SELECTION AND SYNTHESIS OF GENERAL MECHANISMS FOR FORMATION OF CHF IN COMORBID PATHOLOGY

Olga A. Efremova*, Ludmila A. Kamyshnikova, Natalya I. Obolonkova, Olga A. Bolkhovitina, Mariya A. Gayvoronskaya
Belgorod National Research University, Pobeda Street 85, Belgorod, 308000 Russia

Abstract:
The work analyses the pathogenesis of chronic heart failure (CHF) with preserved ejection fraction (EF); General mechanisms of CHF formation in concomitant diseases are outlined; Modern data on the effect of co morbid pathology on cardiac remodelling and dysfunction in patients with chronic heart failure with a preserved EF are summarized.
Russian and foreign literary sources presented in the search engines were analyzed for the work.
Analysis of the scientific literature has shown that an increase in systemic vascular inflammation, endothelial dysfunction and oxidative stress lead to a decrease in the bioavailability of nitric oxide (NO), an increase in LV stiffness and unfavourable remodelling in CHF with a preserved EF. Concomitant diseases such as overweight / obesity, diabetes, hypertension, chronic obstructive pulmonary disease, anaemia and chronic renal dysfunction lead to coronary remodelling through micro vascular endothelial inflammation. Demographic characteristics, such as the elderly age and the female gender, also contribute negatively.
Generalizing the analysis of literature sources of the pathogenesis of CHF with comorbid pathology, it is concluded that in addition to left ventricular (LV) diastolic dysfunction, there are other pathophysiological mechanisms that affect cardiac function: disruption of reserve function, violation of the ventricular-arterial relationship, myocardial energy deficit, pulmonary hypertension, Chronotropic imbalance, inflammation, oxidative stress and endothelial dysfunction.
Keywords: *Chronic heart failure; accompanying illnesses; comorbidity; mortality; endothelial dysfunction; review.*

Corresponding author:
Prof. Olga A. Efremova,
Institute of Medicine,
Belgorod National Research University,
Pobeda Street 85, Belgorod, 308000 Russia
e-mail: efremova@bsu.edu.ru

QR code

INTRODUCTION:

Chronic heart failure with preserved ejection fraction (CHF with preserved EF), i.e. With left ventricular ejection fraction (LV)> 45% is now more than 50% of all patients with CHF, and its prevalence is increased by approximately 1% annually compared with CHF with reduced ejection fraction (systolic CHF) [1]. Modern pharmacotherapy does not improve the outcome in patients with CHF with preserved EF, which is explained by incomplete understanding of the pathophysiology of this condition [2, 3]. In addition, diastolic LV dysfunction is not the only feature in CHF with a preserved PV. In recent years, other mechanisms have been found contributing to the development of LV dysfunction, such as vascular stiffness, a violation of the systemic vasodilator reserve, chronotropic incompetence of the sinus node [4] and pulmonary hypertension [5].Numerous recent studies have shown that CHF patients with preserved PV are generally older, more often female, and have a high prevalence of non-cardiologic comorbidities such as overweight / obesity, essential hypertension (GB), diabetes mellitus (DM), Chronic obstructive pulmonary disease (COPD), anemia and chronic kidney disease [6].Systemic inflammation and endothelial dysfunction are important unifying features of these concomitant diseases [7]. Recently, a new paradigm of CHF with preserved EF has been proposed, which suggests that concomitant diseases lead to myocardial dysfunction and cardiac remodelling through coronary micro vascular endothelial inflammation [8].

Aim

The aim was to analyze the pathogenesis of chronic heart failure (CHF) with preserved ejection fraction (EF); the allocation of common mechanisms for the formation of CHF with concomitant diseases; Generalization of modern data on the effect of co morbid pathology on cardiac remodelling and dysfunction in patients with chronic heart failure with a preserved EF.

RESEARCH METHODOLOGY:

The entire Russian and English literature was analyzed in the search engines, scientific electronic libraries "eLibrary.ru" and MedLine.

RESULTS AND DISCUSSION:

Analysis of the pathogenesis of CHF with preserved ejection fraction.

An analysis of scientific literature has shown that diastolic dysfunction is a delayed LV relaxation and an increase in diastolic stiffness of the heart, which increases diastolic pressure and filling, leading to a worsening of the heart, both at rest and during exercise [9].Diastolic dysfunction was studied in large-scale studies in patients with preserved heart failure with treatment with aldosterone antagonists (TOPCAT study) [10] and treatment with I-Preserve [11], who demonstrated structural heart remodelling in many patients with chronic heart failure with preserved EF including concentric remodelling and hypertrophy of the left ventricle (59-77%), as well as dilatation of the left atrium (LP) (59-66%). At the microscopic level, an increase in the diameter of cardiomyocytes and a change in the extracellular matrix were detected. With CHF with a preserved EF both qualitative and quantitative changes in the extracellular matrix (increased interstitial collagen deposition, higher expression of type 1 collagen and collagen with bridges), which contribute to an increase in myocardial mass and diastolic stiffness are revealed. In addition to myocardial fibrosis, the increased stiffness of cardiomyocytes is also formed, which is determined by the elasticity of the giant sarcomerictitin protein (connectin), functioning as a bi-directional spring and responsible for early diastolic filling and later diastolic stretching [12]. The rigidity of a cardiomyocyte based on titin is the result of dynamic changes in the expression of its isoforms-hard N2B and N2BA, which depend on the status of phosphorylation [12]. In experimental studies on rats with the modelling of diastolic myocardial dysfunction, a decrease in the content of NT (2-3 times), N2BA and N2B (by 1.5-2 times) isoformatein was observed [13]. The obtained data on the increase of expression of protea-musical pain and increase in intracellular concentration of $Ca2+$ in cardiomyocytes Rats explain the detected destructive changes in titin. Myocardial studies in patients with CHF and aortic stenosis (AS) showed significantly higher cardiomyocytes stiffness in patients with CHF with a preserved PV than with systolic CHF in patients with AS [14].

It was shown that the level of the brain natriuretic peptide (BNUP) with CHF with a preserved EF is lower than with systolic CHF. The decrease in myocardial bioavailability of nitric oxide was proposed as a basis for reducing the sensitivity of the myocardium to cyclic guanosine monophosphate signals in CHF with a preserved EF [14]. It was found that an increase in nitrous oxide / oxidative stress was the result of a high prevalence of concomitant diseases, such as AG, obesity and diabetes, which are known to cause inflammatory reactions in chronic heart failure with a preserved EF. Recent results show the important role of endothelial dysfunction [4] and inflammation [15] in the pathophysiology of CHF with a preserved EF.

Endothelial dysfunction leads to disturbances in the vasomotor reaction, cell proliferation, leukocyte-

endothelial interaction, platelet adhesion / aggregation, and increased vascular permeability, which are involved in vascular inflammation [16].

In a study with endomyocardial biopsy, the number of inflammatory cells that release the transforming growth factor (TGF-β), which induces the conversion of fibroblasts to myofibroblasts, increased in patients with preserved heart failure compared with the control group; the production of collagen increased and the expression of matrix metalloproteinases of the 1st type (MMP-1) decreased. The number of inflammatory cells and myocardial collagen correlated with diastolic LV dysfunction [15]. The level of circulating inflammatory biomarkers (interleukin 6 (IL-6), IL8, monocyte of chemo attractant protein 1 (MCP1)), collagen metabolism (collagen aminominal propeptide, collagen I carboxypeterin telopeptide, and intercellular matrix exchange (MMP) -2 and MMP-9) [17]. In addition, MMP9, a tissue type 1 metalloproteinase matrix inhibitor (TIMM-1), the MMP-9 / TIMM-1 ratio correlated with a high left atrial volume index (LV) that reflects chronic LV diastolic dysfunction [18]. In the Heal-ABC study, the authors reported that inflammatory biomarkers, such as IL6 and tumour necrosis factor-alpha (TNF-α), are closely related in elderly patients with CHF with a preserved EF, but not with systolic CHF. The serum IL16 level was elevated in CHF with a preserved EF as compared with systolic CHF and control group and was associated with diastolic LV dysfunction [19]. The increase in cardiac production of IL16 in transgenic mice with induced cardiac fibrosis of the myocardium of the left ventricle was accompanied by an increase in macrophage infiltration [19]. Recently, it has been found that galectin-3, lectins that bind β-galactosides reflect inflammatory and fibrotic processes and are a predictor of mortality from all causes of hospitalization with CHF [20].

Thus, according to the new theory with CHF with a preserved PV, it is suggested that the accompanying diseases promote high diastolic rigidity through the induction of systemic inflammation and oxidative stress, which affects coronary micro vascular endothelial dysfunction and lowers myocardial regulation through NO-cyclic guanosine monophosphate. This chain of events leads to an increase in cardiomyocytes stiffness through titin hypophosphorylation, leading to myocardial hypertrophy and increased interstitial fibrosis [8]. Primarily non-cardiologic concomitant diseases with chronic heart failure with preserved PV have common features of systemic inflammation and oxidative stress and, consequently, can be involved in myocardial dysfunction and myocardial remodelling.

THE INFLUENCE OF COMORBID PATHOLOGY ON THE FORMATION OF CHF WITH A PRESERVED EF

As a syndrome, CHF complicates many non-cardiological diseases and increases the frequency of hospitalizations of these patients. The most important of the diseases that lead to CHF are obesity, diabetes, COPD, anaemia and chronic kidney disease [21]. Recently, co morbid pathology has received much attention in scientific research, as well as the peculiarities of the course of diseases in elderly patients. These studies confirm that non-cardiac diseases can adversely affect myocardial function and myocardial remodelling and probably play a role in the pathophysiology of CHF with a preserved EF.

The decrease in the forced expiratory volume in one second (FEV1) in chronic obstructive pulmonary disease (COPD) is an independent predictor of the decrease in EF. COPD is both a premorbid background in CHF with a preserved PV, and one of the causes of death in CHF with a preserved EF. One of the important factors that cause cardiac remodelling in COPD is low active systemic inflammation in this disease. In a large population study, a more severe COPD stage was linearly associated with a diastolic left ventricular function [22].

Chronic kidney disease is presented in about 30-40% of patients with CHF and is an important predictor of mortality [23, 24]. CHF and chronic renal insufficiency often coexist and may be associated with common risk factors such as hypertension, diabetes and atherosclerosis, as well as with common pathogenetic mechanisms such as neurohumoral activation of inflammation and oxidative stress [25].

The prevalence of arterial hypertension (AH) in patients with heart failure with a preserved PV is about 60-88% [26]. The risk of developing heart failure, adjusted for age and other risk factors, is about 2 times higher in men with hypertension and 3 times higher in women with hypertension than in those with normal arterial bloodpressure (BP). In the study of van Deursen V.M. (2014) in European patients, it is shown that arterial hypertension is an independent predictor of diastolic dysfunction [27]. Adverse cardiovascular effects of hypertension include LV hypertrophy, myocardial fibrosis, and increased arterial stiffness. Increased stiffness of the arteries increases post loading on the myocardium, which leads to a violation of LV relaxation and increased LV filling pressure, increased oxygen consumption. In patients with AH, fibrosis markers are associated with asymptomatic diastolic dysfunction and myocardial collagen metabolism, which was higher in patients with more severe diastolic dysfunction [28, 29].

AH, as a rule, is perceived as a factor capable of causing CHF with a preserved PV through an excess of postload on the myocardium and hypertrophy of the LV - this paradigm was actively discussed by scientists [8]. In a valsartan test with diastolic LV dysfunction (VALIDD), only 3% of hypertensive patients had significant LV hypertrophy. It has been shown that inflammation; oxidative stress and endothelial dysfunction play an important role in hypertension [30]. Endothelial dysfunction in hypertensive patients is associated with an increase in the level of plasma TNF-α, IL-6, intercellular adhesion 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1), E-selectin, C-reactive protein (CRP) and von Willebrand factor, which are markers of endothelial activation. Markers of inflammation (albumin in urine, CRP, TNF-α, TGF-β) were independently associated with asymptomatic diastolic dysfunction in patients with CHF with preserved EF. In another study, high levels of circulating IL6, TNF-α, IL8, and MCP1 were detected in 275 patients with stable arterial hypertension with or without heart failure with a preserved EF [18]. With salt-sensitive hypertension, high intake of salt led to systemic oxidative stress [31], possibly due to the renal production of pro-inflammatory cytokines. RAAS is one of the main activators of NADPH oxidase and the production of reactive oxygen (ROS), with more and more evidence indicating that RAAS is a common pathogenetic link for obesity, metabolic syndrome, insulin resistance (IR), chronic kidney disease and hypertension. In patients with AH, frequent violations of carbohydrate metabolism, dyslipidemia, microalbuminuria and obesity are detected. [32].

Obesity is becoming a global epidemic of our time and is an independent risk factor for the development of cardiovascular complications and mortality [33]. This pathology doubles the risk of CHF [34, 35] and CDII. In CHF with a preserved EF, obesity increases mortality, this follows from the U-shaped relationship between BMI and mortality [36]. Obesity causes unfavourable structural and functional changes in the heart. In a large-scale study (Silver Spring) in magnetic resonance imaging of the heart, obesity is associated with concentric LV remodelling, an increase in the ratio of LV mass / volume, with preserved PV [37] and dilatation of LP [31]. Excess weight and obesity are also associated with diastolic LV dysfunction, regardless of the mass of LV myocardium and associated risk factors. The conducted studies showed that the slowing of myocardial relaxation was the result of myocardial-mitochondrial dysfunction caused by obesity, lipotoxicity, dissociation of oxidative phosphorylation and violation of calcium metabolism

in cardiomyocytes. Compared to normal body weight, obese individuals had impaired myocardial energy (creatine phosphate / ATP ratio) and a violation of the rate of LV filling in the diastole, which deteriorates after inotropic stress [38]. The coronary blood flow, measured with positron emission tomography, was significantly reduced in obese postmenopausal women; this was negatively correlated with the waist / hip ratio. Endothelial dysfunction in obesity is caused by the activation of pro-inflammatory cytokines and increased oxidative stress [39]. The increase in lipid deposits in adipocytes led to the formation of pro-inflammatory cytokines and adipokines, including TNF-α, IL6, leptin and resistin, which in turn led to an increase in the number of monocytes and stimulation of differentiation of monocytes into macrophages. Adiponectin is the most common adipokine, a secreted adipocyte. It affects the regulation of insulin sensitivity and energy metabolism [40]. Decreased adiponectin levels in plasma are observed in patients with obesity, CDII, AH and MS and are largely associated with low levels of chronic inflammation. Adiponectin also stimulates endothelial production of NO and has anti-inflammatory properties. Approximately 30% of obese people do not have MI and cardiovascular diseases that are observed with obesity [41]. In patients with normal BMI, visceral fat deposition was associated with impaired systolic and diastolic function, increased myocardial fibrosis markers, impaired insulin sensitivity and pro-inflammatory activation [17]. In addition, an increase in the level of insulin prIIR can be important for the titin base of cardiomyocytic stiffness, since insulin stimulates a shift towards increased expression of hard titin N2B isoform.

DM is an important risk factor for CHF. Diastolic LV dysfunction is the first indicator of myocardial involvement in diabetes. Among patients with chronic heart failure with a preserved SD, CDII is distributed in the range from 26 to 45% [1, 6]. DM causes diastolic LV dysfunction through several mechanisms. In diabetes, the extracellular matrix of the myocardium changes as a result of enhanced interstitial and perivascular fibrosis, increased expression of type I collagen and deterioration in the regulation of matrix metalloproteinases that destroy collagen. These pathological mechanisms are mediated by hyperglycemia, oxidative stress and elevated levels of aldosterone and angiotensin II. In addition to fibrosis, the deposition of glycation end products in the myocardium also increases diastolic stiffness in diabetes [40]. The glycation products modify proteins or lipids, which become non-enzymatically glycosylated and oxidized after contact with the aldose of sugars with the creation of almost

irreversible bridges. Formation and accumulation of glycation products increases hyperglycemias, oxidative stress, and hypertension and is an independent predictor of hospitalizations and cardiac mortality [40]. Increased deposition of glycation products was also detected in micro vessels of the myocardium of diabetic patients with CHF with a preserved EF. Myocardial deposition of glycation products increased diastolic LV stiffness due to direct and indirect mechanisms, including collagen cross-linking, stimulating the production of collagen and activating receptors for glycation products. In addition, glycation products increase oxidative stress and release proinflammatory cytokines, which leads to endothelial dysfunction and reduced NO-bioavailability [40].

DM aggravates the relaxation of the myocardium in diastole through the violation of calcium metabolism in cardiomyocytes. In diabetes, endothelial dysfunction is induced, NO-bioavailability is reduced, and the vasodilation response is impaired by increasing systemic inflammation and oxidative stress. Hyperglycemia causes oxidative stress through various mechanisms that include auto-oxidation of glucose, the formation of glycation products, the activation of the polyol pathway, and the increase in the level of free fatty acids and leptin.

CONCLUSION:

1. Generalizing the current data on the effect of concomitant diseases on cardiac remodelling and dysfunction in patients with chronic heart failure with a preserved PV, one can single out general pathophysiological mechanisms of cardiac function impairment in co morbid pathology: disruption of reserve function, violation of the ventricular-arterial relationship, myocardial energy deficit, pulmonary hypertension, Chronotropic imbalance, inflammation, oxidative stress and endothelial dysfunction.

2. With CHF with a preserved PV, there are often a number of concomitant X diseases, which in themselves cause a negative effect on the cardiovascular system.

3. The new paradigm of CHF with a safe PV offers an important accumulative role of non-cardiac concomitant diseases leading to myocardial dysfunction and remodelling.

REFERENCES:

1.Steinberg, B.A., Zhao, X., Heidenreich, P.A., Peterson, E.D., Bhatt, D.L., Cannon. C.P. Get with the guidelines scientific advisory committee and investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation, 2012;126(1): 65-75.

2.Kamyshnikova, L.A., Efremova, O.A., Structural and functional changes in myocardial of patients with chronic heart failure treated with spironolactone. Clinical medicine, 2012;90(5): 25-28.

3.Komajda, M., Lam, C.S., Heart failure with preserved ejection fraction: a clinical dilemma. Eur Heart J., 2014;35(16): 1022-1032.

4.Borlaug, B.A., Olson, T.P., Lam, C.S., Flood, K.S., Lerman, A., Johnson, B.D., Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am CollCardiol., 2010;56(11): 845-854.

5.Lam, C.S., Roger, V.L., Rodeheffer, R.J., Borlaug, B.A., Enders, F.T., Redfield, M.M., Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am CollCardiol., 2009;53(13): 1119-1126.

6.Lam, C.S., Donal, E., Kraigher-Krainer, R.S. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail.;2011; 13(1): 18-28.

7.van der Wal, H.H., Grote Beverborg, N., van Veldhuisen, D.J., Voors, A.A., van der Meer, P. 2016. Pharmacotherapy for co-morbidities in chronic heart failure: a focus on hematinic deficiencies, diabetes mellitus and hyperkalemia. Expert OpinPharmacother.,17(11): 1527-1538.

8.Paulus, W.J., Tschöpe C., A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am CollCardiol., 2013;62(4): 263-271.

9.Efremova, O.A., V.M. Nikitin, E.A. Lipunova, I.A. Kochetkova., L.A. Kamyshnikova., Visualization and virtual diagnosis of the cardiovascular system current state by the results of its non-invasive monitoring. Research Journal of Pharmaceutical, Biological and Chemical Sciences: RJPBCS. 2014;5(5): 1000-1005.

10.Pitt, B., Pfeffer, M.A., Assmann, S.F., Boineau, R., Anand, I.S., Claggett, B. TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med., 2014;370(15): 1383-1392.

11.Massie, B.M., Carson, P.E., McMurray, J.J., Komajda, M., McKelvie, R., Zile, M.R., I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med., 2008;359(23): 2456- 2467.

12.Linke, W.A., Hamdani, N. 2014. Gigantic business: titin properties and function through thick and thin. Circ Res., 2014;114(6):1052-1068.

13.Hidalgo, C., Hudson, B., Bogomolovas, J., Zhu, Y., Anderson, B., Greaser M., PKC phosphorylation of titin's PEVK element. A novel and conserved

pathway for modulating myocardial stiffness. Circ Res., 2009;105(7): 631-638.

14. VanHeerebeek, L., Hamdani, N., Falcao-Pires, I., Leite-Moreira, A.F., Begieneman, M.P.V., Bronzwaer, J.G.F., et al., Low myocardial protein kinase G activity in heart failure with preserved ejection fraction. Circulation., 2012;126(7): 830-839.

15. Westermann, D., Lindner, D., Kasner, M., Zietsch, C., Savvatis, K., Escher F., Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. Circ Heart Fail.,2011; 4(1): 44-52.

16. Savoia, C., Schiffrin, E.L. 2007. Vascular inflammation in hypertension and diabetes: molecular mechanisms and therapeutic interventions. ClinSci(Lond)., 2007;112(7): 375-384.

17. Kosmala, W., Jedrzejuk, D., Derzhko, R., Przewlocka-Kosmala, M., Mysiak, A., Bednarek-Tupikowska, G., Left ventricular function impairment in patients with normal-weight obesity: contribution of abdominal fat deposition, profibrotic state, reduced insulin sensitivity, and proinflammatory activation. CircCardiovasc Imaging.,2012; 5(3): 349-356.

18. Collier, P., Watson, C.J., Voon, V., Phelan, D., Jan, A., Mak, G., Can emerging biomarkers of myocardial remodelling identify asymptomatic hypertensive patients at risk for diastolic dysfunction and diastolic heart failure? Eur J Heart Fail., 2011;13(10): 1087-1095.

19. Tamaki, S., Mano, T., Sakata, Y., Ohtani, T., Takeda, Y., Kamimura, D., 2013. Interleukin-16 promotes cardiac fibrosis and myocardial stiffening in heart failure with preserved ejection fraction. PLoS One., 8(7): e68893.

20. Van der Velde, A.R., Gullestad, L., Ueland, T., Aukrust, P., Guo, Y., Adourian, A., Prognostic value of changes in galectin-3 levels over time in patients with heart failure: data from CORONA and COACH. Circ Heart Fail.,2013; 6(2):219-226.

21. Campbell, R.T., Jhund, P.S., Castagno, D., Hawkins, N.M., Petrie, M.C., McMurray, J.J., What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? J Am CollCardiol., 2012;60(23): 2349-2356.

22. Barr, R.G., Bluemke, D.A., Ahmed, F.S., Carr, J.J., Enright, P.L., Hoffman, E.A., Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med., 2010;362(3): 217-227.

23. Hillege, H.L., Nitsch, D., Pfeffer, M.A., Swedberg, K., McMurray, J.J., Yusuf S., Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation,2006; 113(5): 671-678.

24. Sviridova, M.S., Efremova, O.A., Kamyshnikova, L.A., The prevalence of chronic kidney disease stages I-III in the Belgorod region. Scientific bulletin Belgorod State University. Medicine Pharmacy, 2013;4 (147): 182-186.

25. Colombo, P.C., Ganda, A., Lin, J., Onat, D., Harxhi, A., Iyasere J.E., Inflammatory activation: cardiac, renal, and cardio-renal interactions in patients with the cardiorenal syndrome. Heart Fail Rev., 2012;17(2): 177-190.

26. McMurray, J.J., Carson, P.E., Komajda, M., McKelvie, R., Zile, M.R., Ptaszynska, A. 2008. Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. Eur J Heart Fail., 10(2): 149-156.

27. VanDeursen, V.M., Urso, R., Laroche, C., Damman, K., Dahlström, U., Tavazzi, L., Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail.2014; 16(1): 103-114.

28. Müller-Brunotte, R., Kahan, T., López, B., Edner, M., González, A, Díez, J., Myocardial fibrosis and diastolic dysfunction in patients with hypertension: results from the Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol (SILVHIA). J Hypertens., 2007;25(9): 1958-1966.

29. Nikitin, V.M., Efremova, O.A., Churnosov, M.I., Lipunova, E.A., Kamyshnikova, L.A. Efremova, O.A., Risk method assessment of coronary heart disease in carriers of polymorphic cardiogenic. Research Journal of Pharmaceutical, Biological and Chemical Sciences (RJPBCS). 2016;7(6): 3233-3238.

30. Cohen, R.A., Tong, X., Vascular oxidative stress: the common link in hypertensive and diabetic vascular disease. J Cardiovasc Pharmacol, 201055(4): 308-316.

31. Hummel, S.L., Seymour, E.M., Brook, R.D., Kolias, T.J., Sheth, S.S., Rosenblum, H.R., et al., Low-sodium dietary approaches to stop hypertension diet reduces blood pressure, arterial stiffness, and oxidative stress in hypertensive heart failure with preserved ejection fraction. Hypertension, 2012;60(5): 1200-1206.

32. Stritzke, J., Markus, M.R., Duderstadt, S., Lieb, W., Luchner, A., Döring, A., et al., The aging process of the heart: obesity is the main risk factor for left atrial enlargement during aging. J Am CollCardiol.,2009; 54(21): 1982-1989. Doi: 10.1016/j.jacc.2009.07.034.

33. Whitlock, G., Lewington. S., Sherliker, P., Clarke, R., Emberson, J., et al., Prospective Studies Collaboration, Body-mass index and cause specific mortality in 900 000 adults: collaborative analyses of

57 prospective studies. Lancet, 2009373(9669): 1083-1096.

34.Murphy, N.F., MacIntyre, K., Stewart, S., Hart, C.L., Hole, D., McMurray, J.J. 2006. Long-term cardiovascular consequences of obesity: 20-year follow up of more than 15 000 middle-aged men and women (the Renfrew- Paisley study). Eur Heart J., 27(1): 96-106.

35.Efremova, O.A., V.M. Nikitin, E.A. Lipunova, D.A. Anohin, L.A. Kamyshnikova., Estimate or the Effectiveness of Intelligent Information System of Early Diagnosis and Prognosis of Cardiovascular Disease. World Applied Sciences Journal. 2013;26 (9): 1204-1208.

36.Haass, M., Kitzman, D.W., Anand, I.S., Miller, A., Zile, M.R., Massie, B.M., et al., Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail., 2012;4(3): 324-331.

37.Kardassis, D., Bech-Hanssen, O., Schönander, M., Sjöström, L., Karason, K., The influence of body composition, fat distribution, and sustained weight loss on left ventricular mass and geometry in obesity. Obesity (Silver Spring), 2012;20(3): 605-611.

38.Rider, O.J., Francis, J.M., Ali, M.K., Holloway, C., Pegg, T., Robson, M.D, et al., Effects of catecholamine stress on diastolic function and myocardial energetics in obesity. Circulation, 2012;125(12):1511-1519.

39.Schindler, T.H., Cardenas, J., Prior, J.O., Facta, A.D., Kreissl, M.C., Zhang X.L., et al., Relationship between increasing body weight, insulin resistance, inflammation, adipocytokineleptin, and coronary circulatory function. J Am CollCardiol.; 2006;47(6): 1188-1195.

40.Kim, J., Montagnani, M., KonKoh, K., Quon, M.J., Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological pathways. Circulation., 2006;113(15): 1888-1904.

41.Reaven, G.M., Insulin resistance: the link between obesity and cardiovascular disease. Med Clin North Am.;201; 95(5): 875-892.

42.Goldin A., Beckman J.A., Schmidt A.M., Creager M.A. Advanced glycation end products: sparking the development of diabetic vascular injury. Circulation. 2006; 114(6): 597-605.