemented in accordance with Good Clinical Practice [31] and the Declaration of Helsinki. The study protocol was approved by the ethics committee. The study is registered at https://clinicaltrials.gov/(MIBGinCRT (ID: NCT03667989). All subjects signed informed consent forms before being included in the study.

Myocardial perfusion scintigraphy

Single-photon emission computed tomography (SPECT) of the myocardium was performed at rest, on a cadmium zinc telluride (CZT) based detector gamma camera (Discovery NM/CT 570c). 99mTc-technetril 370–450 MBq was used as a radiopharmaceutical agent (RPA). ECG synchronized scintigraphy was performed 1.5 hours after the RPA injection (a representative cardiac cycle was composed of 16 frames). Scintigrams were recorded for 360 seconds using a low-energy collimator (19 projections, 32×32 pixel matrix, 4 mm pixel size), with low-dose computed tomography attenuation correction. The energy window center was set at a 140 keV

photopeak, and the energy window width was 20%. The total effective radiation exposure was 6 mSv.

Image processing

The resulting images were reconstructed on a Xeleris 4.0 workstation using iterative reconstruction (60 iterations, Green OSL Alpha 0.7, and Green OSL Beta 0.3) to obtain perfusion images along the standard cardiac axes (short axis, vertical long axis, and horizontal long axis). The Myovation for Alcyone software with the Butterworth filter (frequency 0.37, order 7) was used for further image reconstruction. The reconstruction was performed in a 70×70 pixel matrix with 50 slices. Myocardial tomograms were processed using the Emory Cardiac Toolbox software package. The following parameters were determined for the analysis of mechanical dyssynchrony: phase standard deviation (PSD), histogram bandwidth (HBW), asymmetry (S), and gradient (G) of the phase histogram [25].

Statistical processing

The data are presented as the median (Me [25th percentile, 75th percentile]) and the absolute number and percentage (n (%)). Samples were checked for compliance with normal distribution using the Shapiro-Wilk test. The significance of differences in quantitative data was checked using the Mann–Whitney test. Spearman's rank correlation coefficient was applied to determine the relationship between variables. Univariate and multivariate logistic regression analysis was performed to assess the effect of MD on the CRT outcome, with subsequent calculation of odds ratio (OR) and its 95% confidence interval (CI). ROC analysis was performed, and characteristic curves were constructed to determine the cut-off value of the baseline scintigraphic parameters for predicting CRT response. Differences were statistically significant at $p<0.05$.

Statistical analysis was performed using the SPSS software suite version 24.0 and Medcalc version 17.4.

Results

Clinical characteristics and ECG-MPS results for the patients included in the study are presented in Table 1.

The study included mainly patients with CHF FC III (NYHA). The QRS duration complex was more than 150 ms in all subjects. All patients received diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors. All patients showed scintigraphic signs of severe CHF with LV dilatation, as well as reduced LVEF and moderate myocardial perfusion abnormalities according to ECG-MPS. MD was defined as the threshold exceeding the following indicators: PSD>24.4° (male) and>22.2° (female); HBW>62.2° (male) and>49.8° (female) [25].

Table 1. Clinical characteristics of patients and the results of ECG-synchronized myocardial perfusion scintigraphy

Parameter	Value (n=32)
Clinical characteristics	
Age, years	54±12
Sex, male %	20 (63%)
Diabetes mellitus	2 (6%)
Hypertensive heart disease	20 (63%)
Dyslipidemia	8 (25%)
Ventricular tachycardia	24 (75%)
CHF FC (NYHA 1/2/3/4)	0/10/22/0
QRS complex duration, ms	165 [155; 175]
CLBBB, %	100
ECG-MPS	
SRS	4 [3; 10]
LVEDV, mL	246 [217; 269]
LVESV, mL	184 [154; 202]
LVEF, %	26 [20; 30]
PSD, °	53 [41; 61]
HBW, °	176 [136; 202]
Asymmetry*	1.62 [1.21; 1.89]
Gradient*	2.81 [1.21; 3.49]

* – non-dimensional value; NYHA, New York Heart Association (classification); ECG-MPS, electrocardiography-synchronized myocardial perfusion scintigraphy; CLBBB, complete left bundle branch block; SRS, summed rest score; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; PSD, phase standard deviation; HBW, histogram bandwidth.

Correlation between MD indicators, LV volumes, and global contractility

Correlations were found between LVEDV and LVMD (LVEDV vs PSD: po=0.77, p=0.0001; LVEDV vs HBW: po=0.79, p=0.001; LVEDV vs S: r=–0.53, p=0.001; LVEDV vs G: po=–0.46, p=0.001). Moderate correlations were also found between LVEF and MD indicators (LVEF vs PSD: po=–0.57, p=0.002; LVEF vs HBW: po=–0.56, p=0.001; LVEF vs S: r=0.61, p=0.001; LVEF vs G: po=0.52, p=0.001). The QRS complex duration significantly correlated with PSD (po=0.57, p=0.003), HBW (po=0.56, p=0.003). Moreover, the size of the perfusion defect at rest was found to be associated with asymmetry and gradient of the phase histogram (S: po=–0.45, p=0.04; G: po=–0.46, p=0.03). At the same time, histogram bandwidth and histogram standard deviation showed no statistically significant relationship with the dimension of the perfusion defect at rest.

Analysis of long-term outcomes

The mean follow-up after the implantation and activation of the cardiac resynchronization device was 6 ± 1.7 months. According to the selected criteria, 20 (63%) and 12 (37%)

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of patients were regarded as CRT responders and non-responders, respectively. Before the device installation, the groups of CRT responders and non-responders were comparable in terms of main clinical characteristics, hemodynamic and myocardial perfusion parameters. At the same time, the groups differed statistically significantly by LVMD (Table 2).

Logistic analysis

An univariate logistic regression analysis found that all the MD indicators estimated were statistically significant predictors of a positive response to CRT (Table 3).

The multivariate logistic model, containing the indicators of MD, LV contractility, age, sex, risk factors, and other clinical variables, found that phase histogram gradient was the only independent predictor of a positive response to CRT (OR 1.196; 95% CI 1.04–1.37). In the predictive model, without the inclusion of the phase histogram gradient and asymmetry, only PSD was an independent predictor of the response to CRT (OR 0.67; 95% CI 0.47–0.97).

ROC analysis was then performed for PSD and histogram gradient, as these scintigraphic indices were statistically significant in the multivariate analysis. It was found that the phase standard deviation (PSD) less than 55° (sensitivity 89% and specificity 100%) and increased gradient of the phase histogram more than 1.54 (sensitivity 89% and specificity 100%) predicted a positive outcome of CRT (AUC=0.92; p=0.0001).

Table 2. Comparative characteristics of the main clinical parameters and ECG-MPS data of CRT responders and non-responders before the implantation of a cardiac resynchronization device

Parameter	Non-responders to CRT (n=12)	Responders to CRT (n=20)	p
Clinical characteristics			
Age, years	54±9	52±9	0.72
Sex, male %	8 (67%)	12 (60%)	0.71
Diabetes mellitus	0	2 (10%)	0.30
Hypertensive heart disease	6 (50%)	14 (70%)	0.75
Dyslipidemia	2 (16%)	6 (30%)	0.55
Ventricular tachycardia	10 (83%)	14 (70%)	0.39
NYHA (1/2/3/4)	0/4/8/0	0/6/14/0	0.84
QRS complex duration, ms	164±22	164±7	0.33
ECG-MPS			
SRS	4 [3; 18]	4 [2; 5]	0.17
LVEDV, mL	249 [235; 341]	237 [198; 254]	0.06
LVESV, mL	179 [172; 273]	185 [142; 201]	0.36
LVEF, %	24 [20; 31]	26 [21; 28]	0.89
PSD, °	63 [58; 72]	44 [35; 54]	0.0001
HBW, °	205 [199; 249]	158 [118; 179]	0.0001
Asymmetry*	1.21 [0.93; 1.31]	1.77 [1.62; 2.02]	0.0001
Gradient*	1.21 [0.19; 1.46]	3.03 [2.60; 3.58]	0.0001

* – non-dimensional value; NYHA, New York Heart Association (classification); CRT, cardiac resynchronization therapy; ECG-MPS, electrocardiography-synchronized myocardial perfusion scintigraphy; SRS, summed rest score; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; PSD, phase standard deviation; HBW, histogram bandwidth.

Discussion

According to our findings, the MD values in patients with non-ischemic CHF determined by ECG-synchronized myocardial SPECT differed statistically significantly between CRT responders and non-responders. The logistic regression analysis showed that LVMD indicators determined by ECG-MPS are prognostically significant in terms of CRT efficacy.

Our findings are consistent with the work by Wang et al. [19], in which DM was more pronounced in patients with dilated cardiomyopathy who did not respond to CRT. In our work, it was additionally shown that the asymmetry and gradient of the phase histogram, determined by ECG-MPS, allow the efficacy of CRT to be predicted. Kano et al. [32] also showed that high entropy values in patients with dilated cardiomyopathy and a narrow QRS complex determined by ECG-MPS are associated with a higher incidence of unfavorable cardiac outcomes. Our work is different in this respect, since the prognostic significance of dyssynchrony indicators was established in patients with a wide QRS complex.

In the majority of previous works on this problem, the opposite results were obtained as CRT responders differed from non-responders by greater values of LV dyssynchrony according to ECG-MPS [16,18, 26]. Attention is drawn to the pronounced variance of the phase standard deviation (from 5° to 22.2°) and histogram bandwidth (from 12.7° to 88.6°) between different trials (Figure 1). In these works, except for Mukherjee et al. [18], the samples consisted mainly of patients with ischemic CHF.

The ischemic changes in the myocardium causing dyssynchrony may be associated with a higher frequency of a positive response to CRT. At the same time, a positive response to CRT is characteristic of non-ischemic CHF with mild LV dyssynchrony.

It is known that LV dyssynchrony in patients with ischemic CHF is due to the presence of a postinfarction scar [33]. The rest of LV myocardium may preserve normal morphology and contractile function in this form of CHF [34]. Therefore, the severity of dyssynchrony reflects the

size and depth of the zone of abnormal postinfarction wall motion. This assumption is confirmed by the direct relationship between the size of the perfusion defect at rest and the value of dyssynchrony in patients with ischemic CHF [35, 36]. It was also found that the size of the metabolic defect affects the efficacy of CRT [37, 38]. In the case of CRT and the placement of a left ventricular electrode outside the postinfarction scar (in the viable myocardium), such a patient is more likely to respond to CRT [35, 39, 40].

Myocardial dyssynchrony in non-ischemic cardiomyopathy is caused by the presence of diffuse myocardial fibrosis [41], which is reflected in increased dyssynchrony values. The direct relationship between the value of dyssynchrony and the severity of intramyocardial fibrosis shown by magnetic resonance imaging (MRI) has been discussed in previous publications [41–43]. The direct relationship between MD and LV volumes and the inverse relationship between MD and LV contractility shown in our study confirm the association between high values of dyssynchrony and a lack of response to CRT.

Modern radionuclide imaging in determining LV dyssynchrony and predicting CRT outcomes

Various imaging techniques are used to assess MD, such as echocardiography, MRI, equilibrium radionuclide ventriculography, myocardial perfusion scintigraphy, and positron emission tomography [33].

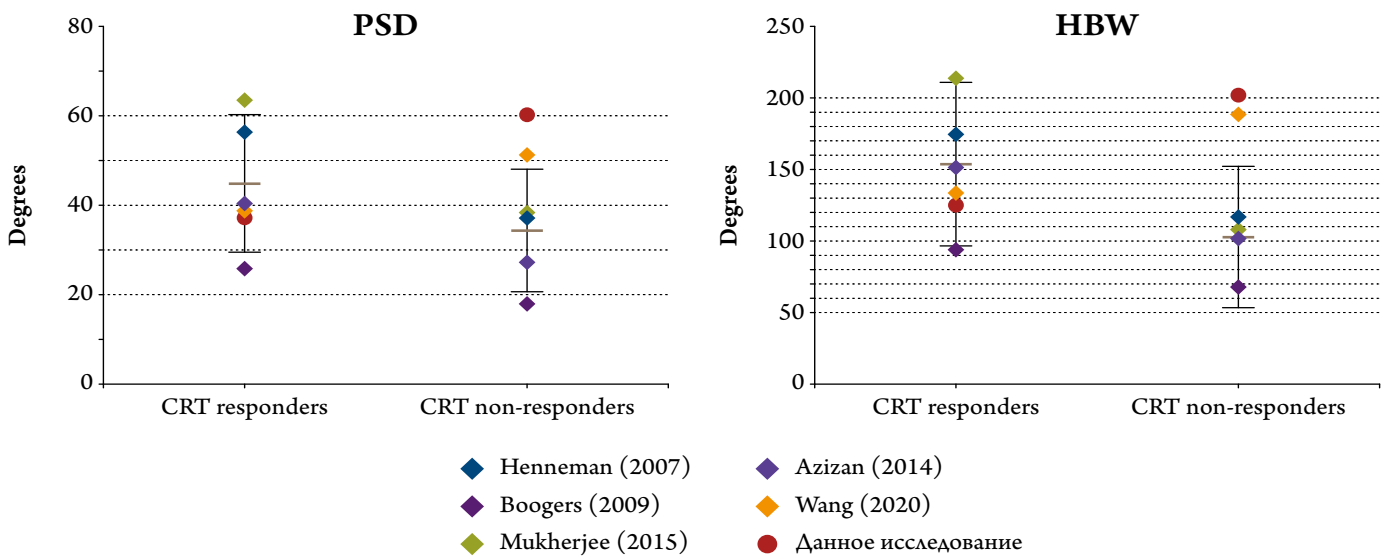
Radionuclide examinations are highly informative and are not inferior to MRI in the accuracy of assessing cardiac

Table 3. Results of univariate logistic analysis of clinical data and indicators of mechanical dyssynchrony used to predict response to CRT

Parameter	Correct classification, %	OR* (95% CI)	p
Clinical characteristics			
Age	62.5	0.93 (0.86–1.00)	0.06
Sex, male %	62.5	1.33 (0.29–5.96)	0.71
Diabetes mellitus	66.7	1.01 (0.59–1.90)	0.84
Hypertensive heart disease	66.7	0.64 (0.13–3.14)	0.59
Dyslipidemia	66.7	1.71 (0.28–10.59)	0.56
Ventricular tachycardia	62.5	2.14 (0.36–12.89)	0.41
NYHA	62.5	0.84 (0.19–3.98)	0.84
QRS duration	62.5	1.00 (0.95–1.06)	0.93
ECG-MPS			
SRS	80.0	0.93 (0.81–1.069)	0.31
PSD	84.6	0.67 (0.48–0.97)	0.03
HBW	92.3	0.88 (0.78–0.99)	0.05
Asymmetry	84.6	2.15 (1.12–3.91)	0.01
Gradient	84.6	1.12 (1.01–1.37)	0.01

OR, odds ratio; CI, confidence interval; SRS, Summed Rest Score; LVEDV, left ventricular end-diastolic volume; CRT, cardiac resynchronization therapy; PSD, phase standard deviation; HBW, histogram bandwidth. ECG-MPS, electrocardiography synchronized myocardial perfusion scintigraphy.

Figure 1. Comparison of MD indicators in CRT responders and non-responders according to this study and the findings of other authors



PSD, phase standard deviation; HBW, histogram bandwidth; MD, mechanical dyssynchrony; CHF, chronic heart failure; CRT, cardiac resynchronization therapy.

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hemodynamics [44]. Other advantages of radionuclide techniques are high reproducibility, independence from the operator, and the possibility of using devices for monitoring the treatment response in patients after the implantation.

In 2005, Chen et al. [45] demonstrated that LVMD values could be obtained retrospectively from previous ECG-synchronized SPECT using phase analysis. These authors developed a base of normal values for the LV dyssynchrony indicators. Later, several papers demonstrated that the LVMD indicators assessed using the phase analysis of ECG-synchronized myocardial SPECT were highly reproducible [46]. Moreover, it was shown that LVMD correlates moderately with electrical dyssynchrony and allows CRT responders to be differentiated more accurately than the QRS duration [22].

Further trials showed that the response to CRT depends on the severity of LVMD. That is, the higher the phase standard deviation and histogram bandwidth (the greater the LVMD), the higher the response rate to CRT [16]. However, these conclusions were obtained in the mixed samples of patients with both ischemic and non-ischemic CHF (except for Mukherjee et al. [18]).

Several previous studies showed that the gradient and asymmetry of the phase histogram were associated with heart diseases, accompanied by conduction and wall motion abnormalities [47–49]. This work established for the first time that the gradient of the phase histogram could be used as an independent predictor of the response to CRT in patients with non-ischemic CHF and a wide QRS complex.

The main limitations of this study are its single-center design and relatively small sample. The follow-up period was 6 months. Instrumental criteria for assessing the response to CRT [28] were used in this study without clinical variables. Using different criteria could have produced different results.

Further research is required in a larger group of patients from different sites for a more accurate assessment of the ECG-MPS effectiveness in predicting CRT outcomes.

Conclusion

The indicators of left ventricular mechanical dissociation, determined by electrocardiogram-synchronized myocardial perfusion scintigraphy, allow the efficacy of resynchronization therapy to be predicted in patients with chronic heart failure of non-ischemic origin. High values of standard deviation and low phase histogram gradients were independently associated in this group of patients, with more frequent non-response to resynchronization therapy within the 6-month follow-up.

No conflict of inter est is reported.

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