Evdokimov D.S., Feoktistova V.S., Boldueva S.A., Ermolov S.Yu., Gaykovaya L.B.
Mechnikov North-Eastern State Medical University, St. Petersburg, Russia

Endothelial Dysfunction in Patients With Takotsubo Syndrome and its Role in Acute and Long Terms Of the Disease

Aim	To evaluate the endothelial function using an Endo-PAT2000 instrument before and after mental stress tests in patients with Tacotsubo syndrome (TS) during acute and long-term periods and to compare the obtained results with laboratory markers of endothelial dysfunction (ED).
Material and Methods	This study included 45 patients with TS (mean age, 63.5±13.7 years) and 40 healthy volunteers (control group, CG). All patients of the main group during the acute period (first 7–14 days) and long-term period (at 1 and 2 years), as well as CG subjects, underwent evaluation of the endothelial function with an Endo-PAT 2000 instrument, and the reactive hyperemia index (RHI) was determined before and after mental stress tests. Also, concentrations of endothelin 1 (ET-1) and numbers of circulating endothelial cells (CEC) were measured after a two-year follow-up of TS patients.
Results	During the acute period of disease, all TS patients (n=45) had ED: RHI was below the threshold level of 1.67; furthermore, 42 (93.3%) patients retained a lower RHI following mental stress. At one year (n=40), 16 (40%) patients showed ED at rest along with a significantly increased mean RHI. Mental stress produced at one year was associated with ED in 28 (70%) TS patients. At two years (n=44), resting RHI was lower than normal in 19 (43.2%) patients. Mental stress tests performed at two years were associated with ED in 29 (65.9%) patients (RHI ≤1.67). Only 10% of CG subjects had a lower-than-normal RHI, which was significantly less than in the main group of TS patients during the acute and long-term periods ($p<0.05$). Mean values of laboratory markers for ED also were significantly different between TS patients during the long-term period of disease (n=41) and CG subjects (n=40; $p<0.01$).
Conclusion	During acute and long-term periods of disease, most of TS patients had impaired vascular reactivity both at rest and during mental stress. The laboratory markers of ED, ET-1 and CEC can be used in clinical practice for evaluation of the risk for TS.

Keywords	Tacotsubo syndrome; endothelial dysfunction; microcirculation; mental stress
For citations	Evdokimov D.S., Feoktistova V.S., Boldueva S.A., Ermolov S.Yu., Gaykovaya L.B. Endothelial Dysfunction in Patients With Takotsubo Syndrome and its Role in Acute and Long Terms Of the Disease. Kardiologiia. 2023;63(3):21–27. [Russian: Евдокимов Д.С., Феоктистова В.С., Болдуева С.А., Ермолов С.Ю., Гайковая Л.Б. Дисфункция эндотелия у больных с синдромом такоцубо и ее роль в остром и отдаленном периодах заболевания. Кардиология. 2023;63(3):21–27].

Corresponding author Feoktistova V.S. E-mail: lerissima@yandex.ru

Takotsubo syndrome (TTS) is a type of acute heart failure that is typically reversible and caused by a variety of stressors in the majority of patients. It is associated with transient predominantly left ventricular (LV) failure with a clinical and electrocardiographic pattern similar to that of acute coronary syndrome [1].

The pathophysiology of TTS is complex and incompletely understood. The underlying mechanisms are being studied, and the direct cardiotoxic effect of catecholamines – which are released in excess in response to physical or emotional stress – along with dysfunction of coronary microvessels, including microvessel spasm caused by excessive catecholamine stimulation of alpha-adrenergic receptors, are considered currently as the main mechanisms. Endothelial dysfunction (ED), which is accompanied by an increase in the synthesis of endothelium-dependent vasoconstrictor factors, particularly endothelin-1 (ET-1), is the main cause of coronary microvascular dysfunction and vasoconstriction [2].

It is generally recognized that ED plays a significant role in the development of numerous cardiovascular diseases. The relevance of microcirculatory disorders in the pathophysiology of TTS has been demonstrated by different methods, despite the lack of studies on this subject in TTS. Transthoracic Doppler and positron emission tomography showed a drop in the coronary flow reserve in patients with acute TTS [2]. Coronary angiography showed the phenomenon of slow blood flow in acute TTS, which is explained by coronary microvascular dysfunction. [2]. Furthermore, findings from cardiac biopsy revealed catecholamine-induced apoptosis of microvascular endothelial cells in patients with TTS [2].

There are still some unanswered questions, including whether ED is permanent or transient after the blood

levels catecholamine are normalized and the LV wall motion is restored, whether the compromised endothelial function is a cause or an effect of the disease, and whether the latter is correlated with laboratory markers of ED.

Objective

Assess the functional activity of the endothelium in TTS patients in acute and remote periods of the disease using the Endo-PAT2000 device before and after mental stress tests, and compare the results with the laboratory indicators of ED.

Material and Methods

A controlled prospective study was conducted in North-Western State Medical University named after I. I. Mechnikov. The study protocol complies with the Declaration of Helsinki and was approved by the local ethics committee.

The interTAK international criteria-based diagnosis of TTS (EOK 2018 Consensus Document) was the inclusion criterion in the main group [1]. The control group included individuals comparable by sex and age with the main group, who did not have acute and chronic cardiovascular diseases, with the exception of moderate arterial hypertension (stage I, grade 1).

The study included 45 patients with TTS, of whom 40 (88.9%) were female, the mean age was 63.5±13.7 years. The control group included 40 patients, of whom 39 (97.5%) were female, the mean age was 66.6±10.4 years (Table 1). Voluntary informed consent was obtained from all subjects.

Endothelial function was studied on the Endo-PAT 2000 device and the reactive hyperemia index (RHI) was determined in all subjects of the main group in the acute (within 7–14 days from the onset of the disease) and remote periods (in 1 year – visit 1 and in 2 years – visit 2) and control subjects. The levels of ET-1 and the number of circulating endothelial cells (CEC) per 3×10^5 leukocytes were determined in patients with TTS at visit 2 and control subjects.

CECs were counted in peripheral blood in a CY TOMICS FC 500 flow cytofluorimeter using fluorochrome-labeled monoclonal antibodies specific for surface cell markers: CD 146 PE (phycoerythrin) as a label for the CECs and CD 45 PC 5 (phycoerythrin + cyanine 5,) as a panleukocyte marker. Whole venous blood collected on an empty stomach in the morning from the ulnar vein into sterile vacuum tubes containing 100 μl of 0.5 M EDTA (pH 8.0) as an anticoagulant.

The serum levels of ET-1 were determined by ELISA using a 680-microplate reader and ET-1 ELISA kit reagents. Blood was collected on an empty stomach in the morning from the ulnar vein into sterile vacuum tubes with a clot activator (silicon dioxide) to accelerate blood clotting.

Table 1. Clinical characteristics of the study groups

Parameter	Main group TTS (n=45)	Control group (n=40)	p
Female, n (%)	40 (88.9)	39 (97.5)	ns
Age, years	63.5 ± 13.7	66.6 ± 10.4	ns
BMI >25 kg/m^2	21 (46.7)	21 (52.5)	ns
Smoking, n (%)	7 (15.6)	6 (15)	ns
Arterial hypertension, n (%)	32 (71.1)	25 (62.5)	ns
Atrial fibrillation/flutter, paroxysms, n (%)	6 (13.3)	0	< 0.05
Postinfarction cardiosclerosis, n (%)	2 (4.4)	0	ns
Chronic heart failure, n (%)	12 (26.7)	0	< 0.05
Cerebrovascular diseases, n (%)	2 (4.4)	0	ns
Diabetes mellitus, n (%)	4 (8.9)	1 (2.5)	ns
Significant family history of cardiovascular diseases, n (%)	36 (80)	25 (62.5)	ns

TTS, Takotsubo syndrome; BMI, body mass index; ns, non-significant.

Instrumental evaluation of endothelial function using the EndoPAT 2000 device was conducted according to the standard technique [3]. The RHI values were ranked into 2 groups: RHI ≤ 1.67 was indicative of ED, RHI within 1.68–3.0 was a criterion of normal endothelial function [3].

Mental stress was simulated in the laboratory by a series of stress tests following the protocol proposed by Alekseeva et al. [4]: Stroop mental stress test (SMST), arithmetic counting (AC) test, anger reproduction/return (AR) test, sick talk (ST) test. These tests are simple enough to perform in people of different ages and levels of education.

A three-stage procedure was used in the experimental protocol to determine the influence of stress tests on the functional activity of the endothelium:

Investigation of endothelial function using the EndoPAT 2000 device at rest (15 min);

Consistent performance of a set of mental stress tests (SMST, AC, AR, ST);

Determination of the presence of ED using the EndoPAT 2000 device after mental stress tests.

The statistical processing of the data obtained was conducted in Statistica 10.0. The values are described as the means and standard deviations (M±SD), with the exception of ET-1 and CEC, which are expressed as the medians and quartile ranges (Me [Q1; Q3]). The chi-

ISSN 0022-9040. Kardiologiia. 2023;63(3). DOI: 10.18087/cardio.2023.3.n2364

square test was used to compare the frequencies in the groups. The statistical significance of differences was assessed using the Mann-Whitney U-test. The correlation analysis was performed using the Spearman's rank correlation. ROC curves were used to determine the threshold blood levels of ET-1 and CECs and assess their diagnostic effectiveness. The generally accepted in medicine p-value < 0.05 was considered the criterion for the statistical significance of the findings.

Results

The examination of the functional activity of the endothelium at rest using EndoPAT 2000 in the acute period of the disease in all patients with TTS showed RHI < 1.67, while a statistically significant progression of ED was observed after mental stress during this period (Table 2).

After one year, the number of patients with reduced RHI (p<0.001) decreased compared to the acute period of the disease: ED (RHI ≤ 1.67) at rest was detected only in 16 (40%) patients, and the mean RHI increased significantly (see Table 2). However, 13 (54.2%) patients had ED after mental stress tests in the subgroup of patients with normal baseline RHI (n = 24), while in the subgroup with low baseline RHI (n = 16), RHI normalized in 1 patient, and the rest still had ED.

Thus, 28 (70%) patients with a history of ST had ED during emotional stress a year after the onset of the disease.

After 2 years, RHI at rest was below normal in 19 (43.2%) patients, which is 50% of patients in the acute period of the disease (p<0.001), but the number of patients with ED did not significantly differ at visit 1 (n=16) and visit 2 (n=19). At the same time, the mean RHI values at visit 2 differed significantly from those in the acute period but remained at the same level compared to visit 1 (Table 2).

ED (RHI ≤ 1.67) was reproduced in 29 (65.9%) patients during mental stress tests 2 years after the acute episode of TTS: 17 patients with reduced baseline RHI and 12 patients who did not have ED before the stress test. In the remaining cases (n=15), RHI was >1.67 after mental stress.

Only 10% of control subjects had RHI below normal at rest, which was significantly fewer than in the main group of TTS patients in the acute period – 100% (p<0.001); furthermore, 40% at visit 1 (p<0.01) and 43.2% at visit 2 (p<0.001). The mean RHI values differed significantly in the main and control groups (Table 2).

After mental stress, only 1 person without ED at baseline in the control group had RHI reduced to the level of dysfunction ≤ 1.67, while the control group generally showed an increase in mean RHI during stress (Table 2).

The comparison of the main and control groups by the number of patients with reduced RHI after stress tests revealed highly significant differences were found in the acute period (p<0.001), in 1 year (p<0.001), and in 2years (p<0.001; Table 2).

Mean values of laboratory markers of ED were statistically significantly different between patients with TTS in the remote period of the disease (n=41) and control subjects (n=40): ET-1 1.25 [0.69; 2.33] and 0.95 [0.43; 1.43] pg/mL, respectively (p<0.01), CEC 5 [2; 7] and 1 [0; 2] cells/3×10^5 leukocytes, respectively (p<0.0001).

The level of ET-1 and CECs was significantly higher in the main group of patients and in subjects with ED (RHI ≤1.67) in the control group compared to those who had normal RHI (Table 3).

The ROC curves (Figure 1) showed that ET-1 >0.48 pg/mL increased 3.4-fold the hazard ratio (HR) of the occurrence of TTS (95% confidence interval (CI) 1.18–9.58; p<0.05) and 3-fold the number of CECs > 5 cells/3×10^5 leukocytes (95% CI 2.10–4.29; p<0.001). The area under the curve (AUC) calculated for both indicators was 0.68 for ET-1 (95% CI 0.57–0.80; p<0.001) and 0.80 (95% CI 0.71–0.90; p<0.001) for CEC, which, according to the expert scale of clinical significance of the test, characterizes the model quality as good.

In the general group of all subjects, a strong direct relationship (r=0.82) was shown between the levels of ET-1 and CECs in the blood (p<0.05) and strong inverse relationship between RHI and ET-1 (r=–0.91; p<0.05), RHI and CECs (r=–0.88; p<0.05). Comparable data were

Table 2. Mean RHI values before and after mental stress tests in the study groups

Parameter	Main group (TTS)			Control group (n = 40)	p
	7–14 days (n = 40)	1year (n = 40)	2years (n = 40)		
RHI before stress test	1.48 ± 0.17	1.74 ± 0.19	1.70 ± 0.21	1.88 ± 0.29	$p_{1-4} < 0.001$; $p_{2-4} < 0.05$ $p_{3-4} < 0.01$; $p_{1-2} < 0.001$ $p_{1-3} < 0.001$; p_{2-3} – ns
RHI after stress test	1.42 ± 0.17	1.57 ± 0.21	1.60 ± 0.17	2.17 ± 0.49	$p_{1-4} < 0.001$; $p_{2-4} < 0.001$ $p_{3-4} < 0.001$; $p_{1-2} < 0.001$ $p_{1-3} < 0.001$; p_{2-3} – ns
p	p < 0.001	p < 0.001	p < 0.001	p < 0.001	–

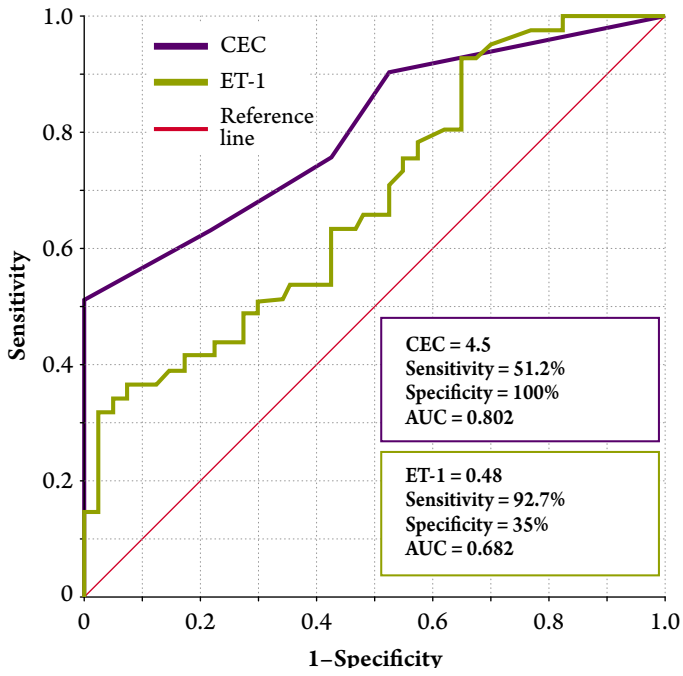
TTS, Takotsubo syndrome; ns, non-significant.; 1 – acute period of TTS (7–14 days); 2 – first visit, 3 – second visit, 4 – control group.

Table 3. Levels of the laboratory markers of endothelial dysfunction respective to RHI in the study groups

Parameter	Group	RHI ≤ 1.67	RHI > 1.67	p
ET-1, pg/mL	TTS	2.42 [1.57; 6.03]	0.77 [0.51; 1.11]	< 0.001
	Control	1.72 [1.62; 2.44]	0.76 [0.41; 1.22]	< 0.01
CEC, cells/3×10^5 leukocytes	TTS	7.0 [6.0; 15.0]	2 [1; 3]	< 0.001
	Control	3.5 [3; 4]	0 [0; 2]	< 0.01

RHI, reactive hyperemia index; ET-1, endothelin-1; CEC, circulating endothelial cells; TTS, takotsubo syndrome.

Figure 1. Sensitivity and specificity ROC-curves for circulating endothelial cells (CECs) and endothelin-1 (ET-1)



obtained in the group of patients with TTS: RHI and ET-1 (r =–0.92; p<0.05), RHI and CECs (r =–0.92; p<0.05), ET-1 and CECs (r=0.89; p<0.05); in the control group: RHI and ET-1 (r = –0.90; p<0.05), RHI and CECs (r= –0.86; p<0.05), ET-1 and CECs (r=0.75; p<0.05).

The obtained relationships between the analyzed laboratory and clinical indicators were preserved when the subjects were divided into subgroups with and without ED. The main group in patients with ED (n=19): RHI and ET-1 (r= –0.83; p<0.05), RHI and CECs (r = –0.75; p<0.05), CECs and ET-1 (r = 0.87; p<0.05); patients without ED (n=22): RHI and ET-1 (r = –0.80; p<0.05), RHI and CECs (r = –0.69; p<0.05), CECs and ET-1 (r = 0.72; p < 0.05).

Discussion

Currently, ED is considered as the leading risk factor for the development of cardiovascular diseases and adverse outcomes [5].

The findings of our study are consistent with previously published data in that all TTS patients had ED in the first 14 days of the disease [6]. Carbonara et al. [6] found that patients with TTS (n = 50) had low FMD (Flow Mediated Dilatation measured by ultrasound Doppler on the brachial artery after 5 minute occlusion with a BP cuff) in the first 12 hours from admission to the hospital, but it was observed to increase in 6.38±1.65 days [6]. Comparable data were obtained by the Russian researchers (Vasilyeva et al.) who evaluated FMD in patients with TTS (n=4), acute myocardial infarction (AMI) with ST-segment elevation (n = 18), and control patients (n = 26) on day 1 and in 7–21 days [7]. In the first 24 hours of the disease, FMD was significantly lower in patients with TTS than in the comparison groups, however, the repeated test study revealed no significant differences between the groups in 1–3 weeks [7].

In this study, ED was assessed using the well-proven plethysmography technique for recording amplitude of peripheral artery tone in a vascular occlusion test using EndoPAT 2000 described above. EndoPAT 2000 is a unique complex for non-invasive assessment of endothelium-dependent vasodilation disorders that produces results comparable with the findings of intracoronary acetylcholine tests [8]. This technique for measuring peripheral arterial tone was approved by the FDA in 2003 [9], has a European CE quality certificate, and listed in the Framingham Heart Study protocol. Bonetti et al. described that the RHI threshold value of ≤ 1.67 calculated on EndoPAT 2000 is indicative of ED with sensitivity of 82% and specificity of 77% [10]. In the study by Lipunova et al. [11], the presence of ED (RHI ≤ 1.67) was confirmed in 91.4% of cases using EndoPAT 2000 in patients with coronary microvascular dysfunction shown by 82Rb-chloride positron emission tomography under stress tests (cold pressor test and dipyridamole). Thus, EndoPAT 2000 can be used for non-invasive assessment of the coronary microvascular dysfunction, specifically abnormalities of endothelium-dependent vasodilation, which was essential to solve our tasks for patients with TTS.

In this study, we examined endothelial function in patients with TTS using mental stress test for the first time. Ghiadoni et al. [12] were among the first to describe in 2000 the occurrence of transient ED in

ISSN 0022-9040. Kardiologiia. 2023;63(3). DOI: 10.18087/cardio.2023.3.n2364

response to mental stress in 10 conditionally healthy men and 8 men with non-insulin-dependent diabetes mellitus. The authors explained the mechanisms of stress-induced ED by sympathetic overstimulation and a local increase in the levels of noradrenaline, reduced synthesis of nitric oxide (NO) by endotheliocytes, lower levels of cyclic adenosine monophosphate (cAMP), and increased secretion of ET-1 vasoconstrictor [13, 14]. Mental stress also provokes oxidative stress, which aggravates ED, causing further release of ET-1 and angiotensin II, and neutralizes the effects of vasodilating molecules [15].

We found that 100% of patients had ED at rest in the acute phase of TTS, which worsened severely when challenged by experimental mental stress in 78% of cases.

It should be noted that Sullivan et al. [16] provide evidence that female patients have more pronounced ED than male patients when reproducing mental stress (anger return). They evaluated ED using EndoPAT but in patients with coronary artery disease. At the same time, Vaccarino et al. [17] who assessed RHI using EndoPAT during and after stress test (anger return) in female and male patients with a history of MI (about 5 months) and control patients, noted that female patients are more prone to post-stress ED. Thus, our findings on a significant decrease in RHI after stress tests in patients with acute TTS, which is more common in women, are what was expected.

In the remote period, ED at rest was less common among our patients: in 40% of cases in 1 year and 43.2% in 2 years. However, acute ED was detected after the reproduction of mental stress in 70% of patients at visit 1 and 66% of patients at visit 2. We found evidence in favor of this information in previously published works. Patel et al. [18] demonstrated that 9 of 10 patients with recovered LV wall motion had signs of coronary microvascular dysfunction during intracoronary challenge with acetylcholine and adenosine 5 months after the onset of TTS. Barletta et al. [19] observed zones of abnormal LV wall motion and reduced coronary blood flow in patients with TTS (n = 17) in response to cold press test 688 days after the onset of the disease, myocardial perfusion was assessed echocardiographically in this study.

Recurrent TTS occurs in 4.7–5% within 10 years [20]. Predictors of the disease recurrence are unknown. However, a decrease in RHI both at rest and after mental stress in the acute and remote periods of TTS, identified in our study, may probably be indicative of an increased risk of recurrence in this patient cohort.

It should be noted that we confirmed the literature data in this study that coronary blood flow should increase in healthy people in response to mental stress as a result of the dilation of the microvascular system [21]. Significant increase in mean RHI was observed after mental stress in apparently healthy women in the control group (Table 2).

In our work,we determined for the first time the levels of ET-1 in patients with TTS in the distant period of the disease and it was shown that it is significantly higher than in CG. The concentrations of ET-1 had been measured previously only in patients with acute TTS. Jaguszewski et al. [22] showed that the levels of ET-1 in TTS patients is higher than in the group of healthy individuals but does not differ between patients with acute STEMI and NSTEMI. These data do not seem surprising given the pathogenesis of TTS and AMI.

To date, no information has been obtained regarding the number of CECs in peripheral blood in TTS patients in the remote period. CECs are mature differentiated cells that separate from the endothelial wall when it is damaged and therefore can act as a direct cellular sign of ED [23]. Healthy people have very little amounts of CECs in peripheral blood, since in the absence of pathological conditions, the process of endothelial renewal is slow, and non-viable endothelial cells are quickly removed from the circulation by the reticuloendothelial system [23]. However, the numbers of CECs increase in patients with cardiovascular diseases [24]. Significantly higher levels of CECs in patients 2 years after the episode of TTS indicate that ED is not a consequence, but the cause of TTS.

As expected, in the group of patients with TTS and the control group, the ET-1 and CEC levels were significantly higher in individuals with ED shown by EndoPAT 2000. Laboratory indicators indicative of ED were strongly correlated between each other and with RHI. In our study, the diagnostic significance in relation to the risk of TTS was demonstrated, according to the ROC analysis, by the ET-1 levels (sensitivity 92.7%, specificity 35%) and CECs (sensitivity 51.2%, specificity 100%). We also found out that ET-1 > 0.48 pg/mL increased HR of TTS 3.4-fold (95% CI) 1.18–9.58; $p<0.05$) and CECs > 5 cells/3×10^5 leukocytes increased it 3-fold (95% CI 2.10–4.29; $p<0.001$). These data suggest that the ET-1 and CEC levels can be used in clinical practice to diagnose ED and assess the likelihood of TTS, however, it should be further confirmed.

Conclusions

1. patients with takotsubo syndrome mostly have abnormal vascular reactivity both at rest and in response to mental stress in the acute and remote periods of the disease.
2. Abnormal vasomotor reaction due to endothelial dysfunction can be considered as a factor contributing to the development of takotsubo syndrome.

3. Laboratory markers of endothelial dysfunction, endothelin-1 and circulating endothelial cells, and the results of EndoPAT2000 testing can be used in clinical practice to assess the risk of takotsubo syndrome.

Funding

No funding was received for this study.

No conflict of interest is reported.

The article was received on 04/12/2022

REFERENCES

1. Ghadri J-R, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ et al. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. European Heart Journal. 2018;39(22):2032–46. DOI: 10.1093/eurheartj/ehy076
2. Boldueva S.A., Evdokimov D.S. Takotsubo cardiomyopathy. Literature review: concept, epidemiology, pathogenesis. Part I. Russian Journal of Cardiology. 2022;27(3S):108–19. [Russian: Болдуева С.А., Евдокимов Д.С. Кардиомиопатия такоцубо. Обзор данных литературы: понятие, эпидемиология, патогенез. Часть I. Российский кардиологический журнал. 2022;27(3S):108-19]. DOI: 10.15829/1560-4071-2022-4993
3. Itamar Medical Ltd. Endo PATTM2000 Device User Manual. Av. at: https://www.itamar-medical.com/wp-content/uploads/2019/07/OM1695214.pdf.
4. Alekseeva D.Yu., Tsurinova E.A., Solntsev V.N., Mamontov O.V., Treshkur T.V. The role of the mental stress-tests examination of patients with ventricular arrhythmia. Translational Medicine. 2016;3(2):6–16. [Russian: Алексеева Д.Ю., Цуринова Е.А., Солнцев В.Н., Мамонтов О.В., Трешкур Т.В. Роль ментальных проб при обследовании больных с желудочковой аритмией. Трансляционная медицина. 2016;3(2):6-16]
5. Kobzeva N.D. Features of endothelial dysfunction in patients with atherosclerotic lesions of various vascular beds. Medical Almanac. 2022;1(70):29–36. [Russian: Кобзева Н.Д. Особенности эндотелиальной дисфункции у пациентов с атеросклеротическим поражением различных сосудистых бассейнов. Медицинский альманах. 2022;1(70):29-36]
6. Carbonara R, Giardinelli F, Pepe M, Luzzi G, Panettieri I, Vulpis V et al. Correlation between endothelial dysfunction and myocardial damage in acute phase of Tako-Tsubo cardiomyopathy: brachial flow mediated dilation as a potential marker for assessment of patient with Tako-Tsubo. Heart and Vessels. 2018;33(3):291–8. DOI: 10.1007/s00380-017-1062-8
7. Vasilieva E, Vorobyeva I, Lebedeva A, Urazovskaya I, Kalinskaya A, Skrypnik D et al. Brachial Artery Flow-mediated Dilation in Patients with Tako-Tsubo Cardiomyopathy. The American Journal of Medicine. 2011;124(12):1176–9. DOI: 10.1016/j.amjmed.2011.05.033
8. Pokrovsky A.V., Kulbak V.A., Fedorov E.E. Evaluation of the index of reactive hyperemia as an indicator of the degree of endothelial dysfunction in patients with atherosclerotic lesions of peripheral arteries. High-tech medicine. 2016;3(4):5–11. [Russian: Покровский А.В., Кульбак В.А., Федоров Е.Е. Оценка индекса реактивной гиперемии, как индикатора степени эндотелиальной дисфункции у больных с атеросклеротическим поражением периферических артерий. Высокотехнологическая медицина. 2016;3(4):5-11]
9. Martin B-J, Gurtu V, Chan S, Anderson TJ. The relationship between peripheral arterial tonometry and classic measures of endothelial function. Vascular Medicine. 2013;18(1):13–8. DOI: 10.1177/1358863X12468194
10. Bonetti PO, Pumper GM, Higano ST, Holmes DR, Kuvin JT, Lerman A. Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. Journal of the American College of Cardiology. 2004;44(11):2137–41. DOI: 10.1016/j.jacc.2004.08.062
11. Lipunova A.S., Boldueva S.A., Leonova I.A., Kolesnichenko M.G., Ryzhkova D.V., Kecherukova A.V. et al. The role of endothelial dysfunction in the genesis of cardiac syndrome X. Preventive and clinical medicine. 2013;1(46):38–42. [Russian: Липунова А.С., Болдуева С.А., Леонова И.А., Колесниченко М.Г., Рыжкова Д.В., Кечерукова А.В. и др. Роль дисфункции эндотелия в генезе кардиального синдрома Х. Профилактическая и клиническая медицина. 2013;1(46):38-42]
12. Ghiadoni L, Donald AE, Cropley M, Mullen MJ, Oakley G, Taylor M et al. Mental Stress Induces Transient Endothelial Dysfunction in Humans. Circulation. 2000;102(20):2473–8. DOI: 10.1161/01.CIR.102.20.2473
13. Sara JDS, Lerman LO, Lerman A. The endothelium is a key player in the vascular response to acute mental stress. European Heart Journal. 2021;42(39):4089–91. DOI: 10.1093/eurheartj/ehab510
14. Sher LD, Geddie H, Olivier L, Cairns M, Truter N, Beselaar L et al. Chronic stress and endothelial dysfunction: mechanisms, experimental challenges, and the way ahead. American Journal of Physiology-Heart and Circulatory Physiology. 2020;319(2):H488–506. DOI: 10.1152/ajpheart.00244.2020
15. Sara JDS, Toya T, Ahmad A, Clark MM, Gilliam WP, Lerman LO et al. Mental Stress and Its Effects on Vascular Health. Mayo Clinic Proceedings. 2022;97(5):951–90. DOI: 10.1016/j.mayocp.2022.02.004
16. Sullivan S, Hammadah M, Al Mheid I, Wilmot K, Ramadan R, Alkhoder A et al. Sex Differences in Hemodynamic and Microvascular Mechanisms of Myocardial Ischemia Induced by Mental Stress. Arteriosclerosis, Thrombosis, and Vascular Biology. 2018;38(2):473–80. DOI: 10.1161/ATVBAHA.117.309535
17. Vaccarino V, Sullivan S, Hammadah M, Wilmot K, Al Mheid I, Ramadan R et al. Mental Stress–Induced-Myocardial Ischemia in Young Patients With Recent Myocardial Infarction: Sex Differences and Mechanisms. Circulation. 2018;137(8):794–805. DOI: 10.1161/CIRCULATIONAHA.117.030849
18. Patel SM, Lerman A, Lennon RJ, Prasad A. Impaired coronary microvascular reactivity in women with apical ballooning syndrome (Takotsubo/stress cardiomyopathy). European Heart Journal: Acute Cardiovascular Care. 2013;2(2):147–52. DOI: 10.1177/2048872613475891
19. Barletta G, Del Pace S, Boddi M, Del Bene R, Salvadori C, Bellandi B et al. Abnormal coronary reserve and left ventricular wall motion during cold pressor test in patients with previous left ventricular ballooning syndrome. European Heart Journal. 2009;30(24):3007–14. DOI: 10.1093/eurheartj/ehp325
20. Santoro F, Mallardi A, Leopizzi A, Vitale E, Rawish E, Stiermaier T et al. Current Knowledge and Future Challenges in Takotsubo Syndrome: Part 2 — Treatment and Prognosis. Journal of Clinical Medicine. 2021;10(3):468. DOI: 10.3390/jcm10030468
21. Ma H, Guo L, Fei H, Yin H, Wang H, Bai B et al. Assessing mental stress on myocardial perfusion and myocardial blood flow in women without obstructive coronary disease: protocol for a mechanistic clinical trial. BMJ open. 2020;10(12):e038362. DOI: 10.1136/bmjopen-2020-038362
22. Jaguszewski M, Osipova J, Ghadri J-R, Napp LC, Widera C, Franke J et al. A signature of circulating microRNAs differentiates takotsubo cardiomyopathy from acute myocardial infarction. European Heart Journal. 2014;35(15):999–1006. DOI: 10.1093/eurheartj/eht392
23. Feoktistova V.S., Vavilova T.V., Sirotkina O.V., Boldueva S.A., Gaikovaia L.B., Leonova I.A. et al. A new approach to assessing dysfunction endothelium: determination of the number of circulat-

ISSN 0022-9040. Kardiologiia. 2023;63(3). DOI: 10.18087/cardio.2023.3.n2364

ing endothelial cells by flow cytometry. Clinical laboratory diagnostics. 2015;60(4):23–39. [Russian: Феоктистова В.С., Вавилова Т.В., Сироткина О.В., Болдуева С.А., Гайковая Л.Б., Леонова И.А. и др. Новый подход к оценке дисфункции эндотелия: определение количества циркулирующих эндотелиальных клеток методом проточной цитометрии. Клиническая лабораторная диагностика. 2015;60(4):23-39]

24. Topuzova M.P., Alekseeva T.M., Vavilova T.V., Sirotkina O.V., Klocheva E.G. Circulating endothelial cells and endothelial progenitor cells as a marker of endothelial dysfunction in hypertensive patients survived after ischemic stroke (review). Arterial Hypertension. 2018;24(1):57–64. [Russian: Топузова М.П., Алексеева Т.М., Вавилова Т.В., Сироткина О.В., Клочева Е.Г. Циркулирующие эндотелиоциты и их предшественники как маркер дисфункции эндотелия у больных артериальной гипертензией, перенесших ишемический инсульт (обзор). Артериальная гипертензия. 2018;24(1):57-64]. DOI: 10.18705/1607-419X-2018-24-1-57-64