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The interrelationship between the alteration of arterial markers and left ventricular diastolic dysfunction in metabolic syndrome subjects

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VILNIAUS UNIVERSITETAS

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Arterijų funkcijos ir struktūros rodiklių pokyčio ir kairiojo skilvelio diastolinės disfunkcijos sąsajų tyrimas metabolinį sindromą turinčių asmenų grupėje

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CONTENT

ABBREVIATIONS

ABI – ankle-brachial index

AH – arterial hypertension

BMI – body mass index

BP – blood pressure

CAVI – cardio–ankle vascular index

CCA – common carotid artery

CI – confidence interval

CVDs – cardiovascular diseases

DM – diabetes mellitus

FPG – fasting plasma glucose

HDL-C – high-density lipoprotein cholesterol

HF – heart failure

HFpEF – heart failure with preserved left ventricular ejection fraction

hsCRP – high sensitivity C-reactive protein

IMT – intima-media thickness

IVST – interventricular septal end-diastolic thickness

LDL-C – low-density lipoprotein cholesterol

LitHiR – the Lithuanian High Cardiovascular Risk Primary Prevention Program

LPWT – left ventricular posterior wall end-diastolic thickness

LVDd – left ventricular end-diastolic dimension

LV – left ventricular

LVMI – left ventricular mass index

MetS – metabolic syndrome

OR – odds ratio

PP – pulse pressure

PWV – pulse wave velocity

QCS – quality carotid stiffness

RWT – relative wall thickness

SD – standard deviation

TC – total cholesterol

TG – triglycerides

WC – waist circumference

WHO – World Health Organization

1. INTRODUCTION

1.1 The Problem of the Study

Cardiovascular diseases (CVDs) are the main cause of mortality, morbidity and decreasing working capacity worldwide and accounts for 31% of all deaths [1]. According to the World Health Organization (WHO), around 17.5 million people died of CVDs in 2012. Myocardial infarction or vertebrobasilar circulatory disorders were the cause of death in 80% of these cases. Based on the data of the Lithuanian Department of Statistics, 56.2% of the residents of Lithuania died of vascular diseases in 2016. The majority of them died of ischemic heart disease (65.6%) and cerebrovascular disease (24.2%). Most of the deceased (i.e., 87%) who were diagnosed with vascular disorders were over 65 years old. Among them, 47.8% were males and 64.4% were females, which showed a higher mortality rate in women compared to men.

Risk factors of cardiovascular diseases are analyzed extensively in developed countries. According to the available scientific research, the following are some of the most important risk factors of CVDs: arterial hypertension (AH), glucose metabolism disorders, especially, diabetes mellitus (DM), dyslipidemia, smoking and obesity. These risk factors are most often brought about by unhealthy diet, lack of physical activity and high levels of stress. INTER-HEART, a case-control study on the effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries, revealed that standard risk factors accounted for approx. 90% of acute CVDs [2].

As soon as it was noticed that patients with several cardiometabolic risk factors had a higher probability of developing CVDs, a new term was suggested: “metabolic syndrome”, also called “syndrome X” and “insulin resistance syndrome” [3, 4, 5].

Metabolic syndrome (MetS) is a cluster of risk factors (e.g. arterial hypertension, abdominal obesity, insulin resistance, atherogenic dyslipidemia) and is considered one of the major problems in our modern world. More economically developed countries deem it a priority to prevent and treat these pathological conditions in a timely manner, as cases of obesity, AH and MetS seem to keep increasing in number and frequency [6, 7]. Diagnosis of MetS has a high clinical significance as, on one hand, the syndrome can be slowed down by employing preventive means and treating patients in a timely manner, but on the other hand, the syndrome can cause or accelerate the development of type 2 diabetes and atherosclerosis, which are

the top causes of death worldwide [8, 9]. With respect to the increase of the cases of people diagnosed with DM and MetS both in Europe and the United States, the prevalence of Mets is forecasted to grow as high as 40% on a global scale in 2020. The occurrence and progress of such highly prevalent diseases as CVDs and type 2 diabetes mellitus are closely connected to metabolic and hormonal disorders that constitute the basis of MetS [10, 11]. According to the results of epidemiological studies, MetS is highly prevalent and its risk group is constantly growing [12, 13].

The prevalence of MetS in Lithuania depends on the age, sex and type of respondents and, at the moment, the frequency of MetS cases tends to range from 10.3% to 36.6%. According to the data of the Lithuanian High Cardiovascular Risk (LitHiR) Primary Prevention Program, as many as 31.5% of the respondents in the group aged 40-65 years old were diagnosed with MetS [14].

Arterial stiffness is another important independent risk factor for CVDs and cardiovascular mortality, which is being researched more and more widely all over the world [15, 16, 17]. Arterial stiffness occurs as a consequence of aging and progressing atherosclerosis. It is related to certain functional and morphological changes in arterial walls which start with the endothelial dysfunction and may progress to intima-media thickening and, ultimately, formation of atherosclerotic plaques. Furthermore, current research suggests that increased arterial stiffness and atherosclerosis might be two interdependent but not identical pathways to increased cardiovascular morbidity and mortality [18]. Accumulating data suggests the link between increased aortic stiffness with the occurrence and progressing of the left ventricular (LV) diastolic dysfunction [19, 20]. Higher arterial stiffness results in increased pulse wave velocity (PWV) and earlier (systolic rather than diastolic) arrival of reflected wave at the ascending aorta. Systolic blood pressure increases and the diastolic blood pressure drops in the aorta, the left ventricular afterload increases, myocardial hypertrophy starts developing, coronary perfusion worsens, and normal flow is replaced with pulsatile flow heading towards the small arteries in the peripheral vascular system. The small arteries degenerate causing microcirculation disorders and target organ (e.g. heart, kidney, brain, etc.) damage. Worsening coronary perfusion and LV myocardial hypertrophy result in abnormal ventricular relaxation and development of diastolic dysfunction. It has been proven that increased left ventricular stiffness is diagnosed more often in patients with increased arterial stiffness. Both of these factors are closely connected to the occurrence and progression of heart failure [21, 22].

About 40–50% of the patients with heart failure (HF) are also diagnosed with preserved left ventricular ejection fraction. Certain structural and functional changes in the left ventricle are inherent to heart failure with preserved LV ejection fraction (HFpEF). Abnormal LV diastolic function is one of the most important of such changes [23, 24] and is conditioned by various factors, e.g. aging, AH, DM, chronic kidney disease, metabolic syndrome and high arterial stiffness. LV diastolic function is an important factor causing HFpEF [25, 26]. Furthermore, it has been demonstrated that the increase of arterial stiffness in patients with HF is related to a worse health prognosis, thus, determination and decrease of arterial stiffness could become a goal in both prevention and treatment of heart failure [27].

Since LV diastolic dysfunction is considered to be an early preclinical marker of cardiovascular disorders which cause HF over time, the determination of the pathogenetic factors for LV diastolic dysfunction is of key importance for choosing an optimal medical treatment. Several studies confirm a significant connection between the LV diastolic dysfunction and the various indices of arterial stiffness (pulse wave velocity [PWV], cardio-ankle vascular index, augmentation index) in different CVDs risk groups (patients with AH, DM). W. P. Abhayaratna *et al* [28, 29] determined that high arterial stiffness in the older patients group was related to the LV diastolic dysfunction and that the strength of the correlation was dependent on the indices used for assessment of arterial stiffness. The PWV turned out to be a better marker of LV diastolic dysfunction, compared to the central or peripheral pulse pressure. Another population–based study on 1233 participants revealed that the LV diastolic dysfunction parameters have significant correlations with the carotid-femoral PWV and central pulse pressure measured by applanation tonometry [30]. Data of 5799 patients were analyzed during Framingham Heart Study. A significant correlation was found between the carotid-femoral PWV, central pulse pressure and LV diastolic dysfunction parameters (e', E/e' ratio) [31]. Yet, data on the correlation between arterial stiffness and LV diastolic dysfunction in subjects with metabolic syndrome are insufficient: the studies are of a small size and only single indices of arterial stiffness are analyzed [32, 33].

Increasingly greater body of scientific evidence confirms the relevance of metabolic syndrome and its components for the development of heart failure [34]. The frequency of LV diastolic dysfunction occurrence was determined to be significantly higher in subjects with MetS [35, 36]. However, scientific literature lacks reliable data on the early clinical diagnosis of heart

failure with preserved LV ejection fraction, and on its association with the progression of arterial stiffness, in subjects with metabolic syndrome.

1.2 Relevance and Significance

Scientific literature provides an impressive amount of evidence showing the link between arterial stiffness and the development and progression of CVDs. Over 50% of middle-aged Lithuanian residents are afflicted with arterial hypertension and related risk factors, such as MetS, that induce early arterial function impairment and over time result in the morphological changes of the arterial wall. In case of further progressing of this pathological condition, heart failure with preserved left ventricular ejection fraction (HFpEF) develops. Possibilities of treating HFpEF are low due to insufficient research of pathogenetic mechanisms; thus, early detection of left ventricular diastolic dysfunction is of utmost significance.

According to available research, LV diastolic dysfunction and heart failure with preserved ejection fraction are related to the increase in arterial stiffness [37]. However, it is not known whether an early prevention of the increase of arterial stiffness could in turn prevent the development of HF nor is it established how the slowing down of the increase in arterial stiffness affects the left ventricular remodeling. To answer these questions is important for practical cardiology as it would allow for choosing the optimal medications for treatment and forecasting the occurrence and progression of heart failure. In the search for an answer, examining the dynamics of arterial parameters (e.g., assessment of the arterial stiffness, endothelial function, intima-media thickness and plaque of the carotid arteries) and their correlation with the left ventricular diastolic dysfunction, HFpEF and other cardiac diseases is of crucial importance.

The results of research carried out during the past decade revealed that it was the central rather than peripheral arterial blood pressure that correlated better with the cardiovascular outcome in certain patient groups. However, the prognostic relevance of central blood pressure in patients with MetS was not widely researched. Successful studies in this field would most probably change treatment plans: physicians would first choose antihypertensive drugs that effectively lower central blood pressure instead of the peripheral.

It should be noted that MetS is a potentially curable condition. Early diagnosis and adequate early intervention might dramatically reduce the

prevalence of MetS, consequently decreasing the risk of developing CVDs and DM. The available research suggests that cardiovascular diseases associated with MetS comprise vascular and myocardial abnormalities that are initially manifested as impaired relaxation of the left ventricle. This myocardial dysfunction is characterized predominantly by diastolic dysfunction consisting of relaxation abnormalities that are prevalent and have prognostic importance in patients with MetS [38].

A number of cross-sectional studies have been carried out with the intent to analyze the relation between arterial stiffness and LV diastolic dysfunction. However, there is a lack of longitudinal studies, the results of which could demonstrate the predictive value of the increased arterial stiffness for the development of LV diastolic dysfunction, a potential precursor to heart failure in MetS subjects. Such studies could help to choose the optimal treatment geared towards the prevention of occurrence and progress of CVDs and heart failure.

The paper presents an analysis of a large cohort, comprised of 1208 subjects with MetS. Follow-up and repeated tests were carried out on 573 participants after three or more years of observation. The relationship between the arterial indices and their changes, and the dynamics of LV diastolic function were assessed.

Currently, little is known about an early development and early clinical diagnosis of heart failure with preserved ejection fraction (HFpEF) in subjects with MetS. Given the high prevalence of LV diastolic dysfunction in this population, it can be reasonably expected that a significant number of subjects with MetS already have unrecognized HFpEF. To uncover the early phase of HFpEF we tested a HF biomarker, BNP, and evaluated the exercise capacity of our cohort subjects by performing the cardiopulmonary stress test. Additionally, we examined an association of markers of arterial stiffness with early HFpEF.

1.3 Research Objective and Tasks

Research Objective

To evaluate the interrelationship between the alterations of arterial markers and left ventricular diastolic dysfunction in metabolic syndrome subjects.

Research Tasks

1. To evaluate the relationship between arterial markers and left ventricular diastolic dysfunction in the cross-sectional study.

2. To determine how the alteration of arterial stiffness affects the dynamics of left ventricular diastolic dysfunction during longitudinal observation.

3. To investigate the frequency of left ventricular diastolic dysfunction and to uncover the early phase of heart failure with preserved left ventricular ejection fraction in subjects with metabolic syndrome. Then, to examine an association of arterial markers with early heart failure with preserved left ventricular ejection fraction.

1.4 Statements to be Defended

1. Left ventricular diastolic dysfunction is significantly associated with elevated arterial stiffness in metabolic syndrome subjects.

2. The increase in arterial stiffness, measured as carotid to femoral pulse wave velocity, is significantly related to the deterioration of the left ventricular diastolic function.

3. A significant number of patients with metabolic syndrome already have left ventricular diastolic dysfunction and unrecognized early heart failure with preserved left ventricular ejection fraction. These subjects exhibit higher aortic augmentation index.

1.5 Novelty of the Study

One of the gratest methodological assets of our study was that, as compared to other studies, we analysed a relatively large group of MetS subjects. The paper presents the cross-sectional study of 1208 subjects with MetS. The study assessed the relationship between different indices of arterial wall function and structure (e.g. pulse wave velocity, aortic augmentation index, and central blood pressure indices, cardio-ankle vascular index, carotid artery stiffness and intima-media thickness) and LV diastolic dysfunction. The carotid-femoral PWV was found to be a significant independent prognostic marker of the LV diastolic dysfunction in metabolic syndrome subjects.

The longitudinal study was carried out by observing 573 participants. The effects of the change in arterial stiffness on the dynamics of the LV diastolic dysfunction were assessed (average monitoring duration: 3.8 ± 0.6 years). Our findings show that carotid-femoral PWV is more closely correlated with LV diastolic function parameters than other indices of arterial stiffness, namely AIx, ABI, CAVI or aortic pulse pressure. The results of longitudinal observation allowed to better understand the relation between arterial stiffness and LV diastolic dysfunction. We found that the increase of carotid-femoral PWV and aortic augmentation index are strongly associated with negative dynamics of LV diastolic function. Aortic pulse pressure, heart ratio, BMI, weight, and calcium channel blockers might also have an important prognostic value. According to the published research available our study is the first of this type of the longitudinal observation study in MetS subjects.

The possibility of early detection of heart failure in subjects with MetS was analyzed for the first time. The study results revealed that patients diagnosed with early heart failure demonstrated increased arterial stiffness and abnormal oxygen metabolism. The assessment of pulmonary ventilation, oxygen metabolism during physical exertion and natriuretic peptide levels showed that more than half of the patients with MetS may develop heart failure with preserved left ventricular ejection fraction. Physical capacity test might be useful in early detection of heart failure. The results of our study are useful for timely detection of the heart failure with the preserved LV ejection fraction.

2. METHODOLOGY

2.1 Study Subjects

A study was carried among 1208 metabolic syndrome subjects. All of the study cohort participants were recruited between 2009 and 2015 years as paticipants of the Lithuanian High Cardiovascular Risk (LitHiR) primary prevention programme at the Vilnius University Hospital Santaros Clinics. This long-term programme has focused on women (aged 50–65 years) and men (aged 40–55 years) without overt cardiovascular disease [39, 40]. Subjects with systolic dysfunction (LV ejection fraction < 50%), significant valvular disease, cardiomyopathy, renal failure, atrial fibrillation, infection, malignancy were excluded. Prior to formal enrollment in the study, all interested subjects signed an informed consent form. The study was authorized by the Vilnius Regional Biomedical Research Ethics Commitee (No. 158200–13–641–205).

The cross sectional study included all the 1208 MetS subjects. The follow-up visit of 573 subjects was carried out after 3.8 ± 0.6 years. For additional assessment of cardiopulmonary stress test and BNP we prospectively enrolled 148 patients with MetS from 573 follow-up subjects. For comparison of study parameters between early and clinically obvious stages of HFpEF, 38 patients with MetS and confirmed HFpEF were enrolled retrospectively (Fig.1).

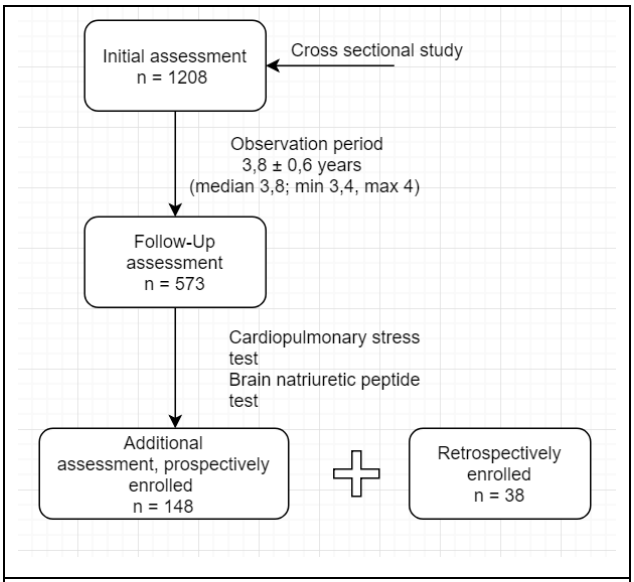


Fig.1. Model of the study.

All participants at initial and follow-up assessments underwent a physical examination, risk profile (smoking) analysis, anthropometry (height, weight, waist circumference [WC] and body mass index [BMI], defined as weight in kilograms divided by height), blood pressure and pulse determination. Twelve lead electrocardiogram was registered. After a 12–hour fast serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL–C), triglycerides (TG), low-density lipoprotein cholesterol (LDL–C), high sensitivity C–reactive protein (hsCRP) levels were assessed. Fasting plasma glucose (FPG) was sampled. The Abbott ARCHITECT immunoassay analyzer was used for the diagnosis of BNP concentration in plasma (units of measure – ng/l).

Each participant at initial and follow-up assessments also underwent echocardiography, and the detailed assessment of arterial function and wall properties. The latter consisted of evaluation of the ankle-brachial index (ABI) and cardio–ankle vascular index (CAVI), carotid wall assessment for the measurement of common carotid artery (CCA) intima-media thickness (IMT) and stiffness, aortic pulse wave velocity (PWV) for aortic stiffness evaluation, and the pressure wave reflection measurements. Vascular assessment was carried out in supine position after 20 minutes bed rest in a temperature–controlled room at 23°C. Study subjects abstained from drinking alcoholic beverages, coffee and vasoactive drugs for 12 hours before the examination.

Brain natriuretic peptide (BNP) test and cardiopulmonary stress test were performed for additional assessment in 148 subjects.

2.2 Definition of Metabolic Syndrome, Hypertension, Dyslipidaemia, and Smoking Status

MetS was diagnosed according to AHA/IDF updated National Cholesterol Education Program Adult Treatment Panel III definition [41]. Participants were classified as having MetS if they satisfied at least 3 of the following 5 criteria:

- Central (abdominal) obesity with a waist circumference > 102 cm in men, or > 88 cm in women;
- Triglycerides of ≥ 1.7 mmol/l;
- Fasting serum glucose ≥ 5.6 mmol/l;
- HDL-cholesterol level ≤ 1.03 mmol/l in men, and ≤ 1.29 mmol/l in women;
- Blood pressure of ≥ 130/85 mmHg.

Hypertensives were defined as subjects with a history of hypertension in whom the sustained elevation of blood pressure (> 140 mmHg systolic and/or > 90 mmHg diastolic BP) has been observed in at least three separate measurements obtained on different days (or antihypertensive treatment).

Dyslipidemia was defined as TC > 5mmol/L, or LDL–C > 3 mmol/L, or HDL–C < 1.0mmol/L in men or < 1.2 mmol/L in women, or TG > 1.7 mmol/L (or receiving of hypolipidaemic medications).

Smoking was classified as never, former, or current smoking.

2.3 Signs of Early Heart Failure With Preserved Left Ventricular Ejection Fraction

Objective parameters of oxygen uptake during peak exercise and biomarker of myocardial wall stress were used for the establishment of the initial phase of HF. Individuals were considered as having early HFpEF if during cardiopulmonary stress test the peak VO2 was ≤ 90% of predicted value or/and BNP was 35 ng/l or higher. Based on these two criteria

prospective patients were divided into two subgroups: without (HFpEF–) and with signs of early HFpEF (HFpEF+).

2.4 Methods

2.4.1 Echocardiographic Examination

Two–dimensional echocardiography was performed using ultrasonic system equipped with a 1.0–5.0 MHz transducer (GE Vivid 4; GE Healthcare, New York, USA). The following measures were obtained: interventricular septal end-diastolic thickness (IVST), left ventricular posterior wall end-diastolic thickness (LPWT), and left ventricular end-diastolic dimension (LVDd).

The following formulas were used:

body surface area = 0,0061 × body height (cm) + 0.128 × body weight (kg) – 0.1529 (m^2),

left ventricular mass (LVM)= 0.8 × 1.04 × [(IVST + LPWT + LVDd)^3 – LVDd^3] + 0.6 (g),

and relative wall thickness (RWT) = (IVST + LPWT)/LVDd.

According to recommendations for chamber quantification LV hypertrophy was diagnosed when LV mass index was ≥ 95 g/m² in women and ≥ 115 g/m² in men and/or relative wall thickness ≥ 0.42 [42]. Based on measurments of left ventricular mass index (LVMI) and relative wall thickness (RWT) 3 patterns of LV remodeling were defined: concentric remodeling (normal LVMI and increased RWT), eccentric hypertrophy (increased LVMI and normal RWT) and concentric hypertrophy (increased LVMI and increased RWT).

Assessment of LV diastolic function included transmitral pulse wave Doppler with evaluation of peak velocities of early diastolic flow (E) and peak flow of atrial contraction (A), E/A ratio, E wave deceleration time (DT) as well as tissue Doppler imaging parameters with early (e') and late (a') diastolic mitral septal and lateral annular velocities, E/e' ratio. Isovolumic relaxation time (IVRT) was measured from the end of aortic flow to the beginning of mitral inflow with the simultaneous visualization of aortic and mitral flow.

The left atrial volume (LAV) was measured by the biplane area-length

method and indexed to the body surface area.

Diagnosis of LV diastolic dysfunction

Left ventricular diastolic dysfunction was defined according to the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [43] (Table 1). Impaired relaxation was described as E/A < 1.0 and E/e' mean < 13. Participants were considered as having pseudonormal or restrictive diastolic dysfunction if the E/e' mean ratio was ≥ 13. In case of E/A > 1.0 and e'septal ≥ 8 cm/s and e'lateral ≥ 10 cm/s diastolic function was interpreted as normal.

Table 1. Left ventricular diastolic dysfunction.

Parameter	**Impaired relaxation**	**Pseudonormal filling**	**Restrictive filling**
E/A ratio	< 1.0	1.0 – 2.0	> 2.0
DecT, ms	> 220	140 – 220	< 140
IVRT, ms	> 110	60 – 100	< 60
e'septal, cm/s	< 8	< 8	< 8
e'lateral cm/s	< 10	< 10	< 10
E/e' mean ratio		≥ 13	≥ 13

Abbreviations: DecT – deceleration time, IVRT – isovolumetric relaxation time, e' – early diastolic tissue velocity of mitral annular.

According to the cardiac ultrasound findings study subjects were divided into two groups: with LV diastolic dysfunction (LV DD+, n = 915) and with normal LV diastolic function (LV DD–, n = 293).

2.4.2 Arterial Stiffness and Wave Reflection Measurements

Parameters of arterial stiffness and wave reflection was assessed by applanation tonometry (SphygmoCor, AtCor Medical, v.8.0, Sydney, Australia) system with high-fidelity micromanometer (Millar R, Millar Instruments, Houston, TX), which is placed on the skin surface at the projection of radial, carotid and femoral arteries in order to obtain pulse pressure wave curves [44]. Brachial blood pressure was recorded and the distance between the surface markings of the sternal notch and the femoral artery was measured. These data and simultaneously recorded electrocardiogram allows the system from pulse wave curves to compute the main parameters of arterial stiffness (carotid-femoral pulse wave velocity

[cfPWV], also called aortic PWV), aortic augmentation index, and central blood pressure.

2.4.3 Carotid Artery Wall Assessment

Carotid intima-media thickness (IMT), cross-sectional carotid artery distensibility (both calculated in μm) and non-dimensional index Quality Carotid Stiffness (QCS) of common carotid artery (CCA) were measured using high-resolution echo-tracking technology (Art.Lab, Esaote Europe B.V., Maastricht, the Netherlands).

2.4.4 Assesment of the Ankle-brachial Index and Cardio-ankle Vascular Index

The ankle-brachial index (ABI) and cardio-ankle vascular index (CAVI) were calculated using the Fukuda Vascular Screening system VaSera VS-1000 (Fukuda Denshi Co. Ltd., Tokyo, Japan) [45]. CAVI < 8 and an ABI between 0.9 and 1.3 in both legs were considered as normal.

2.4.5 Cardiopulmonary Stress Test

The cycle ergometer was set to a ramp mode for individually fitted incremental tests, each increment varied from 15 to 30 W per minute. The exercise protocol was designed to last approximately 8-12 minutes. Throughout the test, blood pressure and constant eletrocardiogram monitoring was applied. Prior to the exercise test, spirometry was performed for each subject using a manually calibrated spirometer (SensorMedics, USA). Expired gases during the test were measured and analyzed using a “breath-by-breath” respiratory mass spectrometry system (Vmax® Encore 229, SensorMedics, USA), that was automatically calibrated before each test. The anaerobic threshold and VAT were determined by the “V-slope” method (VCO2/VO2 ratio) – the first curve inflection [46]. Peak oxygen consumption (peak VO2) was considered to be achieved if VO2 reached a plateau in the presence of a growing power output (W) [47]. If the subject was exhausted before the attainment of peak VO2, the VO2 value was accepted as a reasonable maximum if the heart rate was > 85 % of the predicted maximum rate and a

respiratory quotient (RQ) > 1.00 was recorded.

2.5 Statistical Analysis

Variables were presented as mean ± standard deviation (SD). Statistical analysis was performed using STATISTICA (StatSoft, version 10) and SPSS (version 17.0 *for Windows*). Comparison between subjects groups was made using t test or Wilcoxon test. Spearman's rank test was used to test the correlation between indices of arterial stiffness and the determinants of LV diastolic function and LV filling pressure (E/A ratio, E/e' ratio). Subsequently, significantly correlated variables in the univariate logistic regression analysis were further analyzed by the forward stepwise logistic regression analysis to assess independent association with LV diastolic dysfunction. Receiver-operating characteristic (ROC) curves were obtained to calculate the cut-off values of a statistical models to reach the best prediction of LV diastolic dysfunction. Optimal cut-off was defined as a threshold where the sum of sensitivity and specificity was maximal. To assess prediction of LV diastolic dysfunction conditional random forests analysis was performed. A key advantage of random forest variable importance measures, as compared to univariate screening methods, is that they cover the impact of each predictor variable individually as well as in multivariate interactions with other predictor variables. Random forests are able to better examine the contribution and behavior that each predictor has, even when one predictor's effect would usually be overshadowed by more significant competitors in simpler models. The statistical significance was set at $p < 0.05$ (two-sided tests), and for multiple testing we used a statistical significance of $p < 0.01$.

3. RESULTS

3.1 The Relationship Between Arterial Markers and Left Ventricular Diastolic Dysfunction in the Cross-sectional Study

In the study cohort, there were 423 men (35%) and 785 women (65%), the average age 54.5 ± 6.17 years. Ninety five percent of study subjects were overweight (BMI > 25kg/m^2) and 60% had BMI > 30kg/m^2. Ninety eight percent of men and ninety nine percent of women with a BMI > 30 kg/m^2 had an inceased waist circumference > 102 cm in men and > 88 cm in women. High blood pressure was found in 92% of study subjects, increased fasting glucose in 58%, decreased HDL-C in 36.5%, and elevated TG in 58.5% of subjects. The carotid-femoral pulse wave velocity (cfPWV) was 8.78 ± 1.6 m/s, the mean stiffness of carotid artery was 3.82 ± 1.42, and the carotid artery mean IMT was 651.9 ± 103 μm. We found that 915 (75.7%) subjects had LV diastolic dysfunction (LV DD+) and 293 (24.3%) participants had normal LV diastolic function (LV DD–). The main characteristics of our cross-sectional cohort and its LV DD+ and LV DD– subgroups are presented in Tables 2 and 3.

Table 2. The clinical characteristics in groups of subjects with (LV DD+) and without (LV DD–) left ventricular diastolic dysfunction.

Parameters	**All subjects (n=1208)**	**LV DD+ (n= 915)**	**LV DD– (n=293)**	**p value**
Age, years	54.54 ± 6.17	54.7 ± 6.00	52.0 ± 6.28	< 0.0001
Sex, men, %	425 (35.1)	293 (32.0)	132 (45.2)	< 0.001
Hipertensives, %	1115 (93.3)	856 (93.7)	257 (88.3)	0.005
Diabetes mellitus, %	195 (16.1)	152 (15.7)	43 (14.7)	0.466
Never smoked, %	339 (28.1)	242 (26.6)	95 (32.9)	0.043
Dyslipidemia, %	1204 (99.7)	909 (99.7)	290 (99.7)	1.000
Weight, kg	88.84 ± 16.79	89.1 ± 16.69	87.9 ± 17.12	0.2941
BMI, kg/m2	31.72 ± 4.98	32.1 ± 5.06	30.5 ± 4.52	< 0.0001
Waist circumference, cm	106.04 ±10.74	106.8 ± 10.76	103.6 ± 10.40	< 0.0001
TC, mmol/L	6.98 ± 1.44	7.0 ± 1.45	7.0 ± 1.41	0.7586
LDL-C, mmol/L	4.61 ± 1.29	4.6 ± 1.29	4.6 ± 1.31	0.8125
HDL-C, mmol/L	1.33 ± 0.36	1.3 ± 0.35	1.3 ± 0.40	0.8255

TG, mmol/L	2.21 ± 1.31	2.2 ± 1.27	2.2 ± 1.42	0.8623
Fasting glucose, mmol/L	6.0 ± 1.22	6.0 ± 1.29	5.9 ± 0.99	0.0231
hsCRP, mg/dL	4.06 ± 28.83	4.5 ± 33.11	2.5 ± 3.08	0.0697
Abbreviations: BMI – body mass index; TC – total cholesterol; LDL-C – low density lipoprotein cholesterol; HDL-C – high density lipoprotein cholesterol; TG – triglycerides; hsCRP – high sensitivity C-reactive protein.				

Table 3. The arterial and hemodynamic properties in subjects with (LV DD+) and without (LV DD–) left ventricular diastolic dysfunction.

Parameters	**All subjects (n=1208)** Mean ± SD	**LV DD+ (n= 915)** Mean ± SD	**LV DD– (n=293)** Mean ± SD	**p value**
HR, beats/min	65.77 ± 9.23	66.4 ± 9.44	63.8 ± 8.25	< 0.0001
cfPWV, m/s	8.78 ± 1.6	9.0 ± 1.65	8.2 ± 1.34	<0.0001
AIx/HR, %	24.36 ± 10.27	25.4 ± 9.96	21.1 ± 10.84	<0.0001
Arterial blood pressure, mmHg	107.36 ± 12.35	108.6 ± 12.85	103.4 ± 10.13	<0.0001
Aortic pulse pressure, mmHg	43.89 ± 10.68	44.5 ± 10.69	41.9 ± 10.80	0.0004
CAVI	7.99 ± 1.62	8.0 ± 1.67	7.8 ± 1.55	0.0721
CCA IMT, μm	651.92 ± 103.08	656.6 ±105.29	637.6 ± 98.49	0.0069
CCA stiffness	3.82 ± 1.42	3.9 ± 1.47	3.5 ± 1.32	<0.0001
Mean ABI	1.09 ± 0.09	1.1 ± 0.59	1.2 ± 0.55	0.5652
Abbreviations: HR – heart rate, cfPWV – carotid-femoral pulse wave velocity; AIx/HR – augmentation index, automatically normalized for a heart rate of 75 bpm; CAVI – cardio-ankle vascular index; CCA – common carotid artery; IMT – intima-media thickness; ABI – ankle-brachial index.				

We found significant differences between the groups with LV diastolic dysfunction (LV DD+) and without LV diastolic dysfunction (LV DD–). Subjects with LV diastolic dysfunction were older (54.7 ± 6 vs. 52 ± 6.28 years, $p < 0.0001$), had higher BMI (32.1 ± 5.06 vs. 30.5 ± 4.52 kg/m^2, $p < 0.0001$) and WC (106.8 ± 10.76 vs. 103.6 ± 10.40 cm, $p < 0.0001$), arterial blood pressure (108.6 ± 12.85 vs. 103.4 ± 10.13 mmHg, $p < 0.0001$), heart rate (66.4 ± 9.44 vs. 63.8 ± 8.25 beats/min, $p < 0.0001$), and aortic pulse pressure (44.5 ± 10.69 vs. 41.9 ± 10.80 mmHg, $p = 0.0004$). The LV DD+ subjects, as compared to LV DD– group, had higher prevalence of hypertensives (93.7% of subjects in LV DD+ group compared to 88.3% in LV DD– group, $p = 0.005$), female subjects (68% in LV DD+ group compared to

54.8% in LV DD– group, p < 0.001), and smokers (73.4% of subjects in LV DD+ group compared to 67.1% in LV DD– group, p = 0.043).

Subjects with LV diastolic dysfunction displayed higher cfPWV (9.0 ± 1.65 vs. 8.2 ± 1.34m/s, p < 0.0001), AIx/HR (25.4 ± 10 vs. 21.1 ± 10.84%, p < 0.0001), and mean carotid artery IMT (656.6 ± 105.29 vs. 637.6 ± 98.49 μm, p = 0.0069) (Table 3). The LVMI (109.88 ± 24.56 vs. 101,96 ± 21.5 g/m^2, p < 0.0001) and RWT (0.43 ± 0.05 vs. 0.42 ± 0.05, p = 0.0023) were higher in the LV DD+ group (Table 4).

Table 4. The echocardiographic parameters in subjects with (LV DD+) and without (LV DD–) left ventricular diastolic dysfunction.

Parameters	**All subjects (n=1208)** Mean ± SD	**LV DD+ (n=915)** Mean ± SD	**LV DD– (n=293)** Mean ± SD	**p value**
LV index, cm/m2	2.59 ± 0.27	2.59 ± 0.28	2.55 ± 0.26	0.142
LVMI, g/m2	107.96 ± 24.08	108.82 ± 24.04	97.11 ± 21.96	<0.001
RWT	0.43 ± 0.05	0.43 ± 0.05	0.41 ± 0.05	0.003
LA length, cm	5.25 ± 0.5	5.26 ± 0.51	5.19 ± 0.43	0.229
LA width, cm	4.73 ± 0.59	4.75 ± 0.58	4.48 ± 0.54	<0.001
LA volume index, ml/m2	32.64 ± 9.29	32.78 ± 9.38	30.84 ± 7.83	0.059
LA volume, ml	64.32 ± 20.25	64.66 ± 20.48	60.14 ± 16.55	0.044
Transmitral peak early diastolic flow (E-wave velocity), m/s	0.8 ± 0.17	0.8 ± 0.17	0.84 ± 0.15	0.014
Transmitral peak flow of atrial contraction (A-wave velocity), m/s	0.85 ± 0.17	0.87 ± 0.16	0.65 ± 0.12	<0.001
E/A ratio	0.97 ± 0.27	0.94 ± 0.25	1.32 ± 0.24	<0.001
Transmitral E-wave DT, millisec	210.81 ± 37,60	212.58 ± 38.48	199.4 ± 29.71	0.145
Early (e'sept) diastolic tissue velocity of septal	7.15 ± 1.86	6.92 ± 1.68	9.97 ± 1.72	<0.001

mitral annular, cm/sec				
Early (e'lat) diastolic tissue velocity of lateral mitral annular, cm/sec	9 ± 2.56	8.74 ± 2.39	12.18 ± 2.45	<0.001
E/e'sept ratio	11.91 ± 4.08	12.17 ± 4.09	8.65 ± 2.02	<0.001
E/e'lat ratio	9.63 ± 3.67	9.83 ± 3.7	7.18 ± 1.93	<0.001
E/e'mean ratio	10.47 ± 3.44	10.69 ± 3.46	7.72 ± 1.66	<0.001
Mean pulmonary capillary wedge pressure (mmHg) by Nagueh formula	13.84 ± 4.55	14.09 ± 4.59	10.81 ± 2.39	<0.001
Abbreviations: LV – left ventricular, LVMI – left ventricular mass index, RWT - relative wall thickness, LA - left atrium, DT - deceleration time.				

We found statistically significant correlations between arterial stiffness indices and LV diastolic function parameters: cfPWV and aortic augmentation index negatively correlated with E/A ratio (r_{cfPWV}= –0.19 [Figures 2], $r_{AIxHR75}$= – 0.15, $p < 0.001$), and positively correlated with E/e' mean ratio (r_{cfPWV} = 0.17, $r_{AIxHR75}$ = 0.14, $p < 0.001$). Also the positive significant correlation was found between E/e'mean ratio and age (r = 0.190, $p < 0.001$), BMI (r = 0.216, $p < 0.001$), LVMI (r = 0.324, $p < 0.001$), arterial blood pressure (r = 0.159, $p < 0.001$), aortic pulse pressure (r = 0.265, $p < 0.001$) (Figure 3), and mean carotid artery IMT (r = 0.163, $p < 0.001$) (Table 5). The strongest correlation was found between the LVMI and E/e' mean ratio.

Table 5. The correlations between various variables and left ventricular diastolic function parameters.

Parameters	E/A ratio		E/e'mean ratio	
	r	p value	r	p value
Age, years	-0.178	<0.001	0.190	<0.001
BMI, kg/m2	-0.054	0.062	0.216	<0.001
cfPWV, m/s	-0.190	<0.001	0.167	<0.001
AIx/HR, %	-0.151	<0.001	0.136	<0.001
Arterial blood pressure, mmHg	-0.125	<0.001	0.159	<0.001
Aortic pulse pressure, mmHg	-0.053	0.068	0.265	<0.001
CCA IMT, µm	-0.014	0.632	0.163	<0.001
HR, beats/min	-0.198	<0.001	-0.062	0.031
CAVI	-0.065	0.024	0.003	0.922
LVMI, g/m2	-0.037	0.199	0.324	<0.001

Abbreviations: BMI – body mass index; cfPWV–- carotid-femoral pulse wave velocity; AIx/HR – augmentation index, automatically normalized for a heart rate of 75 bpm; CCA – common carotid artery; IMT – intima–media thickness; HR – heart rate; CAVI – cardio-ankle vascular index; LVMI – left ventricular mass index.

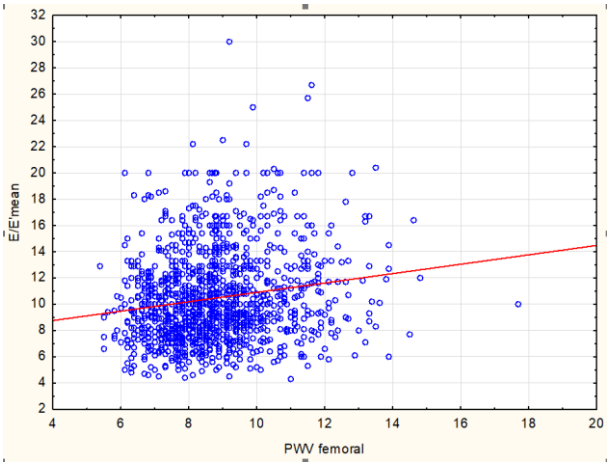


Figure 2. Scatter plot showing the assotiation between carotid-femoral pulse wave velocity and E/e'mean ratio in 1208 subjects.

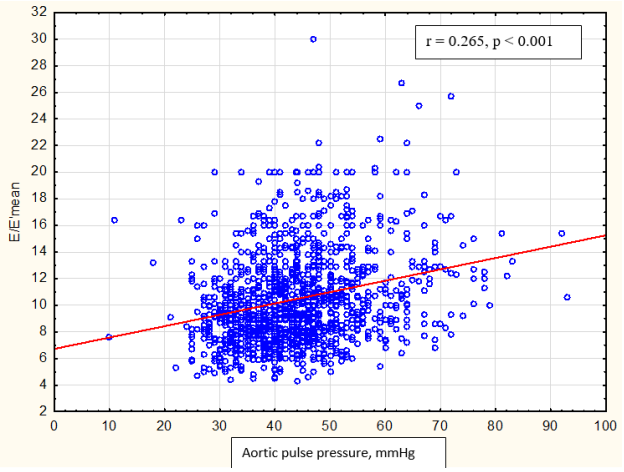


Figure 3. Scatter plot showing the assotiation between aortic pulse pressure and E/e'mean ratio in 1208 subjects.

Univariate logistic regression analysis (Table 6) revealed that the probability of LV diastolic dysfunction is increasing with age. Also, we found that the increase of carotid-femoral PWV, aortic augmentation index, heart rate, arterial blood pressure, aortic pulse pressure, carotid artery IMT, BMI, WC, LVMI, and hsCRP is associated with the presence of the LV diastolic dysfunction (all $p < 0.05$). Women also had a higher probability of the LV diastolic dysfunction than men, namely by 43%. We have found that the carotid-femoral PWV threshold value of 8.2 m/s helps to distinguish subjects with the increased risk for the development of LV diastolic dysfunction. An increase in carotid-femoral PWV higher then 8.2 m/s was associated with a significantly higher probability of LV diastolic dysfunction by 41% (AUC 0.642, sensitivity 0.715, specificity 0.596).

Table 6. Univariate logistic regression analysis for the association between LV diastolic dysfunction and various variables.

Characteristics	Cut-off	OR	95% CI	p value	AUC
Age, years	≥ 54	1.073	1.050 – 1.097	< 0.001	0.623
Sex	men	0.571	0.436 – 0.747	< 0.001	0.566
BMI, kg/m2	≥ 32.2	1.078	1.046 – 1.111	< 0.001	0.599
WC, cm	≥ 106	1.030	1.016 – 1.043	< 0.001	0.587
B–Ch, mmol/l	≥ 7.7	1.014	0.926 – 1.112	0.759	0.497
Fasting glucose, mmol/l	≥ 6.87	1.142	1.000 – 1.303	0.05	0.536
hsCRB, mg/dl	≥ 3.0	1.064	1.019 – 1.112	0.005	0.570
cfPWV, m/s	≥ 8.2	1.412	1.280 – 1.557	< 0.001	0.642
AIx/HR, %	≥ 19.6	1.041	1.027 – 1.054	< 0.001	0.617
Mean arterial BP, mmHg	≥ 99.5	1.039	1.027 – 1.052	< 0.001	0.616
Aortic pulse pressure, mmHg	≥ 36.9	1.024	1.011 – 1.038	< 0.001	0.573
CAVI mean	≥ 8.4	1.078	0.993 – 1.171	0.072	0.558
IMT mean, μm	≥ 662	1.002	1.000 – 1.003	0.007	0.563
CCA stiffness mean	≥ 3.7	1.244	1.119 – 1.383	< 0.001	0.588
HR, beats/min	≥ 63.8	1.032	1.017 – 1.048	< 0.001	0.575
ABI mean	≥ 2.0	0.940	0.759 – 1.163	0.568	0.552
LVMI, g/m^2	≥ 103	1.015	1.009 – 1.021	< 0.001	0.595
Smoking status	Current	0.741	0.557 – 0.986	0.040	0.531

Abbreviations: OR – odds ratio; CI – confidence interval; BMI – body mass index; TC – total cholesterol; hsCRP – high sensitivity C-reactive protein; HR – heart rate; cfPWV – carotid-femoral pulse wave velocity; AIx/HR – augmentation index, automatically normalized for a heart rate of 75 bpm; BP – blood pressure, CAVI – cardio-ankle vascular index; CCA – common carotid artery; IMT – intima–media thickness; ABI – ankle-brachial index; LVMI – left ventricular mass index; AUC – area under the curve.

In order to further clarify the significant predictors of LV diastolic dysfunction, a stepwise multiple logistic regression analysis with all significant variables was performed. Due to high correlation between BMI, WC, two stepwise logistic regression models were constructed including either BMI or WC (Table 7, Model 1 and Model 2). Age, gender and HR were included in all regression models as covariates. In Model 1, we included BMI, hsCRP, cfPWV, AIx, mean aortic BP, aortic PP, mean CCA IMT, mean ABI,

LVMI, and smoking as independent variables. In Model 2, BMI was replaced with WC. Stepwise multiple logistic regression analyses demonstrated that cfPWV, age, sex (only in Model 1), BMI or WC, and LV MI remained significant predictors of the presence of LV diastolic dysfunction ($p < 0.05$).

Table 7. The predictors of left ventricular diastolic dysfunction in the cross-sectional data: multiple logistic regression analysis.

	Model 1			Model 2		
Characteristics	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age, years	1.068	1.031 – 1.107	0.003	1.053	1.023 – 1.083	<0.001
Sex, men	1.61	1.016 –2.551	0.043	No significance		
BMI, kg/m2	1.077	1.042 – 1.114	<0.001			
WC, cm				1.039	1.023 – 1.055	<0.001
hsCRB, mg/dl						
cfPWV, m/s	1.186	1.066 – 1.320	0.002	1.182	1.062 – 1.315	0.002
AIx/HR, %	1.031	1.014 – 1.049	<0.001	1.029	1.013 – 1.046	0.001
Arterial BP, mmHg						
Aortic pulse prssure, mmHg						
CCA IMT mean, μm						
HR, beats/min						
ABI mean						
LVMI, g/m^2	1.031	1.014 – 1.048	<0.001	1.030	1.013 – 1.048	0.001
Smoking status, current						
AUC			0.706			0.707

Abbreviations: OR – odds ratio; CI – confidence interval; BMI – body mass index; WC – waist circumference; TC – total cholesterol; hsCRP – high sensitivity C-reactive protein; HR – heart rate; cfPWV – carotid-femoral pulse wave velocity; AIx/HR – augmentation index, automatically normalized for a heart rate of 75 bpm; BP – blood pressure, CAVI – cardio-ankle vascular index; CCA – common carotid artery; IMT – intima–media thickness; ABI – ankle-brachial index; LVMI – left ventricular mass index; AUC – area under the curve.

As the odds ratios in Table 7 show, carotid-femoral PWV was the strongest predictor of the LV diastolic dysfunction: increase of cfPWV by 1SD is associated with significantly higher probability of LV diastolic dysfunction, namely, by 18.6% and 18.2% in Models 1 and 2 respectively. The ROC curve analysis showed that the areas under the ROC (AUC) of the statistical models for predicting of LV diastolic dysfunction were 0.706 in

Model 1 (Figure 4) and 0.707 in Model 2 (Figure 5), thus indicating slightly higher predictive value of WC over BMI in MetS subjects.

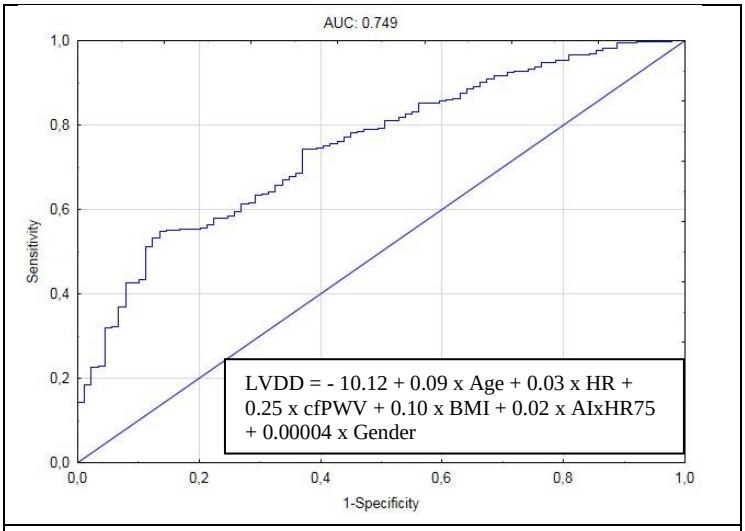


Figure 4. ROC curve of Model 1 for prediction of LV diastolic dysfunction (Sensitivity 0.566; Specificity 0.820)

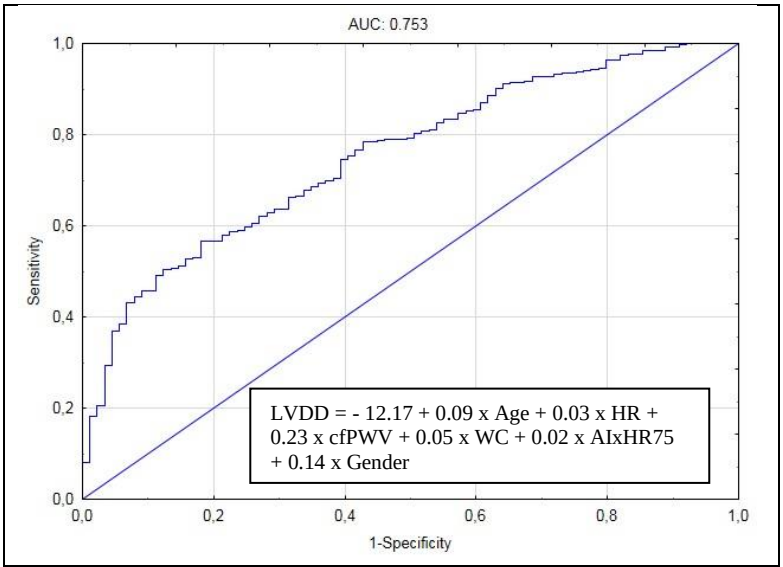


Figure 5. ROC curve of Model 2 for prediction of LV diastolic dysfunction. (Sensitivity 0.549; Specificity 0.865)

In conlusion, left ventricular diastolic dysfunction is significantly associated with elevated arterial stiffness in metabolic syndrome subjects.

Non-invasively measured carotid-femoral pulse wave velocity, an index of aortic stiffness, is a significant and independent determinant of the LV diastolic dysfunction in patients with metabolic syndrome without overt cardiovascular disease. Age, BMI, aortic augmentation index, gender and LV mass index also are significant predictors of the presence of LV diastolic dysfunction.

3.2 The Influence of Arterial Stiffness Alteration on the Dynamics of Left Ventricular Diastolic Dysfunction during Longitudinal Observation

The longitudinal study of 3.8 ± 0.6 years was carried out in 573 subjects randomly selected from the general cohort of 1208 participants. The data of this study was used to analyze the effects of the alteration of arterial stiffness on the dynamics of the left ventricular diastolic dysfunction.

3.2.1 Longitudinal Observation: The Subjects Profile at Baseline and Follow-up Visit

In the longitudinal study cohort there were 36.8% (n = 211) men and 63.2% (n = 362) women, an average age of the study participants was 53.4 ± 5.8 years. High blood pressure was found in 92.7% (n = 531) of subjects. The obesity (BMI > 30 kg/m^2) was found in 62.8% (n = 360) of study subjects.

During the longitudinal observation, we have observed a significant reduction in waist circumference (from 105.77 ± 9.94 to 104.65 ± 10.99 cm, $p < 0.001$), total cholesterol (from 6.83 ± 1.45 to 6.57 ± 1.59 mmol/L, $p = 0.002$), LDL cholesterol (from 4.49 ± 1.25 to 4.27 ± 1.34 mmol/L, $p = 0.003$) and hsCRP (from 3.12 ± 4.13 to 2.58 ± 3.00 mg/L, $p = 0.009$) (Table 8).

Table 8. Baseline and follow-up indeces of obesity, lipid and fasting glucose profile, and inflammation.

Parameters	**At baseline (n = 573)** Mean ± SD	**Follow-up (n = 573)** Mean ± SD	**Change** Mean ± SD	**p value**
Weight, kg	89.38 ± 15.68	89.22 ± 16.03	0.25 ± 6.95	0.495
BMI, kg/m^2	31.53 ± 4.24	31.37 ± 4.28	– 0.16 ± 2.05	0.065
Waist circumference, cm	105.77 ± 9.94	104.65 ± 10.99	– 1.12 ± 6.74	< 0.001
TC, mmol/l	6.83 ± 1.45	6.57 ± 1.59	– 0.26 ± 1.67	0.002
LDL–C, mmol/l	4.49 ± 1.25	4.27 ± 1.34	– 0.22 ± 1.43	0.003
HDL–C mmol/l	1.31 ± 0.34	1.27 ± 0.33	– 0.03 ±0.03	< 0.001
TG, mmol/l	2.30 ± 1.91	2.39 ± 4.15	0.09 ± 3.75	0.623
Fasting glucose, mmol/l	5.99 ± 1.22	6.19 ± 1.42	0.19 ± 1.28	0.001
hsCRB, mg/l	3.12 ± 4.13	2.58 ± 3.00	– 0.54 ± 4.08	0.009
Abbreviations: BMI – body mass index; TC – total cholesterol; LDL-C – low density lipoprotein cholesterol; HDL-C – high density lipoprotein cholesterol; TG – triglycerides; hsCRP – high sensitivity C-reactive protein.				

The treatment data were collected only at follow-up visit. In our follow-up cohort, 89.3% (n = 512) of subjects were on treatment. The most frequently used medications were ACE inhibitors, BB, CCB and statins (Table 9).

Table 9. The data of medications used.

Medication	**n**	**%**
ACE inhibitors	233	40,7
ARB	89	15,5
Diuretics	130	22,7
CCB	198	34,6
BB	206	36
α blockers	4	0,7
Other	32	5,6
Statins	412	71,9
Abbreviations: ACE – angiotensin converting enzyme inhibitors, CCB – calcium channel blockers, ARB – angiotensin receptor blockers, BB – beta blockers.		

3.2.2 Arterial Wall Functional and Structural Parameters at Baseline and Follow-up Visit

The baseline evaluation of arterial wall parameters revealed that the subjects with LV diastolic dysfunction (LV DD+) had higher heart rate (67.97 ± 10.81 vs. 64.70 ± 9.23 beats/min, p = 0.002), carotid-femoral PWV (8.71 ± 1.48 vs. 8.10 ± 1.20 m/s, p < 0.001), AIx/HR (23.90 ± 10.07 vs. 20.48 ± 10.48%, p < 0.001), mean arterial BP (106.63 ± 10.65 vs. 102.53 ± 10.17 mmHg, p < 0.001), aortic pulse pressure (43.33 ± 9.80 vs. 40.57 ± 9.96 mmHg, p = 0.003), carotid artery stiffness (3.92 ± 1.41 vs. 3.55 ± 1.31, p = 0.006), and carotid artery IMT (663.26 ± 100.87 vs. 634.04 ± 95.44 μm, p = 0.002) (Table 10).

Table 10. The comparison of arterial wall parameters between subjects groups at baseline.

Parameters	**LV DD+ (n = 418)** mean ± SD	**LV DD– (n = 155)** mean ± SD	**p value**
HR, beats/min	67.97 ± 10.81	64.70 ± 9.23	0.002
cfPWV, m/s	8.71 ± 1.48	8.10 ± 1.20	< 0.001
AIx/HR, %	23.90 ± 10.07	20.48 ± 10.48	< 0.001
Mean arterial BP, mmHg	106.63 ± 10.65	102.53 ± 10.17	< 0.001
Aortic pulse pressure, mmHg	43.33 ± 9.80	40.57 ± 9.96	0.003
CAVI	7.73 ± 1.57	7.90 ± 1.69	0.258
CCA IMT , μm	663.26 ± 100.87	634.04 ± 95.44	0.002
CCA stiffness	3.92 ± 1.41	3.55 ± 1.31	0.006
ABI	1.07 ± 0.09	1.10 ± 0.09	0.002

Abbreviations: LV – left ventricular, DD – diastolic dysfunction, HR – heat rate, cfPWV – carotid-femoral pulse wave velocity; AIx/HR – augmentation index, automatically normalized for a heart rate; BP – blood pressure, CAVI – cardio-ankle vascular index; CCA – common carotid artery; IMT–- intima-media thickness; ABI – ankle-brachial index.

After 3 years, we have observed a significant decrease in heart rate (– 3.61 ± 10.6 k/min, p < 0.001) and mean arterial BP (– 3.71 ± 15.22 mmHg, p < 0.001) and a significant increase in cfPWV (0.15 ± 1.59 m/s, p = 0.019), AIx/HR (1.44 ± 9.55 proc., p < 0.001), carotid artery stiffness (0.78 ± 1.46, p < 0.001) and carotid artery IMT (38.33 ± 90.86 μm, p < 0.001) (Table 11).

Table 11. The changes of haemodynamic and arterial wall parameters during the longitudinal observation.

Prameters	**At baseline (n = 573)** Mean± SD	**Follow-up (n = 573)** Mean ± SD	**Change** Mean ± SD	**p value**
HR, beats/min	67.00 ± 10.29	63.35 ± 8.67	– 3.61 ± 10.6	< 0.001
cfPWV, m/s	8.55 ± 1.44	8.71 ± 1.61	0.15 ± 1.59	0.019
AIx/HR, %	22.83 ± 10.37	24.27 ± 10.82	1.44 ± 9.55	< 0.001
Mean arterial BP, mmHg	105.63 ± 10.62	101.59 ± 14.72	– 3.71 ± 15.22	< 0.001
Aortic pulse pressure, mmHg	42.62 ± 9.94	43.31 ± 10.61	0.68 ± 11.15	0.146
CAVI	7.77 ± 1.61	7.78 ± 1.55	0.01 ± 1.9	0.916
CCA IMT , µm	652.77 ± 102.11	691.11 ± 103.04	38.33 ± 90.86	< 0.001
CCA stiffness	3.78 ± 1.40	4.56 ± 1.60	0.78 ± 1.46	< 0.001
ABI	1.08 ± 0.09	1.09 ± 0.10	0.01 ± 0.10	0.077

Abbreviations: cfPWV – carotid-femoral pulse wave velocity; AIx/HR – augmentation index normalized for a heart rate; BP – blood pressure, CCA – common carotid artery; IMT – intima–media thickness; HR – heart rate; CAVI – cardio-ankle vascular index; ABI – ankle-brachial index.

After 3 years, carotid-femoral PWV increased in 310 subjects, decreased in 241 subjects; aortic augmentation ndex increased in 295 and decreased in 218 subjects; and arterial BP increased in 221 and decreased in 318 subjects.

3.2.3 Echocardiographic Parameters and Their Changes during the Longitudinal Observation

At the baseline evaluation 72.9% (n = 418) of the longitudinal cohort subjects had LV diastolic dysfunction. The subjects with LV diastolic dysfunction (LV DD+) had higher LV mass index (106.77 ± 22.59 vs. 102.25 ± 21.99 g/m^2, p = 0.033) and relative wall thickness (0.43 ± 0.06 vs. 0.42 ± 0.06, p = 0.020) (Table 12).

Table 12. Comparison of echocardiographic parameters in subjects with (LV DD+) and without (LV DD–) left ventricular diastolic dysfunction at baseline.

Parameters	**LV DD+ n = 418** Mean± SD	**LV DD– n = 155** Mean± SD	**p value**
LV index, cm/m^2	2.55 ± 0.28	2.54 ± 0.24	0.481
LVMI, g/m^2	106.77 ± 22.59	102.25 ± 21.99	0.033
RWT	0.43 ± 0.06	0.42 ± 0.06	0.020
LA volume index, ml/m^2	33.13 ± 9.54	31.93 ± 7.56	0.120
LA volume, ml	65.89 ± 21.54	63.88 ± 18.02	0.264
E, cm/s	0.76 ± 0.16	0.91 ± 0.13	< 0.001
A, cm/s	0.87 ± 0.16	0.73 ± 0.13	< 0.001
E/A ratio,	0.89 ± 0.22	1.26 ± 0.18	< 0.001
e'$_{sept}$, cm/s	6.71 ± 2.87	8.65 ± 1.87	< 0.001
e'$_{lat}$, cm/s	8.39 ± 2.43	11.14 ± 2.34	< 0.001
E/e' mean ratio	10.85 ± 3.91	9.40 ± 2.01	< 0.001
E/e'$_{lat}$ ratio	10.16 ± 6.55	8.52 ± 2.29	< 0.001
E/e'$_{sept}$ ratio	12.32 ± 4.43	10.97 ± 2.86	< 0.001
PKpr, mmHg	14.50 ± 8.12	12.47 ± 2.83	< 0.001

Abbreviations: LV – left ventricular, LVMI – left ventricular mass index, RWT – relative wall thickness, LA – left atrium, E – transmitral peak early diastolic flow, A – transmitral peak flow of atrial contraction, sept – septal part of mitral annular, lat – lateral part of mitral annular, PKpr – mean pulmonary capillary wedge pressure (mmHg) by Nagueh formula.

After 3 years, we have observed the significant reduction of LV index from 2.55 ± 0.27 cm/m^2 to 2.51 ± 0.33 cm/m^2 (p = 0.008), LVMI from 105.56 ± 22.5 to 99.11 ± 23.67 (p < 0.001) and RWT from 0.43 ± 0.06 to 0.42 ± 0.06 (p = 0.002). Also, during the longitudinal observation, we have found the significant positive dynamics of LV diastolic function parameters: E/e'$_{mean}$ decreased from 10.46 ± 3.55 to 9.43 ± 2.87 (p < 0.001), E/e'$_{lat}$ decreased from 9.72 ± 5.77 to 8.54 ± 3.05 (p < 0.001), and E/e'$_{sept}$ decreased from 11.95 ± 4.11 to 10.89 ± 3.19 (p < 0.001) (Table 13).

Table 13. Changes of echocardiographic parameters during the longitudinal observation.

Parameters	**At baseline (n = 573)** Mean± SD	**Follow-up (n = 573)** Mean ± SD	**Change** Mean ± SD	**p value**
LV index, cm/m^2	2.55 ± 0.27	2.51 ± 0.33	– 0.03 ± 0.32	0.008
LVMI, g/m^2	105.56 ± 22.5	99.11 ± 23.67	– 6.39 ± 26.28	< 0.001
RWT	0.43 ± 0.06	0.42 ± 0.06	– 0.01 ± 0.07	0.002
LA volume index, ml/m^2	32.76 ± 9.02	33.36 ± 8.65	0.60 ±10.5	0.172
LA volume, ml	65.28 ± 20.6	66.42 ± 19.40	1.14 ± 21.49	0.206
E, cm/s	0.99 ± 0.27	0.93 ± 0.23	– 0.05 ± 0.27	< 0.001
A, cm/s	7.24 ± 2.77	7.14 ± 1.75	0.21 ± 2.74	0.402
E/A ratio,	9.13 ± 2.70	9.35 ± 2.56	– 0.10 ± 2.86	0.063
e'$_{sept}$, cm/s	10.46 ± 3.55	9.43 ± 2.87	– 1.03 ± 3.84	< 0.001
e'$_{lat}$, cm/s	9.72 ± 5.77	8.54 ± 3.05	– 1.18 ± 5.78	< 0.001
E/e' mean ratio	11.95 ± 4.11	10.89 ± 3.19	– 1.06 ± 4.57	< 0.001
E/e'$_{lat}$ ratio	13.95 ± 7.15	12.49 ± 3.79	– 1.46 ± 7.17	< 0.001

Abbreviations: LV – left ventricular, LVMI – left ventricular mass index, RWT – relative wall thickness, LA – left atrium, E – transmitral peak early diastolic flow, A – transmitral peak flow of atrial contraction, sept – septal part of mitral annular, lat – lateral part of mitral annular, PKpr – mean pulmonary capillary wedge pressure (mmHg) by Nagueh formula.

The dynamics of LV diastolic function are presented in Table 14. During the longitudinal observation, in 243 (74.7%) subjects impaired LV relaxation remained unchanged, in 54 (16.6%) subjects LV diastolic dysfunction improved and in 28 (8.61%) – worsened.

Notably, in 77.2% (n = 72) subjects with advanced LV diastolic dysfunction (pseudonormal or restrictive LV filling) at baseline we observed the improvement of LV diastolic function and LV morphometric parameters, such as LVMI and RWT. In 16.6% (n = 54) subjects with impaired LV relaxation at baseline, we observed normal LV diastolic function at follow-up visit.

Table 14. Dynamics of left ventricular diastolic function.

		Follow-up LV diastolic function			
		Normal	**Impaired relaxation**	**Pseudonormal filling**	**Overall**
At baseline LV diastolic function	**Normal**	73	69	13	155
	Impaired relaxation	54	243	28	325
	Pseudonormal LV filling	13	58	21	92
	Restictive LV filling	0	1	0	1
Overall		140	371	62	573

Abbreviations: LV – left ventricular.

The baseline evaluation of LV morphometric parameters revealed normal LV geometry in 26.9% (n = 154) of longitudinal cohort subjects. LV remodeling was evaluated in 73.1% (n = 419) of subjects at baseline. The LV geometry at baseline and changes during the longitudinal observation presented in Figure 6. After 3 years, in 21.1% (n = 121) of subjects with LV remodeling at baseline, we found normal LV geometry. In 14% (n = 88) of subjects with normal LV geometry at baseline we found LV remodeling at follow-up visit.

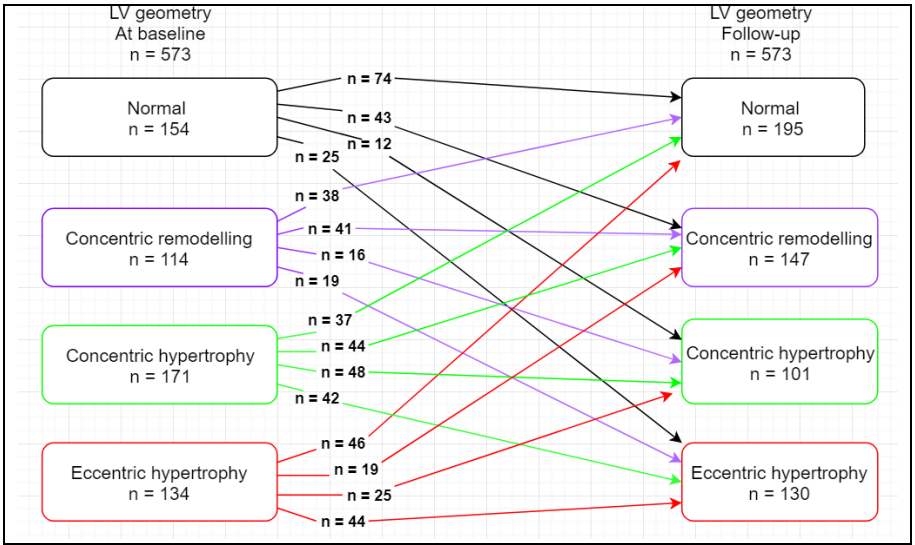


Figure 6. Changes in left ventricular geometry during the longitudinal observation.

3.2.4 Changes in Aortic Pulse Wave Velocity and Left Ventricular Diastolic Function Dynamics

Depending on the LV diastolic function dynamics, our further analysis focused on the comparison of the arterial hemodynamic markers, in the 3 subgroups (Figure 7):

- Group I: LV diastolic dysfunction improved (22.0, n = 126),
- Group II: LV diastolic function unchanged (58.8 %, n = 337),
- Group III: LV diastolic function worsened (19.2 %, n = 110).

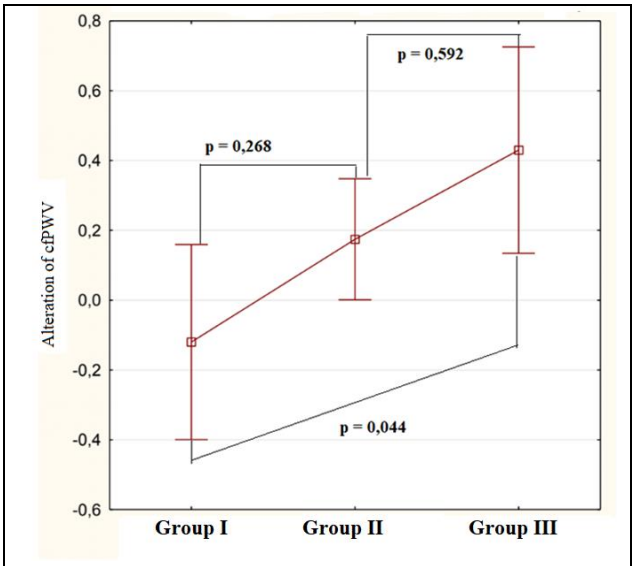


Figure 7. The dependence of the left ventricular diastolic function on the alteration of carotid-femoral pulse wave velocity (cfPWV).

After 3 years, we have observed the following significant changes in the subjects of Group I (LV dastolic dysfunction improved): BMI decreased from 32.06 ± 4.34 to 31.60 ± 4.31 kg/m^2 (p = 0.013), and WC decreased from 106.85 ± 9.99 to 105.57 ± 10.34 cm (p = 0.040).

In Group III we have found a significant increase of weight from 88.21 ±15.58 to 89.35 ±16.85 kg (p = 0.041). Notably, BMI (31.02 ± 4.08 vs. 31.27 ± 4.45, p = 0,267) and WC (04.96 ± 8.88 vs. 103.88 ± 11.9, p = 0.133) did not change significantly.

After 3 years, in both Groups I and III we found the following change in the hemodynamic and arterial parameters (Table 15):

- A significantly decreased heart rate;
- A significantly decreased arterial blood pressure;
- A significantly increased carotid artery stiffness and IMT.

After 3 years, carotid-femoral PWV and aortic augmentation index significantly increased only in Group III. These results confirm, that the negative dynamics of LV diastolic function is associated with the progression of the arterial stiffening.

Table 15. Comparison of arterial and central haemodynamics indices Between Group I and Group III at baseline and follow-up.

Group I Improved LV DD (n = 126)				**Group III Worsened LV DD (n = 110)**		
At baseline (n = 573) Mean± SD	**Follow-up (n = 573)** Mean ± SD	**p value**	**Parameters**	**At baseline (n = 573)** Mean± SD	**Follow-up (n = 573)** Mean ± SD	**p value**
66.27 ±10.09	62.15 ±8.86	< 0.001	**HR, beats/min**	65.17 ±9.41	62.07 ±8.51	0.003
8.67 ±1.40	8.55 ±1.51	0.489	**cfPWV, m/s**	8.25 ±1.36	8.68 ±1.73	0.004
23.43 ±9.31	23.85 ±10.55	0.450	**AIx/HR, %**	23.16 ±9.94	25.16 ±10.08	0.035
107.60 ±10.89	100.48 ±16.55	< 0.001	**Mean arterial BP, mmHg**	104.07 ±10.94	99.73 ±13.17	0.010
43.14 ±9.41	43.18 ±10.77	0.978	**Aortic pulse pressure, mmHg**	43.30 ±10.08	43.55 ±10.73	1.000
7.76 ±1.61	7.95 ±1.37	0.314	**CAVI**	8.02 ±1.96	7.65 ±1.60	0.070
653.26 ±98.87	688.31 ±103.46	< 0.001	**CCA IMT, μm**	658.31 ±98.40	694.21 ±106.14	0.001
3.72 ±1.35	4.47 ±1.57	< 0.001	**CCA stiffness**	3.75 ±1.39	4.57 ±1.54	< 0.001
1.07 ±0.08	1.07 ±0.11	0.842	**ABI**	1.08 ±0.09	1.09 ±0.10	0.790

Abbreviations: LV – left ventricular, DD – diastolic dysfunction, SD – standart deviation, cfPWV – carotid-femoral pulse wave velocity; AIx/HR – augmentation index normalized for a heart rate; BP – blood pressure, CCA – common carotid artery; IMT – intima–media thickness; HR – heart rate; CAVI – cardio-ankle vascular index; ABI – ankle-brachial index.

The longitudinal observation has demonstrated the following significant changes in ehocardiographic parameters: in Group I a decrease in LVMI ($p < 0.001$) and RWT ($p = 0.001$). In Group III we found no significant changes of LVMI and RWT (Table 16).

Table 16. Comparison of echocardiographic parameters between Group I and Group III.

Group I Improved LV DD (n = 126)				**Group III Worsened LV DD (n = 110)**		
At baseline (n = 573) Mean ± SD	**Follow-up (n = 573)** Mean ± SD	**p value**	**Parameters**	**At baseline (n = 573)** Mean ± SD	**Follow-up (n = 573)** Mean ± SD	**p value**
5.08 ±0.45	5.02 ±0.51	0.193	**LV diastolic diameter, cm**	5.01 ±0.47	5,04 ±0,58	0,556
2.56 ±0.27	2.49 ±0.42	0.217	**LV index, cm/m^2**	2.55 ±0.25	2,55 ±0,27	0,861
109.98 ±20.22	98.92 ±24.37	< 0.001	**LVMI, g/m^2**	105.27 ±23.79	105,08 ±25,72	0,946
0.44 ±0.05	0.42 ±0.05	0.001	**RWT**	0.43 ±0.06	0,43 ±0,08	0,310
33.80±9.65	33.22 ±7.71	0.957	**LA volume index, ml/m^2**	32.32 ±8.44	33,69 ±7,89	0,220
67.72 ±21.13	66.19 ±16.66	0.926	**LA volume, ml**	64.21 ±20.00	67,58 ±20,10	0,158
0.83 ±0.17	0.76 ±0.17	0.003	**E, cm/s**	0.87 ±0.16	0,76 ±0,15	< 0,001
0.85 ±0.16	0.78 ±0.14	< 0.001	**A, cm/s**	0.79 ±0.16	0,83 ±0,16	0,004
0.99 ±0.25	1.00 ±0.26	0.734	**E/A ratio,**	1.13 ±0.26	0,92 ±0,19	< 0,001
6.55 ±4.68	7.46 ±1.70	< 0.001	**e'$_{sept}$, cm/s**	8.10 ±2.05	6,61 ±1,63	< 0,001
7.73 ±2.53	9.77 ±2.44	< 0.001	**e'$_{lat}$, cm/s**	10.00 ±2.43	8,26 ±2,47	< 0,001
12.94 ±4.65	9.07 ±2.08	< 0.001	**E/e' mean ratio**	9.80 ±2.00	10,94 ±3,75	0,007
11.97 ±4.89	8.17 ±2.15	< 0.001	**E/e'$_{lat}$ ratio**	9.07 ±2.32	10,12 ±3,93	0,023
14.53 ±5.11	10.64 ±2.81	< 0.001	**LV index, cm/m^2**	11.25 ±3.06	12,20 ±4,03	0,099
16.75 ±6.06	12.03 ±2.67	< 0.001	**PPKsp, mmHg**	13.15 ±2.88	14,45 ±4,87	0,023

Abbreviations: SD – standart deviation, LV – left ventricular, DD – diastolic dysfunction, LVMI – left ventricular mass index, RWT – relative wall thickness, LA – left atrium, E – transmitral peak early diastolic flow, A – transmitral peak flow of atrial contraction, sept – septal part of mitral annular, lat – lateral part of mitral annular.

The logistic regression analysis was performed to determined which are the independent variablies with a significant influence on the dynamics of LV diastolic function (Table 17). In our regression models, carotid-femoral

PWV remained a significant predictor of LV diastolic dysfunction even after adjusting for arterial blood pressure changes.

Table 17. Logistic regression analysis assessing the association between the change of carotid-femoral pulse wave velocity and left ventricular diastolic dysfunction.

	Coefficient of regression	**OR**	**95% CI**	**p reikšmė**
Δ cfPWV	0.222	1.248	1.045 - 1.492	0.015
Δ aortic BP	0.008	1.008	0.991 – 1.026	0.337
Abbreviations: CI – confidence interval, cfPWV – carotid-femoral pulse wave velocity, OR – odds ratio, BP – blood pressure, Δ – the change.				

For more accurate evaluation of the relationship between alterations of arterial stiffness indices and other analized parameters and the dynamics of LV diastolic function the conditional random forests analysis was performed. In this analysis, the effect of each variable is evaluated. Random forest can be very effective to find a set of predictors that best explains the variance in the response variable. The results of analysis are presented in importance diagrams. To ensure the stability of analysis 4 tests were performed: Test 1 and Test 2 with generated 1000 trees, Test 3 and Test 4 with 5000 trees.

During the analysis, we evaluate two prognostic models. One model was designed to evaluate which variables are most significant for worsening of LV diastolic function. The second model was constructed to evaluate the prognostic markers of E/e' alterations.

Random forests analysis demonstrated that carotid-femoral PWV, BMI, weight, and CAVI had prognostic significance for the worsening of LV diastolic function (Figure 8). The second random forests model demonstrated the significant association between the aortic pulse pressure, heart rate, BMI, weight, and calcium chanel blockers and the changes of E/e'_{mean} ratio (Figure 9).

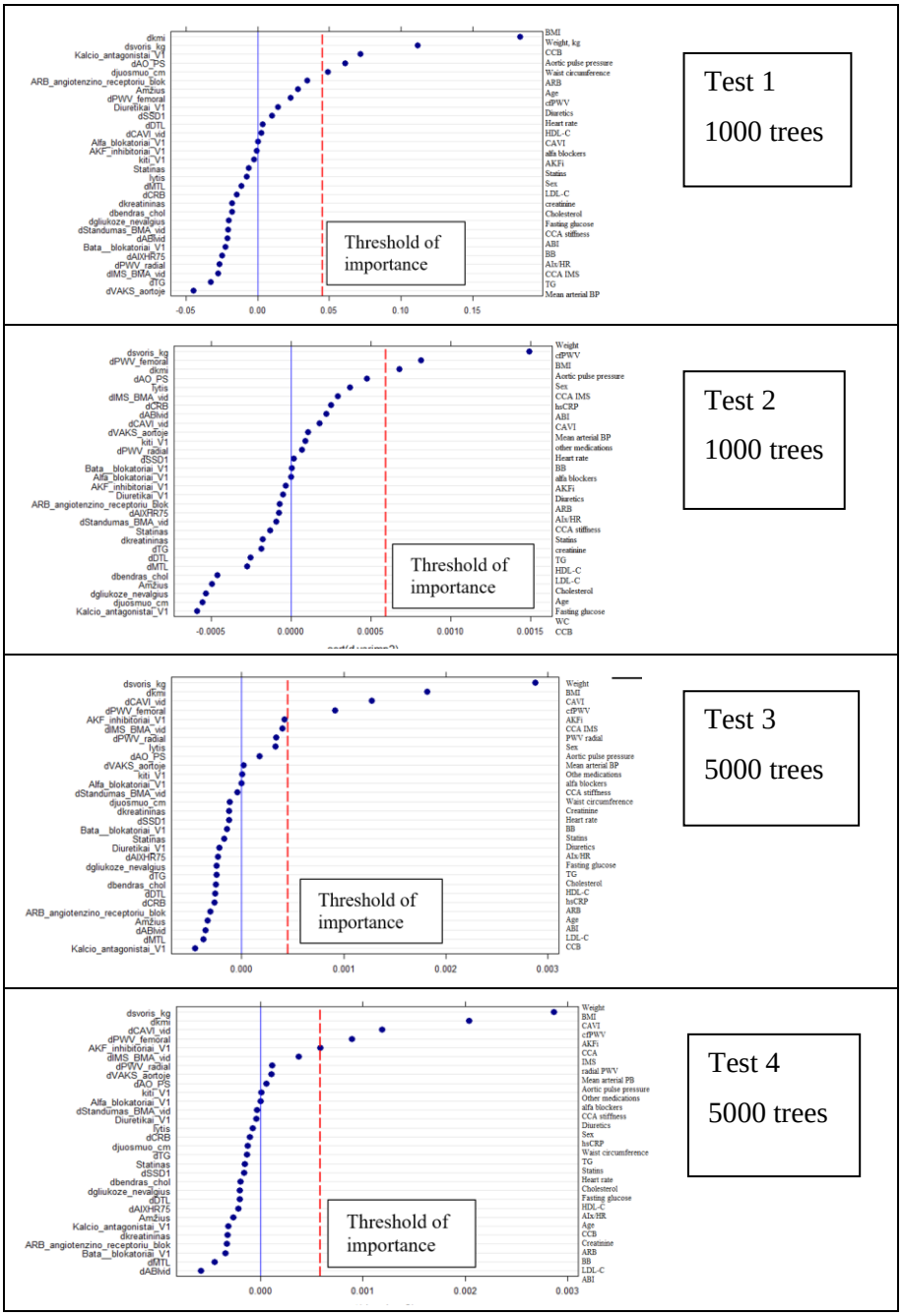
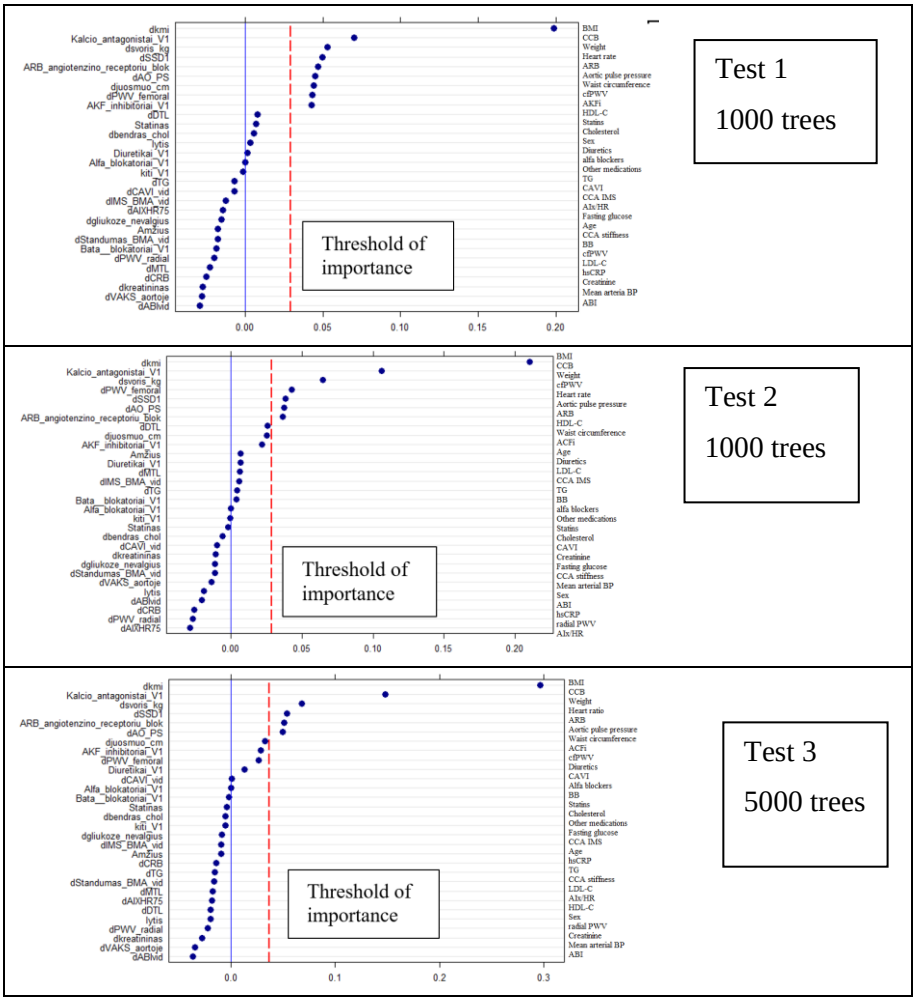


Figure 8. Importance diagrams of conditional random forests analysis for prognosis of LV diastolic function worsening.

Abbreviations and explanations: variables at the right of the threshold are the most important. cfPWV – carotid-femoral pulse wave velocity; AIx/HR – augmentation

index normalized for a heart rate; BP – blood pressure, CCA – common carotid artery; IMT – intima–media thickness, CAVI – cardio-ankle vascular index; ABI – ankle-brachial index, BMI – body mass index; TC – total cholesterol; LDL-C – low density lipoprotein cholesterol; HDL-C – high density lipoprotein cholesterol; TG – triglycerides; hsCRP – high sensitivity C-reactive protein, ACFi – angiotensin converting enzyme inhibitors, CCB – calcium channel blockers, ARB – angiotensin receptor blockers, BB – beta blockers.



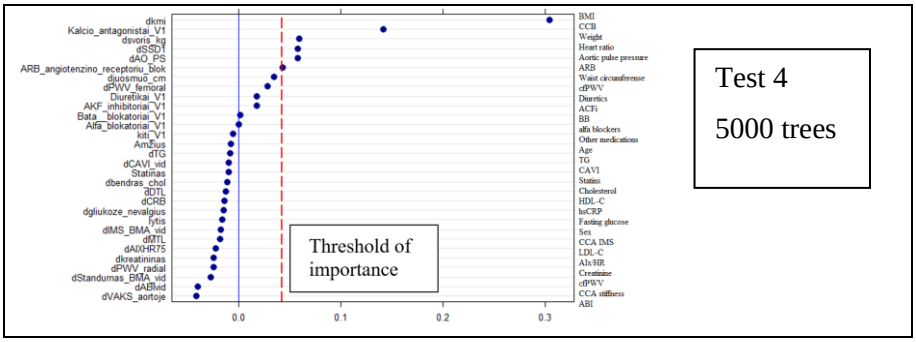


Figure 9. Conditional random forests analysis importance diagrams assessing the association between the changes of E/e'$_{mean}$ and evaluated parameters.

Abbreviations and explanations: variables at the right of the threshold are significantly associated with the changes of the E/e'$_{mean}$. cfPWV – carotid-femoral pulse wave velocity; AIx/HR – augmentation index normalized for a heart rate; BP – blood pressure, CCA – common carotid artery; IMT – intima–media thickness, CAVI – cardio-ankle vascular index; ABI – ankle-brachial index, BMI – body mass index; TC – total cholesterol; LDL-C – low density lipoprotein cholesterol; HDL-C – high density lipoprotein cholesterol; TG – triglycerides; hsCRP – high sensitivity C-reactive protein, ACFi – angiotensin converting enzyme inhibitors, CCB – calcium channel blockers, ARB – angiotensin receptor blockers, BB – beta blockers.

In conclusion, the increase of carotid-femoral PWV and aortic augmentation index are significantly associated with negative dynamics of LV diastolic function. Aortic pulse pressure, heart rate, BMI, weight and calcium channel blockers might also have an important prognostic value.

3.3 Detection of Incipient Heart Failure with Preserved Left Ventricular Ejection Fraction according to Evaluation by Means of Exercise Capacity and Biomarker Testing in Metabolic Syndrome Subjects

According to our cross-sectional study in 1208 subjects with metabolic syndrome, LV diastolic dysfunction is highly prevalent (75.7% [n = 915] of study subjects had LV diastolic dysfunction).

For the additional assessment of early HFpEF, 148 subjects of our follow-up cohort (n = 573) underwent a cardiopulmonary stress (spiroergometry) and an assessment of BNP. The average age of this „prospective" group was 56.4 ± 6.6 years, there were 46 (31.1%) men. For the sake of comparing our findings in this group with the clinical characteristics

of the subjects with clinically HFpEF, we additionally enrolled 38 MetS subjects with confirmed HFpEF, an average age in this „retrospective“ group was 61 ± 10.5 years, 16 (42.1%) men.

According to the BNP values and cardiopulmonary stress test results, subjects from prospective group were divided into two subgroups: with and without early HFpEF. Subjects were assigned to the early HFpEF subgroup (HFpEF+), if, in the cardiopulmonary stress test, they had the peak VO2 ≤ 90% of predicted value or/and BNP ≥ 35 ng/l. According to this classification, the rest of the subjects were considered as HFpEF free (HFpEF– subgroup).

Data on baseline characteristics, echocardiographic parameters, cardiometabolic risk factors, laboratory markers and exercise capacity are presented in Table 18. The most frequent components of metabolic profile were pathological waist circumference (96.0%), blood pressure (90.5%) and fasting serum glucose (70.3%) in the prospective subjects, while – high blood pressure (86.8%), low HDL-cholesterol level (84.2%) and increased fasting serum glucose (76.3%) dominated in retrospective group. In our study the majority of prospective and retrospective subjects presented with LV diastolic dysfunction, and more then half had LV hypertrophy.

As many as 96 subjects from the prospectively enrolled cohort (n = 148) demonstrated reduced exercise capacity and/or elevated BNP consistent with the early signs of HFpEF (Table 18). The BNP level was significantly higher in early HFpEF+ subgroup comparing with the HFpEF– subjects (31.7 ± 23.2 vs. 16.2 ± 6.6 ng/l, $p < 0.05$); in 44 participants (29.7%) of the prospective cohort BNP ≥ 35 ng/l was found. Importantly, retrospective patients with established HFpEF and prospective subgroup with early HFpEF+ demonstrated similarly decreased exercise tolerance, with no difference in oxygen uptake (82.7 ± 14.0 vs. 79.8 ± 22.1%, $p > 0.05$).

Table 18. Metabolic risk factors, echocardiography, laboratory and exercise capacity data of study participants.

	Prospective subgroup without HFpEF– n = 52	Prospective subgroup with early HFpEF+ n = 96	Retrospective group with HFpEF n = 38
Men	27 (51.9 %)	19 (19.8 %)	16 (42.1 %)
Age, years	55.4 ± 6.4	57.1 ± 6.6	61 ± 10.5
MetS components			
Waist circumference, men	108.8 ± 10.4	107.3 ± 7.3	107.5 ± 6.4
Waist circumference, women	105.0 ± 11.2	98.7 ± 9.7*	103.0 ± 12.8
Triglycerides, mmol/l	2.6 ± 2.3	2.2 ± 2.0	2.4 ± 1.4
Fasting serum glucose, mmol/l	6.4 ± 1.3	6.1 ± 0.9	6.5 ± 1.5
HDL-cholesterol, mmol/l	1.2 ± 0.3	1.3 ± 0.4*	1.0 ± 0.3≈
Mean systolic BP, mmHg	152.2 ± 18.9	155.1 ± 21.8	146.1 ± 15.5≈
Mean diastolic BP, mmHg	97.2 ± 11.7	95.6 ± 11.7	90.2 ± 10.1≈
Symptoms, %			
Dyspnoea or fatigue	7 (13.5)	11 (11.5)	27 (71.1)
Chest pain	8 (15.4)	19 (19.8)	11 (28.9)
Arrhythmias	4 (7.7)	8 (8.3)	6 (15.8)
Echocardiographic parameters			
E/e'mean ratio	9.6 ± 2.6	9.5 ± 3.0	11.4 ± 4.6≈
E/A ratio	0.9 ± 0.2	0.9 ± 0.2	1.4 ± 2.1
LA volume index, ml/m²	34.0 ± 9.0	31.8 ± 9.1	46.7 ± 13.7≈
LVMI, man, g/m²	104.0 ± 27.8	101.8 ± 28.3	119.1 ± 25.5
LVMI, women, g/m²	97.5 ± 16.7	94.6 ± 22.2	104.5 ± 33.4
RWT	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
LVH, %	29 (55.8)	61 (63.5)	26 (68.4)
LV diastolic function, %			
Normal	2 (3.8)	3 (3.1)	1 (2.6)
Impaired LV relaxation	29 (55.8)	56 (58.3)	15 (39.5)
Pseudonormal LV filling	21 (40.4)	37 (38.5)	20 (52.6)
Restrictive LV filling	0 (0)	0 (0)	2 (5.3)
Cardiopulmonary stress test			
Peak VO2, %.	103.1 ± 7.6	82.7 ± 14.0*	79.8 ± 22.1
VE/VCO2	28.3 ± 2.8	29.1 ± 2.9	33.0 ± 4.4≈
BNP, ng/l	16.2 ± 6.6	31.7 ± 23.2*	191.2 ± 49.8≈

Abbreviations: HFpEF – heart failure with preserved ejection fraction; VE/VCO_2 - ventilation/carbon dioxide production slope; LVMI - left ventricular mass index; RWT - relative wall thickness; LAVI – left atrial volume index; LVH - left ventricular hypertrophy; BNP - brain natriuretic peptide.
early HFpEF was considered if peak VO2 was ≤ 90% of predicted value or/and BNP was 35 ng/l or higher;
* - statistically significant ($p < 0.05$) difference between prospective group without HFpEF– and with early HFpEF+;

≈- statistically significant ($p < 0.05$) difference between prospective group with early HFpEF+ and retrospective group with HFpEF.

We have found that prospective subjects with early heart failure (HFpEF+ subgroup) were older (57.1 ± 6.6 to compared with 55.4 ± 6.4 years in HFpEF– subgroup), women dominated (80.2% to compared of 48.1% in HFpEF– subgroup). Notably, only 11.5% of HFpEF+ subgroup subjects had complaints, in contrast, 84.3% demonstrated decreased exercise tolerance during the cardiopulmonary stress test. Early HFpEF+ subjects were characterized by significantly lower waist circumference in women and higher HDL-cholesterol compared to HFpEF– subgroup subjects.

Remarkably, significantly higher values of BNP (191.2 ± 49.8 vs. 31.7 ± 23.2 ng/l, $p < 0.05$), E/e' ratio (11.4 ± 4.6 vs. 9.5 ± 3.0, $p < 0.05$), LA volume index (46.7 ± 13.7 vs. 31.8 ± 9.1 ml/m^2, $p < 0.05$), and VE/VCO_2 (33.0 ± 4.4 vs. 29.1 ± 2.9, $p < 0.05$) as well as significantly lower HDL-C was observed in retrospective group as compared to the HFpEF+ prospective subgroup.

The analysis of arterial indices in the prospective group revealed that the HFpEF+ subgroup had significantly higher aortic augmentation index as compared to the HFpEF– subgroup (31.2 ± 9.9 vs. 27.3 ± 7.4%, $p < 0.05$). There were no significant differences between carotid-femoral PWV, mean systolic and mean diastolic blood pressure in HFpEF+ subjects as compared with HFpEF– subjects. The data of the hemodynamic and arterial parameters are presented in Table 19.

Table 19. Arterial indices of preclinical atherosclerosis in prospective group (n = 148).

	PROSPECTIVE GROUP		
	All prospective group n=148 Mean ± SD	Prospective group HFpEF– n=52 Mean ± SD	Prospective group HFpEF+ n=96 Mean ± SD
sBP, mmHg	152.2 ± 18.9	152.2 ± 18.9	155.1 ± 21.8
dBP, mmHg	97.2 ± 11.7	97.2 ± 11.7	95.6 ±11.7
cfPWV, m/s	9.0 ± 1.3	9.0 ± 1.3	9.0 ± 1.3
AIx/HR, %	29.8 ± 9.2	27.3 ± 7.4	31.2 ± 9.9*

CCA IMT, μm	670.1 ± 98.1	682.1 ± 88.7	663.4 ± 102.7
CCA stiffness	4.8 ± 1.5	4.7 ± 1.6	4.8 ± 1.5
ABI	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1
Abbreviations: SD – standart deviation, cfPWV – carotid-femoral pulse wave velocity; sBP – systolic blood pressure, dBP – diastolic blood pressure, CCA IMT– common carotid artery intima–media thickness; ABI – ankle-brachial index. * - statistically significant ($p < 0.05$) difference between prospective group without HFpEF– and with early HFpEF+.			

An analysis on interdependence of the arterial indices and early heart failure markers revealed significant positve correlation between BNP and aortic augmentation index ($r = 0.148$, $p = 0.074$) and carotid artery stiffness ($r = 0.248$, $p = 0.003$). We also observed a significant negative correlation between peak VO2 and aortic augmentation index ($r = – 0.264$, $p = 0.001$) and carotid arterty stiffness ($r = – 0.270$, $p = 0.001$) (Table 20).

Table 20. Correlation between arterial indices and heart failure markers.

	BNP, ng/l		**Peak VO2, %**	
	r	**p value**	**r**	**p value**
Peak VO2, %	–0,354	< 0,001		
cfPWV, m/s	0,011	0,899	–0,071	0,393
AIx/HR, %	0,148	0,074	–0,264	0,001
CCA stiffness	0,248	0,003	–0,270	0,001
CCA IMT , μm	–0,014	0,632	0,030	0,718
Abbreviations: BNP - brain natriuretic peptide; cfPWV – femoral–carotid pulse wave velocity; AIx/HR – aortic augmentation index; CCA IMT– common carotid artery intima–media thickness. * - statistically significant ($p<0.05$) difference between prospective group without HFpEF and with early HFpEF.				

In order to further investigate the dependence of the early HFpEF on arterial indices in the prospective cohort with MetS, we performed an univariate logistic regression analysis (Table 21). This analysis has demonstrated that the presence of an early HFpEF was significantly associated with aortic augmentation index ($p = 0.030$), BNP ($p < 0.001$), and peak VO2

($p < 0.001$). However, in the stepwise multiple logistic regression analysis aortic augmentation index did not remain a significant predictor of early HFpEF (Table 22).

Table 21. Univariate logistic regression analysis assessing the association between arterial indices and early heart failure with preserved left ventricular ejection fraction.

	OR	**95% CI**	**p value**
BNP, ng/l	1,084	1,044 – 1,124	< 0,001
Peak VO2, %	0,076	0,032 – 0,179	< 0,001
cfPWV, m/s	1,003	0,775 – 1,299	0,982
AIx/HR, %	1,045	1,004 – 1,087	0,030
CCA stiffness	1,048	0,926 – 1,112	0,690
CCA IMT, µm	0,998	0,834 – 1,316	0,269
Abbreviations: CI – cofidence interval; OR – odds ratio; BNP - brain natriuretic peptide; cfPWV – femoral–carotid pulse wave velocity; AIx/HR – aortic augmentation index, automatically ; CCA IMT– common carotid artery intima–media thickness.			

Table 22. Stepwise multiple logistic regression analysis assessing the association between significant variables and early heart failure with preserved left ventricular ejection fraction.

	OR	**95% CI**	**p value**
BNP, ng/l	1,068	1,024 - 1,114	0,002
Peak VO2, %	0,093	0,037 - 0,230	<0,001
AIx/HR, %	Not significant		
Abbreviations: CI – cofidence interval; OR – odds ratio; BNP - brain natriuretic peptide; AIx/HR – aortic augmentation index.			

In conclusion, our results show that the considerable proportion of subjects with MetS have signs of the early stage of heart failure. In metabolic syndrome population initial stage of heart failure with preserved ejection fraction might be associated with increased arterial stiffness.

4. DISCUSSION

Cardiovascular diseases remains one of the main causes of death worldwide. According to the World Health Organization (WHO), around 17.5 million people died of CVDs in 2012. Metabolic syndrome represents a cluster of cardiovascular risk factors, such as obesity, hypertension, diabetes, hyperlipidemia and has a growing prevalence worldwide. As a result, this syndrome contributes to development of cardiovascular events.

It has been demonstrated that increased arterial stiffness is associated with increased morbidity and both all-cause and cardiovascular mortality in hypertensive patients, in patients with impaired glucose tolerance and/or diabetes [48, 49, 50]. Besides, increased arterial stiffness is associated with multiple cardiovascular risk factors, such as hypertension, dyslipidemia, obesity, smoking, diabetes, and aging, which contribute to the development of atherosclerosis [6, 51]. These observations suggest that arterial stiffening might be mediating the adverse cardiovascular outcome in MetS subjects.

The research available suggests that cardiovascular diseases associated with MetS comprise vascular and myocardial abnormalities that are initially manifested as impaired relaxation of the left ventricle. This myocardial dysfunction is characterized predominantly by diastolic dysfunction consisting of relaxation abnormalities that are prevalent and have prognostic importance in subjects with MetS [8]. The correlation between the intensity of metabolic syndrome and both the presence and the grade of diastolic dysfunction is reported in several studies [52, 53, 54, 55].

Although the relationship between arterial stiffness and left ventricular diastolic function in patients with hypertension [56], diabetes mellitus [57], in general [58] or eldery population has been previously reported [59], data in subjects with high cardiovascular risk and MetS without overt cardiovascular disease are limited to small sample studies assessing some arterial wall properties [60, 61]. Therefore, in the present study, we evaluated the relationship of a variety of arterial stiffness parameters and left ventricular diastolic dysfunction development and longitudinal alterations in large cohort of MetS subjects. There are invasive and noninvasive methods of evaluating arterial stiffness, including vascular catheterization, ultrasound, magnetic resonant imaging and arterial tonometry [62, 44]. In our study we used an arterial tonometry method and measured the carotid-femoral PWV (the „gold standart“ for aortic stiffness), aortic augmentation index, arterial blood pressure and aortic pulse pressure. Arterial tonometry is an accessible,

nonivasive assessment of arterial stiffness that can be done at the bedside. For assessment of carotid artery stiffness and IMT we used a highly accurate echotracking system (Art. Lab, Esaote Europe B.V.) [63]. The research available of association between arterial markers and LV diastolic dysfunction have had ralatively small sampe sizes and showed the different strengths of the correlation of arterial indeces with LV diastolic dysfunction. In our study we have analysed much more numerous cohort of 1208 subjects with MetS. Currently, little is known about an early development and early clinical diagnosis of heart failure with preserved ejection fraction in subjects with metabolic syndrome. Given the high prevalence of diastolic dysfunction in this population, we hypothesized that a significant number of subjects with MetS already have unrecognized HFpEF. In our study we uncovered the early phase of HFpEF by means of exercise capacity evaluation and biomarker testing. Additionally, we evaluated an association of arterial indices with early HFpEF.

For assessment of the LV diastolic dysfunction we used Doppler echocardiography. Although cardiac catheterization and measuring of LV filling pressure during the procedure remain the primary methods for diagnosing LV diastolic dysfunction; however, the application of this invasive method is limited in daily clinical practice. It was determined that the values of LV filling pressure measured during cardiac ultrasound coincided with the results collected during cardiac catheterization using the Swan-Ganz catheter [64]. The LV filling pressure can be assessed precisely by determining the ratio of the blood flow via the mitral valve and the speed of the mitral annular displacement (E/e' ratio) during cardiac ultrasound [242, 65]. LV filling pressure measured as E/e' ratio is an important diagnostic criterion in determining LV diastolic dysfunction [66]. In our study we evaluated the association between E/A ratio (an important echocardiography index for characterizing the severity and staging LV diastolic dysfunction) and E/e' ratio with arterial indices in MetS subjects.

4.1 Characteristics of the Study Participants

The cohort was comprised of 1208 subjects of both genders with MetS. Arterial hypertension (93.3%, n = 1115) and dyslipidemia (99.7%, n = 1204) were highly prevalent among them. Approximately 60% of the subjects (63% of men and 58% of women) were obese (BMI $\geq$ 30 kg/m^2) at the time of the evaluation. Impaired LV diastolic function was diagnosed in the

majority of the participants (915 [75.7%] patients compared to 292 [24.2%] subjects with normal LV diastolic function). According to the scientific literature, the prevalence of LV diastolic dysfunction tends to increase with the presence of MetS and can reach as many as 35-65% compared to 11-27% without Mets in the general population of adults [67, 68]. Such a difference in results might be caused by the chosen diagnostic criteria. In our study the LV diastolic dysfunction was determined according to the most recent HF diagnosis and treatment recommendations released by the European Society of Cardiology in 2016 [282]. The studies described in scientific literature mostly used the criteria suggested by S. F. Nagueh *et al* in 2009 to determine the LV diastolic dysfunction.

The study subjects with impaired LV diastolic function were older than those without LV diastolic dysfunction (54.7 ± 6.0 vs. 52.0 ± 6.2 years , $p < 0.0001$). Age is one of the risk factors of LV diastolic dysfunction and early HF [69]. LV relaxation slows down with age in both males and females [70]. All organs are afflicted with normal aging which causes certain morphological and functional changes. The impairment of the LV diastolic function during normal aging is caused by structural (increase the size of cardiomyocytes, higher degree of apoptosis, decrease in the number of cardiomyocytes, impaired regulation of growth factors, accumulation of collagen in myocardium) and functional (impaired response to β-adrenergic stimulation, lower number and activity of Ca^{2+} ions transporting albumin) changes in the heart. Our study revealed a significant correlation between age and the ultrasound parameters of LV diastolic function, e.g. blood flow via the mitral valve (E/A ratio, $p < 0.001$) and LV filling pressure (E/e' ratio, $p < 0.001$). Age has remained significantly associated with LV diastolic dysfunction in stepwise logistic regression models ($p < 0.001$).

Our study revealed that the majority of the respondents with LV diastolic dysfunction were women (68%, n = 622, compared to 54.8% in subjects without LV diastolic dysfunction, $p < 0.0001$). However in stepwise logistic regression analysis sex in one of analysis models lost its significance. According to the available literature gender impact on LV diastolic dysfunction is controversial. F. Ceis *et al* determined that women sex is a significant risk factor in developing LV diastolic dysfunction and HFpEF. The prevalence of HFpEF among women tends to increase more with age compared to heart failure [71]. Based on available studies, sex influences both the arterial wall and LV stiffness. However S. A. Carrubbas *et al* analysed the 3936 subjects data did not reveal a significant sex effects on prevalence of LV diastolic dysfunction [72]. Probably gender can influence cardiac changes

during physiological aging [73]. In our opinion, the gender impact on the development of LV diastolic dysfunction and HFpEF requires further detailed research that may be a continuation of this study.

Our study showed that 95% of subjects were overweight (BMI > 25 kg/m^2) and 60% had BMI > 30kg/m^2. Subjects with LV diastolic dysfunction displayed a higher BMI (32,1 ± 5,06 vs. 30,5 ± 4,52 kg/m^2, $p < 0,0001$) and waist circumference (106,8 ± 10,76 vs. 103,6 ± 10,40 cm, $p < 0,0001$). We found statistically significant correlations between BMI and LV filling pressure (E/e' ratio) ($r = 0,216$, $p < 0,001$). In stepwise logistic regression analysis BMI and waist circumference remained as predictors of LV diastolic dysfunction in MtS subjects. The studies discussed bellow showed that obesity is associated with LV diastolic dysfunction and heart failure. S. Kenchaiah et al in longitudinal study of 5881 subjects (average follow-up period was 14 years) determined a significant association between BMI and higher risk of heart failure [74]. The risk of heart failure increased in men by 5% and in women by 7% when BMI increase per 1 kg/m^2. M. R. Movahed *et al* determined a significant correlation between obesity (BMI ≥ 30 kg/m^2) and LA enlargement, LV hypertrophy LV mass and RWT [75]. In the case of BMI ≥ 30 kg/m^2 the risk of heart failure increased (the ORs were 2.5, $p < 0,0001$). The results of *Framinghame Heart Study* confirm the association of obesity and changes in KS geometry independently on age and arterial blood pressure [76]. It should be noted that insulin resistance, hyperinsulinemia and oxidative stress [77] can promote LV remodeling in obesity [78].

Our study has demonstrated that, as compared to subjects with normal LV diastolic function, subjects with LV diastolic dysfunction had higher fasting glucose (6.0 ± 1.29 vs. 5.9 ± 0.99 mmol/l, $p = 0,0231$). Earlier studies have shown that hyperglycaemia may cause arterial wall and myocardial damage and functional impairment. Hyperglycaemia increases the activity of inducible nitric oxide synthase and promotes inflammation, oxidative stress, AGE accumulation that can lead to atherosclerosis progression and myocardial damage [79]. M. K. Rutter *et al* found a higher LV mass and RWT in subjects with impaired glucose tolerance [80]. Some studies indicate that hyperglycaemia may be a significant risk factor for the development of chronic heart failure [81]. In our study in univariate logistic regression analysis fasting glucose did not remained significant factor for LV diastolic dysfunction ($p = 0,05$).

4.2 The Relationship between Arterial Markers and Left Ventricular Diastolic Dysfunction in the Cross-sectional Study

This study represents the association of noninvasive indices of arterial wall parameters (carotid-femoral PWV, aortic augmentation index, mean arterial blood pressure, aortic pulse pressure, common carotid artery IMS and stiffness, cardio-ankle index) with ultrasound measurements of LV diastolic function in a large cohort (n = 1208) of MetS subjects without overt coronary artery disease. Notably, the majority of study participats were demonstrated to have subclinical LV diastolic dysfunction.

The relationship between arterial stiffness and LV diastolic function has been previously reported in subjects with hypertension, diabetes mellitus, in general or eldery populations [82, 83, 84], but similar data in MetS subjects are lacking. The main determinants of arterial wall pathological changes in MetS are endothelial dysfunction, increased collagen production, accumulation of collagen molecules and AGE's, activation of the renin-angiotensin-aldosterone system and inflammatory response [92, 93, 94, 95, 96]. It has been demonstrated that increased arterial stiffness is associated with increased morbidity and both all-cause and cardiovascular mortality [83]. Carotid-femoral PWV is the "gold standard" for measuring large artery stiffness. The additive value of PWV above and beyond traditional risk factors, including SCORE and the Framingham risk score, has been suggested by European Society of Cardiology [102]. As described earlier (pp. 9), the independent prognostic value of increased aortic stiffness for LV diastolic dysfunction and higher CV risk has been theoretically explained by the elevation of central systolic and pulse pressure and the diminishment of the diastolic component in the central blood pressure curves. Our study has demonstrated, that subjects with LV diastolic dysfunction displayed a higher cfPWV (8.8 ± 1.6 compared to 7.9 ± 1.34 m/s in group without LV diastolic dysfunction, $p < 0{,}0001$). The analysis of the relationship between arterial markers and LV diastolic function parameters showed statistically significant correlations between carotid-femoral PWV and E/A ratio ($r_{cfPWV} = -0.190$, $p<0.001$), and E/e' ratio ($r_{cfPWV} = 0.167$, $p<0.05$). Our results confirms those of the earlier studies conducted in several smaller and other than MetS cohorts. The study conducted by C. J. Roos *et al* revealed a significant negative correlation between aortic PWV and E/A ratio ($r = -0{,}350$, $p < 0{,}001$) in 148 patients with diabetes [85]. Abhayaratna *et al* [86] in 233 elderly adult, also Hack-Lyoung Kim at al. [87] in a healthy population, demonstrated a significant correlation between PWV and E/e'. A study of 70 hypertensive

patients [88] showed a significant association between arterial stiffness measured as central pulse pressure and E/e', however, the significant correlation was found only in the univariate logistic regression analysis. In our study, there was a significant positive correlation between cfPWV and E/e' ratio in a larger cohort of 1208 participants and these findings suggests usefulness of cfPWV for early detection of increased LV filling pressure in MetS subjects.

In a multiple regression analysis, we have demonstrated that cfPWV, an index of aortic stiffness, is a significant and independent determinant of the LV diastolic dysfunction in MetS population ($p = 0.002$). Though, in a univariate logistic regression analysis, subjects with MetS and LV diastolic dysfunction also displayed higher aortic augmentation index, ABI, carotid artery IMT, LVMI, RWT, and left atrium width, after adjustment for other significant variables, these associations did not remain significant. Thus, the aortic PWV is an independent prognostic marker of LV diastolic dysfunction. Our results showed that increase of cfPWV by 1.3 m/s is associated with 18.6% higher probability of LV diastolic dysfunction ($p = 0.002$). The determined cfPWV threshold value 8.2 m/s allows to distinguish subjects with the higher risk of LV diastolic dysfunction (AUC 0.642, sensitivity 0.715, specificity 0.596).

In our study cohort subjects with LV diastolic dysfunction displayed a higher aortic augmentation index (25.4 ± 9.96 compared to 21.1 ± 10.84 % in LV DD– group, $p < 0.0001$), which was also reflected in the statistically significant correlations between AIx/HR and LV diastolic function parameters: E/A ($r = – 0.151$, $p < 0.001$) ir E/e' ratio ($r = 0.136$, $p < 0.001$). In the stepwise multiple logistic regression analysis aortic augmentation index remained significant predictor of LV diastolic dysfunction ($p = 0.001$). Previous studies have shown contradictory results in association between augmentation index and LV diastolic dysfunction. Similarly to our data, N. Cauwenberghs *et al* found that AIx was significantly related with increased LV filling pressure [89]; however, their study was carried out in general population, not MetS subjects. C. Luers *et al* [90] in 257 subjects group (mean age 66 years) demonstrated that increased AIx is related with increasing of LV filling pressure. In multiple regression analysis, however, after adjustment for age, gender and carotid-femoral PWV, association between AIx and increased LV filling pressure did not remain. In distinction, our study has shown that both aortic augmentation index and carotid-femoral PWV remained significant for prediction of LV diastolic dysfunction in middle aged

subjects with MetS and therefore their combination should be taken into account for CV risk assessment.

In our study, we also investigated the relationship between arterial blood pressure, aortic pulse pressure and LV diastolic dysfunction. Some previous studies have shown that arterial blood pressure and aortic pulse pressure are clinically more significant in comparison to peripheral blood pressure. For instance, J. Hashimoto *et al* described the association between aortic pulse pressure and regression of LV remodeling [91]. Our findings complement these studies by showing that subjects with LV diastolic dysfunction displayed a higher arterial blood pressure (108.6 ± 12.85 vs. 103.4 ± 10.13 mmHg, $p < 0.0001$) and aortic pulse pressure (44.5 ± 10.69 vs. 41.9 ± 10.8 mmHg, $p = 0.0004$) compared to those with normal LV diastolic function. Furthermore, our results revealed a statistically significant positive correlation between arterial blood pressure, aortic pulse pressure and LV filling pressure, measured as E/e' ratio: $r_{aBP} = 0.159$, $r_{aPP} = 0.265$, $p < 0.001$. However, in the stepwise multivariate regression analysis, the relationship between these parameters of central BP and the presence of LV diastolic dysfunction did not remain significant, thus suggesting that the effect of increase central pulse pressure is not an independent predictor: it is derivative of aortic stiffness.

The relationship between carotid artery IMT, stiffness and LV diastolic dysfunction has been demonstrated in different populations other than MetS. In a cohort of the *Multi-Ethnic Study of Atherosclerosis* of 58 subjects free of cardiovascular diseases (mean average age 64 years), carotid artery IMT was associated with the incipient systolic and diastolic myocardial dysfunction [92]. Similar results were obtained by Garcia *et al* [93] in 48 healthy subjects in whom the relation between carotid artery IMT and LV diastolic dysfunction was evaluated. In contrast, Y. Mizuguch *et al* [94] have shown no significant association between carotid artery IMS and the echocardiographic LV systolic and diastolic parameters. In our cohort subjects with LV diastolic dysfunction displayed higher carotid artery IMT (656.6 ± 105.29 vs. 637.6 ± 98.49 μm, $p = 0.007$) and carotid artery stiffness (3.9 ± 1.47 vs. 3.5 ± 1.32, $p < 0.0001$) compared to participants with normal LV diastolic function. Once more, after adjustment for other significant variables by performing a stepwise logistic regression analyses, this relationship lost its statistical significance, foregrounding that, in contrast to aortic stiffness indices, the carotid IMT and the local stiffness in the carotid artery do not have an independent predictive value for LV diastolic dysfunction.

The cardio-ankle vascular index (CAVI) has been recently promoted as easy-to-obtain marker of aortic stiffness, which is automatically adjusted for the BP at the time of measurement. K. Sakane *et al* in total of 119 subjects (mean average age 62 ± 11 years) demonstrated significant assotiation between CAVI and E/A ratio, LA diameter, age, BMI and systolic blood pressure [95]. The study conducted by Y. Mizuguchi *et al* [96] in small 30 subjects group (mean average age 59 ± 5.7 years) showed significant positive correlation between CAVI and the peak early diastolic transmitral flow velocity, E/A ratio, deceleration time of the early diastolic transmitral flow velocity, peak early diastolic mitral annular motion velocity. Our study showed no significant difference of CAVI values between LV DD+ and LV DD– groups subjects (8.0 ± 1.67 in LV DD+ subjects compared to 7.8 ± 1.55 in LV DD–, p = 0,0721). Likewise, in the univariate logitic regression analysis CAVI was not associated with the presence of LV diastolic dysfunction (p = 0,178). Thus, in our study, CAVI did not demonstrate superiority over other indices of arterial stiffness for predicting of LV diastolic dysfunction in MetS. This might be explained by the fact that CAVI is a derivative index that reflects a complex interaction of arterial properties beyond aortic PWV.

To sum up, our study has shown that left ventricular diastolic dysfunction is significantly associated with elevated arterial stiffness in metabolic syndrome subjects. Non–invasively measured carotid-femoral pulse wave velocity, an index of aortic stiffness, is a significant and independent determinant of the LV diastolic dysfunction. Based on our results, in subjects with MetS, the adequate measures for preventing the development of LV diastolic dysfunction are especially urgent when carotid-femoral PWV is higher than 8.2 m/s. Since LV diastolic dysfunction is highly prevalent in middle aged MetS subjects, implementing these measures is of key importance for preventing the future development of heart failure with preserved LV ejection fraction.

4.3 The Influence of Arterial Stiffness Alteration on the Dynamics of the Left Ventricular Diastolic Dysfunction during Longitudinal Observation

Left ventricular diastolic dysfunction is an early pre-clinical marker of cardiovascular diseases. Any kind of heart disease that leads to myocardial structural alteration may cause LV diastolic dysfunction [97]. Early subclinical LV diastolic dysfunction has leads to the elevation of LV filling pressures and has been shown to be associated with development of heart failure. To clarify the relationship between arterial stiffness and LV diastolic

dysfunction we aimed to determine how the alteration of arterial stiffness affects the dynamics of LV diastolic dysfunction during longitudinal observation.

Our study has shown that over a 3 ± 0.6 years period, LV diastolic function remained unchanged in 58.8 % MetS subjects. In 22% of subjects LV diastolic dysfunction improved, and in 19% – has worsened. Some previous studies determined age–related changes in LV diastolic dysfunction dynamics. G. C. Kan *et al* in a cohort of 1402 subjects, over a 4 ± 0.3 years period, found unchanged LV diastolic dysfunction in 67.8% patients, and only in 8.8% subjects LV diastolic dysfunction normalized and in 23.4% - worsened [98]. In their study the worsening of LV diastolic dysfunction was associated with age 65 years or older. Left ventricular diastolic dysfunction was also associated with incident heart failure during 6 years period after adjustment for age, hypertension, diabetes, and coronary artery disease. Our study showed no significant age difference between subjects with improved vs. worsened LV diastolic dysfunction at baseline (respectively 53.25 ± 5.28 vs. 53.16 ± 5.7, $p = 0.857$). During the longitudinal observation we found no significant difference in age changes between subjects with improved vs. worsened LV diastolic dysfunction (age changes 3.85 ± 0.54 vs. 3.9 ± 0.56 years, $p > 0.05$). Furthermore, in logistic regression analyses, age did not remained significant for dynamics of LV diastolic function ($p = 0.605$) neither for alteration of E/e' ratio ($p = 0.653$). This suggests that age–related changes might blurred and acceleratedby the presence of MetS and its various cluster. This hypothesis is supported by the acceleration of arterial stiffness in MetS subjects, recently demonstrated in large follow–up study [99].

In our study we evaluated how the alteration of arterial markers, LV geometry and LA echocardiographic parameters affect the improvement or the worsening of LV diastolic function. We have found that main factor associated with the worsening of LV diastolic function was the carotid-femoral PWV. In a group of improved LV diastolic dysfunction, cfPWV did not increase; there was, in fact a decrease in cfPWV, however, not statisticaly significant ($p = 0.489$). In a group of worsened LV diastolic dysfunction, cfPWV significantly increased ($p = 0.004$). Logistic regression analysis demonstrated that alteration of cfPWV remained a significant predictor of the deterioration of LV diastolic function even after adjustment for other potentially explanatory variables ($p = 0{,}015$). In order to more accuratly evaluate the prognostic markers of the LV diastolic dysfunction progression, we performed conditional random forests analysis. According to the available literature, random forests have become a popular and widely-used tool for

non-parametric regression in many scientific areas. They show high predictive accuracy and are applicable even with highly correlated variables [100]. In our study conditional random forests analysis confirmed the high significance of the elevated arterial stiffness alteration for the development of LV diastolic dysfunction. It has been shown that cfPWV alteration stands out among other arterial stiffness indices as a significant predictor of the dynamics of the LV diastolic function.

Our study demonstrated significant reduction of LVMI (from 109.98 ± 20.22 to 98.92 ± 24.37, $p < 0.001$) and relative wall thickness (from 0.44 ± 0.05 to 0.42 ± 005, $p = 0.001$) in a group of improved LV diastolic dysfunction. According to the literature, development of an abnormal LV geometric pattern is associated with increased CVDs risk [101]. *Multi-Ethnic Study of Atherosclerosis* showed the significant progression in the increase of LV mass during the 9.4 years period [102]. In our study progression of LV remodeling was found in 24.2% of cohort subjects, regression of LV remodeling – in 39.4% subjects. Findings from other studies demonstrated the association between AH with LV hypertrophy and LV diastolic dysfunction [103]. In a group of LV diastolic dysfunction, our study demonstrated the significant higher values of LVMI (106.77 ± 22.59 compared to 102.25 ± 21.99 g/m^2 in LV DD– group, $p = 0.033$) and RWT (0.43 ± 0.06 compared to 0.42 ± 0.06 in LV DD– group, $p = 0{,}020$) at baseline. We found significant correlation between LVMI and LV filling pressure, measured as E/e' ratio ($r = 0.324$, $p < 0.001$). In stepwise multiple logistic regession analysis, LVMI remained significant predictor of the LV diastolic dysfunction together with cfPWV, BMI, waist circumference, and age.

Previous studies revealed that left atrium volume index increases as an expression of LV diastolic dysfunction severity and is independently associated with age, LV hypertrophy, LV systolic dysfunction and increased LV filling pressure [104]. In our study, no sigificant difference was found in LV volume and LV volume index between LV DD+ and LV DD– groups at baseline. During the longitudinal observation, no significant differences were found in respect to the alteration of LA volume and volume index between subjects with improved LV diastolic dysfunction and LV diastolic function deterioration. It might be explained by the fact that, the majority of study patients (74.7%, n = 243) had an impaired LV relaxation with normal LV filling pressure at baseline.

It should be noted, that the conditional random forests analysis demonstrated a number of drugs used by our study subjects, such as calcium channel blockers, angiotensin converting enzyme inhibitors, and angiotensin

receptor blockers might influence E/e' ratio. Univariate logistic regression analysis, however, revealed that alteration of E/e' ratio was associated only with calcium channel blockers: the use of calcium channel blockers during the follow–up period was related to LV diastolic dysfunction improvement ($p = 0.012$). No significant association was found between LV diastolic function dynamics and angiotensin converting enzyme inhibitors ($p = 0.195$) and angiotensin receptor blockers ($p = 0.504$). The possible limitation for an accurate evaluation of the treatment effect was that we collected data on medical treatment only at follow-up visit. Further longitudinal studies designed specifically to assess various medical treatment strategies are needed to determine the relationship between the dynamics of LV diastolic function and medications.

In summary, our findings show that the alterations of arterial indices, namely, carotid–femoral PWV and aortic pulse pressure are the independent predictors of LV diastolic dysfunction in MetS subjects. Our findings suggest that increased arterial stiffness is a pathogenetic factor of LV diastolic dysfunction. These results have important clinical implications. Since PWV is modifiable with medical therapy [105,106], it can be used as a surrogate endpoint for assessing the treatment efficiency in subjects with MetS and LV diastolic dysfunction. Moreover, the identification of subjects with increased aortic stiffness should be considered in primary prevention of LV diastolic dysfunction, a condition associated with adverse prognosis in the community.

4.4 Detection of Early Heart Failure with Preserved Left Ventricular Ejection Fraction in Subjects with Metabolic Syndrome

To the best of our knowledge, this is the first study that addresses the early detection of HFpEF in MetS patients using a combination of BNP and peak VO_2. In our cross–sectional study of 1208 participants, highly prevalent of LV diastolic dysfunction was demostrated. We hypothesized that subjects, who are at high risk of heart failure development, a focused testing will reveal a very early phase of HFpEF. Indeed, up to two thirds of our prospectively enrolled MetS subjects ($n = 148$) without established overt cardiovascular disease, had an impaired functional capacity, elevated neurohormonal activation and ultrasound evidence of elevated LV filling pressure. Heart failure diagnosis in such patients is largely in accordance with HFpEF definition by the recent guidelines [107]; the components of the diagnosis include increased BNP, left ventricular mass, diastolic dysfunction and objectively documented impaired exercise capacity. A certain peculiarity is

the use of exercise test in order to elicit objective decrease of exercise tolerance, which frequently is not adequately appreciated by the patients themselves.

It has been shown that the usage of self-rated health (SRH), assessed through a single question [108, 109], is of limited value in patient with left ventricular diastolic dysfunction for a subjetive self–evaluation tends to underestimate the heart failure symptoms. A Swedish study has shown that the majority of participants with asymptomatic left ventricular diastolic dysfunction rated their health status as good or very good, despite the high prevalence of co-morbidities [110]. Therefore, there is a need for comprehensive diagnostic methods that would help to highlight the symptoms. Cardiopulmonary stress test is an established tool for the evaluation of the disease severity and prognosis in heart failure patients. Our study suggests its value for the early detection of reduced exercise tolerance in subjects enrolled in the prevention program. Though only 11.5% of patients with the signs of early HFpEF had documented complaints of dyspnoea, the cardiopulmonary stress test revealed reduced exercise tolerance in 83.3% of these patients.

The latest ESC heart failure guidelines require the elevated BNP level for establishment of HFpEF diagnosis. In our study 96 (64.8%) subjects from 148 prospectively enrolled participants with MetS, have shown modest but statistically significant elevation of BNP: 31.7 ± 23.2 in the subgroup with early HF compared to 16.2 ± 6.6 ng/l in the subgroup without early HF ($p < 0.05$). BNP ≥ 35 ng/l was found in 28.3% subjects with early HFpEF. It can be expected that subjects with hidden HFpEF could be identified with even greater accuracy if not the inverse impact of MetS on BNP – as it was previously demonstrated, BNP values are significantly lowered in persons affected by MetS [111]. Several hypotheses attempt to explain the inverse relationship between BNP levels and obesity. Renal theory states that BNP levels are depressed because of higher glomerular filtration rates which lead to more efficient molecular clearing [112]. Adipose tissue theory states that the reason for lowered BNP values in MetS is natriuretic peptide clearance receptor-C (NPR-C) [113]. On the contrary, the *Framingham Heart Study* [114] and the *Dallas Heart Study* [115] questioned this theory showing that NT–proBNP values in obesity are also reduced even though it is not cleared by NPR-C. The Dallas Heart Study authors found that both BNP and NT-proBNP values were more closely associated with lean mass than with BMI. Due to this finding they theorized that not the adipose tissue itself is the main factor causing lowered BNP values but a substance produced in the lean mass

which could suppress either BNP synthesis either its release from cardiomyocytes.

Two MetS criteria, insulin resistance and lipid abnormalities, are considered as the main components that influence progression of the disease, whereas obesity and high blood pressure are linked to the outcomes in HF patients [116]. Recently presented new paradigm for HFpEF emphasizes the importance of obesity as one of the main comorbidities which induces a systemic inflammatory state that sequentially leads to diastolic LV dysfunction [117].

Left ventricular diastolic dysfunction as a leading mechanism in the formation of HFpEF was detected in most of the study patients. Only 3.4% of prospective and 2.6% of retrospective individuals had normal diastolic function. The most common grade of diastolic dysfunction in both prospective subgroups was impaired relaxation, whereas retrospective group mostly presented with pseudo-normal filling.

Arterial markers of preclinical atherosclerosis are used for early prediction of cardiovascular risk and the impact of MetS on arterial elastic properties is discussed in many current scientific papers [118, 119]. In our study we found a markedly higher AIxHR75 in early HFpEF patients compared to those without (31.2 ± 9.9% vs. 27.3 ± 7,4%, $p < 0,05$). The analysis of the relationship between arterial markers and the markers of early HFpEF has shown a statistically significant correlation between aortic augmentation index and peak VO2 ($r = – 0.264$, $p = 0.001$). However, in the multiple logistic regression analysis, the association between AIx/HR and the presence of HFpEF lost its significance. This controversial finding might be explained by the relatively small number of participants, and the negative association between BNP and obesity. Thus, increasing the sample size and using an heart failure biomarker which is not affected by obesity is desirable in further studies.

5. CONCLUSIONS

1. In metabolic syndrome subjects without overt cardiovascular disease, arterial stiffness, asessed by measuring the "gold standard" index of carotid-femoral pulse wave velocity, is significantly and independently associated with the LV diastolic dysfunction.

2. In subjects with metabolic syndrome, the progression in arterial stiffening, assessed as an increase in carotid-femoral pulse wave velocity, significantly predicts the worsening of the left ventricular diastolic function. Our findings suggest that increased arterial stiffness is a pathogenetic factor of left ventricular diastolic dysfunction.

3. A considerable portion of subjects with metabolic syndrome exhibit signs of an early heart failure with preserved left ventricular ejection fraction. In metabolic syndrome population, initial stage of heart failure with preserved ejection fraction might be associated with the increased arterial stiffness.

6. RECOMMENDATIONS FOR CLINICAL PRACTICE

1. Based on our results, in subjects with metabolic syndrome, the adequate measures for preventing the development of LV diastolic dysfunction are especially urgent when carotid–femoral PWV is higher than 8.2 m/s. Since LV diastolic dysfunction is highly prevalent in the middle aged MetS subjects, implementing these measures is of key importance for preventing the future development of heart failure with preserved LV ejection fraction.

2. Carotid–femoral pulse wave velocity can be used as a surrogate endpoint for assessing the treatment efficiency in subjects with metabolic syndrome and LV diastolic dysfunction.

3. In addition to the assessment of clinical complaints, cardiopulmonary stress test can be used for the early detection of the reduced exercise tolerance and for identifying of an early heart failure with the preserved LV ejection fraction in subjects with metabolic syndrome.

7. PUBLICATION

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8. ANNEXES

8.1 Curriculum Vitae

Brief information about the author

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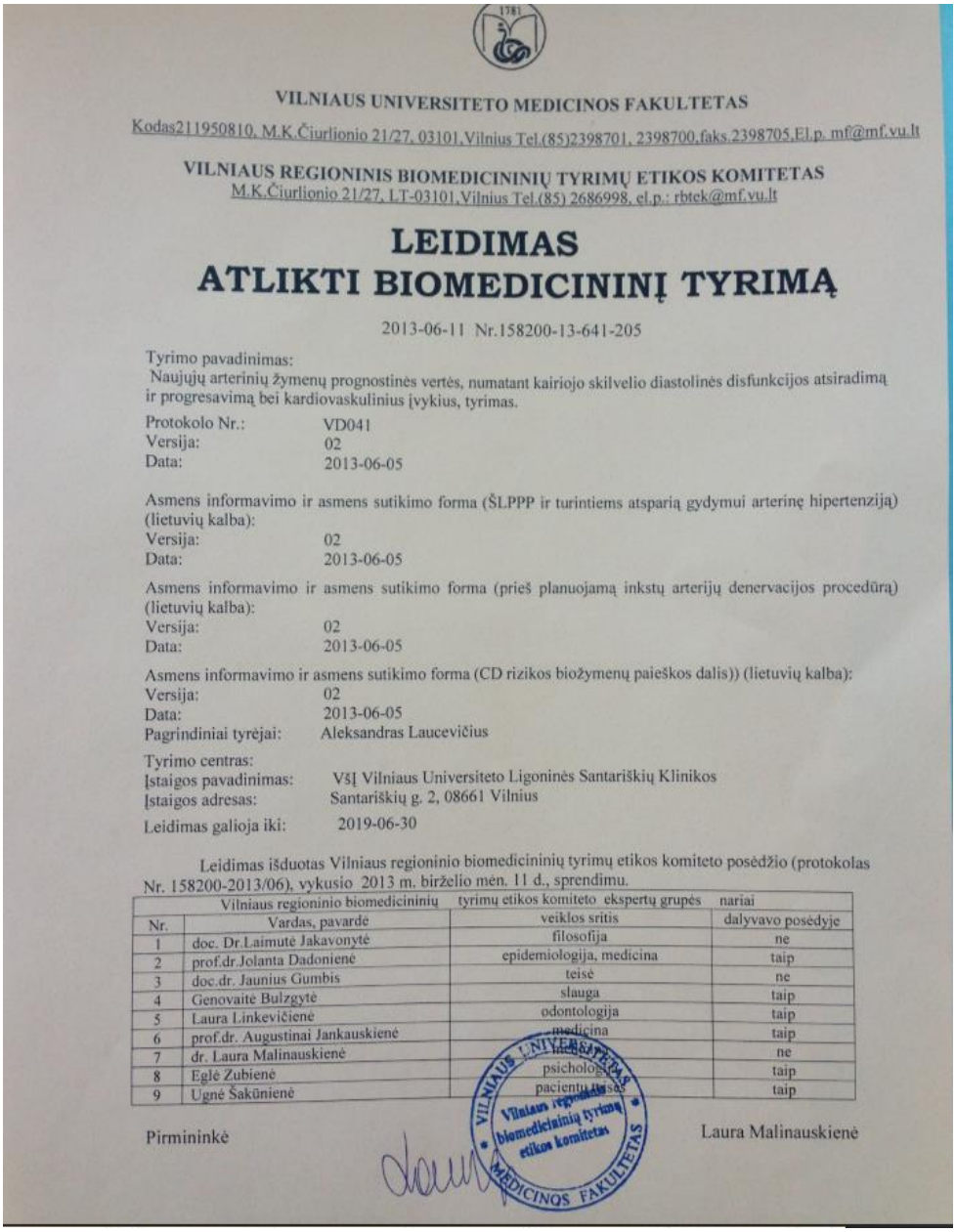
8.2 Authorization Provided by the Vilnius Regional Biomedical Research Ethics Committee



VILNIAUS UNIVERSITETO MEDICINOS FAKULTETAS

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LEIDIMAS ATLIKTI BIOMEDICININĮ TYRIMĄ

2013-06-11 Nr.158200-13-641-205

Tyrimo pavadinimas:
Naujųjų arterinių žymenų prognostinės vertės, numatant kairiojo skilvelio diastolinės disfunkcijos atsiradimą ir progresavimą bei kardiovaskulinius įvykius, tyrimas.

Protokolo Nr.: VD041
Versija: 02
Data: 2013-06-05

Asmens informavimo ir asmens sutikimo forma (ŠLPPP ir turintiems atsparią gydymui arterinę hipertenziją) (lietuvių kalba):
Versija: 02
Data: 2013-06-05

Asmens informavimo ir asmens sutikimo forma (prieš planuojamą inkstų arterijų denervacijos procedūrą) (lietuvių kalba):
Versija: 02
Data: 2013-06-05

Asmens informavimo ir asmens sutikimo forma (CD rizikos biožymenų paieškos dalis)) (lietuvių kalba):
Versija: 02
Data: 2013-06-05
Pagrindiniai tyrėjai: Aleksandras Laucevičius

Tyrimo centras:
Įstaigos pavadinimas: VšĮ Vilniaus Universiteto Ligoninės Santariškių Klinikos
Įstaigos adresas: Santariškių g. 2, 08661 Vilnius

Leidimas galioja iki: 2019-06-30

Leidimas išduotas Vilniaus regioninio biomedicininių tyrimų etikos komiteto posėdžio (protokolas Nr. 158200-2013/06), vykusio 2013 m. birželio mėn. 11 d., sprendimu.

Vilniaus regioninio biomedicininių		tyrimų etikos komiteto ekspertų grupės	nariai
Nr.	Vardas, pavardė	veiklos sritis	dalyvavo posėdyje
1	doc. Dr.Laimutė Jakavonytė	filosofija	ne
2	prof.dr.Jolanta Dadonienė	epidemiologija, medicina	taip
3	doc.dr. Jaunius Gumbis	teisė	ne
4	Genovaitė Bulzgytė	slauga	taip
5	Laura Linkevičienė	odontologija	taip
6	prof.dr. Augustinai Jankauskienė	medicina	taip
7	dr. Laura Malinauskienė	medicina	ne
8	Eglė Zubienė	psichologija	taip
9	Ugnė Šakūnienė	pacientų teisės	taip

Pirmininkė Laura Malinauskienė

VILNIAUS UNIVERSITETAS Vilniaus regioninio biomedicininių tyrimų etikos komitetas MEDICINOS FAKULTETAS

ĮVADAS

Širdies ir kraujagyslių ligos (ŠKL) – tai pagrindinė pasaulio gyventojų mirtingumo ir sergamumo bei mažėjančio darbingumo priežastis, lemianti 31 proc. visų mirčių. Pagal Pasaulinės sveikatos organizacijos (PSO) duomenis, 2012 metais nuo ŠKL mirė apie 17,5 milionų žmonių, 80 proc. mirčių sąlygojo miokardo infarktas ir galvos smegenų kraujotakos sutrikimai. Lietuvos Respublikos Statistikos departamento duomenimis, 2016 metais nuo kraujotakos sistemos ligų mirė 56,2 proc. gyventojų. Didžiausią dalį sudarė asmenys, mirę nuo išeminės širdies ligos (65,6 proc.) ir cerebrovaskulinių ligų (24,2 proc.). Didžioji dalis (87 proc.) mirusiųjų nuo kraujotakos sistemos ligų buvo 65 metų ir vyresnio amžiaus asmenys.

Širdies ir kraujagyslių ligų rizikos veiksniai (RV) plačiai tyrinėjami ekonomiškai išsivysčiusiose šalyse. Metabolinis sindromas (MetS) – rizikos veiksnių (arterinė hipertenzija, pilvinio tipo nutukimas, atsparumas insulinui ir aterogeninė dislipidemija) derinys – viena iš opiausių problemų šiuolaikiniame pasaulyje. Dėl didėjančio nutukimo, AH ir MetS dažnio, šių patologinių būklių profilaktika ir laiku suteiktas gydymas tampa prioritetu ekonomiškai stipriose šalyse. MetS nustatymas turi didelę klinikinę reikšmę, kadangi, viena vertus, tai sindromas, kurio pasireiškimą taikant prevencines priemones ir laiku suteiktą gydymą galima sulėtinti, kita vertus, jis sąlygoja 2 tipo CD ir aterosklerozinių ligų, pirmaujančių pasaulyje tarp gyventojų mirties priežasčių, atsiradimą ir progresavimą.

Kitas stiprus ir nepriklausomas ŠKL sergamumo ir mirtingumo rizikos veiksnys – arterijų standumas – vis plačiau tyrinėjamas pasaulyje. Svarbiausi ikiklinikiniai arterijų sienelės funkciniai ir morfologiniai pakitimai apima endotelio disfunkciją, arterijų standumo padidėjimą, intimos-medijos sluoksnio storėjimą, tačiau arterijų standumui šiuo metu skiriamas didžiausias dėmesys. Esant MetS, padidinto arterijų standumo reikšmė ypač pabrėžiama. Kaupiasi duomenys, rodantys, kad padidėjęs aortos standumas daro įtaką kairiojo skilvelio (KS) diastolinės disfunkcijos atsiradimui bei progresavimui. Padidėjus arterijų sienelės standumui, didėja pulsinės bangos plitimo greitis (PBG) ir ankstyvas (sistolėje, o ne diastolėje) atspindėtos pulsinės bangos grįžimas į kylančią aortą. Aortoje didėja sistolinis, mažėja diastolinis kraujospūdis, didėja kairiojo skilvelio pokrūvis, vystosi miokardo hipertrofija, blogėja koronarinė perfuzija, pulsuojanti, ne vientisa tėkmė pasislenka toliau periferijos, smulkiųjų arterijų link. Smulkios arterijos degeneruoja, sutrinka mikrocirkuliacija, vystosi organų–taikinių pažeidimas (inkstų, smegenų ir kt.).

Blogėjanti koronarinė perfuzija ir kairiojo skilvelio miokardo hipertrofija lemia KS atsipalaidavimo sutrikimą bei diastolinės disfunkcijos atsiradimą. Atliktų tyrimų duomenys rodo, kad pacientams, padidėjus arterijų standumui, dažniau nustatomas sutrikęs KS atsipalaidavimas, ir abu šie veiksniai kartu su arterijų senėjimu (angl. *vascular aging*) yra siejami su širdies nepakankamumo atsiradimu ir progresavimu.

Tarp sergančiųjų širdies nepakankamumu apie 40–50 proc. pacientų nustatoma išsaugota kairiojo skilvelio išstūmio frakcija. Išsaugotos kairiojo skilvelio išstūmio frakcijos širdies nepakankamumui (IIFŠN) būdingi tam tikri kairiojo skilvelio struktūriniai ir funkciniai pokyčiai, kurių vienas svarbiausių – sutrikusi KS diastolinė funkcija. Įvairūs veiksniai, tokie kaip senėjimas, arterinė hipertenzija, cukrinis diabetas, lėtinė inkstų liga, metabolinis sindromas ir padidėjęs arterijų sienelės standumas sąlygoja kairiojo skilvelio diastolinės funkcijos sutrikimą ir gali būti svarbūs vystantis IIFŠN. Arterijų standumo didėjimas pacientams su ŠN siejamas su blogesne prognoze, tad arterijų standumo nustatymas ir jo sumažinimas galėtų būti taikiniu ir ŠN prevencijoje, ir gydyme.

Kadangi kairiojo skilvelio diastolinė disfunkcija literatūroje įvardinama ankstyvuoju ikiklinikiniu širdies ir kraujagyslių sistemos sutrikimų žymeniu, kuriai progresuojant išsivysto ŠN (o tai savo ruožtu sąlygoja blogėjančią pacientų gyvenimo kokybę mažėjant fiziniam pajėgumui bei tolerancijai krūviui), jos patogenetinių veiksnių nustatymas yra svarbus parenkant tinkamą medikamentinį gydymą. Tačiau vis dar trūksta duomenų apie arterijų standumo ir kairiojo skilvelio diastolinės funkcijos sąsajas tarp asmenų su nustatytu metaboliniu sindromu: atlikti tyrimai yra mažos imties, analizuojami tik atskiri arterijų standumo rodikliai.

Kaupiasi duomenys, patvirtinantys metabolinio sindromo ir jo komponentų svarbą išsivystant širdies nepakankamumui. Esant MetS, nustatytas reikšmingai didesnis kairiojo skilvelio diastolinės disfunkcijos dažnis. Tačiau literatūroje vis dar trūksta duomenų apie IIFŠN vystymosi eigą ir ankstyvąją klinikinę diagnostiką asmenims, turintiems metabolinį sindromą. Iki šiol nebuvo tirtos galimybės taikyti tikslingą ištyrimą (kardiopulmoninį krūvio mėginį, natriuretinio peptido koncentracijos vertinimą), siekiant nustatyti tikrąjį ankstyvojo širdies nepakankamumo dažnį asmenų, turinčių MetS, grupėje.

Nors pasaulyje atlikta nemažai skerspjūvio tyrimų, analizuojančių ryšį tarp arterijų standumo ir KS diastolinės disfunkcijos, vis dar trūksta išilginio stebėjimo tyrimų, išaiškinančių ryšį tarp arterijų standumo didėjimo ir KS diastolinės disfunkcijos progresavimo bei širdies nepakankamumo

išsivystymo. Tokių tyrimų atlikimas padėtų geriau parinkti optimalų gydymą sumažinant ŠKL ir širdies nepakankamumo atsiradimą ir progresavimą.

Darbo tikslas

Darbo tikslas – nustatyti sąsajas tarp arterijų funkcijos ir struktūros rodiklių pokyčių ir kairiojo skilvelio diastolinės disfunkcijos asmenų, turinčių metabolinį sindromą, kohortoje.

Darbo uždaviniai

1. Įvertinti sąsajas tarp arterinių rodiklių ir kairiojo skilvelio diastolinės disfunkcijos skerspjūvio tyrime.
2. Išilginio stebėjimo tyrime nustatyti, kaip arterijų standumo pokytis daro įtaką kairiojo skilvelio diastolinės disfunkcijos dinamikai.
3. Ištirti ankstyvojo širdies nepakankamumo paplitimą tarp asmenų, turinčių metabolinį sindromą, vertinant krūvio deguonies suvartojimą ir natriuretinio peptido koncentraciją. Įvertinti sąsajas tarp arterinių rodiklių ir išsaugotos kairiojo skilvelio išstūmio frakcijos širdies nepakankamumo.

Ginamieji teiginiai

1. Asmenims, turintiems metabolinį sindromą, kairiojo skilvelio diastolinė disfunkcija reikšmingai siejasi su padidintu arterijų standumu.
2. Arterijų standumo, išmatuoto vertinant miego-šlaunies arterijų pulsinės bangos greitį, didėjimas reikšmingai siejasi su kairiojo skilvelio diastolinės funkcijos blogėjimu.
3. Esant metaboliniam sindromui, dalis asmenų turi neatpažintą ankstyvąjį širdies nepakankamumą, objektyviai nustatomą vertinant fizinio pajėgumo ir neurohormoninės aktyvacijos žymenis.

Tyrimo naujumas ir aktualumas

Šiame darbe atlikta didelės 1208 asmenų, turinčių MetS, kohortos duomenų skerspjūvio analizė, kurios dėka įvertintos skirtingų arterijų sienelės struktūros ir funkcijos rodiklių (pulsinės bangos greičio, aortos augmentacijos indekso, centrinio AKS, centrinio pulsinio spaudimo, širdies-kulkšnies indekso, bendrosios miego arterijos standumo ir intimos-medijos storio) sąsajos su KS diastoline disfunkcija. Nustatyta, kad miego-šlaunies arterijų pulsinės bangos greitis yra reikšmingas nepriklausomas veiksnys prognozuojant KS diastolinę disfunkciją asmenims, turintiems metabolinį

sindromą. Kaip minėta, MetS turinčiųjų kohortoje, tokios didelės apimties tyrimų šioje srityje iki šiol labai trūksta.

Atliktas 573 asmenų išilginio stebėjimo tyrimas, kuriame įvertinta arterijų standumo pokyčio įtaką KS diastolinės disfunkcijos dinamikai (stebėjimo trukmės vidurkis 3,8 ± 0,6 metai). Nustatyta, kad arterijų standumo didėjimas yra nepriklausomas KS diastolinės funkcijos blogėjimo prognostinis veiksnys. Taip pat atskleista, kad KS diastolinės disfunkcijos dinamika reikšmingai siejasi su kūno masės indekso ir širdies susitraukimų dažnio pokyčiais. Remiantis šiuo metu prieinamų mokslinių tyrimų duomenimis, mūsų darbas yra pirmas tokio pobūdžio stebėjimo tyrimas asmenų, turinčių MetS, grupėje.

Mūsų darbe tai pat pirmą kartą objektyviai įvertinti ankstyvojo širdies nepakankamumo požymiai asmenų, turinčių MetS, grupėje. Vertinant pikinį deguonies suvartojimą per fizinį krūvį ir natriuretinio peptido (BNP) koncentraciją, nustatyta, kad daugiau nei pusė mūsų tirtų asmenų turėjo širdies nepakankamumo su išsaugota KS išstūmio frakcija požymių.

Šiame darbe naujai atskleistos ir patvirtintos sąsajos gali ženkliai pasitarnauti mokslo tiriamajame ir klinikiniame darbe, ypač užtikrinant savalaikį širdies nepakankamumo nustatymą ir perspėjant jo vystymąsį.

METODIKA

Biomedicininiam tyrimui atlikti gautas Vilniaus regioninio biomedicininių tyrimų etikos komiteto leidimas Nr. 158200-13-641-205. Visi tyrime dalyvaujantys asmenys buvo informuoti apie tyrimo eigą ir pasirašė informuoto asmens sutikimo formą.

Tiriamųjų grupę sudarė abiejų lyčių asmenys, 2009 - 2015 metais tirti Vilniaus universiteto ligoninėje Santaros klinikose pagal Asmenų, priskirtų ŠKL didelės rizikos grupei, atrankos ir prevencijos priemonių finansavimo programą (angl. *The Lithuanian high cardiovascular risk primary prevention program, LitHiR*). Į tyrimą buvo įtraukti 50 – 65 metų moterys ir 40 – 55 metų vyrai, kuriems buvo nustatytas metabolinis sindromas.

Metabolinis sindromas nustatytas remiantis 2005 metų NCEP ATP III modifikuotais kriterijais (kai nustatyti bet kurie trys iš žemiau išvardintų penkių kriterijų):

- Liemens apimtis: vyrams ≥ 102 cm, moterims ≥ 88 cm;
- Arterinis kraujo spaudimas: ≥ 130/85 mmHg, arba gydymas vaistais, esant AH anamnezėje;

- Gliukozės koncentracija kraujyje (nevalgius): ≥ 5,6 mmol/l, arba gydymas vaistais esant hiperglikemijai;
- DTL – Ch koncentracija serume: vyrams < 1,03 mmol/l; moterims < 1,30 mmol/l;
- TG koncentracija serume : ≥1,7 mmol/l, arba gydymas vaistais.

Pirmame etape atlikta 1208 tiriamųjų duomenų skerspjūvio analizė. Antrame etape, po 3,8 ± 0,6 metų, 573 tiriamieji buvo ištirti pakartotinai. Tiek pradinio, tiek pakartotino vertinimo metu atliktas pilnas asmenų ištyrimas pagal LitHiR programos protokolą. Pakartotino ištyrimo metu, siekiant įvertinti ankstyvojo ŠN dažnį, 148 tiriamiesiems papildomai nustatyta B tipo natriuretinio peptido (BNP) koncentracija kraujyje ir atliktas kardiopulmoninis krūvio mėginys (spiroergometrija).

Atlikti antropometriniai matavimai – matuotas tiriamųjų svoris, ūgis, juosmens apimtis, apskaičiuotas kūno masės indeksas (KMI), matuotas arterinis kraujo spaudimas (AKS), atlikta didelio jautrumo C-reaktyvaus baltymo (djCRB), BNP, lipidograma, gliukozė nevalgius. Atliktas arterijų sienelės parametrų vertinimas: pulsinės bangos greičio (PBG), vidutinio arterinio kraujo spaudimo, pulsinio spaudimo, augmentacijos indekso aortoje matavimas aplanacinės tonometrijos metodu, miego arterijų intimos ir medijos sluoksnio storio ir miego arterijų standumo nustatymas ultragarsiniu metodu, kulkšnies-žasto ir širdies-kulkšnies indeksų matavimas. Atlikus echokardiografiją vertinta KS diastolinė funkcija, KS geometrija. Atliekant spiroergometriją vertintas fizinis pajėgumas, degonies suvartojimas per laiko vienetą.

REZULTATAI IR JŲ APTARIMAS

Šiame darbe pirmą kartą Lietuvoje įvertinom KS diastolinės disfunkcijos paplitimą didelės kardiovaskulinės rizikos asmenų grupėje, esant nustatytam MetS. Tyrimo kohortą sudarė 1208 abiejų lyčių asmenys. Atlikus echokardiografiją didžiajai tirtų asmenų daliai (75,7 proc., n = 915) nustatėm sutrikusią KS diastolinę funkciją.

Atlikę tyrimą ir palyginę tiriamųjų grupes nustatėme, kad tiriamieji, esant sutrikusiai KS diastolinei funkcijai, buvo vyresnio amžiaus, vyravo moterys, turėjo didesnę gliukozės koncentraciją nevalgius. Taip pat šioje grupėje nustatėme didesni AH sergančiųjų procentą (93,7 proc. vs. 88,3 proc., p = 0,005).

Tiriamųjų, esant sutrikusiai KS diastolinei funkcijai, grupėje nustatyti reikšmingai didesni KMI (32,1 ± 5,06 vs. 30,5 ± 4,52 kg/m^2, p < 0,0001) ir liemens apimtis (106,8 ± 10,76 vs. 103,6 ± 10,40 cm, p < 0,0001). Vertinant analizuojamų kintamųjų tarpusavio priklausomybes ir skaičiuojant koreliacijos koeficientus nustatėme, kad KMI reikšmingai susijęs su E/e'$_{vid}$ santykiu (r = 0,216, p < 0,001). Pažingsninės daugialypės regresinės analizės modeliuose, prognozuojant KS diastolinę disfunkciją, KMI ir liemens apimtis išliko reikšmingais rizikos veiksniais (p < 0,001).

Siekiant įvertinti sąsajas tarp KS diastolinės funkcijos ir arterijų sienelės rodiklių atlikome 1208 tiriamųjų duomenų skerspjūvio analizę. Mūsų žiniomis tai pirmas didelės kohortos, esant MetS, tyrimas, per kurį vertinom neinvaziniais metodais išmatuotus pagrindinius arterijų sienelės struktūros ir funkcijos rodiklius – miego-šlaunies arterijų PBG, augmentacijos indeksą, centrinį kraujospūdį, centrinį pulsinį spaudimą, bendrosios miego arterijos standumą ir intimos-medijos storį, širdies-kulkšnies indeksą.

Mūsų darbe tiriamųjų, esant sutrikusiai KS diastolinei funkcijai, grupėje miego-šlaunies arterijų PBG buvo reikšmingai didesnis (9,0 ± 1,65 vs. 8,2 ± 1,34 m/s, p < 0,0001). Nustatėme reikšmingas koreliacijas tarp miego – šlaunies arterijų PBG ir KS diastolinės finkcijos parametrų: atvirkštinis ryšys su E/A (r = – 0,190, p < 0,001) ir teigiamas ryšys su E/e'$_{vid}$ (r = 0,167, p < 0,001) santykiais. Mūsų darbe atskleidėme, jod miego-šlaunies arterijų PBG yra reikšmingas veiksnys prognozuojant KS diastolinę disfunkciją asmenų, esant nustatytam MetS, grupėje. Atliekant žingsninės daugialypės logistinės regresijos analizę kartu su arterijų sienelės rodikliais įvertinome klasikinius ŠKL rizikos veiksnius (KMI ir liemens apimtį, centrinį vidutinį AKS, rūkymą). Koregavus analizės rezultatus pagal amžių, lytį ir ŠSD, miego-šlaunies arterijų PBG išliko reikšmingu nepriklausomu KS diastolinės disfunkcijos išsivystymo rizikos veiksniu (p = 0,002). Nustatėme, kad padidėjus miego-šlaunies arterijų PBG per 1,3 m/s, tikimybė pasireikšti KS diastolinei disfunkcijai padidėja 18,6 proc..

Mūsų tiriamųjų grupėje, esant KS diastolinei disfunkcijai, nustatytas didesnis augmentacijos indeksas aortoje (25,4 ± 9,96 vs. 21,1 ± 10,84 proc., p < 0,0001). Augmentacijos indeksas reikšmingai koreliavo su KS diastolinės funkcijos parametrais: E/A (r = – 0,151, p < 0,001) ir E/e'$_{vid}$ (r = 0,136, p < 0,001). Daugialypės regresinės analizės modeliuose AIx, automatiškai koreguotas pagal ŠSD, šalia mšPBG, išliko reikšmingai susijęs su KS diastoline disfunkcija.

Mūsų darbe tiriamųjų grupėje, esant KS diastolinei disfunkcijai, nustatėme reikšmingai didesni centrinis vidutinis AKS (108,6 ± 12,85 vs.

103,4 ± 10,13 mmHg, p < 0,0001) ir centrinis pulsinis spaudimas (44,5 ± 10,69 vs. 41,9 ± 10,8 mmHg, p = 0,0004). Taip pat atskelidėme, kad centrinis AKS ir centrinis pulsinis spaudimas reikšmingai susiję su KS prisipildymo spaudimu, vertintu kaip E/e'_{vid} santykis (r_{cAKS} = 0,159, p < 0,001; r_{cPP} = 0,265, p < 0,001). Tačiau, tęsiant analizę, pažingsninės daugialypės regresijos modeliuose centrinio AKS ir centrinio pulsinio spaudimo sąsajos su KS diastoline disfunkcija neišliko reikšmingos.

Mūsų darbe įvertinome centrinės hemodinamikos ir arterijų sienelės rodiklių pokytį ir jo įtaką KS diastolinės funkcijos dinamikai. Šiai užduočiai atlikti po 3,8 ± 0,6 metų laikotarpio pakartotinai ištyrėme 573 asmenys iš bendros 1208 tiriamųjų kohortos. Nustatėme, kad pagrindinis veiksnys, susijęs su KS diastolinės funkcijos blogėjimu, yra miego-šlaunies arterijų PBG. Šio rodiklio pokytis buvo skirtingas tarp tiriamųjų grupių: KS diastolinės disfunkcijos gerėjimo grupėje stebėtas, nors ir statistiškai nereikšmingas, mšPBG sumažėjimas. Tuo tarpu KS diastolinės disfunkcijos blogėjimo grupėje mšPBG reikšmingai didėjo (p = 0,004). Įdomu tai, kad ne tik visoje pakartotinai tirtų asmenų kohortoje, bet ir KS diastolinės funkcijos blogėjimo grupėje nustatytas reikšmingas ŠSD (nuo 65,17 ± 9,41 iki 62,07 ± 8,51 k/min, p = 0,003) ir centrinio vidutinio AKS (nuo 104,07 ± 10,94 iki 99,73 ± 13,17 mmHg, p = 0,010) sumažėjimas. Tačiau atlikę logistinės regresijos analizę, jos modeliuose tik miego-šlaunies arterijų PBG išliko reikšmingu, prognozuojant KS diastolinės funkcijos blogėjimą (p = 0,015).

Mūsų stebėjimo rezultatai patvirtina skerspjūvio analizės išvadas, kad mšPBG yra KS diastolinės disfunkcijos atsiradimą lemiantis patogenetinis veiksnys. Manome, kad atsakėme į svarbų klausimą – ar aortos standumo didėjimas lemia KS diastolinės funkcijos sutrikimą nepriklausomai nuo amžiaus, AKS ir kitų tradicinių ŠKL rizikos veiksnių. Galime teigti, kad mšPBG (aortos standumo rodiklis) yra KS diastolinės disfunkcijos atsiradimą lemiantis patogenetinis veiksnys. Todėl terapinės priemonės, kurios galėtų sulėtinti arba sustabdyti amžinius ir (arba) patologinius arterijų sienelės pakitimus ir standumo didėjimą, turėtų būti vertingos KS diastolinės disfunkcijos iš ŠN prevencijai ir regresijai.

Mūsų žiniomis, šiame darbe pirmą kartą pabandyta nustatyti galimybę aptikti ankstyvąjį ŠN, remiantis deguonies apykaita ir plaučių ventiliacija per fizinį krūvį bei BNP koncentracija kraujyje, tiriamųjų, esant MetS, grupėje. Atlikus tyrimą, didžiajai daliai (64,8 proc.) tiriamųjų šalia didelio KS diastolinės disfunkcijos dažnio (73,6 proc.) nustatėme sumažintą fizinio krūvio toleranciją ir (arba) padidintą natriuretinio peptido koncentraciją. Šiems asmenims mes diagnozavom ankstyvąjį ŠN.

Palyginus tiriamųjų duomenis, ankstyvojo širdies nepakankamumo pogrupyje nustatėme patikimai didesnį augmentacijos indeksą (31,2 ± 9,9 vs. 27,3 ± 7,4 proc., $p < 0,05$). Augmentacijos indeksas buvo reikšmingai susijęs tik su $VO2_{piko}$ ($r = – 0,264$, $p = 0,001$). Atlikę vienfaktorinę logistinę regresiją nustatėme, kad ankstyvojo ŠN buvimas reikšmingai susijęs su BNP, $VO2_{piko}$ ir augmentacijos indeksu aortoje. Tačiau įtraukus šiuos reikšmingus kintamuosius į pažingsninės logistinės regresijos analizę, augmentacijos indeksas prarado reikšmingumą prognozuojant ankstyvąjį ŠN.

IŠVADOS

1. Skerspjūvio tyrime nustatyta, kad trims ketvirtadaliams tiriamųjų, turinčių metabolinį sindromą, randama sutrikusi kairiojo skilvelio diastolinė funkcija.
2. Asmenims, turintiems metabolinį sindromą, arterijų standumas, vertintas matuojant miego-šlaunies pulsinės bangos greitį, yra nepriklausomas kairiojo skilvelio diastolinės disfunkcijos prognostinis veiksnys, kurio reikšmingumas išlieka net ir atsižvelgus į tradicinius kardiometabolinės rizikos veiksnius.
3. Miego-šlaunies pulsinės bangos greičio didėjimas, esant metaboliniam sindromui, yra reikšmingas kairiojo skilvelio diastolinės funkcijos blogėjimo veiksnys. Tai atskleidžia jo svarbą kairiojo skilvelio diastolinės disfunkcijos patogenezėje.
4. Pritaikius objektyvų fizinio pajėgumo ir neurohormoninės aktyvacijos vertinimą, daugiau nei pusei tirtų asmenų, turinčių metabolinį sindromą, nustatytas ankstyvasis išsaugotos kairiojo skilvelio išstūmio frakcijos širdies nepakankamumas. Ankstyvojo širdies nepakankamumo asmenų grupėje nustatytas statistiškai reikšmingas arterijų standumo, vertinto matuojant augmentacijos indeksą aortoje, padidėjimas.

PRAKTINĖS REKOMENDACIJOS

1. Efektyviam asmenų, turinčių metabolinį sindromą, kardiovaskulinės rizikos įvertinimui ir gydymo taktikos parinkimui tikslinga nustatyti arterijų standumo ir centrinės hemodinamikos rodiklius, ypač pulsinės bangos greitį aortoje ir centrinį pulsinį spaudimą.
2. Remiantis šio darbo rezultatais nustatyta slenkstinė 8,2 m/s miego-šlaunies pulsinės bangos greičio reikšmė, padedanti atskirti asmenis, esant didesnei

kairiojo skilvelio diastolinės disfunkcijos galimybei. Nustačius miego-šlaunies arterijų pulsinės bangos greitį > 8,2 m/s asmenims, turintiems metabolinį sindromą, rekomenduojame taikyti ankstyvesnę ir efektyvesnę kardiovaskulinių ligų prevenciją. Tai padėtų sumažinti kairiojo skilvelio diastolinės disfunkcijos išsivystymo riziką.

3. Asmenims, turintiems metabolinį sindromą, šalia klinikinių simptomų vertinimo ir echokardiografijos, siekiant laiku aptikti besivystantį išsaugotos kairiojo skilvelio išstūmio frakcijos širdies nepakankamumą, būtų tikslinga nustatyti natriuretinių peptidų koncentraciją kraujyje ir atlikti kardiopulmoninį krūvio mėginį.

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