https://doi.org/10.23873/2074-0506-2025-17-3-281-290

Stress-induced rhythm disturbances in patients with dilated cardiomyopathy

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Abstract

Background. *Dilated cardiomyopathy (DCM) accounts for more than 50% of all forms of cardiomyopathy and is one of the main causes of chronic heart failure, heart transplantation and the development of life-threatening arrhythmias. Some patients with DCM who do not have rhythm disturbances at rest remain at risk for their development during physical exertion.*

Objective. *To study the structure of rhythm disturbances in patients with DCM with indications for heart transplantation and to identify predictors of the occurrence of ventricular extrasystoles (VEs) according to cardiopulmonary exercise testing (CPET).*

Material and methods. *The study included 82 male patients with DCM who were on the waiting list for heart transplant and admitted for examination and conservative treatment aimed at compensating for heart* *failure. Their mean age was 45 (37;54.2) years old. All patients underwent clinical and instrumental examinations, as well as CPET with the analysis of peak oxygen consumption, anaerobic threshold level, minute ventilation volume, ventilatory equivalent for carbon dioxide, oxygen pulse, threshold load power (W), and load duration.*

Results. *CPET conducted at baseline to patients with DCM demonstrated the presence of rhythm disturbances in the form of atrial fibrillation, VEs, and left bundle branch block in 63.4%. Newly occurring rhythm disturbances in the form of single and paired VEs were recorded in 19.5% of cases. The logistic regression analysis of echocardiography data showed that the linear size of the right atrium, the indexed parameters of the left ventricular end-systolic and end-diastolic volumes were directly correlated to VEs occurrence during CPET: OR 2.41 (95% CI [1.85-5.82]; p=0.01), OR 2.26 (95% CI [1.34-7.51]; p=0.03), OR 1.84 (95% CI [1.09-5.42]; p=0.02), respectively. Oxygen pulse was inversely related to VEs occurrence during CPET, OR 0.52 (95% CI [0.11-0.76]; p=0.02).*

Conclusion. *The patients with DCM having indications for heart transplantation are characterized as a group of a potential risk for developing VEs during physical exertion. During CPET, newly identified single and paired VEs were registered in 19.5% of cases. The linear size of the right atrium, the indexed parameters of the end-systolic and end-diastolic volumes of the left ventricle in patients with DCM are directly related to VEs occurrence during CPET. The oxygen pulse parameter is inversely related to VEs occurrence during CPET.*

Keywords: dilated cardiomyopathy, rhythm disturbances, cardiopulmonary exercise test

Conflict of Interest. No conflict of interest to declare.

Financial disclosure: The study was conducted within the framework of State Assignment No. 124022000090-0 from the Ministry of Health of the Russian Federation

For citation: Loginova IYu, Kamenskaya OV, Klinkova AS, Porotnikova SS, Doronin DV, Lomivorotov VN, et al. Stress-induced rhythm disturbances in patients with dilated cardiomyopathy. *Transplantologiya. The Russian Journal of Transplantation.* 2025;17(3):281–290. (In Russ.). https://doi.org/10.23873/2074-0506-2025-17-3-281-290

AF, atrial fibrillation
AT, anaerobic threshold
BP, blood pressure
CD, confidence interval
CHF, chronic heart failure
CPET, cardiopulmonary exercise testing
DCM, dilated cardiomyopathy
EDV, end-diastolic volume
ESV, end-systolic volume
HR, heart rate
LV, left ventricle
LVEF, left ventricular ejection fraction
OR, odds ratio
PE, physical exertion
RA, right atrium
TTEcho, transthoracic echocardiography
MV, minute ventilation
VEs, ventricular extrasystoles
VE/VCO_{2max}, ventilatory equivalent for carbon dioxide
VO_{2peak}, peak oxygen uptake
VO_{2pulse}, oxygen pulse
VA, ventricular arrhythmia
W, load power

Introduction

Dilatational cardiomyopathy (DCM) accounts for more than 50% of all forms of cardiomyopathy and is one of the main causes of chronic heart failure (CHF), heart transplantation, and the development of life-threatening arrhythmias (ventricular tachycardia, atrial fibrillation) [1, 2]. The DCM prevalence ranges from 10 to 37 cases per 100,000 of population per year. The annual mortality rate is 7–14% [3]. This disease is most often found in young people of working age and is not uncommon in the practical work of outpatient cardiologists [4].

In patients with DCM on the waiting list for heart transplantation, a sudden cardiac death is one of the most common risk factors for death, in addition to the ineffectiveness of drug therapy for CHF. The risk of sudden cardiac death increases many times over with a combination of frequently occurring ventricular extrasystoles (VEs) and a low left ventricular (LV) ejection fraction [5, 6].

As noted above, DCM often leads to the development of rhythm disturbances, including atrial fibrillation (AF), ventricular extrasystoles. At the same time, some patients with DCM, who do not have rhythm disturbances at rest, remain at risk of developing them on physical exertion (PE). Studying the problem of ventricular extrasystoles in patients with DCM awaiting heart transplantation is rather important because of their high incidence in clinical practice, and their role as a predictor of life-threatening tachyarrhythmia developments and CHF worsening [5].

To date, ventricular arrhythmias (VAs) provoked by PE remain poorly studied. Meanwhile, VAs during physical exercise make the most unfavorable factors, including sudden cardiac death, compared to VA at rest [7].

The objective of the study was to examine the structure of rhythm disturbances in DCM patients with indications for heart transplantation and to identify the predictors of VEs occurrence based on the cardiopulmonary exercise test (CPET).

Material and methods

This retrospective study included 82 male patients with DCM who had been placed on the heart transplant waiting list and admitted to the

E.N. Meshalkin National Medical Research Center from 2018 to nowadays for a routine examination and conservative treatment aimed at compensation for heart failure. The median age of the patients was 45 (37;54.2) years. The study was conducted in accordance with the standards of Good Clinical Practice and the Declaration of Helsinki principles. The study protocol was approved by the local Ethics Committee. Written informed consent was obtained from all patients prior to inclusion in the study.

The inclusion criteria were the following: male patients with DCM over 18 years of age placed on the heart transplant waiting list. The exclusion criteria were as follows: patient's refusal to participate in the study; congenital and acquired heart defects, chronic obstructive pulmonary disease, musculoskeletal disorders that prevented CPET, female patients.

The examination protocol for patients with DCM included complete blood count and biochemistry blood tests, hemostasis parameters, urinalysis, chest X-ray, and transthoracic echocardiography (TTEcho) [8]. The right heart catheterization parameters were assessed: pulmonary artery pressure, cardiac index, and pulmonary vascular resistance. In order to identify rhythm disturbances, all patients underwent a 24-hour continuous electrocardiographic (ECG) Holter monitoring of the heart [9].

To assess the reserves of the cardiovascular and respiratory systems, patients with DCM underwent CPET using the Oxycon Pro device (Jaeger, Germany) complete with a 12-channel ECG monitoring module. Gas exchange was studied using the breath-by-breath method with the analysis of each respiratory cycle by the RAMP protocol with a continuously increasing load (20 W/min) [10]. During the CPET, the pulmonary gas exchange and the cardiovascular system parameters were recorded. The analysis included: the peak oxygen consumption ($VO_{2peak,}$ mm/min/kg); the anaerobic threshold level (VO_{2peak} at AT) measured by the V-slope method [11]; minute ventilation (MV, L/min); ventilatory equivalent for carbon dioxide (VE/VCO_2 max) showing the efficiency of minute ventilation; oxygen pulse (O_{2pulse}) being an index of stroke volume; the threshold load power (W), and the load duration (min). During CPET the following were also recorded: arterial pressure; heart rate; arterial saturation using a pulse oximeter; rhythm disturbances. Patient subjective sensations were assessed using the 10-point Borg scale. Indications for CPET cessation included: reaching submaximal age-related heart rate; shortness of breath; fatigue; dizziness; ischemic changes in the ECG; life-threatening rhythm disturbances; chest pain; decreased arterial pressure. Tolerance to PE was determined by the threshold load power and test duration. The obtained data interpretation was performed according to clinical guidelines for CPET assessment [11].

The analysis of the obtained results was made using the Statistica 6.1 statistical software (USA). Nonparametric statistical methods were used to calculate the medians (Me), interquartile ranges (the 1st and 3rd quartiles); qualitative variables are presented as absolute values and percentages. To identify the patient clinical and medical history data, CPET and echocardiographic parameters associated with the occurrence of rhythm disturbances during CPET, the univariate logistic regression analysis with the calculation of the odds ratio (OR) and 95% confidence interval [CI] was used. The values were considered statistically significant at the level of $p<0.05$.

Results

The clinical and functional status of DCM patients is presented in Table 1.

Table 1. Clinical and functional parameters of patients with dilated cardiomyopathy

Parameter		Value, n=82
Age, years, Me (Q_1;Q_3)		45 (37;54.2)
NYHA Functional Class of chronic heart failure, n (%)	III	68 (83.0)
	IV	14 (17.0)
Rhythm disturbances	Atrial fibrillation	24 (29.2)
	Ventricular extrasystoles	25 (30.4)
	Complete left bundle branch block	3 (3.6)
Presence of an implanted pacemaker		23 (28.0)
History of stroke, n (%)		2 (2.4)
Obesity, n (%)		28 (34.1)
Type 2 diabetes mellitus, n (%)		6 (7.3)
Chronic kidney disease, n (%)		15 (18.2)
Pulmonary angiography parameters		
Mean pulmonary artery pressure, mm Hg		23.5 (18.0;28.4)
Cardiac index, L/min/m^2		1.7 (1.4;2.0)
Pulmonary vascular resistance, dyn s/cm^{-5}		238.0 (130.0,0;285.0)

In the studied cohort of DCM patients, rhythm disturbances in the form of AF, VEs, and left bundle branch block were registered in 63.4% of cases. Among other comorbidities, obesity and chronic kidney disease were predominant.

TTEcho parameters in DCM patients are presented in Table 2.

Table 2. Transthoracic echocardiography parameters in patients with dilated cardiomyopathy, Me (Q_1;Q_3)

Parameter	Value, n=82
RA, longitudinal axis, cm	5.7 (5.2;6.8)
RA area, cm^2	29.4 (21.4;35.0)
LA, longitudinal axis, cm	6.0 (5.3;6.7)
LA area, cm^2	32.2 (22.1;38.1)
RV EDV/ Body surface area, mL/m^2	29.8 (24.2;41.1)
RV end-diastolic area, cm^2	23.8 (22.6;32.5)
RV fractional area change (FAC) (%)	38.2 (30.6;40.5)

LV EDV/Body surface area, mL/m^2	122.9 (110.1;178.4)
LV ESV/Body Surface Area, mL/m^2	98.3 (83.1;109.2)
IVST in diastole, cm	1.0 (0.8;1.2)
LVPWT in diastole, cm	1.0 (0.8;1.2)
LVEF (Simpson method) (%)	25.0 (21.0;30.0)

Notes: RA, right atrium; LA, left atrium; EDV, end-diastolic volume; RV, right ventricle; LV, left ventricle; ESV, end-systolic volume; IVST, interventricular septum thickness; LVPWT, left ventricular posterior wall thickness; LVEF, left ventricular ejection fraction

Table 2 shows that DCM patients had the increased sizes of all heart chambers, with a significant increase in the LV. The fractional change in the RV area was slightly reduced, and the LVEF was abruptly reduced.

The data of the CPET in the studied cohort of patients with DCM are presented in Table 3.

Table 3. Cardiopulmonary exercise test parameters in patients with dilated cardiomyopathy, Me (Q_1;Q_3)

Parameter	Values at rest, n=82	Values at threshold load power, n=82
SpO_2, % (N >95%)	97.0 (96.0;97.0)	96.0 (95.0;97.0)
VO_{2peak}, mL/min/kg	3.4 (2.6;3.8)	10.2 (9.6;11.7)
O_{2pulse}, mL/beat	3.5 (3.2;4.1)	8.2 (6.6;9.5)
MV, L/min	12 (10.5;14.0)	36 (32.0;41.0)
VE/VCO_2 (N < 34)	43.7 (41.8;50.1)	40.5 (32.0;42.0)
Heart rate, per min	72.0 (66.0;82.0)	119.0 (100.0;130.0)
Systolic blood pressure, mm Hg	110.0 (100.0;120.0)	130.0 (120.0;145.0)
Blood pressure, mm Hg	70.0 (60.0;75.0)	80.0 (70.0;90.0)

Notes: SpO_2, arterial saturation; N, normal values; VO_{2peak}, peak oxygen uptake; O_{2pulse}, oxygen pulse; MV, minute ventilation; VE/VCO_2, ventilatory equivalent for carbon dioxide; HR, heart rate; BP, blood pressure

The DCM patients displayed low tolerance to physical activity during CPET. The threshold load power was 62.0 (60.0–65.0) W, the load duration was 7.0 (5.0–9.0) min. Such values can be explained by low reserves of the cardiovascular and respiratory systems. Thus, VO_2 at the peak of the load was within 10 mL/min/kg, which characterizes severe heart failure (class C by Weber classification). Low O_{2pulse} and high VE/VCO_2 at the peak of physical activity also indicated insufficient oxygen supply to the body on physical exertion. The anaerobic threshold was reached in 67 patients (81.7%).

Stress-induced rhythm disturbances during CPET were registered in the form of AF or VEs in 63.4% of cases. Of these, in 20 patients (24.4%), rhythm disturbances were detected for the first time, including VEs-type rhythm disturbances in 16 patients (19.5%). Previously, no arrhythmias were detected at rest or in previous history of those patients. By type, VEs occurred with a frequency of 8 to 20 per minute, single and paired.

The main reasons for discontinuing CPET included: achieving submaximal heart rate in 46 patients (56%), dyspnea and weakness in the legs in 23 patients (28%), decrease in blood pressure in 5 patients (6%), frequent VEs in 8 patients (10%). These adverse events resolved spontaneously during the recovery period.

Table 4 presents a univariate logistic analysis of the relationship between the heart structural and functional parameters based on the TTEcho data, concomitant pathology, parameters of right heart catheterization and the occurrence of VEs during CPET.

Table 4. The relationship between clinical and structural-functional parameters of the heart in patients with dilated cardiomyopathy who displayed extrasystoles during cardiopulmonary exercise testing

Parameter	OR	[95% CI]	p
Age	0.68	[0.05–4.23]	0.87
History of stroke, n (%)	1.32	[0.39–4.56]	0.64
Obesity, n (%)	2.42	[0.46–3.71]	0.74
Type 2 diabetes mellitus, n (%)	0.41	[0.02–3.53]	0.58
Chronic kidney disease, n (%)	1.44	[0.68–4.11]	0.24
Mean pulmonary artery pressure, mm Hg.	0.72	[0.05–3.21]	0.57
Cardiac index, L/min/m^2	2.23	[0.51–4.38]	0.37
Pulmonary vascular resistance, dyn s/cm^{-5}	0.48	[0.11–2.98]	0.51
VO_{2peak}, mL/min/kg	1.54	[0.92–3.87]	0.09
O_{2pulse}, mL/beat	0.52	[0.11–0.76]	0.02
MV, L/min	0.32	[0.08–2.98]	0.47
VE/VCO_2 (N<34)	3.87	[0.24–6.56]	0.61
RA longitudinal axis, cm	2.41	[1.85–5.82]	0.01
RA area, cm^2	0.98	[0.22–4.86]	0.62
LA, longitudinal axis, cm	1.45	[0.63–3.51]	0.12
LA area, cm^2	0.87	[0.17–7.63]	0.41
RV EDV/Body surface area, mL/m^2	0.94	[0.08–3.65]	0.51
RV End-diastolic area, cm^2	1.02	[0.21–2.54]	0.37
RV fractional area change (FAC) (%)	0.27	[0.07–1.58]	0.55
LV EDV/Body surface area, mL/m^2	1.84	[1.09–5.42]	0.02
LV ESV/Body surface area, mL/m^2	2.26	[1.34–7.51]	0.03
IVST in diastole, cm	0.87	[0.32–1.64]	0.24
LVPWT in diastole, cm	1.32	[0.85–2.31]	0.11
LVEF (Simpson method) (%)	1.68	[0.96–4.32]	0.09

Notes: OR, odds ratio; CI, confidence interval; VO_2, oxygen uptake; O_{2pulse}, oxygen pulse; MV, minute ventilation; VE/VCO_2, ventilatory equivalent for carbon dioxide; RA, right atrium; LA, left atrium; EDV, end-diastolic volume; RV, right ventricle; LV, left ventricle; ESV, end-systolic volume; IVST, interventricular septum thickness; LVPWT, left ventricular posterior wall thickness; LVEF, left ventricular ejection fraction

The data of logistic regression analysis showed that the linear size of the RA, indexed parameters of LV ESV and LV EDV in DCM patients are directly correlated to the occurrence of VEs during CPET. At the same time, the O_{2pulse} parameter is inversely related to the occurrence of VEs during CPET.

Discussion

The mechanisms of VA development on PE are associated with an increase in catecholamine concentrations, which leads to an increase in the rate of excitation conduction through myocardiocytes and a decrease in the duration of their action potential. These changes can lead to increased automatism and the development of premature myocardial contractions with the activation of the repeated impulse entry (re-entry) phenomenon [7]. Frequent ventricular ectopic complexes at PE and in the first three minutes of the recovery phase after physical exertion are associated with a high risk of adverse cardiovascular events [5].

Our study demonstrated that rhythm disturbances during the exercise test were registered in 63.4% of DCM patients on the heart transplant waiting list. Newly identified arrhythmias in the form of single and paired VEs were registered in 19.5%. Meanwhile, no rhythm disturbances were recorded in these patients at rest or seen in the previous history. At baseline, the proportion of rhythm disturbances in the form of AF, VEs and left bundle branch block was 63.4% of patients in the studied cohort. The logistic regression analysis revealed that the RA linear dimension, the indexed parameters of LV ESV and LV EDV at TTEcho in DCM patients are directly correlated to the occurrence of VEs during CPET. The O_{2pulse} parameter was inversely related to the occurrence of VEs in CPET. We should note that we could hardly find studies investigating the structure of rhythm disturbances in DCM patients during CPET and the relationships between arrhythmias and clinical and functional parameters.

Some authors have established a relationship between the occurrence of persistent episodes of ventricular tachyarrhythmia in non-ischemic cardiomyopathy patients and the indexed end-systolic LV dimension [12]. In this study, it was suggested that increased linear LV dimensions in a systole may characterize a more pronounced intraventricular mechanical dyssynchrony, which the authors described as a predictor of the development of ventricular tachyarrhythmias. In a subsequent study, the authors found that in patients with CHF and low LV EF, the structural and electrophysiological remodeling of the right and left atria may predict not only AF, but also VAs [13]. In our study, in DCM patients, the LV volumetric parameters, as well as the RA longitudinal dimension correlated to the occurrence of VEs during CPET.

In the present study, the DCM patients showed the reduced O_{2pulse} during CPET. The O_{2pulse} parameter is an indirect characteristic of the cardiac stroke volume and should increase adequately on PE to provide tissues with oxygen [14, 15]. In the study cohort, an inverse relationship was found between O_{2pulse} and the occurrence of VEs during CPET. Obviously, this is due to insufficient oxygen supply to the myocardium against the background of structure-functional and electrophysiological remodeling of the heart.

The results of this study showed that DCM patients with indications for heart transplantation are characterized as patients with a potential risk of developing VAs on PE. This indicates the need to conduct CPET in these patients for identifying rhythm disturbances in order to reduce the risks of an unfavorable outcome.

The limitation of the study was its retrospective design.

Conclusions

1. In patients with dilated cardiomyopathy and indications for heart transplantation against the background of structure-functional and electrophysiological myocardium remodeling, rhythm disturbances in response to a challenge by physical activity were detected in 63.4% of cases.

2. Patients with dilated cardiomyopathy are characterized as a group with a potential risk of developing life-threatening rhythm disturbances when challenged by physical exertion. When conducting a cardiopulmonary exercise test in patients with dilated cardiomyopathy, newly identified rhythm disturbances were recorded in 19.5% of cases, in the form of single and paired ventricular extrasystoles, without the previous history of rhythm disturbances.

3. The right atrium linear dimension, the indexed parameters of the left ventricular end-systolic and end-diastolic volumes, according to transthoracic echocardiography data, in patients with dilated cardiomyopathy are directly correlated to the occurrence of ventricular extrasystoles during the cardiopulmonary exercise test; OR 2.41 (95% CI [1.85-5.82], p=0.01), 2.26 (95% CI [1.34-7.51], p=0.03), and 1.84 (95% CI [1.09-5.42], p=0.02), respectively. The O_{2pulse} parameter is inversely related to the occurrence of ventricular extrasystoles during the cardiopulmonary exercise test; OR 0.52 (95% CI [0.11-0.76], p=0.02).

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The article was received on April 23, 2025;

Approved after reviewing on June 5, 2025;

Accepted for publication on June 25, 2025