DOCTORAL SCHOOL IN MEDICAL SCIENCES

Manuscript title:
U.D.C: 616.123:616-008.9 (043.2)

SEDAIA ECATERINA

THE IMPACT OF METABOLIC SYNDROME AND ITS COMPONENTS ON RIGHT CHAMBERS OF THE HEART

321.03 – CARDIOLOGY

Summary of Ph.D. Thesis in Medical Sciences

CHISINAU, 2021

The thesis was designed at the Department of Internal Medicine, Discipline of Cardiology, clinical base at Institute of Cardiology, PI „Nicolae Testemitanu" State University of Medicine and Pharmacy

Scientific advisor:

Revenco Valeriu
Habilitated Doctor of Medical Sciences, University professor
Members of the guidance group
Grib Livi, Habilitated Doctor of Medical Sciences, Associate professor
Ochișor Viorica, Ph.D., Associate professor
Mihalache Georgeta, Ph.D., Associate professor

Ph.D. thesis defense will take place on February 11th, 2021, at 14.00 online : https://meet.google.com/rkt-oroa-qts , in the meeting of the Commission for the public defense of the Ph.D. thesis, approved by the decision of the Scientific Council of the Consortium from _14.12.2020_____ (protocol nr._14_)

Nominal structure of the Specialized Scientific Council:
Chair:
Cobeț Valeriu, Habilitated Doctor of Medical Sciences, University professor
Members:
Grib Livi, Habilitated Doctor of Medical Sciences, Associate professor
Grosu Aurel, Habilitated Doctor of Medical Sciences, University professor
Revenco Valeriu, Habilitated Doctor of Medical Sciences, University professor
Ciobanu Nicolae, Habilitated Doctor of Medical Sciences, Research professor
Mătrăgună Nelea, Habilitated Doctor of Medical Sciences, Associate professor
Carauș Alexandru, Habilitated Doctor of Medical Sciences, Research professor

Official Reviewers:
Ciobanu Nicolae, Habilitated Doctor of Medical Sciences, University professor
Mătrăgună Nelea, Habilitated Doctor of Medical Sciences, Associate professor
Grib Livi, Habilitated Doctor of Medical Sciences, Associate professor

The Ph.D. thesis and the summary can be consulted at the library of "Nicolae Testemitanu" State University of Medicine and Pharmacy and on the ANACEC website.

The summary submitted on January 11th , 2021.

Scientific advisor:
Revenco Valeriu, Habilitated Doctor of Medical Sciences, University professor

Author:
Sedaia Ecaterina

CONTENTS

Introduction. Metabolic syndrome (MS) is associated with increased cardiovascular mortality risk. Thus, population studies have shown that in patients with MS the risk of cardiovascular disease is 2 times higher, and in non-diabetic patients MS would increase 5 times the risk of developing type 2 diabetes (DM) [9].

Each component of the MS represents a factor that can cause an increased cardiovascular risk, but it is also important to highlight the overall cardiovascular risk in these patients. In addition, the components of MS that are not found in the definition criteria (proinflammatory and prothrombotic status, insulin resistance etc.) are also determinants of increased cardiovascular risk [10].

According to the new concepts, developed by the Cardiometabolic Health Alliance of America (the Cardiometabolic Think Tank), currently it is proposed to highlight specific subtypes of MS depending on the target organ damage and a classification of MS in 4 stages [11]. Moreover, the emphasis is on the role of obesity in MS and ectopic adipose tissue (AT) excess, which would be fundamental in the pathophysiology of MS [12]. New evidence appears in the literature that the accumulation of AT is associated with metabolic and cardiovascular pathologies even among people with body mass index (BMI) 18.5-22.9 kg / m2, one of the explanations being that BMI does not directly indicate the distribution and accumulation of AT. The clinical relevance of BMI, abdominal circumference (AC) is discussed, and also the development and possible introduction of other markers of visceral obesity into daily practice is argued in medical literature [13].

Cardiometabolic risk is widely discussed in the specialized medical literature. Cardiometabolic risk factors include insulin resistance, elevated AC, low HDL cholesterol, high triglycerides (TG) and high blood pressure (BP) and are associated with an increased risk of the developing of atherosclerosis and DM. The MS includes the majority of cardiometabolic risk factors.

The pathophysiological processes in MS are closely related not only to AT but also to its distribution in the human body [16]. AT includes subcutaneous AT and visceral AT, which differ in its function and morphology, fact which is proven in several clinical studies [7, 1]; excessive accumulation of visceral AT seems to contribute more significantly to the development of metabolic disorders. Moreover, in some studies, it has been reported that visceral obesity *per se* is closely linked to hypertension (HTN), impaired glucose tolerance, dyslipidemia and other cardiovascular risk factors. Thus, pericardial and epicardial AT have a direct relationship with increased cardiometabolic risk. Epicardial adipose tissue (EAT) is considered as a visceral fat deposit of the heart [17]. Some authors propose the use of EAT as a new marker of visceral and myocardial adiposity [14]. EAT can be easily determined by echocardiography (ECOCG), multidetector computed tomography (MDCT) or magnetic resonance imaging (MRI). Ultrasonographic determination of EAT is the most accessible method of evaluation in terms of cost-effectiveness.

Some clinical studies showed that EAT thickness is independently related to MS. Iacobellis G. et al. [15] found that the thickness of EAT was influenced by the main clinical and anthropometric components of MS. Thus, the thickness of EAT, determined by ECOCG, correlates with the induced insulin resistance and impaired glucose tolerance in obese patients. Patients with MS had a higher thickness of EAT compared to people who were not present with this syndrome and this value of EAT was influenced by some components of MS [13]. Moreover, other studies showed that EAT thickness was dependent on myocardial mass in patients with and without heart

hypertrophy [2]. Thus, it was demonstrated, that the thickness of EAT was related to the mass of the left ventricular myocardium, the dimensions of the right ventricular cavity and the enlargement of both atria [2, 3]. The pathogenic mechanisms that could completely elucidate this link at the moment are not entirely clear. One of the hypotheses by which EAT could have an effect on the myocardium is that EAT has a direct contact with the underlying myocardial tissue, having the same source of blood irrigation - the coronary bed. Considering that EAT is a metabolically active organ, it is assumed that the main effect occurs due to adipokines and by paracrine mechanisms [4]. On the other hand, it is of great importance the beneficial effects of EAT in physiological conditions, such as: local energy source; the "buffer" system between the myocardium and the coronary circulation [13]. However, in some pathological conditions such as: coronary heart disease (CHD) and obesity, the MS contributes to increasing of the volume of EAT, which leads to reduced production and elimination of protective cytokines and significantly increases the expression of adipokines with pro-inflammatory and pro-atherogenetic effects [5, 6].

Considering the major impact of MS on a patient's prognosis, many clinical studies have been launched to evaluate the effect of MS and its components on left ventricular (LV) function and structure. There are several clinical studies that demonstrate a close relation between diastolic and global LV myocardial dysfunction, hypertrophy and LV dilation in MS patients [22, 23]. Also, in the specialized literature there are several studies dedicated to the assessment of the influence of EAT on the geometry and function of LV in MS and obesity. At the same time, there are a few researches about the impact of MS on the right chambers of the heart.

The right ventricle (RV) for a long period of time was considered as the "passive chamber" of the heart [18]. It was thought that the main role of RV consisted only in the accumulation and transport of blood to the lungs [28]. In clinical practice there is often a tendency to minimize the evaluation of RV function, making a more qualitative assessment. Recent studies show that systolic and global RV function are independent predictors of cardiovascular mortality in congenital heart disease, valvular diseases, pulmonary hypertension, left ventricular failure, heart transplantation and myocardial infarction [19]. According to the MESA study [20], RV hypertrophy is associated with a double risk of heart failure and sudden death in the multiethnic population. Different imaging techniques were used for RV evaluation, each of them presenting important complementary information about RV function. ECOCG and MRI are the most used methods, the latter being the "gold standard" in non-invasive RV assessment. However, cardiac ultrasound is considered the basic examination in assessing the structure and function of RV and RA, given its cost-effectiveness and availability.

The possible influence of MS on the remodeling of the right compartments of the heart is currently being discussed [19]. If this hypothesis is demonstrated, then the idea of a relationship between MS mortality and the remodeling of the right compartments of the heart, especially the RV, could be launched [21].

Of particular interest is the relationship between EAT thickness and subclinical dysfunction of the right ventricle in patients with MS [15, 29]. Recently, Gökdeniz et al. [13] demonstrated that in patients with MS, the thickness of EAT had a direct relationship with systolic and diastolic RV dysfunction. Other studies emphasize the importance of the correlation between the volume of EAT and the size of the RV cavity [24]. It is less studied whether the hypertrophy of the myocardium of the free wall of the RV could have interconnections with the thickness of EAT, evaluated by echocardiography.

Thus, the patients with MS have a global cardiovascular risk higher than people in general population. On the other hand, MS can be associated with the remodeling of the right chambers of the heart, especially the RV, which in turn can represent an independent predictor of cardiovascular mortality. In light of what was said, the studies that would assess the relationship between MS and the right compartments of the heart are welcome. In this context, the following **purpose of the research** was established:

To evaluate the impact of metabolic syndrome and its components on right heart geometry and function.

The study objectives:

1. To evaluate structural remodeling of right heart chambers in patients with metabolic syndrome according to its components.
2. To study the impact of the components of metabolic syndrome and sex on right heart mechanics.
3. Sonographic evaluation of the epicardial fat thickness in patients with metabolic syndrome and its relation to other sonographic and anthropometric parameters of visceral obesity.
4. To evaluate the correlation of epicardial fat thickness, visceral obesity, insulin resistance and dysfunction and remodeling of right ventricle and atrium in metabolic syndrome.

Scientific novelty of the research. The novelty and originality of the study consists in focusing of the scientific work on the determination of specific components of MS responsible for remodeling of right heart chambers. More of that, taking into account that MS is composed of several cardiovascular risk factors, we highlighted the particular impact of systolic blood pressure, parameters of visceral obesity (AC, EAT thickness) and fasting glucose level on remodeling. Besides the fact that that MS includes several cardiovascular risk factors, we highlighted the particular impact of systolic blood pressure, parameters of visceral obesity (AC, EAT) and fasting blood glucose in remodeling and affecting the mechanical function of the right heart, with a more special role for women with MS.

Thus, the approach to the patient with MS seems to be much more complex and requires a more in-depth attitude, considering right heart functional parameters and RV remodeling in the context of cardiometabolic risk assessment and prognosis of the patient with MS.

Theoretical significance. In this study we demonstrated important correlations between MS and remodeling of right heart chambers. Recent studies demonstrate the particular importance of mechanical function of RV and RV hypertrophy as determinant factors of prognosis of the patients with present and absent concomitant cardiovascular pathology, which makes the assessment of the right parts of the heart very important. The hypothesis of the special role of some specific components of MS and their effect on different geometric and functional parameters of RV and RA depending on sex was advanced – a statement which we proved in our study. A special role belongs to the importance of evaluating of new markers of visceral obesity to assess early cardiometabolic risk, especially in patients with MS. Among that markers we were able to demonstrate the efficacy of such a parameter as EAT thickness, and its correlation with impaired global and diastolic function of the right ventricle in patients with MS.

Application value of the topic. The results of the study argued the need for mandatory determination of hypertrophy, systolic and diastolic function of RV myocardium, especially in patients with MS, in which could be rational the assessment of the need for therapeutic intervention as early as possible to improve the prognosis.

The introduction into daily practice of new parameters for quantifying the visceral obesity, such as EAT thickness, also plays an important role in choosing the appropriate approach to the patients at increased cardiometabolic risk.

Implementation of scientific results. The results of the study were implemented in the clinical activity of the PMI Institute of Cardiology, as well as in the didactic activity of the Cardiology Discipline, within the Department of Internal Medicine, of the State University of Medicine and Pharmacy "Nicolae Testemitanu".

1. MATERIAL AND RESEARCH METHODS

The study was approved by the State University of Medicine and Pharmacy "Nicolae Testemitanu" Research Ethics Committee, being examined at the briefing of November 7, 2016, with the issuance of favorable notice no. 33 from 14.11.2016. To achieve the proposed goal, an analytical case-control study was performed, which was conducted during the years 2016-2019 in accordance with the Principles of the Helsinki Declaration - WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human subjects. The following research methods were used: questionnaire, objective clinical examination, biochemical examinations, electrocardiography (ECG), echocardiography (ECOCG), ECG exercise test, ultrasonography (USG) of the abdominal organs. The design of the study was developed, which was carried out in three stages.

Stage 1. The required number (pattern volume) of participants was collected for inclusion in the study according to the following formula:

$$n = \frac{1}{(1-\mathrm{f})} \frac{2(Za + Zb)^2 \mathrm{P}(1-\mathrm{P})}{(P0 - P1)^2}$$

Where: P = (P0 + P1)/2 = 0,45

Zα – tabular value (significance threshold / probability of type I error) = 1.96

Zβ – tabular value (significance threshold / probability of type II error) = 1.28 (for power of 90%)

P0 – proportion of patients who are subject to a known risk factor (a value from bibliographic sources) = 35% (0.35)

P1 – proportion of patients expected to detect a known risk factor (to be determined by the researcher) = 70.0% (0.70)

f – proportion of study subjects who quite the study for different reasons (non-response sample volume adjustment factor) = 10% (0.1)

If we use the existing data in accordance with respective formula, we obtain that the size of the research group must be not less than 47 respondents (L1 = 47). As a rule, the ratio between groups must be 1:1, then the size of the control group is the same - 47 respondents (L0 = 47).

Criteria for inclusion in the study: age 30-65 years; voluntary agreement to participate in the study.

Criteria for exclusion from the study:

- heart failure with intermediate and reduced left ventricular ejection fraction,
- the presence of regional myocardial contractility abnormalities,
- ischemic heart disease,
- history of stroke,

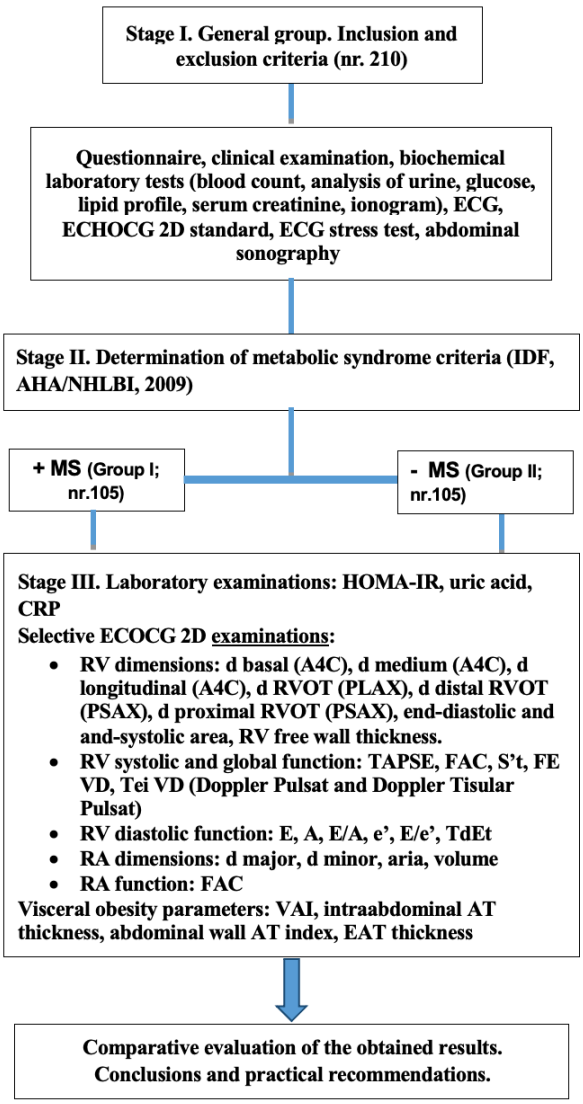
• atrial fibrillation or atrial flutter,
• major left bundle branch block,
• major surgery in the last month (intervention with a major risk of bleeding),
• congenital heart defects,
• severe valvopathies (presence of prosthetic valves, any degree of stenosis, moderate or severe valvular regurgitation),
• pericarditis,
• secondary hypertension,
• pulmonary hypertension (patients with moderate or high echocardiographic probability),
• liver cirrhosis,
• renal insufficiency (estimated glomerular filtration rate <60 ml / min / 1.73 m2),
• endocrinological pathologies (except type 2 diabetes mellitus),
• severe obesity (BMI ≥ 35),
• obstructive sleep apnea syndrome (according to the STOP BANG questionnaire),
• chronic obstructive pulmonary disease or other chronic lung disease.

Stage 2. Basic examinations of the general study group with the following distribution in 2 groups according to the presence of criteria for MS.

The diagnosis of MS in patients included in the study was established according to the presence of ≥ 3 IDF criteria, AHA / NHLBI (2009) [12]:

1. Abdominal obesity (abdominal circumference ≥ 94 cm for men and ≥ 80 cm for women)
2. Triglycerides > 1.7 mmol / l (or specific lipid-lowering treatment)
3. HDL cholesterol: men <1 mmol / l (40 mg / dL), women <1.3 mmol / l (50 mg / dL) (or specific treatment)
4. BP s ≥ 130 mmHg or BP d ≥ 85 mmHg OR antihypertensive therapy
5. Basal blood glucose ≥ 5.6 mmol / l

Stage 3. Selective echocardiographic evaluations of the right chambers of the heart and additional anthropometric and sonographic parameters of visceral obesity with comparison of the obtained results between the groups (Study design).



Legend: *MS – metabolic syndrome, d-diameter, CRP- C-reactive protein, RVOT- right ventricle outflow tract, VAI – visceral adiposity index, TdEt - E wave deceleration time at the tricuspid level, AT– adipose, FAC – fractional area change, EF –Ejection fraction, S't – tricuspid annular systolic velocity measured by pulse wave tissue Doppler*

Study design.

1.1. Research methods used in the study

Subjects included in the study underwent a complex clinical, paraclinical and instrumental examination. Initially, each participant went through an interview, registering the received data in a questionnaire developed for the research. The questionnaire included questions about general patients data: age, demographics, smoking status, alcohol consumption, administration of antihypertensive, hypoglycemic, hypolipemic drugs or other treatment, duration of hypertension or diabetes. Subsequently, the clinical examination was performed. The anthropometric parameters evaluated were height, body mass, AC, hip perimeter (HP), AC / HP ratio, BMI, body surface area (BSA). Laboratory analyzes were performed in all participants of the study and included: blood count, general urine test, basal blood glucose, urea, creatinine, lipid profile, ionogram (potassium, sodium), uric acid and C-reactive protein (PCR), HOMA -IR.

Among the non-invasive instrumental evaluations in all participants were performed: ECG, 2D ECOCG, abdominal USG, ECG exercise test.

The statistical analysis of the results was performed using Jamovi 1.2.27.0 software, specialized in scientific statistical calculations.

2. STUDY OUTCOMES

The current study focused on the assessing of the impact of MS on the structure and function of the right compartments of the heart. Comparative selective analysis of the structure and function of RA and RV was performed depending on the association with MS. Special attention was also paid to some parameters of visceral obesity, evaluated by sonographic and anthropometric methods.

2.1. The analysis of echocardiographic parameters of the right compartments of the heart

Analyzing the data obtained by ECOCG 2D we concluded that the dimensions (d longitudinal and d transverse; area) and RA volume were significantly higher in the group with MS ($P < 0.001$ for all parameters). At the same time there was no statistically significant difference between the RA function estimated as FAC between the research groups ($P = 0.089$) (Table 2.1). Using the univariate analysis of the RA volume related to the body surface and the interconnections with the MS components, we found that in research group I there was important positive correlations with AC ($r = 0.330$, $P < 0.001$) and systolic blood pressure (BP) ($r = 0.204$, $P = 0.037$). The same components of MS correlated positively with the RA area: AC ($r = 0.321$, $P < 0.001$), systolic BP ($r = 0.334$, $P < 0.001$).

By analyzing the morphological parameters of RV (table 2.1) we found that: d basal (A4C), medium (A4C), proximal TEVD PLAX, and proximal TEVD PSAX - did not show significant differences between the research groups (for all parameters $P > 0.05$). At the same time, d longitudinal of RV ($P < 0.001$) and d distal TEVD PSAX ($P < 0.001$) were significantly higher in subjects with MS. Similarly, the data in table 2.1 shows that the end-diastolic and end-systolic area of RV (even being indexed to the body surface area), are statistically significantly lower in group I vs control group ($P < 0.001$). Also to note, that there is an important difference in the thickness of the free wall of RV, it is significantly higher in the group of subjects with MS ($P < 0.001$). Thus, RV free wall hypertrophy was present in 87 subjects in the first research group (34 men (39.1%) and 53 women (60.9%)), and 27 subjects in the control group (13 men (48.1%) and 14 women (51.9%).

The risk of RV free wall hypertrophy was 4 times higher among women with MS vs. men (OR 4.05, 95% CI: 1.33-12.4, $P = 0.010$). To note, that there were observed statistically significant interdependencies between the thickness of the RV free wall and the MS components: AC ($r = 0.670$, $P < 0.001$), systolic BP ($r = 0.786$, $P < 0.001$), diastolic BP ($r = 0.703$, $P < 0.001$), basal glycemia ($r = 0.269$, $P < 0.001$), HDL cholesterol ($r = -0.204$, $P = 0.003$), TG ($r = 0.342$, $P < 0.001$). Univariate analysis of RV free wall thickness in the group of patients with MS showed the following statistically significant positive correlations with LV morphological and functional ultrasound parameters: LV Tei index ($r = 0.545$, $P < 0.001$), IVS ($r = 0.627$, $P < 0.001$), RWT ($r = 0.466$, $P < 0.001$), LV mass ($r = 0.612$, $P < 0.001$), LV mass / BSA ($r = 0.651$, $P < 0.001$), LV mass / $h^{2,7}$ ($r = 0.682$, $P < 0.001$) and significant negative correlation with LVEF ($r = -0.205$, $P = 0.036$).

Table 2.1. **Structural and functional echocardiographic parameters of the right compartments of the heart in patients with metabolic syndrome vs control group**

Parameter	MS (n=105), M±DS	Control group (n=105), M±DS	P
Right atrium			
d longitudinal, mm	46,1±2,7	42,2±3,2	<0.001
d transversal, mm	38,3±2,6	35,4±3,0	<0.001
Area, cm^2	17,3±1,1	14,2±1,5	<0.001
Volume/BSA, ml/m^2	24,7±2,7	17,4±2,1	<0.001
FAC, %	43,5±3,5	44,4±3,8	0.089
Right ventricle			
d basal A4C, mm	31,2±2,0	30,5±4,4	0.160
d medium A4C, mm	28,7±2,1	27,9±4,1	0.061
d longitudinal A4C, mm	72,6±3,5	69,9±4,0	<0.001
d proximal RVOT PLAX, mm	26,8±1,8	26,2±2,7	0.084
d proximal RVOT PSAX, mm	30,5±2,1	29,9±3,5	0.118
d distal RVOT PSAX, mm	24,0±1,5	22,0±2,0	<0.001
End-diastolic area, cm^2	16,4±1,5	19,1±1,5	<0.001
End-diastolic/BSA ratio, cm^2/m^2	7,6±1,12	9,9±1,03	<0.001
End- systolic area, cm^2	7,8±1,1	9,5±1,2	<0.001
End-systolic area/BSA ratio, cm^2/m^2	3,7±0,5	4,9±0,6	<0.001
Free wall thikness, mm	6,2±0,9	4,6±1,1	<0.001
TAPSE, mm	20,9±1,9	21,4±2,2	0.087
EF, %	53±3	54±4	0.092
S't, m/s	0,114±0,03	0,117±0,01	0.259
FAC, %	52±6	51±4	0.100
Et, cm/s	46,5±12,5	54,3±13,2	<0.001
At, cm/s	58,6±11,5	49,6±9,5	<0.001
Et/At	0,84±0,37	1,15±0,41	<0.001
TdE, msec	231±9	210±18	<0.001
e't, cm/s	9,2±1,7	12,6±4,0	<0.001
Et/e't	5,0±1,1	4,4±0,6	<0.001
Tei index (PW Doppler)	0,47±0,04	0,37±0,05	<0.001
Tei index (PW tisular Doppler)	0,58±0,04	0,47±0,06	<0.001

Legend: *d – diameter, RVOT – right ventricle outflow tract, A4C – apical 4 chamber view, PSAX – parasternal short axis view, EF – ejection fraction, FAC – fractional area change, BSA – body surface area*

We found it logical and interesting to look further and analyze in the group of patients with MS interconnection between RV free wall thickness and tolerance to physical activity, evaluated by cycloergometry (respectively, we received statistically important correlation: r = -0.504, P

<0.001). Along with the evaluation of the morphological indices of the RV, the functional echocardiographic evaluation of the RV was performed. The parameters responsible for right ventricular systolic function (TAPSE (P = 0.087), EF (P = 0.092), S't (P = 0.259), FAC (P = 0.100), (table 2.1) did not show statistically significant differences between the groups of research. The evaluation of diastolic function, according to table 2.1, revealed important changes in the first research group compared to the control group. All parameters of diastolic function were statistically significantly modified in the group with metabolic syndrome vs. control group, respectively: Et 46,5 ± 12.5 cm / s vs. 54,3 ± 13,2 cm / s, P <0,001; At 58,6 ± 11,5 cm / s vs. 49,6 ± 9,5 cm / s, P <0,001; Et / At ratio 0,84 ± 0,37 vs. 1,15 ± 0,41, P <0,001; TdE 231 ± 9 msec vs. 210 ± 18 msec, P <0,001; e't 9,2 ± 1,7 cm / s vs. 12,6 ± 4,0 cm / s, P <0,001; the ratio Et / e't 5,0 ± 1,1 vs. 4,4 ± 0,6, P <0,001. According to the data obtained we can observe that the most patients with MS had diastolic dysfunction of RV such as impaired relaxation 77,1% (81 cases); at the same time pseudonormal diastolic dysfunction was present in 19% (20 cases) and restrictive type in 1% (1 case). The normal diastolic function of RV was detected in only 2,9% (3 cases) of participants in the MS group. In the control group, most subjects had normal RV diastolic function (61%, 64 cases), the rest was diagnosed with affected RV myocardial relaxation. The correlational analysis of the echographic parameters responsible for determining of the diastolic function of the RV myocardium (Et / At and Et / e't) and the MS components reported several significant associations. Thus, a negative statistically significant correlation was noted between: Et / At and AC (r = -0.427, P <0.001), systolic BP (r = -0.442, P <0.001), diastolic BP (r = -0.397, P < 0.001), TG (r = −0.162, P = 0.019). The Et / e't ratio showed a positive, statistically significant correlation with the following MS components: AC (r = 0.259, P <0.001), systolic BP (r = 0.311, P <0.001), diastolic BP (r = 0.258, P <0.001), basal glycemia (r = 0.291, P <0.001), TG (r = 0.215, P = 0.002), and significant negative correlation with HDL (r = −0.166, P = 0.016). Of major importance we consider the presentation of the univariate analysis of the parameters of the diastolic RV (Et / e't) function and the RV free wall hypertrophy (figure 2.1).

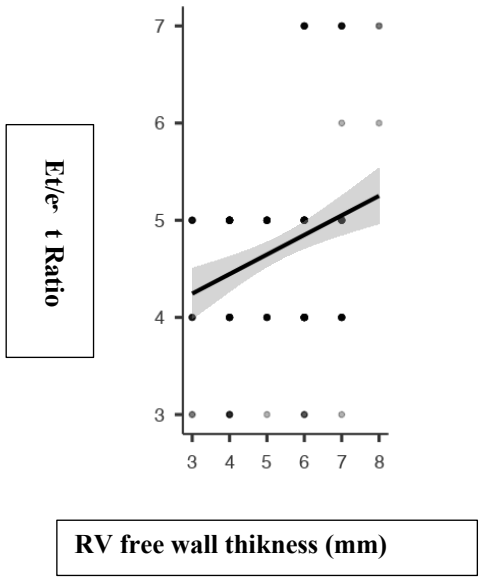


Figure 2.1. **The correlations of the Et / e't ratio with the right ventricle free wall thickness (mm) (r = 0.268, P <0.001)**

According to our study, we could report that in the MS patients group RV free wall myocardial hypertrophy was found in 81.5% of patients with impaired RV myocardial relaxation as well as in 100% of patients with pseudonormal pattern of RV diastolic dysfunction and respectively in 100% of patients with restrictive-type of diastolic dysfunction (Table 2.2).

Table 2.2. **The association of right ventricle free wall myocardial hypertrophy related to the degree of diastolic right ventricular dysfunction in the group of patients with metabolic syndrome (n = 105)**

Diastolic function of the RV miocardium	Presence of RV free wall hypertrophy					
	Yes			No		
	Men, n (%)	Wemen, n (%)	Total, n (%)	Men, n (%)	Wemen, n (%)	Total, n (%)
Normal	0 (0)	0 (0)	0 (0)	3 (100)	0 (0)	3 (100)
Impaired relaxation	29 (43,9)	37 (56,1)	66 (81,5)	10 (66,6)	5 (33,4)	15 (18,5)
Pseudonormal	5 (25)	15 (75)	20 (100)	0 (0)	0 (0)	0 (0)
Restrictive	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)

Legend: *RV – right ventricle*

By analyzing the interdependence between the Tei index determined by pulsed Doppler and the MS components, statistically important positive correlation was noted with: AC (r = 0,709, P <0,001), systolic BP (r = 0,736, P <0,001), diastolic BP (r = 0,628, P <0,001), basal glycemia (r = 0,409, P <0,001). Global RV myocardial function, assessed by calculation of the Tei index, was affected in group I. For the Tei index determined by pulsed tissue Doppler, the correlational analysis showed the following statistically significant interconnections with the MS components: AC (r = 0.705, P <0.001), systolic BP (r = 0.709, P <0.001), diastolic BP (r = 0.618, P <0.001), basal glycemia (r = 0.399, P <0.001), HDL (r = -0.270, P <0.001), TG (r = 0.367, P <0.001). According to the data obtained in the study, we found that in the group of subjects with MS, the overall RV dysfunction, determined by the altered Tei index was present at 86,1% (93 cases: 38 men and 55 women) vs. 13,9% (15 cases; 7 men, 8 women) in the control group. In the first research group, we determined that the risk of the developing of global RV dysfunction is approximately 4 times higher among women with MS vs. men with MS (OR 4.34, 95% CI 1.10-17.1, P = 0.025). Using univariate analysis in the group of patients with metabolic syndrome we determined a statistically important interconnection between the RV myocardium performance index and RV free wall hypertrophy, respectively for the Tei index by pulsed Doppler (r = 0.623, P <0.001), for the Tei index by tissue Doppler pulsat r = 0.658, P <0.001. Based on the data described above, we proposed the idea to analyze the prevalence of RV hypertrophy among patients with global RV dysfunction in the first research group. Thus, we can conclude that the risk for the development of global RV dysfunction among patients with MS and RV free wall hypertrophy is approximately 7 times higher (OR 6.75, 95% CI 1.87-24.4, P = 0.001) than in those who are without RV hypertrophy. Analysis of the correlation between RV Tei index by pulsed Doppler and pulsed tissue Doppler and echocardiographic parameters of LV morphology and function in the group with MS subjects showed the following statistically important interconnections: LV EF (statistically significant data only for Tei index determined by pulsed Doppler, respectively r = −0.216, P = 0.027), Tei index VS (r = 0.593, P <0.001; r = 0.594, P

<0.001), RWT (r = 0.341, P <0.001; r = 0.339, P <0.001), IVS (r = 0.425, P <0.001; r = 0.420, P <0.001), LV mass (r = 0.359, P <0.001; r = 0.350, P <0.001), LV mass / BSA (r = 0.394, P < 0.001; r = 0.407, P <0.001), LV mass / h2.7 (r = 0.456, P <0.001; r = 0.488, P <0.001). We would like to mention that among people with MS, in 83 persons with altered Tei index specific for global dysfunction of RV was present LV myocardial hypertrophy, and only 10 persons with impaired global RV function were without LV hypertrophy. 7 participants from the MS group had the overall RV function preserved, but at the same time had increased LV myocardial mass and 5 persons with MS had the Tei index within the norm without increased LV mass association. Thus, we could conclude that the risk of developing global RV dysfunction is almost 6 times higher (OR 5.93, 95% CI 1.58-22.2, P = 0.004) in people with MS and LV myocardial hypertrophy. By excluding patients with hypertension from research group I, we obtain that in 3 persons with LV hypertrophy was associated global RV dysfunction vs. 1 person with affected Tei index and normal LV myocardial mass. Biventricular hypertrophy was present in 79 patients with MS and impaired overall RV function (P <0.001). Analyzing the interdependencies between the overall performance index of the RV and LV myocardium, we can see the following data among patients with MS: concomitant association between the affected Tei index of both ventricles was present in 84 patients (33 men, 51 women) vs. 7 persons (5 men, 2 women) with preserved overall biventricular function; 5 participants (4 men, 1 woman) had only the impairment of the LV Tei index and 9 patients (5 men, 4 women) with MS had exclusively the impairment of the global RV function.

Also, it is important to mention that a statistically important interconnection was detected between the RV myocardial performance index and the tolerance to physical exertion in subjects with MS (respectively, for Tei index by pulsed Doppler r = -0.538, P <0.001; by Doppler pulsed tissue r = −0.517, P <0.001).

2.2. Analysis of echocardiographic parameters of the left compartments of the heart

The comparative analysis of the data obtained from the 2D ECOCG evaluation of the left side of the heart in both research groups noted some important features for subjects with MS. Thus, according to table 2.3, we can see that the dimensions of LA (longitudinal and transverse diameters, volume, including relative to BSA and h2) are larger in group I compared to the control group (for all parameters the value P <0.001). On the other hand, the FAC that was proposed for the evaluation of LA function did not show a statistically significant difference between both research groups (P = 0.101). Similar data were received for RA (described above). Analyzing the morphological parameters of LV in Table 2.3 we can conclude that the end diastolic diameter and end-systolic diameter of LV, as well as interventricular septal (IVS) thickness and LV posterior wall (PW) – relative wall thickness (RWT), LV mass relative to body surface area and height 2,7 are higher in the group of MS patients. In the group with MS, end-diastolic diameter of LV showed a positive correlation with the following parameters of MS: systolic BP (r = 0.244, P = 0.012), diastolic BP (r = 0.415, P <0.001). Through the univariate analysis of the interdependencies between IVS, LVPW, LV mass and MS components in group I we found positive correlations with systolic BP (respectively, r = 0.495, P <0.001; r = 0.395, P <0.001; r = 0.497, P < 0.001) and diastolic BP (respectively, r = 0.332, P <0.001; r = 0.266, P = 0.006; r = 0.428, P <0.001). LV myocardial hypertrophy in the group of patients with MS was present in 90 subjects, 32 men

(35.6%) and 58 women (64.4%). In the control group, LV myocardial hypertrophy was detected in 40 subjects, 9 men (22.5%) and 31 women (77.5%).

Table 2.3. **Structural and functional echocardiographic parameters of the left compartments of the heart in patients with metabolic syndrome and the control group**

Parameter	MS (n=105), M±DS	Control group (n=105), M±DS	P
Left atrium			
d longitudinal, mm	52,6±2,37	47,0±2,79	<0.001
d transversal, mm	42,4±2,67	37,4±2,8	<0.001
Volume, ml	77,4±7,33	57,6±13,18	<0.001
Volume/BSA, ml/m^2	36,7±2,8	29,5±5,1	<0.001
Volume/h^2, ml/m^2	27,5±2,6	19,5±4,2	<0.001
FAC, %	52±5	53±4	0.101
Left ventricle			
DTD (end-diastolic diameter), mm	50,7±3,1	48,3±3,3	<0.001
DTS (end-systolic),mm	32,2±3,9	29,9±3,7	<0.001
VTD (end-diastolic),ml	100±21,2	95±20,5	0.083
VTS (end-systolic), ml	38±11,1	35±9,6	0.056
IVS, mm	12,2±1,4	10,5±1,2	<0.001
LVPW, mm	11,4±1,1	10,0±0,9	<0.001
RWT	0,45±0,045	0,42±0,036	<0.001
EF, %	59±2,9	60±2,5	0.080
Tei index (Doppler pulsed)	0,49±0,051	0,37±0,046	<0.001
Masa/BSA, g/m^2	112,7±24,0	92,6±15,9	<0.001
Masa/$h^{2,7}$, g/$m^{2,7}$	58,8±14,1	42,1±8,8	<0.001
E/A	1,11±0,47	1,41±0,41	<0.001
E/e’	8,52±4,10	7,39±1,91	0.011

Note: *h – height, BSA – body surface area, FAC – fractional area change, IVS – interventricular septum, RWT – relative wall thickness, EF – ejection fraction, LVPW – left ventricular posterior wall.*

It is important to note that the systolic function reflected by the ejection fraction (EF) of LV did not show statistically significant differences in both research groups (P = 0.080). Univariate correlational analysis of LV diastolic function (E / e ') parameters in the group of MS subjects showed true interconnections with the following MS components: systolic BP (r = 0.223, P = 0.022), basal glycemia (r = 0.196, P = 0.045). The LV Tei index in the same group of patients correlated positively with the following MS parameters: AC (r = 0.217, P = 0.026) and systolic BP (r = 0.367, P <0.001). It is also important to mention that the LV Tei index correlated negatively, statistically important with the tolerance to physical effort among patients with MS: r = -0.423, P <0.001.

2.3. Anthropometric and sonographic parameters of obesity, insulin resistance, diabetes mellitus, lipid spectrum and their effect on the function and structure of the myocardium of the right and left compartments of the heart in patients with and without metabolic syndrome

Increasing attention is being paid to visceral obesity as a major risk factor in the occurrence of several pathological conditions, including cardiovascular diseases. Thus, we decided to analyze the anthropometric and sonographic parameters of visceral obesity. The summary of the obtained data is represented in table 2.4. Analyzing the data from table 2.4, we can conclude that all obesity parameters are statistically significantly higher in the group of patients with MS vs. control (for all parameters P <0.001).

Table 2.4. **Anthropometric and ultrasound parameters of obesity in patients with metabolic syndrome and the control group**

Parameter	MS (n=105), M±DS	Control group (n=105), M±DS	P
Body mass (kg)	94,8±8,2	79,9±12,6	<0.001
BMI (kg/m^2)	33,6±1,3	27,0±3,4	<0.001
AC (cm)	102,1±5,6	85,3±10,8	<0.001
Hip perimeter (cm)	106,0±4,4	99,0±6,8	<0.001
AC/hip perimeter ratio	0,96±0,05	0,86±0,06	<0.001
IAV	2,5±1,4	1,2±0,6	<0.001
Abdominal AT thickness, cm	5,9±1,1	3,3±1,0	<0.001
Minimal thickness of subcutaneous AT, mm	22,5±10,2	11,5±5,9	<0.001
Maximal thickness of subcutaneous AT, mm	23,5±10,3	11,0±6,3	<0.001
AT abdominal index	1,05±0,06	0,94±0,07	<0.001
EAT thickness, mm	7,7±0,8	5,6±1,1	<0.001

Legend: *EAT – epicardial adipose tissue, AC – abdominal circumference, IAV – index of visceral adiposity, BMI – body mass index*

When we assesed the interrelationship between EAT thickness and the echocardiographic morphological parameters of RA in the group of patients with MS, the following statistically significant positive correlations were determined: with longitudinal and transversal d of RA (respectively, r = 0.506, P <0.001; r = 0.477 , P <0.001); area and volume / BSA (respectively, r = 0.674, P <0.001; r = 0.558, P <0.001). On the other hand, the RA function determined by FAC did not seem to have an important correlation with the thickness of EAT (r = -0.180, P = 0.067). Analyzing the correspondence of other indicators of visceral obesity with the echocardiographic morphological parameters of RA in the first research group, statistically veridical correlations were also found. Thus, d longitudinal of the RA correlated to BMI (r = 0.273, P = 0.005), AC (r = 0.307, P = 0.001), hip perimeter (r = 0.202, P = 0.039), intra-abdominal AT thickness (r = 0.206, P = 0.035); d transversal had correlation with BMI (r = 0.302, P = 0.002), AC / hip perimeter ratio (r = 0.206, P = 0.035), intra-abdominal AT thickness (r = 0.316, P = 0.001); and area correlated with BMI (r = 0.336, P <0.001), AC (r = 0.321, P <0.001), AC / hip perimeter ratio (r = 0.352, P <0.001), intra-abdominal AT thickness (r = 0.367, P <0.001), abdominal AT index (r = 0.363, P <0.001).

Based on the objectives of the study, we studied the interconnections between the morphological parameters of RV and obesity indices in the first research group. We would like to emphasize the importance of visceral obesity in remodeling of the free wall of RV (Table 2.5). The data in Table 2.5 show a statistically significant correlation between RV wall thickness and BMI (P <0.001), AC (P <0.001), hip perimeter (P = 0.006), intra-abdominal AT thickness (P

<0.001), AT minimal subcutaneous thickness (P = 0.015), pre-peritoneal AT maximum thickness (P = 0.008), abdominal AT index (P = 0.009) and EAT thickness (P <0.001).

Table 2.5**. Correlation of anthropometric and ultrasound indices of obesity and free wall thickness of the right ventricle in the group of patients with metabolic syndrome (n = 105)**

Indices	Pearson correlation coefficient (r)	P
Body mass (kg)	-0.154	0.118
BMI (kg/m^2)	0.513	<0.001
AC (cm)	0.343	<0.001
Hip perimeter (cm)	0.265	0.006
AC/hip perimeter ratio	0.188	0.055
IAV	-0.089	0.365
Intra-abdominal AT thickness, cm	0.370	<0.001
Subcutaneous minimum AT, mm	0.237	0.015
Pre-peritoneal subcutaneous maximum AT, mm	0.259	0.008
AT abdominal index	0.253	0.009
EAT thickness, mm	0.539	<0.001

Legend: *EAT – epicardial adipose tissue, AC – abdominal circumference, IAV – index of visceral adiposity, BMI – body mass index*

Moreover, according to the results obtained in our study we could report important data about the interdependence between obesity parameters and diastolic function of RV. Thus, statistically significant interconnections were found between the ratio Et / At, Et / e't and TdE t and body mass (respectively, r = -0.395, P <0.001; r = 0.145, P = 0.035; r = 0.424, P <0.001), BMI (respectively, r = -0.431, P <0.001; r = 0.260, P <0.001; r = 0.635, P <0.001), AC (respectively, r = -0.427, P <0.001; r = 0.259, P <0.001; r = 0.551, P <0.001), HP (respectively, r = -0.321, P <0.001; r = 0.226, P <0.001; r = 0.447, P <0.001), AC / HP ratio (respectively, r = -0.437, P <0.001; r = 0.227, P <0.001; r = 0.533, P <0.001), IAV (respectively, r = -0.171, P = 0.013; r = 0.207, P = 0.003; r = 0.281, P <0.001), intra-abdominal AT thickness (respectively, r = -0.342, P <0.001; r = 0.335, P <0.001; r = 0.592, P <0.001), minimum subcutaneous AT thickness (respectively r = -0.139, P = 0.045; r = 0.389, P <0.001; r = 0.507, P <0.001), maximum thickness of pre-peritoneal AT (respectively, r = -0.162, P = 0.019; r = 0.400, P <0.001; r = 0.532, P <0.001), abdominal AT index (respectively, r = -0.426, P <0.001; r = 0.212, P = 0.002; r = 0.538, P <0.001) and EAT thickness (respectively r = - 0.524, P <0.001; r = 0.291, P <0.001; r = 0.692, P <0.001). Figure 2.2 highlights statistically important interdependencies between visceral obesity indices and RV Et / e't ratio.

Also, based on the proposed objectives, in the group of patients with MS we analyzed the link between global RV myocardial function and obesity. Both parameters, either the Tei index determined by pulsed Doppler or pulsed tissue Doppler, showed a statistically significant correlation with the following obesity indices: AC (respectively, r = 0.370, P <0.001; r = 0.426, P <0.001), BMI. (respectively, r = 0.566, P <0.001; r = 0.611, P <0.001), AC / HP (respectively, r = 0.321, P <0.001; r = 0.373, P <0.001), intra-abdominal AT thickness (respectively, r = 0.498, P <0.001; r = 0.530, P <0.001), abdominal AT index (respectively, r = 0.313, P = 0.001; r = 0.307, P = 0.001). Particular attention should be paid to the interdependence between the thickness of the EAT and the overall function of the RV, with a significant positive correlation (Figure 2.3).

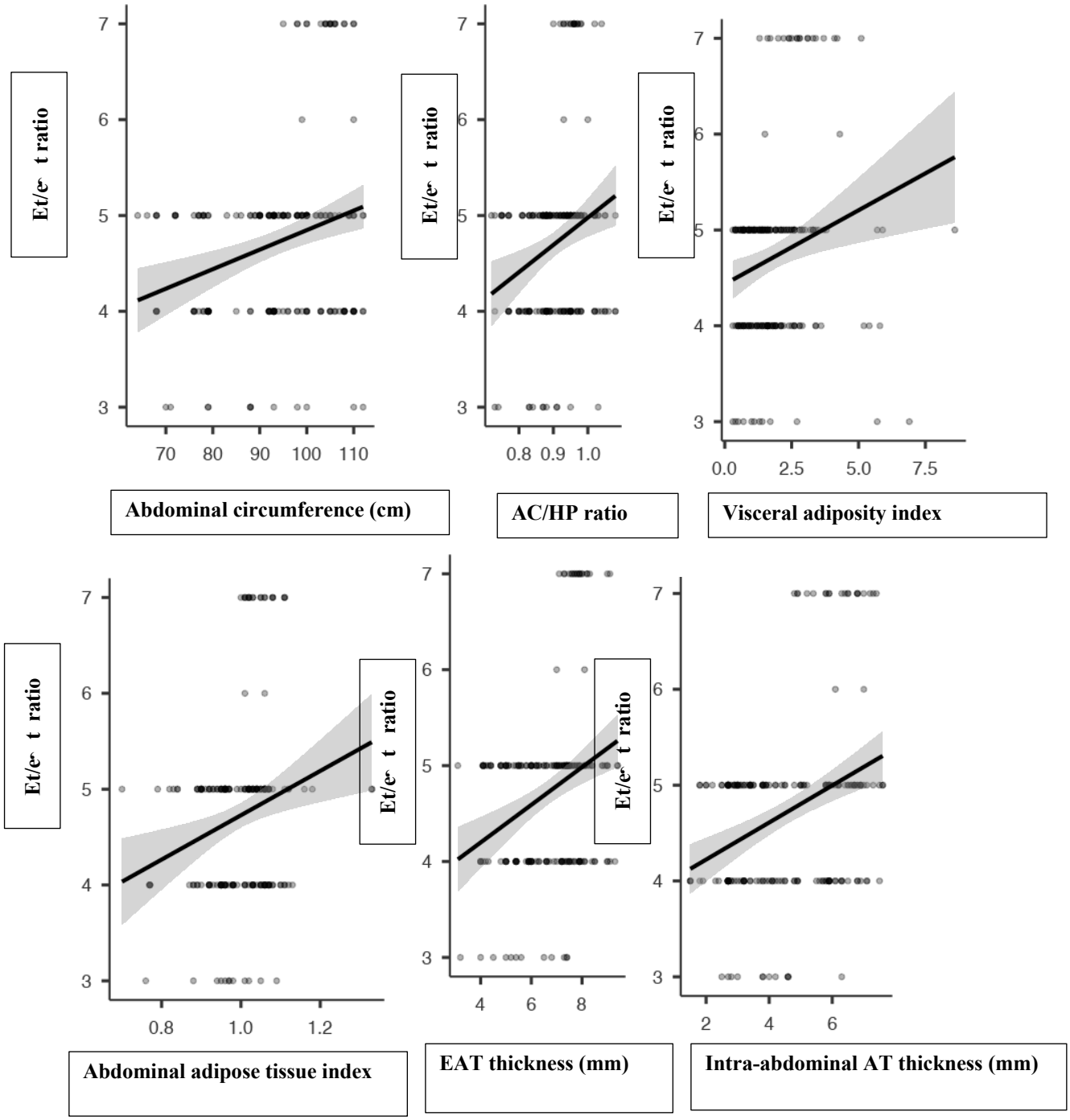


Figure 2.2. **Correlations of visceral obesity indices and Et / e't ratio (P <0.05)**

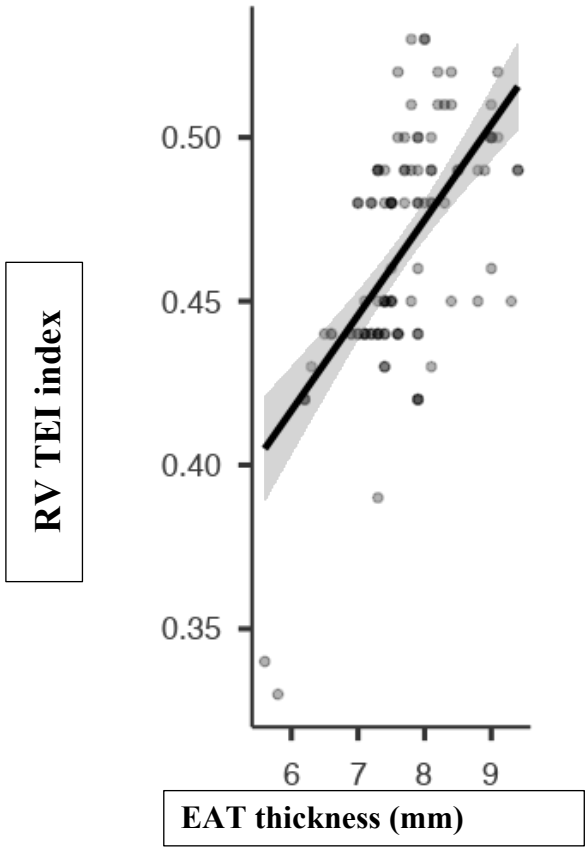


Figure 2.3. **Correlations of the myocardial performance index by pulsed Doppler of the right ventricle with the thickness of the epicardial adipose tissue (mm) in the group of patients with metabolic syndrome (r = 0.623, P <0.001)**

The analysis of RV systolic function in the group of subjects with MS reported some relatively important but statistically true interconnections only for the TAPSE parameter and some obesity indices, such as: AC (r = -0.337, P <0.001), AC / HP (r = -0.242, P = 0.013), intra-abdominal AT thickness (r = -0.301, P = 0.002), abdominal AT index (r = -0.236, P = 0.015), AT thickness (r = -0.319, P < 0001).

In some of the study participants (total 34 persons: 15 in group I and 19 in the control group) the insulin resistance status was assessed using the HOMA-IR index, which presented the following statistically important interconnections with: intra-abdominal AT thickness (r = 0.515, P = 0.002), EAT thickness (r = 0.661, P <0.001), AC (r = 0.503, P = 0.002), AC / HP (r = 0.426, P = 0.012), Tei index of the LV (r = 0.577, P <0.001), LV mass / h2.7 (r = 0.425, P = 0.012),RV free wall thickness (r = 0.532, P = 0.001), Et / At ratio (r = -0.427, P = 0.012), Tei index of the RV determined by pulsed Doppler (r = 0.500, P = 0.003) and pulsed tissue Doppler (r = 0.505, P = 0.002). In the group of participants with MS, the values of the HOMA-IR index did not show statistically significant differences between men (8 cases) and women (7 cases), respectively 3.48 ± 1.33 vs. 3.40 ± 1.02, P = 0.895. The same data were true for the control group, respectively the HOMA-IR index in men (9 cases) was 2.05 ± 0.59 and in women (10 cases) 2.24 ± 0.60, P = 0.497. In the general study group, insulin resistance status (HOMA-IR index ≥ 2.5) was confirmed in 17 participants. The risk for diastolic RV dysfunction (14 people with confirmed insulin resistance) is 5 times higher for those with HOMA-IR ≥ 2.5 (OR 5.25, 95% CI: 1.09-25.2, P = 0.031). But if

we analyze exclusively women (9 people with insulin resistance), then this risk increases up to 22 times (OR 22.5, 95% CI: 1.61-31.5, P = 0.009) vs. approximately 2 times in men (5 people) (OR 1.67, 95% CI: 0.210-13.2, P <0.05). In the patients in whom the HOMA-IR index was assessed, insulin resistance was associated with RV-free wall hypertrophy in 35.3% (12 cases) of participants vs. 20.6% (7 cases) of participants with HOMA-IR ≥ 2.5 and no association of RV hypertrophy or 8.8% (3 cases) with RV hypertrophy and normal HOMA-IR index. So, we can observe that the risk for the development of RV hypertrophy is approximately 1.5 times higher (OR 1.46, 95% CI: 0.303-7.02, P = 0.012) in people with insulin resistance. Statistically significant differences between the association of insulin resistance with RV myocardial hypertrophy according to gender were not noted (P> 0.05).

Multiple linear regression analysis for RA area and associated factors revealed the following statistically significant independent links with: body mass (P = 0.016), AC / HP (P = 0.013), systolic BP (P = 0.024), basal glycemia (P = 0.030)), LV mass / h2.7 (P = 0.006). Moreover, the multivariate analysis reported that the LA volume is independently associated with: body mass (P <0.001), systolic BP (P <0.001), triglycerides (P = 0.007), LV mass / h2.7 (P <0.001).

By studying the factors that would influence the global function of the RV myocardium, the multivariate analysis reported the following data: the LV Tei index (P = 0.001), the RV free wall thickness (P <0.001) and the EAT thickness (P = 0.047) are independently associated with the Tei index of RV determined by pulsed Doppler in men. For women, the multivariate analysis marked the following statistically true independent associations for the RV Tei index: systolic BP (P = 0.048), basal glycemia (P = 0.049), LV Tei index (P <0.001), RV free wall thickness (P = 0.017), EAT thickness (P = 0.014) (table 2.6).

Table 2.6. **Clinical and ultrasound predictors of global right ventricular myocardial function (Tei index determined by pulsed Doppler) in sex dependence**

Predictors	Multivariate analysis			
	Men		Women	
	Coefficient (F)	P	Coefficient (F)	P
Body mass	0.130	0.720	1.318	0.254
BMI	1.495	0.226	0.937	0.335
AC	0.006	0.940	3.497	0.064
AC/HP	0.114	0.737	0.226	0.635
Systolic BP	1.147	0.288	4.078	0.048
Dyastolic BP	2.354	0.130	0.176	0.676
Basal glycemia	1.316	0.255	4.045	0.049
Tryglicerids	0.048	0.828	1.213	0.273
HDL cholesterol	0.005	0.983	0.007	0.935
non-HDL cholesterol	0.457	0.501	3.391	0.068
IAV	0.038	0.796	2.157	0.145
Intra-abdominal AT thickness	0.641	0.426	0.250	0.618
AT abdominal inde	0.068	0.796	0.359	0.550
LV Tei index	11.675	0.001	11.702	<0.001
LV Mass /$h^{2,7}$	3.270	0.075	0.135	0.714
RV free wall thickness	13.605	<0.001	5.900	0.017
EAT thickness	4.088	0.047	6.265	0.014

Legend: *BMI – body mass index, AC – abdominal circumference, BP – blood pressure, LV – left ventricle, EAT – epicardial adipose tissue*

Via the multivariate analysis we determined independent predictors for RV myocardial diastolic function (assessed by the Et / e't ratio): BMI (F = 5,623, P = 0.019), basal glycemia (F = 7,300, P = 0.008), serum triglyceride level (F = 4.525, P = 0.035), non-HDL cholesterol (F = 4.036, P = 0.046), LV mass / h2.7 (F = 7.395, P = 0.007). From the morphological parameters of RV, the multivariate analysis reported that the free wall thickness was independently associated with systolic BP (F = 11,931, P <0.001), LV mass / h2.7 (F = 26,703, P <0.001) and EAT thickness (F = 41.631, P <0.001). When the sex-dependent analysis was performed, the same parameters remained statistically true for men and women, with one exception - body weight seems to be more important in men in determining the free wall thickness of RV (P = 0.050).

SUMMARY OF THE OBTAINED RESULTS

The important problem for the public health represents MS, especially in case of an associate visceral obesity, which, according to several epidemiological studies, is in constant gro. Moreover, MS is also a real problem due to the complexity of pathophysiological mechanisms and the difficulty in therapeutic approach. MS is a complex of metabolic risk factors (hypertension, carbohydrate metabolism disorders, dyslipidemia with elevated TG levels, low HDL-C levels and abdominal obesity), which provides the development of atherosclerotic cerebrovascular diseases, and is one of the etiological factors that can cause type 2 diabetes mellitus. The prevalence of MS increases with age and weight gain.

The results obtained in the study emphasize the important role of MS and its components in heart remodeling. The impact of MS does not stop only at the morphological parameters of the heart, but also influences the diastolic and global function of the RV and LV myocardium.

There are just several clinical trials that studied the impact of MS on the right heart chambers [20, 21, 26]. Our study showed that the patients with MS had significantly altered morphology and function of the right ventricle, that was also mentioned by other authors (Cuspidi et al., Tadic et al.) [25, 27]. Also, we would like to report that our study makes some new accents on right heart remodeling in the context of visceral obesity, that is an important component of MS, the fact confirmed not only by classical anthropometric parameters such as AC, but also by additional sonographic and anthropometric measurements. More of that, even fewer studies exist in the medical scientific literature, which have analyzed the association of MS with RV function and visceral obesity, and the available data are contradictory [8, 24].

Therefore, the patients with MS are with a high global cardiovascular risk. On the other hand, MS can be associated with remodeling of the right compartments of the heart, especially the RV, which in turn can represent an independent predictor of cardiovascular mortality. In this context, studies that would assess the relationship between MS and the right compartments of the heart are welcome.

GENERAL CONCLUSIONS

1. In patients with metabolic syndrome were determined important connections between some components of the syndrome (waist circumference, glycemia a jeun, systolic arterial pressure) and structural echocardiographic parameters of the right ventricle (dimensions and the thickness of the free wall of the right ventricle).

2. The right atrium is also involved in the processes of remodeling of the right heart in patients with metabolic syndrome by changing its dimensions (diameters, area and volume, all $P<0.001$), and among these parameters the aria and volume of right atrium have the important correlations with systolic blood pressure ($r=0.334$, $P<0.001$; $r=0.204$, $P=0.037$, respectively) and waist circumference ($r=0.321$, $P<0.001$; $r=0.330$, $P<0.001$), while the contraction function of the right atrium remains unchanged ($P=0.089$).

3. The major impact of systolic blood pressure and waist circumference on diastolic and global right ventricular function was found, with higher risk in women, while right ventricular systolic function remained unaffected in patients with metabolic syndrome.

4. By echocardiographic determination of epicardial adipose tissue thickness, important interconnections between this parameter of visceral obesity and right ventricular remodeling parameters (especially, right ventricular hypertrophy, $r=0.539$, $P<0.001$) and function (diastolic, $P<0.001$; systolic, $P<0.001$ and global, $P<0.001$) were demonstrated in patients with metabolic syndrome, which allows to propose this easily measurable parameter as an additional marker in clinical evaluation and follow-up of patients with metabolic syndrome.

5. The analysis of interconnections of epicardial adipose tissue thickness with other sonographic and anthropometric parameters of visceral obesity and insulin resistance status showed the important links between these parameters, which in turn presented important connections with indices of diastolic and global function of right ventricle and right atrium diameters.

PRACTICAL RECOMMENDATIONS

1. In patients with metabolic syndrome or cardiovascular risk factors (hypertension, diabetes, visceral obesity, etc.) a comprehensive and standardized echocardiographic evaluation of the right compartments of the heart is also required.

2. Sonographic assessment of epicardial adipose tissue thickness (including other sonographic parameters of visceral obesity) is recommended as a standard method for the assessment of the cardiometabolic risk in all patients, and especially those with metabolic syndrome or as a marker for monitoring of the effectiveness of initiated treatment (manifested by a reduction in the thickness of epicardial adipose tissue over a period of time).

3. In the screening of asymptomatic patients with metabolic syndrome, before the symptomatic phase of impaired right ventricular function, it is recommended to introduce in the usual echocardiographic practice the determination of diastolic function of the right ventricle.

4. The practical recommendations based on study outcomes could be proposed for daily routine and used by cardiologists, endocrinologists, family doctors, internists.

SELECTIVE BIBLIOGRAPHY

1. Guo, X., Xu, Y., He, H. et al. Visceral fat reduction is positively associated with blood pressure reduction in overweight or obese males but not females: an observational study. In *Nutrition and Metabolism (London)*. 2019, 16:44. ISSN:1743-7075.
2. Bakkum, M.J., Danad, I., Romijn, M.A.J. et al. The impact of obesity on the relationship between epicardial adipose tissue, left ventricular mass and coronary microvascular function. In *European Journal of Nuclear Medicine and Molecular Imaging*. 2015. Vol.42, 1562–1573. ISSN:1619-7089.
3. Gaborit B., Sengenes C., Ancel P., Jacquier A., Dutour-Meyer A. Role of Epicardial Adipose Tissue in Health and Disease: A Matter of Fat? In *American Physiological Society. Comprehensive physiology.* 2017. Vol. 18;7(3), 1051-1082. ISSN:2040-4603.
4. Aldiss P, Davies G, Woods R, Budge H, Sacks HS, Symonds ME. "Browning" the cardiac and peri-vascular adipose tissues to modulate cardiovascular risk. In *International Journal of Cardiology*. 2017. Vol. 228, 265–274. ISSN:0167-5273.
5. D.S. Jiang, H.L. Zeng, R. Li, B. Huo, Y.S. Su, J. Fang, et al., Aberrant epicardial adipose tissue extracellular matrix remodeling in patients with severe ischemic cardiomyopathy: insight from comparative quantitative proteomics. In *Scientific Reports*. 2017. Vol. 7, 43787. ISSN: 2045-2322.
6. V.B. Patel, J. Mori, B.A. McLean, R. Basu, S.K. Das, T. Ramprasath, et al. ACE2 deficiency worsens epicardial adipose tissue inflammation and cardiac dysfunction in response to diet-induced obesity. In *Diabetes*. 2016. Vol. 65, 85–95. ISSN:1939-327X
7. Ji B, Qu H, Wang H, Deng H. Association between the visceral adiposity index and homeostatic model assessment of insulin resistance in participants with normal waist circumference. In *Angiology*. 2017. Vol.68, 716-721. ISSN:1940-1574.
8. Anna Nadulska, Dominik Szwajgier, Grzegorz Opielak. Obesity and metabolic syndrome. In *MEDtube Science.* 2017. Vol. 1, 35 – 43. ISSN:2353-5695.
9. Francesco Cosentino, Peter J Grant, Victor Aboyans, Clifford J Bailey, et al. ESC Scientific Document Group, 2019 ESC Guidelines on diabetes, pre-diabetes, and

cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). In *European Heart Journal. 2020.* Vol. 41 (2), 255–323. ISSN:1522-9645.

10. L.Grib. Sindromul metabolic: considerații patogenetice,clinice și diagnostic. Monografie. Chișinău, 2010. 20-26. ISBN: 978-9975-78-878-6.
11. Sperling L.S. et al. The cardiometabolic health alliance: working toward a new care model for the metabolic syndrome.In *Journal of the American College of Cardiology.*, 2015. Vol.66, 1050–1067. ISSN:0735-1097.
12. Alberti K.G et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. In *Circulation.* 2009. Vol. 120, 1640–1645. ISSN:1524-4539.
13. Tayyar Gokdeniz et al. Relation of Epicardial Fat Thickness to Subclinical Right Ventricular Dysfunction Assessed by Strain and Strain Rate Imaging in Subjects with Metabolic Syndrome: A Two-Dimensional Speckle Tracking Echocardiography Study. In *Echocardiography.* 2015. Vol. 32, 248–256. ISSN:1880-344X.
14. H. Yorgun et al. Increased epicardial fat tissue is a marker of metabolic syndrome in adult patients. In *International Journal of Cardiology.* 2013. Vol.165, 308–313. ISSN:1874-1754.
15. Gianluca Iacobellis, Antonio C. Bianco. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. In *Trends in Endocrinology and Metabolism*. 2011. Vol. 22 (11), 450-457. ISSN:1043-2760.
16. Revenco V. și al. Este țesutul adipos un organ endocrin? Materialele congresului al 5-lea al Cardiologilor. În *Buletinul Academiei de Științe a Moldovei*, Chișinău. 2008. Vol. 4 (18), 75-79. ISSN: 1857-0011.
17. Соловьева А.В. și al. Липоматоз межпредсердной перегородки и эпикардиальный жир: клиническое значение. În: *Ожирение и метаболизм.* 2011. Vol.2, 32-35. ISSN:2306-5524.
18. Marijana Tadic et al. The impact of metabolic syndrome, recently diagnosed diabetes and hypertension on right ventricular remodeling. Is there difference between risk factors? In *Clin Exp Hyperten.* 2014. Vol. 36 (5), 295–301. ISSN:1525-6006.
19. Marijana Tadic et al. Metabolic syndrome and right ventricle: An updated review. In *European Journal of Internal Medicine.* 2013. Vol. 24, 608–616. ISSN:1879-0828.
20. Chahal H, McClelland RL, Tandri H, et al. Obesity and right ventricular structure and function: the MESA-Right Ventricle Study. In *Chest.* 2012. Vol. 141, 388-95. ISSN:0012-3692.
21. Serrano-Ferrer et al. Right ventricle free wall mechanics in metabolic syndrome without type-2 diabetes: effects of a 3-month lifestyle intervention program. In *Cardiovascular Diabetology*. 2014. Vol. 13, 116. ISSN:1475-2840.
22. Simone G, Devereux RB, Chinali M, Roman MJ, Lee ET, Resnick HE, et al. Metabolic syndrome and left ventricular hypertrophy in the prediction of cardiovascular events: the

Strong Heart Study. In *Nutr Metab Cardiovasc Dis*. 2009. Vol. 19, 98-104. ISSN:0939-4753.
23. Turhan H et al. The impact of metabolic syndrome on left ventricular function: evaluated by using the index of myocardial performance. Int J Cardiol 2009;132:382-6.
24. Iacobellis G: Relation of epicardial fat thickness to right ventricular cavity size in obese subjects. Am J Cardiol 2009;104:1601–1602.
25. Cuspidi C, Valerio C, Sala C, Negri F, Esposito A, Masaidi M, et al. Metabolic syndrome and biventricular hypertrophy in essential hypertension. J Hum Hypertens 2009;23:168–75
26. Tadic M, Ivanovic B,Grozdic I.Metabolic syndrome impacts the right ventricle: true or false? Echocardiography 2011;28:530–8.
27. Tadic M, Ivanovic B, Petrovic M. Is gender responsible for everything? The relationship between sex and right ventricular remodeling in metabolic syndrome. Echocardiography 2013. http://dx.doi.org/10.1111/echo.12135.
28. Sedaia E. Funcția diastolică, sistolică și globală a ventriculului drept la pacienții cu sindrom metabolic. Buletinul Academiei de Științe a Moldovei. Științe medicale. 2019; 1 (61): 237-240. ISSN 1857-0011
29. Sedaia E., Revenco V. Țesutul adipos epicardic și riscul cardiovascular la pacienții cu sindrom metabolic. Sănătate Publică, Economie şi Management în Medicină. 2016; 2 (66) : 73-75. ISSN 1729-8687

LIST OF PUBLICATIONS

- **Articles published to accredited national scientific journals:**
  - ✓ **articles in B-category journals**

1. **Sedaia E.**, Zota V., Revenco V. Rolul indicelui adipozității viscerale la pacienții cu sindrom metabolic. *Sănătate publică, Economie și Management în Medicină.* 2019; 1(79): 57-60. ISSN 1729-8687.
2. **Sedaia E.,** Guțan I., Revenco V. Indicii obezității viscerale la pacienții cu sindrom metabolic. *Sănătate publică, Economie și Management în Medicină.* 2019; 1(79): 53-56. ISSN 1729-8687.
3. **Sedaia E.** Funcția diastolică, sistolică și globală a ventriculului drept la pacienții cu sindrom metabolic. *Buletinul Academiei de Științe a Moldovei. Științe medicale.* 2019; 1 (61): 237-240. ISSN 1857-0011
4. **Sedaia E.** Sindromul metabolic: abordare contemporană a problemei. *Buletinul Academiei de Științe a Moldovei. Științe medicale.* 2017; 2 (54): 109-113. ISSN 1857-0011
5. **Sedaia E.,** Revenco V. Țesutul adipos epicardic și riscul cardiovascular la pacienții cu sindrom metabolic. *Sănătate Publică, Economie şi Management în Medicină.* 2016; 2 (66) : 73-75. ISSN 1729-8687

- **Abstracts/theses published within national and international scientific conferences**

6. **E. Sedaia**, V. Revenco, I. Gutan, V. Ochisor, A. Vascenco. The impact of epicardial adipose tissue and right ventricular hypertrophy on diastolic and global

function of right ventricle in patients with metabolic syndrome. *European Heart Journal,* Volume 41, Issue Supplement_2, November 2020, ehaa946.0905, https://doi.org/10.1093/ehjci/ehaa946.0905.

7. **E. Sedaia**, V. Revenco, I. Guțan, V. Ochisor, A. Vascenco. The role of epicardial fat thickness and lipid profile in right ventricular remodeling in patients with metabolic syndrome. Atherosclerosis, 2020, volume XXX, page eXXX. (**IF:4.255**)

8. **Sedaia E.**, Revenco V. The role of epicardial fat thickness and other parameters of visceral adiposity in right ventricular diastolic function in patients with metabolic syndrome. *European Heart Journal*, 2019; 40 (Supplement 1). doi: 10.1093/eurheartj/ehz748.0920 (**IF: 22.673**)

9. **Sedaia E.** Evaluation of visceral adiposity and right ventricle diastolic and global function in patients with metabolic syndrome. *Atherosclerosis*, 2019, volume 287, page e138. doi: 10.1016/j.atherosclerosis.2019.06.408 (**IF:4.255**)

10. **Sedaia E**., Revenco V. Right ventricular involvement in patients with systemic arterial hypertension and preserved left ventricular systolic function. *Journal of Hypertension.* 2019; 37: e245 doi: 10.1097/01.hjh.0000573132.75926.8a (**IF: 4.209**)

11. **Sedaia E.**, Revenco V., Eșanu A., Ochișor V. The influence of blood pressure values and other components of metabolic syndrome on right ventricle Tei index. *Journal of Hypertension. 2019;* 37 : e113 doi: 10.1097/01.hjh.0000571468.05382.4d (**IF: 4.209**)

12. **Sedaia E.**, Revenco V., Moiseeva A. Does metabolic syndrome influence right ventricular diastolic function in patients with preserved left ventricular systolic function? *European Journal of Heart Failure*, 2019; 21 (Suppl.S1): 406 (**IF: 13.965**)

13. **Sedaia E.**, Revenco V., Ochișor V., Guțan I. The role of metabolic syndrome in right and left ventricular remodelling and function in patients with preserved left ventricular systolic function. *Romanian Journal of Cardiology*, 2019; 29 (Supplement) 2019:185-186. ISSN 2392-6910, ISSN-L 2392 – 6910

14. Revenco V., Ochișor V., **Sedaia E.** Influența nebivololului asupra spectrului glucidic și lipidic la pacienții hipertensivi cu insulinorezistență. *Materialele Congresului Național de Cardiologie, Sinaia, România* 2015. 286-287

15. **Sedaia E.** Rolul sindromului metabolic în funcția diastolică ventriculului drept și grosimea țesutului adipos epicardic. *Culegere de rezumate științifice ale studenților, rezidenților și tinerilor cercetători. Chișinău* 2018. p.116 ISBN 978-9975-82-103-2

16. **Sedaia E.** The effect of the metabolic syndrome on right ventricular diastolic function. *MedEspera Abstract Book* , 2018, p.46-47 ISBN 978-9975-3028-3-8

17. **Sedaia E.** Rolul ultrasonografiei în evaluarea pacienților cu sindrom metabolic. *Culegere de rezumate științifice ale studenților, rezidenților și tinerilor cercetători.* Chișinău 2017. p.73 ISBN 978-9975-82-103-2

18. **Sedaia E.**, Revenco V., Relația dintre grosimea țesutului adipos epicardial și disfuncția subclinică a ventriculului drept la pacienți cu sindrom metabolic *Culegere de rezumate științifice ale studenților, rezidenților și tinerilor cercetători.*, 2015. 197. ISBN 978-9975-82-103-2

19. **Sedaia E.**, Revenco V., Impactul sindromului metabolic asupra ventriculului drept. *Culegere de rezumate științifice ale studenților, rezidenților și tinerilor cercetători.* 2014 ISBN 978-9975-82-103-2

20. **Sedaia E.**, Revenco V., Right ventricular remodeling in metabolic syndrome. *Medespera Abstract book* 2014. 76-77. ISBN 978-9975-3028-3-8

- **Active participation within scientific forums:**
  - ✓ **national**

21. Ochișor V., **Sedaia E.** Clasificarea hipertensiunii arteriale, evaluarea clinică a pacienților hipertensivi și modificarea stilului de viață. Simpozionul Național de Cardiologie cu genericul: „Actualități în cardiologie prin prisma ghidurilor noi ale Societății Europene de Cardiologie 2018" în cadrul Zilelor Universității de Stat de Medicină și Farmacie "Nicolae Testemițanu". Chișinău, Republica Moldova 18.10.2018

22. **Sedaia E.** Impactul sindromului metabolic asupra ventriculului drept. Simpozion. "Actualități în cardiologie prin prisma medicinei practice". Zilele Universității de Stat de Medicină și Farmacie "Nicole Testemițanu", 2014

- **Poster presentations within scientific forums:**
  - ✓ **international**

23. **E. Sedaia**, V. Revenco, I. Gutan, V. Ochisor, A. Vascenco. The impact of epicardial adipose tissue and right ventricular hypertrophy on diastolic and global function of right ventricle in patients with metabolic syndrome. Accepted as a POSTER for ESC Congress, Digital format, Amsterdam, 29 August – 1 September, 2020

24. **E. Sedaia**, V. Revenco, I. Guțan, V. Ochisor, A. Vascenco. The role of epicardial fat thickness and lipid profile in right ventricular remodeling in patients with metabolic syndrome. Accepted as a POSTER for the EAS Digital Congress 2020 in Geneva, October 04-07, 2020

25. **Sedaia E.**, Revenco V. The role of epicardial fat thickness and other parameters of visceral adiposity in right ventricular diastolic function in patients with metabolic syndrome. *Congres al Societății Europene de Cardiologie, Paris, Franța, 31 Aug – 4 Sept, 2019*

26. **Sedaia E.** Evaluation of visceral adiposity and right ventricle diastolic and global function in patients with metabolic syndrome. *Al 87lea Congres al Societății Europene de Ateroscleroza, Maastricht, Olanda, Mai 26-29, 2019*

27. **Sedaia E**., Revenco V. Right ventricular involvement in patients with systemic arterial hypertension and preserved left ventricular systolic function. *Congres al Societății Europene de Hipertensiune, Milan, Italia, Iunie 21-24, 2019*

28. **Sedaia E.**, Revenco V., Eșanu A., Ochișor V. The influence of blood pressure values and other components of metabolic syndrome on right ventricle Tei index. *Congres al Societății Europene de Hipertensiune, Milan, Italia, Iunie 21-24, 2019*

29. **Sedaia E.**, Revenco V., Ochișor V., Guțan I. The role of metabolic syndrome in right and left ventricular remodelling and function in patients with preserved left ventricular systolic function. *58lea Congres Național de Cardiologie. Sinaia, România,* 18-21 Septembrie, 2019.

30. **E. Sedaia**, V. Revenco, A. Moiseeva. Does metabolic syndrome influence right ventricular diastolic function in patients with preserved left ventricular systolic function? *Congres al Societății Europene de Insuficiență Cardiacă,* 2019, Mai 25-28, Atena, Grecia

31. **Sedaia E.** The effect of the metabolic syndrome on right ventricular diastolic function. *7th International Medical Congress for Students and Young Doctors MedEspera* 2018, May 3-5th, 2018 Chișinău, Republica Moldova

32. **Sedaia E.**, Revenco V., Right ventricular remodeling in metabolic syndrome. *5 th Internetional Medical Congress For Students and Yong Doctors.* May 14-17, 2014 Chișinău, Republic of Moldova

33. Revenco V., Ochișor V., **Sedaia E.** Influența nebivololului asupra spectrului glucidic și lipidic la pacienții hipertensivi cu insulinorezistență. *Congresul Național de Cardiologie, Sinaia, România 2015.*

SEDAIA ECATERINA

THE IMPACT OF METABOLIC SYNDROME AND ITS COMPONENTS ON RIGHT CHAMBERS OF THE HEART

321.03 - CARDIOLOGY

Summary of Ph.D. Thesis in Medical Sciences

Approved for printing: 11.01.2021	Paper size 60x84 1/16
Offset paper. Offset printing.	Tiraj ... ex...
Printing sheets: ...	Order no. ....

Name and address of the institution where the summary was printed