ASSESSMENT OF DIASTOLIC FUNCTION IN PATIENTS WITH CHEST PAIN AND ANGIOGRAPHICALLY NORMAL CORONARY ARTERIES USING ECG-GATED SPECT

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The diagnosis and treatment of patients with angiographically normal or near normal coronary arteries remains a clinically relevant problem. The aim of this study was to assess diastolic function in patients with chest pain and normal/near normal coronary arteries (NECA) using ECG-gated SPECT/CT. The study recruited 49 patients presenting with chest pain, a positive cardiac stress test and normal coronary arteries, as demonstrated by coronary angiography. All patients were ordered a myocardial SPECT/CT scan, which was performed according to a two-day protocol. After the scan, the patients were divided into 3 groups. Group 1 consisted of 17 patients with microvascular angina. Group 2 was composed of 22 patients with borderline-high blood pressure or stage I hypertensive heart disease associated with secondary microvascular dysfunction. Ten seemingly healthy individuals constituted the control group. According to coronary angiography, the controls had no cardiovascular pathologies accompanied by coronary artery disorders or impaired myocardial perfusion (SPECT). The majority of patients from groups 1 and 2 were found to have impaired diastolic function. The impairments were more pronounced in group 2 tended to exacerbate with stress. The most sensitive parameter of diastolic function, MFR/3, was outside the reference range in almost all patients in groups 1 and 2. MFR/3 characterizes the mean filling rate of the left ventricle in the first third of diastole. The control group showed no symptoms of diastolic dysfunction. Thus, the patients with chest pain, a positive stress test and NECA had signs of left ventricular diastolic dysfunction exacerbated with stress. Such patients are at risk for heart failure with preserved ejection fraction.

Keywords: single-photon emission computed tomography, microvascular angina, diastolic function, angiographically normal or near normal epicardial coronary arteries, myocardial perfusion

Acknowledgements: the authors wish to thank Viktor K. Sychev for kindly allowing them to use the equipment of the Laboratory for Radioisotopes.

Author contribution: Khachirova EA recruited patients for the study, prepared the necessary documentation, participated in conducting the cardiac stress test and SPECT/CT, and processed the obtained data; Samoylenko LE controlled the course of the study and double-checked the obtained results; Shevchenko OP made sure inclusion and exclusion criteria were met.

Compliance with ethical standards: the study was approved by the Ethics Committee of Pirogov Russian Medical Research Medical University (Protocol 150 dated December 15, 2015). All patients gave informed consent to participate.

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Received: 17.09.2018 **Accepted:** 11.11.2018 **Published online:** 23.02.2019

DOI: 10.24075/brsmu.2019.001

ОЦЕНКА ДИАСТОЛИЧЕСКОЙ ФУНКЦИИ МИОКАРДА У ПАЦИЕНТОВ С БОЛЕВЫМ СИНДРОМОМ В ГРУДНОЙ КЛЕТКЕ И АНГИОГРАФИЧЕСКИ НЕИЗМЕННЫМИ КОРОНАРНЫМИ АРТЕРИЯМИ МЕТОДОМ СИНХРОНИЗИРОВАННОЙ С ЭКГ ОДНОФОТОННОЙ ЭМИССИОННОЙ КОМПЬЮТЕРНОЙ ТОМОГРАФИИ

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На протяжении многих лет остается актуальной тема диагностики и тактики ведения пациентов с ангиографически неизмененными или малоизмененными коронарными артериями (КА). Целью исследования было оценить диастолическую функцию у пациентов с болевым синдромом в грудной клетке и неизмененными/малоизмененными КА (Н/МКА) по данным синхронизированной с ЭКГ однофотонной эмиссионной компьютерной томографии (С-ОЭКТ/КТ). В исследование вошли 49 пациентов с болевым синдромом в области грудной клетки, положительными результатами нагрузочного теста и Н/МКА по данным коронароангиографии (КАГ). Всем пациентам выполнили С-ОЭКТ/КТ миокарда по двухдневному протоколу. После исследования пациенты были разделены на три группы: 17 пациентов с микрососудистой стенокардией составили группу 1; 22 пациента с пограничной артериальной гипертензией (АГ), или гипертонической болезнью (ГБ) I стадии, ассоциирующейся с вторичной микрососудистой дисфункцией — группу 2. Группу контроля, или группу 3, составили 10 практически здоровых лиц, у которых при КАГ были исключены заболевания со стороны сердечно-сосудистой системы, сопровождающиеся изменениями коронарных артерий и нарушениями перфузии миокарда при проведении ОЭКТ. У большинства пациентов в группах 1 и 2 были выявлены нарушения диастолической функции, при этом в группе 2 они глубже и усугубляются при нагрузке. Наиболее чувствительный параметр диастолической функции — средняя скорость наполнения ЛЖ в первую треть диастолы (MFR/3) — изменен практически у всех пациентов групп 1 и 2. У пациентов группы контроля изменения не выявлены. Таким образом, у пациентов с болью в груди, положительным стресс-тестом и Н\МКА выявлены признаки диастолической дисфункции ЛЖ (ДДФ) и дальнейшее ее ухудшение при нагрузке. Эти пациенты могут представлять собой группу риска развития сердечной недостаточности с сохраненной фракцией выброса.

Ключевые слова: однофотонная эмиссионная компьютерная томография, ангиографически неизмененные/малоизмененные эпикардиальные коронарные сосуды, диастолическая функция, перфузионная сцинтиграфия, микрососудистая стенокардия

Благодарности: авторы благодарят Виктора Константиновича Сычева за возможность воспользоваться радиоизотопной лабораторией и оборудованием в процессе сбора материала.

Информация о вкладе авторов: Э. А. Хачирова подбирала пациентов, оформляла документацию для проведения исследования, участвовала в проведении велоэргометрии и сцинтиграфического исследования, обрабатывала полученные данные; Л. Е. Самойленко контролировала протокол исследования, проверяла полученные результаты; О. П. Шевченко контролировал соблюдение критериев включения в исследование и критериев исключения при отборе пациентов.

Соблюдение этических стандартов: исследование одобрено этическим комитетом РНИМУ им. Н. И. Пирогова (протокол № 150 от 15 декабря 2015 г.). Все пациенты подписали добровольное информированное согласие на проведение исследования.

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Статья получена: 17.09.2018 **Статья принята к печати:** 11.11.2018 **Опубликована онлайн:** 23.02.2019

DOI: 10.24075/vrgmu.2019.001

The use of echocardiography (EchoCG) in clinical diagnostics shed light on the actual prevalence of heart failure (HF) with preserved left ventricular (LV) systolic function (ejection fraction (EF) > 45%), which turned out to be a very widespread condition. According to the Framingham Heart Study (1948–2012), the Rochester Epidemiology Project (1960–1984) and some other research studies, patients with preserved LVEF make up over one-third of all individuals with HF, and their number is growing steadily [1, 2]. Diastolic dysfunction (DD) is believed to be one of the possible causes of HF in such patients [3–5]. Isolated DD is more often diagnosed in patients with angiographically normal or near normal epicardial coronary arteries (NECA) [6].

In spite of the obvious advances in the understanding of DD in patients with NECA, there are questions about the etiology and pathogenesis of diastolic impairment that still need to be answered [7, 8]. The underlying causes of DD and DD-associated HF named in the literature include LV hypertrophy, metabolic shifts, myocardial fibrosis, and coronary microvascular dysfunction (CMD) that many authors also regard as a risk factor for adverse cardiovascular events [9, 10].

Clinical data corroborating the role of CMD in triggering DD in patients with normal epicardial coronary arteries come from limited sources. For example, there was an extensive retrospective study in which the medical histories of 376 patients with LVEF ≥ 50% and without signs of obstructive coronary artery disease were analyzed [11]. Cardiac PET imaging revealed that all patients with HF, preserved LFEF and signs of DD had reduced coronary flow reserve, which, according to the authors of the study, may have indicated an association between a microvascular pathology, DD and HF. Myocardial hypertrophy (MH) is another possible reason of DD in patients with NECA. A transesophageal Doppler study assessing diastolic function in 30 patients with left ventricular hypertrophy (LVH) found that 16 participants had symptoms of ischemia and angiographically normal CA whereas in 14 patients LVH was asymptomatic. Signs of DD were present in both groups, but tended to be more pronounced in group 1 [12].

Ectopic fat deposition referred to as myocardial steatosis may also increase the risk of DD. A team of researchers measured myocardial triglyceride content and assessed diastolic function in 13 women with intact CA using proton magnetic resonance spectroscopy and magnetic resonance tissue tagging [6]. Five women were shown to have signs of CMD and subclinical DD correlated with high triglyceride content in the myocardium. The authors concluded that myocardial steatosis has a distinct association with diastolic dysfunction in the studied cohort of patients.

At the same time, there are reports that such patients do not develop DD. For example, ECG revealed no significant impairment of diastolic function in 99 patients with syndrome X confirmed by a stress test [13].

Given that the literature reports are controversial, research into DD should be continued in order to work out criteria for this condition and to prevent diastolic heart failure in patients with angiographically normal or near normal epicardial coronary arteries. Today, echocardiography remains the most available and popular method for the assessment of systolic and diastolic myocardial function. However, its reproducibility is quite low and depends largely on the operator who performs the scan. In contrast, cardiac radionuclide imaging is characterized by higher reproducibility and high accuracy, and its results only slightly depend on the operator's skills.

Considering the abovesaid, the aim of this study was to measure the left ventricular function in patients with chest pain and normal or near normal epicardial coronary arteries using cardiac single-photon emission computed tomography (C-SPECT).

METHODS

The study recruited 49 participants (24 men and 25 women) aged 43 to 77 years (the mean age was 62.6 ± 8.9 years) with chest pain (CP) and a positive stress test. All patients were examined and received treatment at the facilities of the Department of Cardiology, Pirogov Russian Medical Research Medical University.

The following exclusion criteria were applied: hypertension (systolic blood pressure ≥ 180 mmHg and diastolic blood pressure ≥110 mmHg), cardiac lesions, LVH, hypertrophic and dilated cardiomyopathies, acute myocardial infarction within 6 months preceding our study, LVEF < 45%, persistent flutter and atrial fibrillation, arrythmias, impaired conductivity, valvular/endocrine/neurological/ disorders, kidney or liver failure, and other diseases leading to impaired myocardial perfusion or affecting systolic and diastolic functions of the myocardium.

A detailed medical history was taken from all participants; a full blood count and a blood biochemistry test were also performed. The patients underwent a physical examination, a standard 12-lead ECG, Holter monitoring, a cardiac stress test on a stationary bicycle (CST), coronary angiography, and a C-SPECT/CT scan at rest and with stress. Angiography identified 37 patients with intact coronary arteries and 12 patients with stenosis (<40%) in one artery and normal systolic function (as assessed by EchoCG). Twenty-two participants had borderline-high blood pressure or stage I hypertensive heart disease with a LV mass index of 132 ± 21; the blood pressure was lowered to an average of 125/80 mmHg by the prescribed medication therapy. Seventeen patients had no comorbidities (the LV mass index was 128 ± 27). Twenty-one patient had hypercholesterinemia: total cholesterol levels were 5.4 ± 1.68 mmol/l, concentrations of low-density lipoproteins were 3.3 ± 1.0 mmol/l. Ten participants who did not have any cardiovascular disorders constituted the control group. Clinical characteristics of the patients are given in Table 1.

All patients underwent a myocardial SPECT/CT scan at the Department of Radionuclide Diagnostics. The scans were ordered to assess the systolic and diastolic functions of the heart. Antianginal therapy was temporarily discontinued before the scan for the period of > 5 elimination half-lives of the used drug.

A 2-day C-SPECT/CT protocol was applied. On the first day, the scan was performed at rest; on the second day, stress images were obtained following the exercise ECG test. During the test on the Ergoline bicycle ergometer, the blood pressure was monitored. The test was conducted according to the standard protocol. The initial workload was 25 W; it was increased by 25 W every 3 minutes. Once the maximal workload was achieved, the patients received an intravenous injection of a radiopharmaceutical and then continued exercising for another minute.

The radiopharmaceutical selected for our study was Technetium (^{99m}Tc) sestamibi (Russia). It was administered intravenously via a 444–555 MBq bolus injection. Images were recorded using a gamma camera. Stress images were obtained 45–60 min after the injection administered during the exercise test, whereas rest images were obtained 60–90 min after the injection at rest.

ECG-gated SPECT/CT imaging was assisted by the dual-detector gamma camera Symbia T-16 (Siemens; Germany) connected to a low-dose scanner for computed tomography equipped with a SMARTZOOM collimator for cardiac studies. Image acquisition was triggered by the R wave. During the scan, the patients were lying in the supine position. The detectors were positioned at 90° to each other and were rotating 180° around the patient's body. In total, 32 projections (16 per detector) were obtained for each patient.

Myocardial perfusion and diastolic function were analyzed in QPS\QGS, AutoSPECT (Quark Inc., version 8.5) using a 17-segment model of the left ventricle. The following systolic and diastolic parameters were assessed.

1. Systole:

– EF ≥ 50% at rest and with stress;

– PER (the peak ejection rate of the LV, expressed as end-systolic volume per second, the normal range is from 2 to 3) at rest and with stress.

2. Diastole:

– PFR (the peak filling rate of the LV, expressed as end-diastolic volume per second, the normal range is from 2 to 3); characterizes myocardial diastolic function;

– MFR\3 (the mean filling rate of the LV during the first-third of diastole, expressed as end-diastolic volume per second, the reference range is from 1.5 to 2);

– PFR2 (secondary peak filling rate, not observed in healthy patients); in patients with two or more filling peaks, the peak filling rate during the second peak was calculated;

– TTPF (time from end systole to peak filling, the normal range is 100–150 ms).

If at least parameter of diastolic function fell outside the reference range, DD was presumed [10].

The obtained data were processed in Statistica 6.0 (StatSoft; version 6.0) and are presented in this work as M ± SD (mean ± standard deviation). Qualitative parameters were compared using the Pearson's chi square test. If the number of observations in one of the compared groups was less than 11, the Yates correction was applied. If the number of observations was below 5, the two-sided Fisher's test was used.

Quantitative data were compared using nonparametric tests, including the Mann Whitney U for 2 independent variables and the Kruskal-Wallis for 3 or more independent variables.

RESULTS

The study participants were examined and divided into 3 groups. Group 1 consisted of 17 patients with microvascular angina (MA) who complained of chest pain but had no comorbidities that could lead to impaired myocardial perfusion; their coronary arteries appeared intact during the coronary angiography, and C-SPECT/CT verified transient myocardial ischemia. Group 2 was composed of 22 patients with borderline-high blood pressure or stage I hypertensive heart disease confirmed by the results of 24-h blood pressure monitoring. The patients in group 2 had no LVH (LV mass index was 132 ± 21) and no cardiac lesions; their blood pressure was lowered to the desired values, and C-SPECT/CT verified transient myocardial ischemia associated with secondary CMD. The control group included 10 seemingly healthy individuals with no cardiovascular conditions, intact coronary arteries and normal myocardial perfusion. In each group, the patients were comparable in terms of age, BMI, heart rate (HR) and blood pressure measured at rest. No significant differences were observed between the groups regarding heart rate, blood pressure, ESD, and EDD (measured by echocardiography) determined at rest (Table 1). In the controls, the systolic and diastolic parameters of the left ventricle fell within the normal reference range both at rest and after exercise.

No significant differences were found in the parameters characterizing the systolic function of the LV between the patients with NECA. EF and peak ejection rate at rest and after the stress test did not differ significantly between groups 1 and 2. At rest, EF was 58.5 ± 6.6 and 59.5 ± 6.8 ($p > 0.05$) in groups 1 and 2, respectively, whereas after the stress test, it reached 65.6 ± 7.8 and 66.4 ± 8.8 ($p > 0.05$), respectively. In

Table 1. Clinical characteristics of the study participants

Parameter	Group 1 (MVA), n = 17	Group 2 (CMD), n = 22	Group 3 controls, n = 10
Age	62.7 ± 7.8 (50–77)	60.6 ± 8.1 (44–75)	63.2 (43–74)
Sex, male/female	6/11	12/10	6/4
BMI (kg/m²)	25.8 ± 3.6	26.7 ± 3.2	25.7 ± 3.47
Duration of disease, years	3.4 ± 2	3.8 ± 1.9	3.2 ± 1.7
Systolic blood pressure (mmHg)	122 ± 9.2	130 ± 6.8	126 ± 6.4
Diastolic blood pressure (mmHg)	73 ± 5.8	74 ± 4.0	72 ± 6.0
LV mass index	128 ± 27	132 ± 21	127 ± 18
Resting heart rate	67 ± 8	72 ± 6	66 ± 8
Pain type:			
Nonanginal (localized, lasting for several hours or more. not relieved by nitroglycerin)	5	7	10
Anginal	12	15	0
Holter monitoring results:			
NORM	6	11	10
ST depression ≥ 2.0 mm	4	5	0
ST depression ≤ 2.0 mm	7	6	0
EchoCG of LV:			
EF (biplane Simpson's method), %	64.5 ± 9.5	60.7 ± 4.0	67.4 ± 10.2
ESD, cm	3.5 ± 0.3	3.6 ± 0.3	2.77 ± 0.5
EDD, cm	4.8 ± 0.3	4.9 ± 0.4	4.65 ± 0.2
PWT, cm	1.0 ± 0.06	1.04 ± 0.08	0.98 ± 0.15

Note: MVA stands for microvascular angina; ESD is end-systolic dimension; EDD is end-diastolic dimension; PWT is posterior wall thickness; HR is heart rate.

group 1, PER at rest was 2.5 ± 0.2, increasing up to 2.7 ± 0.3 after the stress test. In group 2, PER was 2.4 ± 0.3 and 2.7 ± 0.4 ($p > 0.05$) at rest and after the stress test, respectively.

Left ventricular systolic function was normal in both groups.

Diastolic abnormalities were detected in the majority of the patients with NECA both at rest and with stress. At least one measured parameter fell outside the normal range in all patients from group 1 and 17 patients from group 2, indicating DD. MFR/3 was aberrant almost in all participants. However, deviations from the norm were more often observed for more than one measured parameter. At rest, 5 patients from group 1 had abnormal MFR/3 only; 6 patients had abnormal MFR/3+another parameter; in another 5 patients 3 parameters fell outside the reference range; and in 1 patient 4 measured parameters deviated from the norm. After the stress test, deviations from the normal range affecting only 1 parameter were observed in 3 patients; 2 parameters, in 4 patients; 3 parameters, in 7 patients; and 4 parameters, in 2 patients. To sum up, after the stress test the majority of the patients had abnormal values of 3 to 4 parameters characterizing myocardial function, as compared to the same parameters measured at rest.

In group 2, one parameter measured at rest fell outside the normal range in 2 patients; 2 parameters, in 7 patients; 3, in 5 patients; and 4, in 3 patients. In another 5 patients all studied parameters were perfectly normal. However, after the stress test, only one patient still had only one abnormality in the measured parameters; 2 abnormal parameters were detected in 7 patients; 3, in 6 patients; and 4, in 4 patients.

Mean values characterizing myocardial function in patients with normal or near normal epicardial coronary arteries and healthy controls are presented in Table 2.

There were significant differences between groups 1 and 2 in the values of PFRrest, MFR/3stress, TTPFrest, and PFR2stress. At rest, secondary filling peaks were detected in 3 (17%) patients from group 1 and 5 patients (23%) from group 2; after the stress test, secondary filling peaks were present in 4 (23%) and 7 (32%) patients from groups 1 and 2, respectively. No significant difference in MFR/3 at rest and with stress was observed between groups 1 and 2. Perhaps, this is because in both groups this parameter was initially abnormal both at rest and with stress.

When comparing groups 1 and 2 with the controls, we discovered significant differences in all parameters except for PFRrest in group 1. Importantly, EchoCG identified DD signs in 11 (65%) patients from group 1 and 14 (82%) patients from group 2. Echocardiographic criteria for DD include a decline in peak early-diastolic velocity e` (e` < 9 cm/s on average), an increased ratio of early to late diastolic annular velocities (> 15), and a combination of a few other parameters [12]. All cases of diastolic dysfunction suggested by EchoCG were confirmed by C-SPECT.

Below we describe a clinical case of a female patient aged 69 who presented with chest pain and shortness of breath lasting for up to 25 min that appeared following emotional stress and could not be relieved by nitroglycerin. The coronary arteries were intact. The established diagnose was class II effort angina. The patient had had this condition for about 2 years, with almost daily episodes of pain. The patient had no history of familial cardiovascular diseases or addictions.

The patient was in a satisfactory condition at admission. BMI was 20. Blood count and biochemistry, as well as thyroid hormone levels, were within the reference range. ECG revealed normal sinus rhythm and HR of 68 beats/min. EchoCG findings: EDD = 4.6 cm, ESD = 3.2 cm, PWT = 1.0 cm. EF was > 60%, local contractility was without abnormalities. The stress test revealed episodes of ST depression of up to 1.5 mm. Coronary angiography showed that the coronary arteries were intact.

According to C-SPECT scans (Fig. 1, 2) performed at rest (1) and with stress (2), left ventricular systolic function was intact: EF was 67% at rest and 76% after the exercise test. No LV wall motion abnormalities were observed; LV PER was 2.7 at rest and 2.94 after the stress test.

LV PFR was within the reference range: 2.71 at rest and 3.04 after the stress test; MFR/3 was 0.77 at rest and 0.91 after the stress test. LV TTPF was impaired (286 at rest and 287 after the stress test). Additional LV filling peaks were not detected.

The patient exhibited signs of diastolic dysfunction suggested by abnormal MFR/3 and TTPF. Perfusion myocardial SPECT registered signs of transient myocardial ischemia in the upper and medial regions of the anterior wall.

DISCUSSION

It was established that the majority of patients with NECA participating in our study had diastolic dysfunction. What factors can contribute to the impairment of the diastolic cycle in such patients? One of the causes named in the literature is myocardial fibrosis accompanied by changes in cardiac contractility [3, 6]. All patients recruited in our study did not have problems with their left ventricular systolic function; EF and PER measured at rest and after the cardiac test were within

Table 2. Quantitative parameters of diastolic function in the studied groups of patients

Parameters	Parameters of diastolic function				Difference between the groups (*p*-value)			
	Groups 1 and 2, *n* = 39	Group 1, *n* = 17	Group 2, *n* = 22	Group 3 (controls), *n* = 10	Columns 1 and 4	Columns 2 and 3	Columns 2 and 4	Columns 3 and 4
	1	2	3	4				
PFRstress, EDV/s	1.89 ± 0.21	1.93 ± 0.17	1.86 ± 0.24	2.75 ± 0.31	**0.000001**	0.5	**0.00002**	**0.000009**
PFRrest, EDV/s	1.97 ± 0.27	2.12 ± 0.28	1.86 ± 0.20	2.32 ± 0.32	**0.002**	**0.003**	0.14	**0.0001**
MFR/3stress, EDV/s	1.12 ± 0.22	1.01 ± 0.23	1.20 ± 0.17	1.77 ± 0.14	**0.000001**	**0.009**	**0.00002**	**0.000009**
MFR/3rest, EDV/s	1.26 ± 0.24	1.26 ± 0.24	1.26 ± 0.25	1.60 ± 0.15	**0.0003**	0.9	**0.0008**	**0.001**
TTPFrest, ms	164.1 ± 18.1	156.0 ± 13.1	170.4 ± 19.2	138.4 ± 9.5	**0.000047**	**0.015**	**0.001**	**0.00005**
TTPFstress, ms	172.3 ± 24.9	166.3 ± 13.5	176.9 ± 30.5	153.0 ± 6.8	**0.01**	0.3	**0.009**	**0.04**
PFR2stress, number of patients, abs. number, %	14 (35.9%)	3 (17.6%)	11 (50.0%)	0	–	**0.049**	–	–
PFR2rest, number of patients, abs. number, %	8 (20.5%)	1 (5.9%)	7 (31.8%)	0	–	0.1	–	–

Note: significant differences are shown in bold; stress stands for the measurements done after the stress test; rest stands for the measurements at rest.

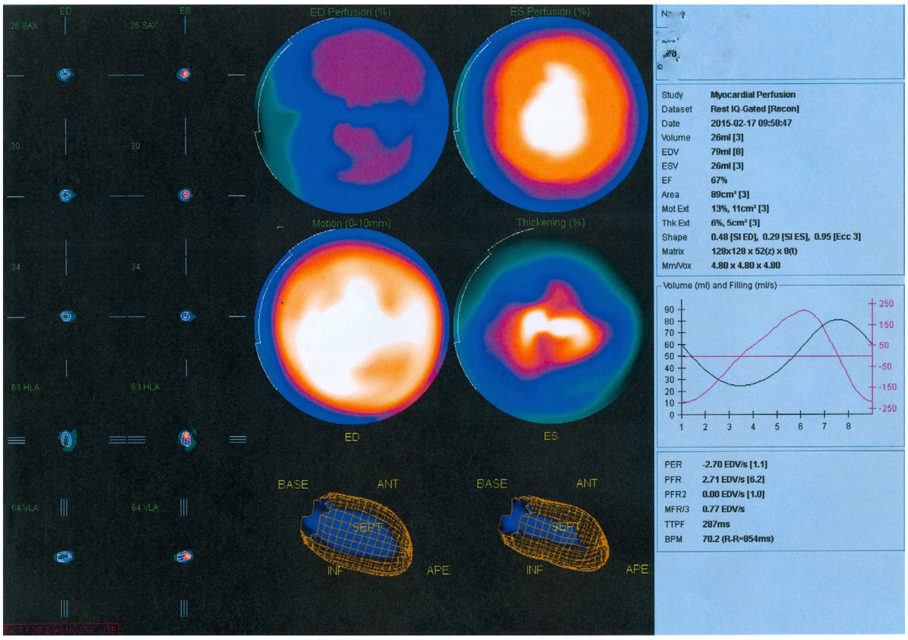

Fig. 1. A resting C-SPECT scan of a female patient aged 69 who presented with chest pain and intact coronary arteries (class II effort angina)

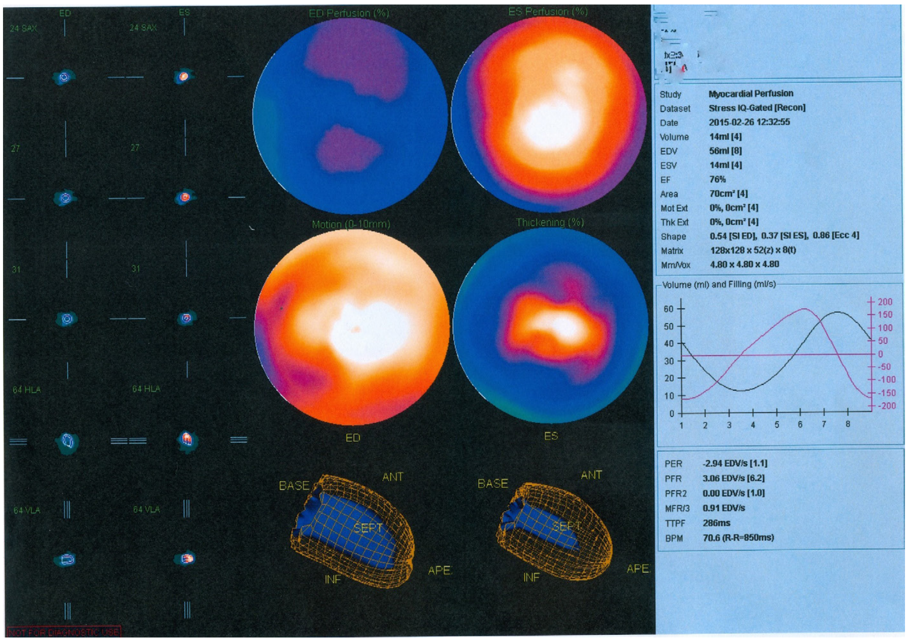

Fig. 2. A stress C-SPECT scan of a female patient aged 69 who presented with chest pain and intact coronary arteries

the normal reference range. No local impairment of LV wall motion was observed. Therefore, we conclude that diastolic dysfunction in our patients is not associated with impaired contractility (myocardial fibrosis).

LV hypertrophy is another possible cause underlying DD. Patients with myocardial hypertrophy were not included in the present study. LV mass index was within the reference range in all patients, reaching 128 ± 27, 132 ± 21 and 127 ± 18 in groups 1 and 2 and the controls, respectively.

Metabolic shifts can also be regarded as a factor contributing to DD. However, our study did not include patients suffering from the conditions associated with metabolic shifts, except for those accompanying transient myocardial ischemia.

The most probable cause of DD in the studied cohort of patients is microvascular dysfunction. Although coronary arteries were intact in all examined patients, C-SPECT/CT verified the diagnosis of transient ischemia in groups 1 and 2.

Patients from group 2 had abnormal left ventricular PFR and TTPF. Those deviations from the norm were more noticeable in group 2 than in patients from group 1 who did not have hypertension. MFR/3, the most sensitive parameter of diastolic function, was abnormal at rest in groups 1 and 2, as compared with the controls, but did not differ significantly between the groups. The abnormalities became more pronounced after the stress test in the absence of any LV wall motion pathology. This could be explained by reduced myocardial perfusion and transient myocardial ischemia.

Besides, a secondary filling peak was detected in some patients from both groups at rest; the number of peaks increased in response to physical exercise.

Our findings are consistent with other studies of diastolic function in patients with intact coronary arteries. For example, an echocardiographic Doppler study demonstrated that diastolic function was impaired in female patients with microvascular angina [14]. In another study, diastolic function was assessed using C-SPECT, EchoCG and heart MRI [15]. Importantly, those C-SPECT findings are consistent with the results of the present study. In [15] EchoCG suggested DD in more than 60% of patients with DD detected by C-SPECT, which also concurs with our findings (65% and 82% in groups 1 and 2, respectively). According to Y.W. Wu et al, C-SPECT is less sensitive to DD than Doppler echocardiography. At the same time, the authors point to high sensitivity of 64-slice computed tomography in the assessment of DF [15].

In conclusion, we would like to stress that all studies listed above, including our own, were performed on a small sample, meaning they have serious limitations. Therefore, research into the causes of diastolic dysfunction should be continued.

CONCLUSIONS

The present study has demonstrated that diastolic function is impaired in patients with intact coronary arteries and chest pain. Given that the literature on the subject is scarce and controversial, we believe that research into the causes of diastolic dysfunction should be continued.

References

1. Hogg K, Swedberg K, McMurray J. Heart Failure with preserved left ventricular systolic function. Epidemiology, Clinical Characteristics, and Prognosis. J Am Coll Cardiol. 2004; 43 (3): 317–27.
2. Fomin IV, Belenkov JuN, Mareev Vju, et al. Rasprostranennost' hronicheskoj serdechnoj nedostatochnosti v Evropejskoj chasti RF (dannye issledovanija «JePOHA – HSN»). ZhSN. 2006; 3 (7): 112–5.
3. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013; 62: 263–71.
4. Taqueti VR, Ridker PM. Inflammation, coronary flow reserve, and microvascular dysfunction: moving beyond cardiac syndrome X. JACC Cardiovasc Imaging. 2013; (6): 668–71.
5. Crea F, Merz CNB, Beltrame JF, et al. Coronary Vasomotion Disorders International Study Group. The parallel tales of microvascular angina and heart failure with preserved ejection fraction: a paradigm shift. Eur Heart J. 2017; (38): 473–77.
6. Wei J, Nelson MD, Szczepaniak EW, et al. Myocardial steatosis as a possible mechanistic link between diastolic dysfunction and coronary microvascular dysfunction in women Am J Physiol Heart Circ Physiol. 2016; 310 (1): H14–H1.
7. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; (37): 2129–200.
8. Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med. 2016; (375): 1868–77.
9. Van Krajj DJ, van Pol PE, Ruiters AW, et al. Diagnosing diastolic heart failure. Eur J Heart Fail. 2002; 4 (4): 419–30.
10. Kato S, Saito N, Kirigaya H, et al. Impairment of coronary flow reserve evaluated by phase contrast cine-magnetic resonance imaging in patients with heart failure with preserved ejection fraction. J Am Heart Assoc. 2016; (5): e002649.
11. Srivaratharajah K, Coutinho T, Liu P, et al. Reduced myocardial flow in heart failure patients with preserved ejection fraction. Circ Heart Fail. 2016; 9 (7): e002562.
12. Isaaz K, Bruntz JF, Paris D, et al. Abnormal coronary flow velocity pattern in patients with left ventricular hypertrophy, angina pectoris, and normal coronary arteries: A transesophageal Doppler echocardiographic study. American Heart Journal. 1994; 128 (3): 500–10.
13. Kaski JC, Rosano GMC, Collins P, et al. Cardiac syndrome X: clinical characteristics and left ventricular function. Journal of the American College of Cardiology. 1995; (25): 807–14.
14. Nelson MD, Szczepaniak LS, Weiet J, al. Diastolic Dysfunction in Women With Signs and Symptoms of Ischemia in the Absence of Obstructive Coronary Artery Disease A Hypothesis-Generating Study. Circ Cardiovasc Imaging. 2014; (7): 510–6.
15. Wu Y, Tadamura E, Yamamuro M, et al. Estimation of global and regional cardiac function using 64-slice computed tomography: a comparison study with echocardiography, gated-SPECT and cardiovascular magnetic resonance. Int J Cardiol. 2008; 128 (1): 69–76.

Литература

1. Hogg K, Swedberg K, McMurray J. Heart Failure with preserved left ventricular systolic function. Epidemiology, Clinical Characteristics, and Prognosis. J Am Coll Cardiol. 2004; 43 (3): 317–27.
2. Фомин И. В., Беленков Ю. Н., Мареев В. Ю. и др. Распространенность хронической сердечной недостаточности в Европейской части РФ (данные исследования «ЭПОХА — ХСН»). ЖСН, 2006; 3 (7): 112–15.
3. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013; 62: 263–71.
4. Taqueti VR, Ridker PM. Inflammation, coronary flow reserve, and microvascular dysfunction: moving beyond cardiac syndrome X. JACC Cardiovasc Imaging. 2013; (6): 668–71.
5. Crea F, Merz CNB, Beltrame JF, et al. Coronary Vasomotion Disorders International Study Group. The parallel tales of microvascular angina and heart failure with preserved ejection fraction: a paradigm shift. Eur Heart J. 2017; (38): 473–77.
6. Wei J, Nelson MD, Szczepaniak EW, et al. Myocardial steatosis as a possible mechanistic link between diastolic dysfunction and coronary microvascular dysfunction in women Am J Physiol Heart Circ Physiol. 2016; 310 (1): H14–H1.
7. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; (37): 2129–200.
8. Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med. 2016; (375): 1868–77.
9. Van Krajj DJ, van Pol PE, Ruiters AW, et al. Diagnosing diastolic heart failure. Eur J Heart Fail. 2002; 4 (4): 419–30.
10. Kato S, Saito N, Kirigaya H, et al. Impairment of coronary flow reserve evaluated by phase contrast cine-magnetic resonance imaging in patients with heart failure with preserved ejection

fraction. J Am Heart Assoc. 2016; (5): e002649.

11. Srivaratharajah K, Coutinho T, Liu P, et al. Reduced myocardial flow in heart failure patients with preserved ejection fraction. Circ Heart Fail. 2016; 9 (7): e002562.
12. Isaaz K, Bruntz JF, Paris D, et al. Abnormal coronary flow velocity pattern in patients with left ventricular hypertrophy, angina pectoris, and normal coronary arteries: A transesophageal Doppler echocardiographic study. American Heart Journal. 1994; 128 (3): 500–10.
13. Kaski JC, Rosano GMC, Collins P, et al. Cardiac syndrome X: clinical characteristics and left ventricular function. Journal of the American College of Cardiology. 1995; (25): 807–14.
14. Nelson MD, Szczepaniak LS, Weiet J, al. Diastolic Dysfunction in Women With Signs and Symptoms of Ischemia in the Absence of Obstructive Coronary Artery Disease A Hypothesis-Generating Study. Circ Cardiovasc Imaging. 2014; (7): 510–6.
15. Wu Y, Tadamura E, Yamamuro M, et al. Estimation of global and regional cardiac function using 64-slice computed tomography: a comparison study with echocardiography, gated-SPECT and cardiovascular magnetic resonance. Int J Cardiol. 2008; 128 (1): 69–76.