

Functional state of cardiovascular system and cardiovascular risk stratification in women with postovariectomy syndrome

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Summary

Objective

To reveal the features of the structural and functional state of cardiovascular system and to stratify cardiovascular risk in women with silent depression of the ST-segment and postovariectomy syndrome.

Materials and methods

The study involved 66 women with perimenopausal metabolic syndrome, including 30 females after surgical menopause (main observation group) and 36 females with naturally occurring menopause (comparison group).

Results

In women with surgical menopause and metabolic syndrome, significant epicardial obesity and coronary calcification were identified; myocardial ischemia was more evident, myocardial hypertrophy and remodeling of the left ventricle was accompanied with violation of its diastolic function. Concentric hypertrophy of the left ventricle prevailed in the structure of geometric model disturbances.

Conclusion

The fact of detection of high risk of adverse cardiovascular events in women with surgical menopause according to single-photon emission computed tomography is clinically significant. Obtained data determine the necessity to search new criteria of cardiovascular risk stratification for the selection of patients with high cardiovascular risk and its timely correction.

Key words

Silent myocardial ischemia, postovariectomy syndrome, single-photon emission computed tomography (SPECT), epicardial adipose tissue

Introduction

In the developed countries postmenopausal period takes more than 1/3 part of women's life, and exactly this period becomes the most socially active one. Investigation of cardiovascular pathology in females is impossible without taking into account cyclic and age-related changes of the endocrine system. Estrogens' deficiency, fat tissue and biologically active molecules produced by it are interrelated, and it is associated with impaired metabolism of fat tissue, development of abdominal obesity, insulin resistance, dyslipidemia, increased activity of sympathetic nervous system and development of arterial hypertension (AH), impaired endothelial function and thrombus formation, changed secretion of neural steroids and neural peptides participating in the regulation of food behavior and providing integrative action of different brain parts and realization of its cognitive function. Even if there is no verified correlation between cardiovascular events and estradiol plasma levels, the crucial role of visceral obesity in coronary heart disease (CHD) that can be triggered by hypoestrogenia is beyond dispute. Surgical menopause may prove the significance of sex hormones as the risk factor of cardiovascular disease (CVD), since the disorders in this condition have more evident manifestations comparing with the natural menopause. Detection of high cardiovascular risk (CVR) and detection of subclinical lesions of target organs in women with hypoestrogenia is an important problem of cardiology that has not been solved yet [1, 2, 3].

Identification of patients belonging to the high risk group of development of CVD caused by atherosclerosis and lacking of evident clinical symptoms is the priority direction of modern medicine. Patients with obesity can be considered as a part of this group

since the growing epidemic of obesity and high risk of cardiovascular complications increase the social importance of this problem. Numerous studies demonstrated elevated risk of stroke and myocardial infarction in case of visceral obesity development and detected correlation between excessive body weight and big amount and early development of atherosclerotic plaques (T. Visscher, 2001, S. Yusuf, 2005, L. De Koning, 2007). Visceral fat is a hormonally active tissue that produces many biologically active molecules participating in the development of metabolic disorders, inflammation and fibrosis, thrombus formation and atherogenesis. At the same time, not all patients with obesity diagnosed according with body mass index (BMI) have high CVR, and not all patients with normal BMI do have low CVR. There are three phenotypes characterizing the role of visceral obesity in cardiovascular continuum: "uncomplicated" obesity, "complicated" obesity and "metabolically obese" but normal weight patients (M. Morelli, 2013) [4, 5]. In this case indirect detection of visceral obesity (VO) using waist circumference (WC) measurement can lead to excessive diagnostics of VO and high CVR (G. Iacobellis, 2003, Y. Chiba, 2007, G.A. Chumakova, 2012). Epicardial fat tissue (EFT) is the deposit of visceral fat around heart located between myocardium and visceral pericardium. EFT correlates with the amount of abdominal visceral fat; it is connected with the levels of C-reactive protein, fibrinogen, plasma lipids, HOMA-IR insulin resistance index and glyce-mic profile, it is also associated with the markers of neurohumoral activity of visceral fat, resistin, leptin, adiponectin, it can play a role in atherosclerosis development and promotes formation of myocardial atherosclerosis and arterial vascular wall (F. Natale, 2009, E. Soliman, 2010) [5, 6, 7, 8]. But up to now-

days the universal quantitative unit of EFT that would have allowed estimating elevated CVR has not been found yet; generalization of existing data about estimation of EFT association with metabolic disorders and cardiovascular remodeling parameters is limited by heterogeneity of visualization techniques and investigated populations of patients. Fat deposits influence adjacent organ's functioning, because of direct mechanical effect and pressure on it and secretion of biologically active molecules. Lipids, accumulated not only in adipocytes, but also in myocytes and endotheliocytes, have lipotoxic impact on them and cause their dysfunction and apoptosis. EFT produces excessive amount of angiotensin II; it increases the synthesis of fibrosis markers, promotes left ventricular myocardium remodeling and impairs cardiac diastolic function, and consequent development of chronic cardiac insufficiency [4, 6].

The objective of this study was to reveal the features of the structural and functional state of cardiovascular system and to stratify cardiovascular risk in women with silent depression of the ST-segment and postovariectomy syndrome.

Materials and methods

This study included 66 female patients in postmenopause with metabolic syndrome and asymptomatic ST segment depression detected with 24-hours electrocardiogram monitoring (24h-ECG). All women were divided in two groups depending on the mechanism of menopause development: main observation group (MOG) included 30 females after surgical menopause, whereas comparison group (CG) consisted of 36 females with naturally occurring menopause. There were no significant differences in age and CHD risk factors between two groups. WC in the main group was 92.5 ± 8.0 cm, and in the comparison group this value was 90.0 ± 6.0 cm.

Instrumental study included 24h-ECG, echocardiography, single-photon emission computed tomography (SPECT) with pharmacological stress test, and coronary computed tomography angiography (CCTA). Episodes of horizontal or descending ST segment depression of at least 1 mm, with duration of at least 0.08 sec after the J-point, lasting for at least 1 minute with a shift of at least 1 minute between episodes [9]. Myocardial SPECT was performed using "Nucline X-Ring" ("Mediso", Hungary) tomographic gamma scanner. ^{99m}Tc - methoxy isobutyl isonitrile (^{99m}Tc -MIBI) was used as a radiopharmaceutical (RP) for these assays. This technique allows verifying coro-

nary ischemia and performing quantitative and qualitative analysis and estimation of the areas with impaired tissue perfusion and intensity of its reduction. Myocardial SPECT was done according with two-day protocol in the following sequence: test in rest (REST) combined with pharmacological stress test (STRESS) with dipyridamole causing vasodilatation and leading to coronary hyperemia. We used 5-points scale for analyzing severity of hypoperfusion: tracer uptake varying from 80 to 95% indicated normal perfusion (0 points), mildly reduced tracer uptake (65-79%) corresponded to 1 point, moderately reduced tracer uptake (50-64%) corresponded to 2 points, evidently reduced tracer uptake (30-49%) – 3 points, and tracer uptake less than 30% corresponded to 4 points. After it we estimated summed stress score (SSS) – the sum of points in all segments obtained using STRESS test [10].

CCTA was performed in axial scanning with prospective cardiac gating: collimation 0,6 mm, tube current 60 mA, voltage 120 kV, tube-sensor turnover time 0.25 ms. Calcium score (CS) was determined semi-automatically using licensed software "Syngo Via" Siemens. EFT was estimated using axial sections (3,0 mm), pericardium contouring was done manually in each fourth section starting 3 mm up from the coronary arterial ostia in cranial direction down to their crossing with inferior myocardial wall. Selection and quantification of tissue volume of fat density (-190 – -30 Hounsfield units) was done automatically.

Results and discussion

According with the results of 24h-ECG, patients of the main group had higher values of ST segment depression amplitude (2.3 ± 0.2 mm), number of episodes (9 [3;13]) and total duration of ischemia within 24h (1900 ± 150 sec) comparing with the comparison group (1.2 ± 0.1 mm; 4 [3; 8] episodes; 1210 ± 110 sec, respectively, $p < 0.05$). Comparison of patients' diaries and monitoring results revealed that physical exercise (MOG: 68% episodes, CG: 42% episodes) and emotional stress (22% of episodes in females with surgical menopause and 20% of episodes in females with naturally occurred menopause) acted as factors provoking significant ST depression in the main observation group. The frequency of spontaneous ST segment deviations (at rest, independent from provoking factors) was higher by 24% in patients with physiological menopause ($p < 0.05$).

Myocardial SPECT results revealed perfusion defects in all female patients with diagnostically signifi-

Table 1. Myocardial SPECT results

Characteristic	SPECT at rest (REST)		SPECT with pharmacological stress test (STRESS)	
	MOG, n=30	CG, n=36	MOG, n=28	CG, n=30
\sum PDV, %	6.2 [4.0; 9.0] ²	4.8 [3.0; 9.4]	15.0 [8.6; 22] ¹	8.0 [4.0; 14]
S_{PD} , cm ²	6.0 [4.2; 10.0] ²	5.0 [3.0; 8.2]	16.0 [8; 24] ¹	8.4 [3.8; 15.2]
SSS	-	-	8 [2; 9]	5 [2; 8]
Percentage of patients having SSS > 8, % of abs.	-	-	46.4% [13]	16.7% [5]

Comment: Significance of differences, $p < 0.05$.

1 – comparing with the CG,

2 – after dynamic comparison.

cant ST depression. Analysis of parameters characterizing dimensions of abnormal perfusion area: perfusion defect value (PDV) as the percentage of an area excluded from total left ventricle (LV) myocardial dimensions (%) and the square of perfusion defect (S_{PD} , cm²), did not detect significant differences between groups during REST test. STRESS testing aggravated coronary circulation in patients of both groups, at the same time patients with surgical menopause (MOG) had more evident dynamics and created differences between groups: total PDV value and perfusion defect square were higher comparing with the CG patients (table 1).

Summed stress score (SSS) estimation is used for the stratification of coronary events' risk. If SSS is less than 4 the probability to develop CHD and possible myocardial infarction (MI) is low; if SSS is between 4 and 8, there is high possibility of CHD, moderate MI risk and low risk of cardiac death; if SSS is above 8, there is high possibility of CHD, moderate MI and cardiac death risk. SSS in the MOG (females with postovariectomy syndrome) was 8 [2; 9] points and corresponded to high probability of CHD development, moderate risk of MI and cardiac death. SSS value in comparison group was 8 [2; 8] points and it matched high probability of CHD, moderate MI risk and low cardiac death risk. The percentage of female patients with SSS value of 8 points and more was 46.4% for the MOG and 16.7% for the CG (Table 1). Thus, around one half of women without ECG symptoms and impaired endocrine homeostasis (postovariectomy syndrome) have high possibility of CHD and moderate risk of MI development and cardiac death.

Several studies demonstrated association of anthropometric characteristics and indexes with the risk of cardiovascular events development: WC is a sign of abdominal obesity and predictor of impaired carbohydrate metabolism, it also correlates with secretory activity of fat tissue and the risk of cardiovascular catastrophes development. At the same time, females with metabolic syndrome included in this study had

significant differences of abnormal myocardial perfusion (SPECT results) and severity of ischemia (CCTA results), even if WC values were comparable between two groups. To evaluate the influence of regional characteristics of fat tissue distribution on cardiovascular risk, we estimated EFT volume, since this tissue is a metabolically active substrate participating in synthesis of biologically active local and systemic action substances involved in CHD pathogenesis. CCTA revealed significant difference of EFT volume: in the MOG this value was 149,13 [82, 28-227, 29] cm³, and in the CG this value was 117.14 [51.11-130.21] cm³, $p < 0,05$. Calcium index quantified using A.S. Agatston (AJ-130) formula was 115 [34; 380] units in females with postovariectomy syndrome and 60 [17, 100] units in the CG patients, another quantification method (Volume) resulted in values of 130 – 140 [41; 354] mm² and 130 – 68 [14; 130] mm², $p < 0,05$, in MOG and CG patients, respectively.

Echocardiography assay demonstrated that LV myocardial mass index (LVMMI) in patients of the MOG was higher than in CG patients (99,5±9,5 g/m²; 88,0±8,4 g/m², $p < 0,05$, respectively). Myocardial hypertrophy (LVMMI more than 95 g/m² for females) and pathologic deviation of LV geometric model were more frequent in patients after surgical menopause. The percentage of patients with LV myocardial hypertrophy (LVMH) in the MOG was 53.3% [16 persons], and 25% in the CG [9 persons]. Concentric LVMH was present in 50% of female patients after surgical menopause, making it the most frequent form of impaired LV geometrical model. We performed the analysis of LV diastolic function using transmitral blood flow peak velocities accessed by Doppler echocardiography in impulse mode. Comparing with CG patients, patients of the MOG had reduced early filling velocity (peak E), increased late filling velocity (peak A), and reduced E/A ratio of transmitral blood flow that indicates diastolic dysfunction of LV myocardium in patients with postovariectomy syndrome (Table 2).

Table 2. LV diastolic function characteristics

Characteristic, Me (25%-75%)	MOG, n=30	CG, n=36
E peak, m/sec	56 (54; 68)*	70 (60; 74)
A peak, m/secc	66 (56; 72)*	62 (50; 64)
E/A ratio	0.8 (0.8; 1.0)*	1.1 (1.0; 1,3)
Symptom, % (abs.)		
LV diastolic dysfunction	83.3% (25)*	53.3% (16)

* Significance of differences comparing with the CG, $p < 0.05$.

Conclusion

Women with metabolic syndrome who went into surgical menopause have evident increase of epicardial fat thickness, coronary calcinosis (EFT volume measured with CCTA was higher comparing with the women with naturally occurring menopause), and more severe myocardial ischemia (according with 24h-ECG results, they had significantly higher amplitude of ST segment depression, higher number of episode and total ischemia duration within 24h, SPECT demonstrated statistically significant increase of total PDV and perfusion defect dimensions). In females with postovariectomy syndrome myocardial hypertrophy and LV remodeling are combined with impaired LV diastolic function, and concentric LVMH is the prevailing form of LV impaired geometrical model.

The fact that females who went into surgical menopause had high risk of unfavorable cardiovascular events (SSS values of 8 (2; 9) points), high percentage of patients with high CHD probability, moderate risk of MI development and cardiac death, is clinically significant. These data determine the necessity to search new criteria of cardiovascular risk stratification for selection of female patients with high cardiovascular risk and its well-timed correction.

Conflict of interest: None declared.

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