Volume 6, № 20, December 2018
ISSN: 2309-0901 (Print)
ISSN: 2311-1534 (OnLine)
http://www.heart-vdj.com

International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation

Late ventricular potentials and their significance for clinical practice

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Results of the most important clinical trials presented at the Congress of the European Society of Cardiology 2018

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Printed in Russia

The Journal is in the List of the leading scitntific journals and publications of the Supreme Examination Board (VAK)

Complete versions of all issues are published: www.elibrary.ru, www.cyberleninka.ru

International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation

Volume 6, № 20, December 2018

DOI: 10.15829/2311-1623-6-20

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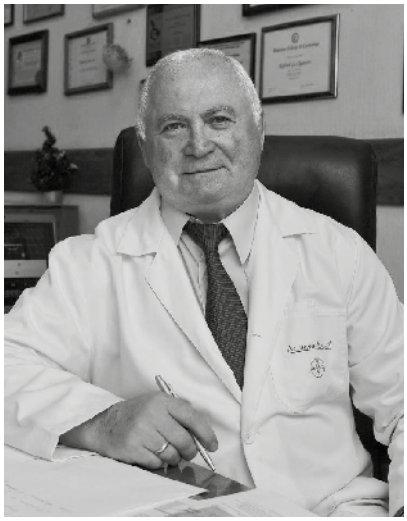

Editor's Welcome

Dear colleagues!

In the 20th issue of the International Heart and Vascular Disease Journal, there are the leading article, original and review articles and experts' opinion on the New statement on chronic heart failure in patients with diabetes mellitus.

The leading article section is dedicated to the problem of methodological questions of late ventricular potentials identification, the data on its sensitivity and specificity in different states, including the questions of prognostic value and late ventricular potentials correction.

Three articles are published in the «Original articles» section. The first article written by the group of authors from Uzbekistan, who studied the dynamics of left ventricular diastolic function in patients with I-III functional classes of chronic heart failure during lisinopril and losartan treatment, depending on stage of chronic kidney disease. The second article is dedicated to clinical and anatomical features of cardiac fat deposits - epicardial fat and interatrial septum lipomatosis during the pathological examination, which revealed that the thickness of interatrial septum lipomatosis and the thickness of epicardial fat tissue correlates with triglyceride blood level, left ventricular myocardial hypertrophy, and calcification of coronary arteries in autopsy. The third article represents the data on the prevalence of certain stress parameters in a workplace in men and women aged 25-64 years in Tumen.

The «Review articles» section represents a quick analysis of the results of the most important clinical trials presented at the Congress of the European Society of Cardiology 2018 (Munich, Germany).

In 2018 the new statement on chronic heart failure in patients with diabetes mellitus was published. It contained the data of major clinical trials on chronic heart failure prevalence, clinical features and complications, pathophysiological aspects and treatment in patients with diabetes mellitus. The comments of the Russian experts on principal positions of this new statement on chronic heart failure in patients with diabetes mellitus is represented in the «Expert opinion» section.

We invite everybody to collaborate with the journal. We are waiting for your original papers, review articles, discussions, and opinions about problems, treatment and prophylaxis recommendations.

Rafael G. Oganov
Editor-in-Chief
President of the "Cardioprogress" Foundation

International Heart and Vascular Disease Journal • Volume 6, № 20, December 2018

Journal of the Cardioprogress Foundation

LEADING ARTICLE

Late ventricular potentials and their significance for clinical practice

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Cardiovascular diseases (CVD) keep the leading position among the mortality causes in the developed countries, and in the Russian Federation within the last 10 years around 60 % of deaths have been caused by CVD. Various arrhythmias and/or acute myocardial ischemia are one of the main causes of cardiovascular mortality. Therefore, it is particularly important to provide the early diagnostics of myocardial electric instability with its consequent correction and secondary prevention. One of the methods for determining the electrical instability of the myocardium is the registration of late ventricular potentials using signal-averaged electrocardiography. There are numerous evidences demonstrating that late ventricular potentials registration may be used as an available, non-invasive, and safe method of risk stratification in patients with cardiovascular disease in terms of aggravation of principal disease, risk of developing ventricular tachycardias and sudden cardiac death. However, the attitude to the phenomenon of late ventricular potentials is ambiguous, and information about its influence on the prognosis of cardiovascular diseases is contradictory. This article reviews methodologic aspects of late ventricular potentials registration, data on their sensitivity and specificity in different conditions (coronary artery disease, including unstable angina, acute myocardial infarction, ventricular tachycardias, etc), and the questions of prognostic importance and possibility of late ventricular potentials correction.

Keywords: *late ventricular potentials, sudden cardiac death, ventricular tachycardia, signal-averaged electrocardiography.*

Conflict of interest: None declared.

Received: 01.10.2018 **Accepted:** 20.10.2018

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Introduction

Over the last years cardiovascular mortality has decreased in high-income countries in response to adoption of preventive measures to reduce burden of CAD and heart failure. Despite these results, cardiovascular diseases are responsible for approximately 17 million deaths every year in the world, approximately 25 % of which are sudden cardiac death (SCD) [1].

In the structure of total mortality in Russian Federation over the last 10 years cardiovascular diseases occupy about 60 %. Approximately in 70 % of cases the death from CAD is sudden [2] and in 25–30 % of cases SCD is the first and last manifestation of CAD [3]. The main causes of SCD in young patients are the pathologies of ion channels, cardiomyopathies, myocarditis, several intoxications, including narcotic intoxication, while in older patients the main causes of SCD are degenerative diseases (CAD, valvular heart diseases and heart failure). Prediction of sudden cardiac death is the insoluble and everlasting question of arrhythmology, which promoted several studies attempting to find reliable prognostic markers of sudden cardiac death over the last 10 years.

The basis for the development of arrhythmogenic death mechanisms is the electrical instability of myocardium, which can be detected by the method of registration of late ventricular potentials (LVP) by using high-resolution signal-averaged electrocardiography (SA-ECG) [4]. Signal averaged ECG has been included to diagnostic approach for family members of sudden unexplained death syndrome or sudden arrhythmic death syndrome victims due to ESC guidelines (2015) [1].

Methodological aspects

LVP are low-amplitude potentials due to fragmented electrical activity at the terminal part of QRS complex or at the beginning of ST segment during the diastole of ventricles appearing at the region of delayed excitation of myocardium also known as «delayed myocardial depolarization potentials», which creates arrhythmogenic zones and contributes to the appearance of malignant ventricular tachyarrhythmias (VTA). Back in the 70s of the XX century E. Berbary et al., L. Fontain et al. discovered delayed ventricular electrical activity that preceded ventricular tachyarrhythmias while analyzing the records from epi- and endocardial electrodes [5].

The mechanism of micro-reentry is considered to be the cause of LVP phenomenon at the regions of local delayed excitation with different origin: ischemic zone of myocardium, local electrolyte balance disturbances, sympathetic activation and other impacts that cause local conduction delay and the appearance of spontaneous electrical activity focuses [6–8].

LVP are detected during SA-ECG with the ECG signal frequency of 1000 Hz and more. Quantitative criteria for LVP can be calculated by three parameters: a) duration of the filtered QRS complex (totQRS); b) duration of low-amplitude signals (< 40 mkV) at the end of the QRS complex (LAS-40); c) root-mean-square amplitude of last 40 ms of the filtered QRS complex (RMS-40). The appearance of at least two of three of these criteria allows to diagnose LVP. It is remarkable that every criterion is considered to be specific, while its sensitivity varies depending on the operation conditions of filters, interference and other external conditions.

Processing of the data obtained during SA-ECG involves the averaging of cardiac signal or sequential analysis of complexes The Simpson method is the most common method of temporal signal averaging which includes the summation of hundreds of sequential cardiac cycles [9]. ECG registration is conducted using three orthogonal leads (X, Y, Z) with the following filtering of the signal. The important advantage of this high-resolution ECG averaging method is the ability to extract the signal from the noise (to stabilize LVP by extracting it from accidental noise).

However, this method has significant disadvantages, such as: the probability of smoothing the high-frequency signals is high because of unstable characteristics of LVP (duration, configuration, frequency of occurrence); the risk of signal distortion by filters and other external sources; deformed and wide QRS complex can obscure late potentials in patients with interventricular conductance disturbances [10].

Spatial averaging is another useful method, which involves simultaneous registration of several (4–16) ECG using a large number of closely spaced pairs of electrodes [11–13].

The most interesting and promising method is spectral analysis of SA-ECG. This technique expands the diagnostic possibilities and has a number of advantages: elimination of background and filter noise, the opportunity to investigate patients with His bundle branch blocks and, moreover, no effect of focal myocardium changes localization on the results [10].

Another method of spectral analysis is wavelet transform for time-frequency mapping of the signal. This technique allows to register and analyze LVP

with modern radiophysical methods by using a large number of cardiac cycles without signal averaging [11].

LVP can be analyzed by the next quantitative criteria (Simpson): duration of the filtered QRS complex after averaging (totQRS > 114 ms); duration of low-amplitude signals (< 40 mkV) (LAS-40) longer than 38 ms; c) root-mean-square amplitude of last 40 ms of the filtered QRS complex (RMS-40) less than 25 mkV [6].

The analysis of late ventricular potentials has been suggested to be used according to the results of Holter monitoring since 1989. Using automatic analysis of LVP during Holter monitoring M. Sosnowski et al. identified two different groups of patients: with and without late potentials [14]. The criteria to determine the presence of late potentials were: totQRS ⩾120 ms; RMS-40 ⩽25 mkV; LAS-40 ⩾39 ms. The patients with myocardial infarction had the circadian rhythm of LVP registration. Specificity of parameters detection reached 100 % from 9 to 12 o'clock in the morning and was lower at night (80 %).

However, L. Zhao identified slightly different criteria to determine the presence of LVP in patients with ventricular tachycardia during Holter monitoring: totQRS ⩾114 ms; RMS-40 ⩽12 mkV; LAS-40 ⩾38 ms. The sensitivity of positive ECG criteria in the patients with tachycardia was 95.7 % and the specificity in the patients without arrythmia was 97.8 %.

Consequently, nowadays there is no consensus regarding which analysis (time, spatial or spectral) is the most preferred to determine LVP and which parameters for totQRS, RMS-40, LAS-40 are more diagnostically accurate.

Prognostic value of late ventricular potentials

Registration of LVP is mostly used for prediction of sudden cardiac death and ventricular arrythmias development in survivors of myocardial infarction (MI). It is important to determine the frequency of LVP on different stages of the disease and the correlation between the localization of MI and the development of LVP. SA-ECG is considered to be a useful and promising non-invasive method for identification of myocardial infarction survivors with high risk of arrythmias, especially VTA.

Thus, Rubal B.J., Bulgrin, Gilman J.K. [16] concluded that the sensitivity of SA-ECG in LVP analysis is about 92–100 % and specificity is about 78–92 % in 90 MI survivors with high risk of sudden cardiac death.

The dynamics of LVP is reflected by instability, variability, electrophysiological and morphological characteristics of cardiomyocytes. Delayed ventricular activity is caused by the alteration of vital cardiomyocytes and areas of ischemia, necrosis and fibrosis. Recovery of ischemic myocardium function and ischemic zone demarcation during treatment lead to cessation of LVP. Delayed fragmented ventricular activity is more often detected on the early stages of acute myocardial infarction (AMI) and in 60 % of patients at the stage of ischemia, but the maximum is registered from 10th to 14th day. Thus, in Zhalyunas R. et al. study LVP were detected on the first day after AMI in 40.5 % of patients, on the third day in 28.5 % of patients and on the fourteenth day in 45.2 % of patients [17]. It is remarkable that in patients with Q wave AMI LVP were significantly more common on the 3d and 14th day (39.1 % and 7.7 %, 55.1 % and 23.1 % respectively).

According to some data LVP detection is more common during the first month after AMI with future decreases of frequency. Pozdnyakova N.V. et al. noted that in 31 % of patients with AMI LVP were detected during all days of study, in 25 % LVP were detected only at the acute phase of MI and disappeared completely by the time of discharge from the hospital and in 44 % of patients LVP weren't detected during the next ECG registrations [18]. The reason for the LVP disappearance can be myocardial «stunning» and «hibernation» by the time of discharge. Buziashvili Yu. I. et al. found LVP in 18.7 % of patients with irreversible myocardial dysfunction and in 61.1 % of patients with hibernation of cardiomyocytes [19]. Consequently, the authors showed that myocardial hibernation is more common reason for LVP appearance than cicatricial changes.

According to other data the viable myocardium in patients with EF < 40 % in the early post-infarction period had correlation with the absence of LVP: viable cardiomyocytes were detected in 80 % of patients without LVP and only in 35 % with LVP by the results of stress echocardiography and SA-ECG. Similar results were obtained in another study: patients with LVP had asynergy zones in 47 % of cases, whereas patients without LVP had them only in 28 % of cases [20, 21].

During the investigation of LVP in patients with acute myocardial ischemia and during the coronary angioplasty it was shown that transient, spontaneous or induced by temporal coronary artery occlusion during transluminal balloon angioplasty myocardial ischemia leads to the significant «impairment» of SA-ECG parameters and LVP appearance. Stabilization of

patient's condition had correlation with the «improvement» of SA-ECG parameters and the disappearance of LVP in one-third of patients [6, 7, 8]. At the same time exercise-induced myocardial ischemia wasn't associated with the changes of SA-ECG parameters.

Areas with reduced blood supply, which include isolated necrotic cardiomyocytes or small focuses of necrosis, are the cause of fragmented impulse conduction. Patients with unstable angina in some cases have an increase in end-diastolic pressure, that can cause changes in electrophysiological characteristics of cardiomyocytes, inhomogeneity of the refractory periods, in particular, which can be the reason for micro-reentry and LVP development.

Stabilizing patient's with unstable angina condition is connected with the «improvement» of SA-ECG parameters and the disappearance of LVP in one-third of them. Antianginal pharmacological therapy or transluminal angioplasty does not change SA-ECG parameters or the frequency of LVP registration significantly in patients with stable CAD [7, 9]. It has been shown that CAD patients with unstable angina and ST segment elevation have LVP twice as often as patients with ST segment depression [6, 7].

According to Saveleva I.V. et al. LVP were detected in 25 %, 30 % and 37 % of patients with single-, double- and triple-vessel CAD respectively [7]. In other studies, a statistically significant predominance of LVP frequency was detected in a group of patients with triple-vessel CAD without focal myocardial changes; it is remarkable that the most sensitive parameter of SA-ECG was the duration of low-amplitude signals (LAS40) [6, 7], what can be explained by the increase of myocardium mass with electrophysiological inhomogeneity. Solmon A.J. et al. also revealed significant differences in the quantitative parameters of SA-ECG in patients with CAD and coronary artery stenosis compared to healthy individuals [22].

LVP were registered in 80 % of patients with chronic CAD, focal cardiosclerosis and ventricular tachyarrhythmias [23]. Brembilla-Perrot B. et al. [24] study included 58 patients with dilated cardiomyopathy and LVP were registered in 13 of 14 patients with induced and maintained VTA. The sensitivity of this method for risk factors estimation of VTA maintenance was high (93 %). LVP were also detected in 9 patients with induced trembling or fibrillation of ventricles.

LVP were 3 times more common in patients with stable VTA compared with CAD patients without ventricular rhythm disturbances (29 %) according to a number of authors [17, 20, 25–27]. However, the presence of high grading premature ventricle contractions didn't correlate with the increase of LVP detection.

According to many researches most patients with CAD and VTA had LVP during SA-ECG, which were connected to the focuses of cardiosclerosis, myocardial ischemia and loss of contractility. At the same time, it is possible to identify a group of patients with stable spontaneous VTA who has high frequency of LVP detection permanently. Typically, it is possible to induce VTA in these patients during electrophysiological study [7, 29, 30].

The study of Akasheva D.U. et al. proves the commonality of conditions for the emergence of LVP and VTA. The positive correlation between the presence of LVP and stable VTA induction during electrophysiological study has been demonstrated (the most sensitive parameter was LAS-40) [6]. Authors suggest to expand the possibilities of LVP in clinical practice, for example as a screening test to decide the question of intracardiac EPS necessity.

It is remarkable that patients with «labile» LVP during physical activity had VTA 5.4 times more often compared to the patients with «stable» LVP (27 % and 5 % respectively). Thus, the «lability» of LVP precisely reflects the electrophysiological processes that underpins the development of VTA during exercise.

However, it has been proved that LVP correlate with sudden cardiac death frequency, but only when the mechanism of sudden cardiac death is directly connected with VTA. Authors associate dangerous LVP with electrophysiologically induced VT. Incze A., Cotol S., Carasca E, [31] determined high prognostic value of LVP for predicting the risk of sudden cardiac death. 60 victims of MI aged over 51 year were included into the 5-year study, by the results of which LVP were determined only in 30 patients. During the investigation sudden cardiac death was registered in 6 patients and the episodes of VTA in 2 patients from the group with LVP. In the group without LVP sudden cardiac death wasn't registered. In case of Roithinger F.X., Punzen-gruber C., [32], Sanjuan R., Morell S., et al. [33] study it had been showed that LVP is a great predictor for sudden cardiac death and VTA development.

The great majority of works are dedicated to the analysis of LVP significance in estimation of fatal arrythmias development. Thus, it was shown that LVP increase the probability of life-threatening arrhythmias by 5 times and exceeding instrumental criterion (QRSd > 106 ms) increase the relative risk value by 9 times. Simpson M.B. et al. showed in their study a

positive correlation between life-threatening arrhythmias and LVP development. It is remarkable that the frequency of LVP is increasing with the class of ventricular tachyarrhythmia [29, 30]. The sensitivity of this method for ventricular arrythmia prognosis is about 86–92 % and the specificity varies from 62 to 97.5 % [23].

Gottfridsson C. et al. found that LVP are more often registered in patients with the history of monomorphic ventricular tachycardia than in the ones with ventricular fibrillation. The first group of patients was characterized by shorter duration of RMS40, totQRS and ejection fraction. Thus, the electro-anatomical substrate for LVP development is more pronounced in patient with VT.

Considering the data obtained, as well as the sensitivity of the temporal and spectral SA-ECG characteristics (for patients with monomorphic VT — 90 %, with EF — 58 %) and specificity (63 %), the authors suggest to use a combination of time and spectral SA-ECG analysis to identify patients with an increased risk of VT developing [34]. In the study of D. U. Akasheva et al., devoted to the study of LVP registration frequency in patients with induced VT with the programmable pacemaker, the sensitivity of LVP was 71 %, and specificity was 89 % [6].

Thus, after analyzing the data on LVP we can't confidently link them with the mechanism of sudden death. However, when sudden death is caused by VT directly, there is a significant correlation between dangerous LVP and VTA induced by programmed stimulation.

The work of Steinbigler P. et al. represents the importance of LVP prognostic value as a criterion for early detection and prevention of sudden cardiac death on the example of 756 AMI victims. However, the authors emphasize that the most informative pet-ameters in post-myocardial infarction risk estimation are LVP and LV EF [35]. According to Boldueva S.A. et al. LVP (as well as recurrent MI, hypotension during active standing test, LV EF, ventricular rhythm disturbances according to 24-hour ECG monitoring, heart rate variability) correlate with sudden cardiac death frequency [36].

The observation of Steinbigler P. et al. is very remarkable — MI victims after VT have LVP permanently during the day (regardless on the time of the day), whereas the patients after ventricular fibrillation (VF) have LVP transiently (in the mourning), which can be detected only with 24-hour monitoring [35]. Transient occurrence of LVP in patients with VF was accompanied by acceleration of heart rate in the morning, changes in the ST segment or transient decrease in heart rate variability. The variability of the appearance of trace potentials within 24 hours may depend on patient's activity and autonomic nervous system status and explains the fact that sudden cardiac death usually occurs in the morning or early afternoon hours.

At the same time, some authors during the examination of 1.800 AMI survivors, did not reveal any significant correlation between LVP, life-threatening arrhythmias and sudden cardiac death. The authors concluded that LVP have no significant prognostic value and can be limitedly used for risk-stratification of patients [37].

LVP prognostic value have been demonstrated in the work of Pozdnyakova. et al: during 18 months after AMI 36 % of patients had recurrent AMI, 32 % of patients with LVP died, 20 % of which had sudden cardiac death [18]. 48.9 % of patients with post-infarction cardiosclerosis (PICS) and unstable angina had LVP and stabilizing of their condition led to the decrease of LVP frequency in patients with non-Q wave myocardial infarction from 46.7 % to 13.3 %, and in patients with the history of Q-wave AMI from 50 to 47 % [18].

LVP in patients with PICS can indicate the development of rhythm disturbances, possible disease complications (early post-infarction angina due to return and persistence of ischemia or peri-infarction myocardial ischemia), reduction of myocardial contractility. According to S. Boldueva. et al. LVP in most cases correlated with sustained ventricular tachycardia (74.1 %), LV aneurysm (61.0 %) and reduced EF (52.5 %) [36]. In the work of Pozdnyakova N.V. et al. patients with PICS and LVP had significantly bigger end-stystolic and end-diastolic volumes than patients without LVP. Residual potentials were detected in 65.6 % of patients with LV dilatation. The frequency of recurrent AMI in patients with PICS and LVP was 19.4 % (4.9 % in the control group) and mortality was 32.2 and 8.3 %, respectively [18]. AMI survivors with LVP had early post-infarction angina in 20 % and acute left ventricular failure in 24 % of cases, whereas patients without LVP had these complications in 10.2 % and 10.2 % of cases, respectively.

Interesting data have been published in the study of overweight patients. Increased body mass as well as arterial hypertension, hyperinsulinemia and insulin resistance compose the metabolic syndrome, which increases the cardiovascular complication risk. In addition, arterial hypertension, diabetes mellitus and dyslipidemia, which usually accompany the obesity

are independent risk factors of sudden cardiac death. Lalani A.P. et al. registered LVP in 55% of patients whose body mass index (BMI) exceeded 30 kg / m^2 and showed that the frequency of LVP directly correlated with the Quetelet's index value. Thus, LVP were registered in 35% of patients with a BMI of 31–40 kg/m^2, 86% of patients with a BMI of 41–50 kg/m^2 and 100% of patients with a BMI> 50 kg /m^2 [38].

The possibilities of late ventricular potentials correction

The works that study the effects of stress test, physiotherapeutic methods of treatment and medication treatment on LVP are particularly important. The study of SA-ECG individual dynamics in patients with CAD showed that physical activity can lead to the occurrence or cessation of LVP regardless of myocardial ischemia. The instability of late potentials was greater in the subgroup with PICS than in the subgroup with the history of MI [6, 7]. LVP during the initial SA-ECG monitoring do not affect the results of the stress test: ST-segment depression was registered in patients with chronic CAD with the same frequency as in patients with or without LVP.

There are many researches evaluating pharmacological and non-pharmacological VTA treatment effectiveness. The works on the LVP changes and effectiveness of VTA comparison of treatment are much more uncommon.

According to Boehrer J.D., Glamann D.B., et al. [39], even temporarily performed restoration of blood flow in the arteries that supply the infarction area in patients with acute myocardial infarction may decrease the frequency of future arrhythmias and the risk of sudden cardiac death. The study was conducted on 54 patients with AMI and angiographically confirmed coronary artery occlusion during the first 5 hours. 35 patients who underwent reperfusion (p = 0.038) had a significant decrease in the frequency (by 50%) of LVP occurrence. On the other hand, 19 patients after successful thrombolysis: 8 of 19 patients (42%) during the first 120 minutes of thrombolysis and 7 of 19 patients (37%) after the procedure did not show a significant decrease. Despite the successful performance of thrombolysis LVP persisted or appeared for the first time in 8 of 54 patients (15%). Thus, it can be concluded that successful thrombolysis decreases the frequency of late potentials during SA-ECG, but the sensitivity and specificity of this method is not enough to control the coronary flow during the post-occlusive period.

The frequency of LVP decreased significantly after systemic thrombolysis – from 68.6% during the first 24 hours to 31.4% (on the 10^{th} day) and to 11.4% (by the end of admission), whereas patients who did not underwent thrombolysis for some reason had LVP in 69%, 48.3% and 41.4% of cases respectively [37].

The influence of anti-anginal and antiarrhythmic therapy on the LVP development have been studied in many works [6, 7]. The patients with unstable angina after stabilization of their condition showed the «improvement» of some SA-ECG parameters and the decrease of LVP frequency, what can be connected with the decrease of myocardial electrophysiological inhomogeneity due to perfusion.

78 patients with recurrent VTA and CAD underwent intraoperative registration of LVP frequency in order to determine the scope and clinical significance of epicardial LVP. The ECG averaging was performed in 30 patients. Correlation of VT focus localization and the area of epicardial LVP development was not determined in 4 patients. On the other hand, the place of LVP development was in the immediate vicinity to the origin of VT in 5 patients (3 of them had polymorphic tachycardia). 76% of patients had low-amplitude LVP. 24 patients without post-operative VT showed the reduction of QRS complex duration (from 137±27 to 121±26 ms; p=0.003), the increase of the QRS complex voltage (from 16.5±16.1 to 39.0±29.4 mkV; p=0.003) and the decrease in LVP frequency (from 71% to 33%; p=0.03) after the angioplasty. Filtered QRS complex remained the same in 13 patients with post-operative VT. The absence of LVP after the surgery in 9 out of 10 cases correlated with the absence of VT (p<0.02) [40].

Early administration of pravastatin in patients with AMI reduces the risk of LVP and the probability of ventricular rhythm disturbances [36]. The frequency of LVP registration decreased from 52% to 16% during standard therapy in patients with unstable angina [36].

According to some data the frequency of LVP in patients with chronic CAD at the initial state and before the discharge was 31% and 25%, respectively. Comparing the quantitative criteria of LVP at the initial state and after the therapy no significant difference was found [6, 41]. This investigation confirms the inconsistency of data on the significance of LVP in patients with chronic CAD.

According to Akadysheva D. U. et al. IA, B, C classes of antiarrhythmic medications and amiodarone do not influence LVP parameters [6]. However, other works showed that amiodarone has positive influence

on SA-ECG parameters: as electro- impulse therapy, lidocaine or mexiletine administration suppressed the paroxysm of ventricular tachycardia, LVP succeeded after amiodarone administration [41]. The influence of beta-blockers (atenolol, bisoprolol, sotalol) on the electrical activity of ventricles have been studied: before the medication administration LVP have been detected in 68.6% of AMI survivors and by the 30th day only in 14.3%.

Consequently, many researches demonstrated high influence of LVP on the course of CAD and the estimation of therapy effectiveness. Coronary reperfusion and function of ischemic but viable cardiomyocytes improves and electrophysiological inhomogeneity of myocardium reduces during the medication treatment in patients with unstable angina and AMI.

The frequency of LVP registration significantly reduces after surgical revascularization and myocardium perfusion improvement (which can lead to the reduction of ischemic zone that is the main cause of LVP). In case of persistent ischemia (unsuccessful revascularization) LVP also stay permanent.

Conclusion

Late ventricular potentials can be the predictors of deterioration in the condition of the patient (CAD exacerbation), AMI development, rhythm disturbances, chronic heart failure progression or death. Dynamic LVP detection including the period of medication treatment can be used to prognose the course of CAD and to estimate the effectiveness of the therapy according to some investigations.

LVP are more effective when determined in combination with a number of structural, hemodynamic and functional parameters (systolic and diastolic LV function, heart rate variability, etc.) due to its uncertain predictive value when used separately. It is also possible to use the combination of time and spectral analysis of SA-ECG. Further research is needed in this area to clarify which analysis (time, spatial or spectral) is the most preferred to determine the LVP and which parameters for totQRS, RMS40, LAS-40 are more diagnostically accurate.

Such investigations can make the prognosis the undesirable disease development more accurate (including VTA and sudden cardiac death) and may identify the group of patients with high risk of sudden cardiac death. Pre-syncopal phase with unclear etiology, the history of SCD can be the signs to conduct SA-ECG.

SA-ECG can also be used separately as a method of early, pre-symptomatic and preclinical diagnosis of myocardial lesion due to several somatic diseases and as a method of estimation of cardiotoxic and pro-arrhythmogenic effects of some medications.

Consequently, LVP registration is an affordable, non-invasive method in diagnosing and predicting VTA in patients with acute myocardial infarction and other types of coronary artery disease, cardiomyopathies, patients with SCD risk, which can reduce the risk of sudden cardiac death if used widely. However, nowadays further investigations are needed to determine the range of diseases when it is reasonable to use this method to clarify the sensitivity, specificity and prognostic value of it, including the studies on applying LVP dynamics as the way to determine the effect of pharmacological and non-pharmacological treatment and surgical interventions.

Conflicts of interest: None declared.

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International Heart and Vascular Disease Journal • Volume 6, № 20, December 2018
Journal of the Cardioprogress Foundation

Left ventricular diastolic function characteristics in patients with chronic heart failure, in relation to the degree of chronic kidney disease, and their dynamics during treatment

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Objective. *To study the dynamics of left ventricular diastolic function (LV DF) in patients with I–III functional classes (FC) of chronic heart failure (CHF) during lisinopril and losartan treatment, depending on stage of chronic kidney disease.*

Materials and methods. *We examined 223 patients with coronary artery disease and I–III FC of CHF initially and after 6 months of treatment. The first group (I) contained 118 patients with I–III FC of CHF, who received lisinopril as a standard therapy, whereas the second group (II) received losartan, and included 105 patients with I–III FC of CHF (the average dose of lisinopril was 7.8 ± 2.6, losartan -76.3 ± 25.6 mg/day). All the patients underwent doppler echocardiography, glomerular filtration rate was quantified using MDRD formula (eGFR). Patients were divided into groups according to eGFR levels: 30<cGFR ≤60 mL/min/1.73 m^3 — 67 patients, and 156 patients with eGFR>60 mL/min/1.73 m^3.*

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Results. *The analysis of initial DF characteristics revealed diastolic dysfunction (DD) in 81.8 % of patients with CHF, and in 59.3 % of cases disturbances like delayed relaxation were prevalent. DF correlated with eGFR. Patients with eGFR≤60 mL/min/1.73 m² had significant reduction (by 6.8 %) of E-wave velocity (p<0.05) compared to patients with eGFR>60 ml/min/1.73 m²; there was a moderate positive correlation between eGFR and E-wave velocity. Patients improved their LV DF characteristics after treatment, with better results for losartan group. Patients of the first and second groups with eGFR≤60 ml/min/1.73 m² had an increase of E-wave velocity by 14.8 % and 15.7 % (p<0.02), respectively; patients with eGFR>60 mL/min/1.73 m² had a trend of E-wave increase by 2.7 % and 7.5 %, respectively, compared to baseline.*

Conclusion. *81.8 % of patients had DD with the prevalence of disturbances of delayed relaxation type. DF correlated with eGFR. Patients with I–III FC of CHF had an improvement of LV DF characteristics with better results for the group of losartan therapy. Patients of both groups with eGFR≤60 ml/min/1.73 m² had a significant increase of E-wave velocity during treatment.*

Keywords: *chronic heart failure, left ventricle diastolic function, renal dysfunction.*

Conflicts of interest: None declared.

Received: 08.08.2018 **Accepted:** 21.08.2018

Chronic heart failure (CHF) is one of the most prevalent, progressive and prognostically adverse cardiovascular disease and is one of the main causes of hospital admissions [1, 2]. The connection between cardiac and kidney pathology have captured scientists' attention a long time ago. The decrease of glomerular filtration rate (GFR) adversely affect the prognosis in patients with chronic heart failure (CHF) [3]. According to a number of authors, structural and morphological changes of left ventricle (LV) myocardium depend on the functional class of CHF and renal dysfunction. High frequency of diastolic dysfunction in patients with chronic kidney disease (CKD) is expected due to left ventricular hypertrophy (LVH), which is seen in half of patients in pre-dialysis with creatinine clearance of 15–35 ml/min according to a number of studies in European, Asian and Latin American nephrology centers [4].

Renal dysfunction (RD) progression is accompanied by the decrease of renal size, changes of left ventricular mass index (LVMI) and increase of eccentric hypertrophy of myocardium. Eccentric hypertrophy was associated with high creatinine level compared with patients with normal blood test values [4, 5]. Even though over the last years it became clear that supportive and kidney function refining therapy can improve prognosis in patients with CHF [5, 6, 7], there is not enough comparative researches on the effect of different groups of medications on heart diastolic function and kidney function in patients with CHF.

The objectives of this study were to investigate the correlation between left ventricular diastolic function (LV DF) and GFR and to estimate the effect of lisinopril and losartan treatment on LV DF, depending on CHF class and RD.

Materials and methods

The study included the examination of 223 patients with coronary artery disease and I–III FC of CHF initially and after 6 months of treatment. The first group (I) contained 118 patients with I FC (28), II FC (51) и III FC (39 patients) of CHF, who received lisinopril as a standard therapy, whereas the second group (II) received losartan, and included 105 patients with c I FC (22), II FC (49) и III FC of CHF (34 patients) of CHF (the average dose of lisinopril was 7.8 ± 2.6, losartan — 76.3 ± 25.6 mg/day). Average age of the patients was 62.3±5.6 years. The therapy included: statins, antiplatelet therapy, bisoprolol, spironolactone 25 mg per day, loop diuretics on demand. All the patients underwent doppler echocardiography with LV DF parameters estimation [8]: peak velocity of early left ventricular filling (E, m/s), peak velocity of late atrial filling (A, m/s), E/A ratio, isovolumetric relaxation time of LV (IVRT, ms), deceleration time of flow velocity during early left ventricular filling (DT, ms) and glomerular filtration rate, which was quantified using MDRD formula (eGFR) [9, 10]. Patients were divided into two groups according to eGFR levels: 30<cGFR ≤60 mL/min/1.73 m³ — 67 patients (29 in the first and 38 in the second group), and 156 patients with eGFR>60 mL/min/1.73 m³ (89 in the first and 67 in the second group).

Statistical analysis of obtained data was done using Microsoft Office Excel 2013, including the use of integral functions such as Statistica 6.0 software. We used a combination of parametric and non-parametric statistic methods with the calculation of the mean values of studied parameters (M), standard deviation (SD), standard error of the mean (m), relative values (frequency %). Statistical significance of the calculations in comparison of the average values was based on Student's test (t) with the calculation of the error probability (p) when checking the normality of distribution (according to the kurtosis criterion). Results were considered statistically significant if p-value was < 0.05. Pearson's test with the calculation of linear correlation coefficient was used for evaluation of correlation between quantitative variables.

Results and discussion

The analysis of initial DF parameters in patients with CHF revealed diastolic dysfunction (DD) in 81.1% of patients with CHF, the decrease of E-wave velocity, increase of A-wave velocity ($p<0.05$), the deviation of E/A ratio and the increase of IVRT time ($p<0.05$) compared with the control group. It is remarkable that the I type (delayed relaxation) of DD was detected in 59.3% (134 patients), the II type (pseudo normal) in 19.5% (44 patients) and III type (restrictive) in 3.1% (7) of patients. The initial parameters of LV DF were comparable in both groups of patients with I–III FC of CHF.

LV DF parameters in patients with I–III FC of CHF are presented in Table 1. E-wave velocity was 0.578±0.093, 0.601±0.136 and 0.684±0.372 m/s in patients with I–III FC of CHF respectively, and was significantly ($p<0.05$) higher (by 15, 5%) in patients with III FC of CHF; IVRT time was 89.38±8.63, 84.6±16.5 and 84.03±14.17 ms respectively and significantly decreased (by 5.7%) in patients with II and III FC of CHF by 5.7% ($p<0.05$) and 6.4% ($p<0.05$) respectively compared with the parameters in patients with I FC of CHF. DT time was 201.5±14.76, 181.1±36.8 and 177.15±42.88 ms in patients with I–III FC of CHF respectively and significantly decreased in patients with II and III FC of CHF by 11.3% ($p<0.001$) and 13.7% ($p<0.001$) respectively compared with patients with I FC of CHF.

The analysis of LV DF disturbances type in dependence of FC of CHF showed that patients with I FC of CHF had DF disturbances in 76% (38 patients) of cases in both groups. At the same time 58% of patients (29) had I type (delayed relaxation) of disturbances and 18% of patients (9) had II type (pseudo normal). Patients with II FC of CHF had DD in 80% (80 patients) of cases in both groups. I type (delayed relaxation) was detected in 60% of cases (60 patients), II type (pseudo normal) in 19% (19 patients) and III type (restrictive) in 2% (2 patients). Patients with III FC of CHF had DD in 81.2% of cases (60 patients) in both groups: I type (delayed relaxation) in 60.3% of cases (44 patients), II type (pseudo normal) in 21.9% (16 patients) and III type (restrictive) in 6.8% (5 patients).

GFR was 50.9±8.8 and 52.7±7.3 mL/min/1.73m^2 in patients of the first and second group with eGFR⩽60 mL/min/1.73 m^2 respectively; and — 79.6±14.8 and 76.96±14.1 mL/min/1.73 m^2 in patients with eGFR⩾60 ml/min/1.73 m^2 respectively. According to eGFR, patients had 1–3 stages of CKD. 54 patients (80.6%) had 3A stage of CKD and 13 (19.4%) patients had 3B stage of CKD among patients with 3 stage of CKD. DF and eGFR parameters had correlation: patients with eGFR ⩽ 60 mL/min/1.73 m^2 had significantly lower (by 6.8%) E-wave velocity ($p<0.05$) comparing with patients with eGFR> 60 mL/min/1.73 m^2. Patients with CHF with eGFR⩽60 and eGFR>60 mL/min/1.73 m^2 had moderate positive correlation between eGFR and E-wave velocity — r = 0.38 and r = 0.46, respectively.

DF parameters had tendency to improvement during lisinopril treatment in the first group of patients with I and III FC of CHF, but still did not reach the necessary reliability value. Patients with II FC of CHF had significant increase of E-wave velocity and E/A ratio by 12.6% ($p <0.005$) and 19.6% ($p <0.001$) respectively

Table 1. **Initial parameters of LV diastolic function in patients with I–III FC of CHF**

Parameter	All patients with c CHF (n=223)			All patients with c CHF (n=223)		
	I FC (n=50)	II FC (n=100)	III FC (n=73)	GFR⩽60mL/min/1.73 m^2 (n=67)	GFR>60mL/min/1.73 m^2 (n=156)	p
E, m\s	0.578±0.093	0.601±0.136	0.684±0.372*	57.8±9.03	61.7±13.4*	p<0.05
A, m\s	0.641±0.140	0.633±0.149	0.624±0.172	62.3±16.3	63.3±15.05	p>0.05
E/A	0.944±0.273	1.01±0.363	1.11±0.455*	0.946±0.385	1.036±0.397	p>0.05
IVRT, ms	89.38±8.63	84.6±16.5*	84.03±14.17*	86.3±12.98	85.04±14.97	p>0.05
DT, ms	201.5±14.76	181.1±36.8**	177.15±42.9**	187.3±37.21	183.0±35.8	p>0.05

* differences are significant ($p<0.05$) comparing with the patients with I FC,
** $p<0.001$

and decrease of A-wave velocity by 10.1% (p<0.02) comparing with baseline.

The II group of patients with I FC of CHF had significant increase of E-wave velocity peak and E/A ratio by 22.7% (p<0.001) and 28.4% (p<0.001), and the decrease of IVRT and DT by 4.6% (p<0.01) and 12.4% (p<0.001) respectively during losartan treatment. Patients with II FC of CHF had a decrease of A-wave velocity by 10.1% (p<0.05), and with III FC of CHF had an increase of E-wave velocity and DT by 12.6% (p<0.01) and 12.7% (p<0.05) respectively comparing with baseline. Improvement of E-wave velocity peak parameters was detected in both groups of patients with eGFR≤60 and eGFR> 60 mL/min/1.73 m^2 during treatment. E-wave velocity increased by 14.8% and 15.7% (p<0.02) in patients from the first and second group with eGFR≤60 mL/min/1.73 m^2 respectively during treatment. Patients with and eGFR> 60 mL/min/1.73 m^2 had tendency to increase of E-wave velocity by 2.7% and 7.5% comparing with baseline.

The results of our investigation of patients with CHF showed that RD can be revealed at the subclinical stage of the disease, when most patients don't have clinical signs of kidney failure. It is believed that RD develops in patients with CHF due to cardiac output decrease, followed by a decrease in arterial bed filling, renal hypoperfusion, increased renal vessels resistance and a decrease of renal blood flow [11]. However, a number of studies have shown that there is no correlation between the parameters of myocardial contractile function and RD in patients with CHF [3]. A number of authors have established that the main type of diastolic dysfunction in elderly and senile patients with diastolic HF is delayed relaxation [12, 13]. At the same time, they identified the features of structural and functional heart disturbances depending on the presence of CKD. It was established that reduced kidney function has an adverse effect on CHF course, which is connected with DF deterioration and, in particular, the increase of isovolumetric relaxation time in patients with I–II FC of CHF.

The positive effect of RAAS blockers can be explained by the reduction of initially high pressure in kidney glomeruli, which can stop the development of glomerulosclerosis [14, 15]. According to the results of some investigations (ORACLE-RF, etc.) ACE inhibitors and ARA have organ-protective and anti-remodeling effects [6]. Positive effects of RAAS blockers became the subject of special discussion after the publication of the LIFE and RENAAL investigations results [10, 14].

Consequently, the estimation of the correlation between the clinical course of the disease and structural and geometric parameters and the functional state of the kidneys is very important for early screening, disease course prognosing and treatment optimization [16].

Kidneys involvement can be considered to be the main factor of CHF progression and, thus, the idea of the kidney function maintenance for secondary prevention in CHF as the main determinant is very reasonable [5, 6, 17].

Conclusion

The analysis of initial DF characteristics revealed DD in 81.8% of patients with CHF, and in 59.3% of cases delayed relaxation type of disturbances were prevalent as well as restrictive type of DD disturbances were prevalent in patients with III FC of CHF. DF correlated with E-wave velocity and eGFR. Patients from the first and the second group with I–III FC of CHF improved their LV DF characteristics after 6-month treatment, with better results for losartan group in patients with I and III FC of CHF. Patients from both groups with eGFR≤60 mL/min/1.73 m^2 had significant reduction of E-wave velocity without statistically significant differences.

Conflict of interest: None declared

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International Heart and Vascular Disease Journal • Volume 6, № 20, December 2018

Journal of the Cardioprogress Foundation

Clinical and anatomical features of cardiac fat deposits

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Objective. *To analyze clinical and anatomical features of cardiac visceral fat deposits: epicardial fat and interatrial septum lipomatosis during the pathological examination.*

Materials and methods. *We analyzed the results of autopsy in 27 patients (15 females and 12 males) aged from 53 to 88 years. We estimated the thickness of epicardial fat (EF) and interatrial septum (IAS), prevalence and severity of atherosclerotic lesions of aorta and coronary arteries.*

Results. *Brain stroke was the cause of death in 44 % cases, and 11 % of death cases were due to myocardial infarction. Left coronary artery (LCA) had 40 % stenosis on average (30;50 %), right coronary artery had 44 % stenosis on average (40;60 %), and calcified atherosclerotic plaques were detected in 18 patients (66.6 %). Average EF thickness was 14 millimeters (10; 15) and ranged from 5 to 20 millimeters. Average thickness of AS was 10 millimeters (7;15) and ranged from 4 to 20 millimeters.*

Histological study demonstrated that epicardial fat represented a single layer of adipose tissue surrounding right coronary artery and sinus venosus, and that lipocytes of the EF inner layer grew between the bundles of myocardial muscle fibers.

Adipose tissue permeates the peripheral part of IAS myocardium, which creates a picture of altered bands of muscle and adipose tissue during microscopic examination.

Adipose tissue infiltrates the zone of the greatest thickness of IAS in a range from 30 % to 70 %. We detected a correlation between interatrial and interventricular septum thickness (r=0.47; p=0.012), whereas females demonstrated a correlation between left ventricular mass (r=0.67; p=0.023) and AS thickness.

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Males had a positive correlation between thickness of IAS and blood level of triglycerides (r=0.77; p=0.001). A positive correlation between epicardial fat thickness and left ventricular thickness was also detected (r = 0.59; p = 0.042).

Conclusion. *The thickness of IAS lipomatosis and the thickness of epicardial fat tissue correlates with triglyceride blood level, left ventricular myocardial hypertrophy, and calcification of coronary arteries in autopsy.*

Keywords: *epicardial fat, lipomatosis of interatrial septum*

Conflicts of interest: nothing to declare.

Received: 03.10.2018 **Accepted:** 06.10.2018

Introduction

Local fat deposits attract close attention of clinical practitioners nowadays, for example, some of them suggest to use epicardial fat (EF) as a new marker of cardiovascular diseases [1]. EF plays role in the development of left ventricular myocardial hypertrophy, coronary atherosclerosis, diastolic function disturbances and fibrosis of cardiomyocytes [2, 3, 4]. Lipomatosis hypertrophy of interatrial septum and its role in the development of cardiovascular diseases is studied less by Russian authors.

Interatrial septum lipomatosis or lipomatosis hypertrophy of interatrial septum (LHIAS) is asymptomatic in most cases and is usually seen in elderly and obese patients. The association between LHIAS, supraventricular rhythm disturbances [5, 6, 7, 8] and sudden cardiac death causes the greatest clinical interest [9]. LHIAS prevalence range from 2% to 8% during transthoracic and transesophageal echocardiography respectively, however, true prevalence is unknown [10].

Hypertrophied interatrial septum due to lipomatosis has a «dumbbell» shape during a visualization with two-dimensional echocardiography or computer tomography (CT). Figures 1 and 2 represent the anatomy of IAS normally and during LHIAS.

The question of determining the thickness of interatrial septum (IAS) thickness, when it can be considered to be hypertrophied, is controversial. One study showed that IAS thickness of adipose tissue normally is about 0–9.6 mm anterior and 0–9.9 mm posterior to foramen ovale during the CT [11]. The study of J.D.Gay was dedicated to LHIAS and included patients with IAS thickness less than 1.0 sm [9]. We chose the thickness of 10 mm and more as a marker of lipomatosis hypertrophy, even though some foreign authors chose 20 mm and more.

We did not find any clinico-anatomical studies of local cardiac fat deposits in available domestic literature, when foreign articles mostly describe clinical cases of this disorder.

Objective

To analyze clinical and anatomical features of cardiac visceral fat deposits: epicardial fat and interatrial septum lipomatosis during the pathological examination.

Materials and methods

We analyzed the results of autopsy in 27 patients (15 females and 12 males) aged from 53 to 88 years (median age is 74 (64; 79) years).

During the pathological examination we estimated EF, which was localized perpendicular to the aortic ring along the AS posterior edge and the interventricular septum (IVS). The thickness of IAS was measured at the upper posterior edge of foramen ovale. Furthermore, we estimated the prevalence and severity of atherosclerotic lesions of coronary arteries.

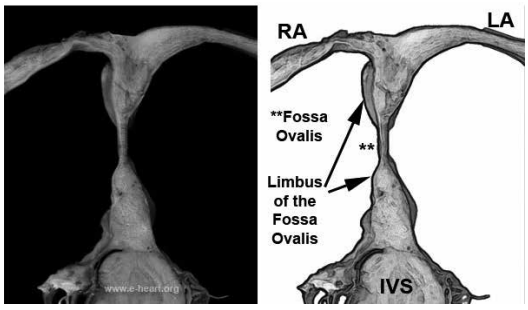

Figure 1. The anatomy of interatrial septum normally (taken from http://www.e-heart.org)

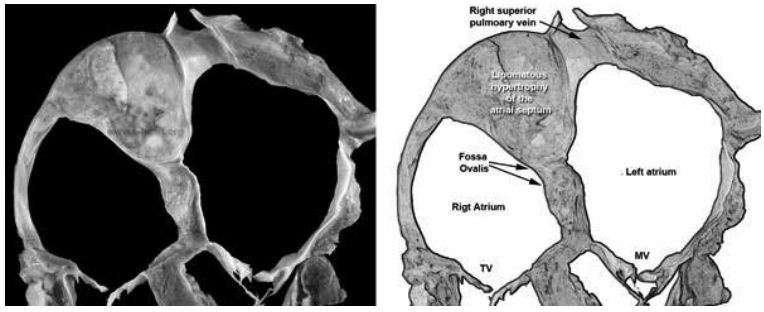

Figure 2. The anatomy of interatrial septum during LHIAS (taken from http://www.e-heart.org)

During the estimation of IAS thickness, we measured diameter of the tissue surrounding foramen ovale (FO) at the upper posterior area. IAS was dissected with transverse diametrical section through FO parallel to fibrous ring. Adipose tissue which surrounds foramen ovale is represented at the section (Figure 3).

The thickness of epicardial adipose tissue was measured at the section from the posterior heart wall along the right edge of IAS and IVS at the coronary sulcus area at the level of inferior coronary sinus wall (Figure 4).

The picture represents the dissected strip of the right ventricular posterior wall along the interventricular septum, the arrows at the cross section point at the level of epicardial fat thickness determination at the coronary sulcus area and along the inferior edge of coronary artery and sinus venosus.

Figure 5 represents the dissection of the heart by A. I. Abrikosov method, and the arrows point at the sections, in which the epicardial fat thickness and the thickness of the tissue surrounding foramen ovale, which represents the lipomatosis hypertrophy of AS, is measured.

Histological examination of all studied heart zones was conducted by standard histological processing of the tissue, followed by hematoxylin and eosin staining.

Statistical analysis was performed using Statistica 10.0 software (StatSoft, Inc., USA). Quantitative parameters are present as median values (Me) and quartiles (25%, 75%). Qualitative parameters are present as frequencies or fractions (in %). Analysis of correlation between two variables was done using Spearman's rank correlation test (r). The level of significance (p) was taken as 0.05.

Results and discussion

Table 1 represents causes of death in patients, where cardiovascular diseases are prevalent.

Table 1. **Causes of death**

Cause of death	Number of patients
Acute cerebrovascular accident	12
Myocardial infarction	3
Cardiosclerosis	2
Lung cancer	2
Chronic glomerulonephritis	1
Chronic bronchitis	1
Chronic obstructive pulmonary disease	1
Pulmonary embolism	1
Endometrial cancer	1
Pleural mesothelioma	1
Breast cancer	1
Encephalopathy	1
TOTAL	27

Figure 3. Dissected AS with radial section from the center of foramen ovale to upper posterior edge

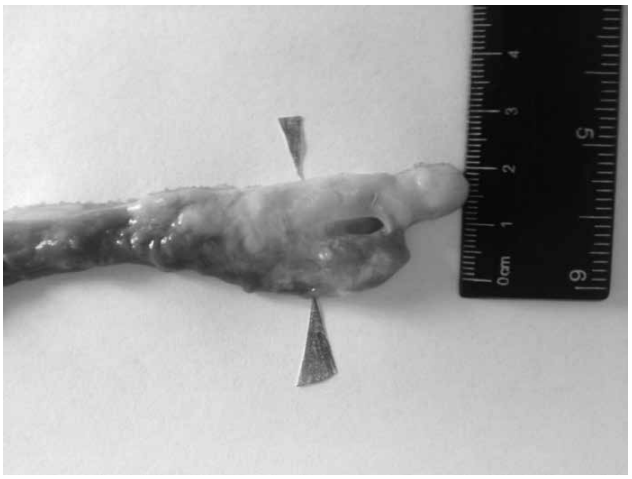

Figure 4. Epicardial fat thickness determination

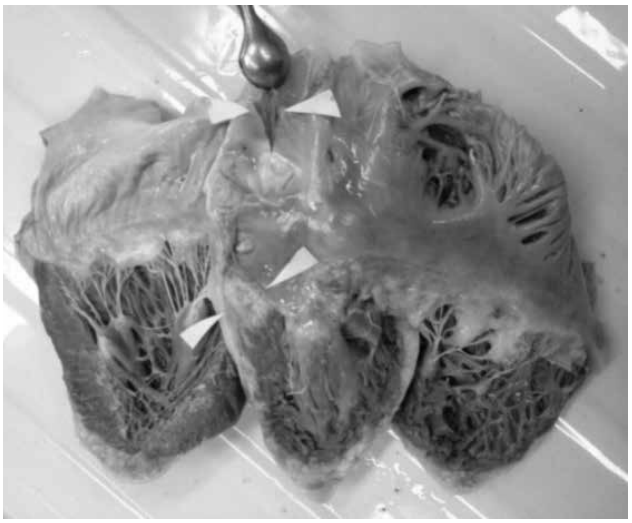

Figure 5. Measurement of IAS thickness (upper arrows) and EF (distal arrows) during autopsy

In addition to the diseases, which caused death, one third of patients had type 2 diabetes, 9 patients had postinfarction cardiosclerosis (33.3 %), 14 patients had arterial hypertension (52 %), 6 patients had heart rhythm disturbances, interatrial fibrillation in particular (22.2 %).

During the pathological examination aortic atherosclerotic plaques occupied 35 (30; 40) % of the area, at the same time, the prevalence of atherosclerotic coronary arteries lesions reached about 90–100 % (50 (35; 60) % for right coronary artery (RCA) and 35 (30; 60) %) for left coronary artery (LCA)). LCA and RCA had 40 (30; 50) % and 44 (40;60) % coronary stenosis, respectively, and calcification of atherosclerotic plaques was found in 18 patients (66.6 %).

Total heart weight was 470.5 (371; 604) g, net heart weight was 374 (258; 471) g, LV mass was 130 (94; 185) g, right ventricular (RV) mass — 69 (54; 90) g, IAS thickness — 17 (14; 19) mm and RV thickness — 3 (3; 5) mm.

The thickness of EF ranged from 5 to 20 mm, and its average value was 14 (10;15) mm. The average IAS thickness was 10 (7;15) mm (ranged from 4 to 20 mm). Lipomatosis of IAS was revealed in 16 patients, in which IAS thickness was ⩾ 10 mm. There were no significant gender differences in the thickness of cardiac fat deposits.

Histological study of posterior heart wall sections at the coronary sulcus area demonstrated that EF represented a single layer of adipose tissue between myocardium and epicardium surrounding RCA and sinus venosus. Epicardium represents a thin layer of fibrous fibers, covered by mesothelium and located at the outer layer of EF tissue. The inner layer of EF is adjacent to myocardium and forms rough boundary line due to lipocytes growth between the bundles of myocardial muscle fibers. The absence of fascia between myocardium and EF allows biologically active substances, such as proinflammatory cytokines, to penetrate into the coronary blood flow from adipose tissue, what causes changes in the walls of coronary arteries, leading to atherosclerosis development [12], and plaque instability in patients with CAD.

During the description of IAS cross sections histological examination results, it is important to mention the following observations. IAS had variable thickness on both sides of the sections due to a layer of fibrous connective tissue. Subendocardial fibrosis represented even wider layer of fibrous tissue at the left atrial area, where cardiomyocyte complexes with irregular shape (mainly fan-shaped and x-shaped) were found among the fibrous fibers, which were spread from FO to periphery. In some cases, small lymphocytic and histiocytic infiltration was observed mostly under the layer of subendocardial fibrosis. Muscular fibers of active myocardium were located at the IAS between subendocardial layers of fibrous tissue and spread from the peripheral zone of the greatest thickness to foramen ovale. Cardiomyocytes had different extent of hypertrophic and dystrophic changes. Adipose tissue permeates the peripheral part of IAS myocardium, which creates a picture of altered bands of muscle and adipose tissue during microscopic examination.

Wider layers of adipose tissue are mostly localized at the inner layer of IAS. There is no lipomatosis of Myocardium at the FO region. Adipose tissue infiltrates the zone of the greatest thickness of IAS in a range from 30 % to 70 %. Consequently, the main reason of the increase of IAS thickness is lipomatosis, and other causes include hypertrophy and swelling of cardiomyocytes.

Since LHIAS is caused more by adipocyte proliferation, than by its hypertrophy, some authors discuss the new name of this pathology, but it is still fair to call it «lipomatosis hypertrophy of interatrial septum». During the correlation analysis, the correlation between interatrial and interventricular septum thickness was detected (r=0.47; p=0.012), whereas females also demonstrated a correlation between left ventricular mass (r=0.67; p=0.023) and IAS thickness.

Males had a positive correlation between thickness of IAS and blood level of triglycerides (r=0.77; p=0.001). We also detected a positive correlation between EF thickness and LV thickness in females (r=0.61; p=0.015) and calcinosis of LCA in males (r=0.59; p=0.042), what confirms the data on the role of epicardial obesity in atherosclerotic lesions of the coronary arteries [3, 12, 13, 14, 15]. According to other investigations, by the results of autopsy, epicardial fat mass correlated with heart mass, and atherosclerotic plaques of the coronary arteries had tendency to be more prominent on the arterial wall, which had contact with EF deposits [16].

Conclusion

According to the correlation of cardiac fat deposits, which were determined using the thickness of IAS lipomatosis and the thickness of epicardial fat tissue, triglyceride blood levels, left ventricular myocardial hypertrophy, and calcification of coronary arteries in autopsy, cardiac fat deposits of visceral adipose tissue can be used as markers of cardiovascular risk in patients.

Conflict of interest: None declared.

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International Heart and Vascular Disease Journal • Volume 6, № 20, December 2018

Journal of the Cardioprogress Foundation

Stress at work in open urban population of different age and gender groups

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Objective. *To study the prevalence of certain stress parameters in a workplace in men and women aged 25–64 years of open urban population in Tumen.*

Materials and methods. *The study was based on cardiological screening among a representative sample of population, the response amounted to 77.7%. The sample of 2000 people was taken from the electoral lists of one of the administrative districts of Tumen and divided into four groups of different age and gender (25–30, 35–44, 45–54, 55–64 years), consisted of 250 persons each. Stress at work was determined using the WHO MONICA psychosocial questionnaire.*

Results. *The results of investigation showed that changes in working specialties were more common in men aged 25–34 and 35–44 years compared to women of the same age. Elder men had significantly less side work compared to younger age groups, it is remarkable that men of elder age significantly diminished the amount of side work compared to women of the same age.*

Conclusion. *The results obtained in this study conducted in unorganized population of Tyumen may be used as the scientific basis for organizing complex socially oriented preventive programs in other moderately urbanized*

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Siberian cities with the main focus on the needs of risk groups — men of young and elder age and women aged 45–54 years.

Keywords: *stress at work, open urban population, gender differences.*

Conflicts of interest: nothing to declare.

Received: 05.10.2018 **Accepted:** 08.11.2018

Many researches have shown, that sometimes every person undergoes stress at work, which is accompanied by many negative factors, such as overwork, physical weakness, loss of concentration, and loss of control. Every specialist has different reaction to stress. It depends on person's character, changes in the workplace, job satisfaction, amount of responsibility during work [1, 2, 3, 4].

According to a global study by World Health Organization, every fourth employee (23 %) has five or more symptoms of depression, only 14 % are truly involved at work and only 12 % show general optimistic attitude. 92 % of research participants admitted, that their psychological state is determined by the results of their work, and not by internal resources, such as, for example, self-reliance [5, 6]. The problem of stress exists in all countries. Thus, in the United States, 20 % of the costs and losses, which are associated with staff turnover, absenteeism, resistance to organizational changes and productivity decrease, are caused by professional neuroses and stresses. Americans claim, that damage from stress factors is about 500 million dollars a year. 33 % of Canadian employees reported, that they had to take days off at their own expense, because they felt exhausted. Another 27 % would do the same, if they were not afraid to lose their job [5, 7].

According to analysts, every third worker at least once a week experiences severe stress in Russia, and 13 % of workers have stress almost every day, and despite this fact, not enough attention is paid to the problem of stress at work nowadays. This leads to a decrease in economic efficiency of the organization, industry in general, and, ultimately, of the government's work. First of all, it is necessary to carry out preventive measures aimed at creating positive work environment for the prevention of occupational stress. Thus, it will increase the productivity and efficiency of employees.

Chronic or acute psycho-emotional stress is the central link in psychosomatic relationships. On the one hand, it connects psychological and social adverse factors and, on the other hand, it also connects psycho-physiological processes, which are involved in pathogenesis of cardiovascular diseases (CVD). Stress at work is one of the most important factors of chronic social stress in working population together with the stress in family, however, gender differences of stress at work in Russian populations are not studied enough, which makes planning and control of preventive measures effectiveness more difficult. The realization of these tasks can be more effective by taking into account the gender characteristics and their prevalence in the population.

The objective of this study was to determine the prevalence of certain stress parameters in a workplace in men and women aged 25–64 years of open urban population in Tumen.

Materials and methods

The study was conducted in the framework of cardiological screening among men and women aged 25–64 years belonging to the open urban working population of Tyumen. A representative population, that involved 2000 participants, was taken from the electoral lists of one of the administrative districts of Tyumen, and included 250 men and women of each age group (25–34, 35–44, 45–54, 55–64 years), the response amounted to 77.7 %.

Questioning of participants was conducted using WHO-MONICA psychosocial questionnaire «Knowledge and attitude towards their health» [8]. Questions of the questionnaire were accompanied by a list of fixed answers, from which the respondents could choose the most correct answer, by their opinion.

Statistical analysis was done using SPSS 11.5 Statistics, Statistica 7.0 software and Microsoft Excel spreadsheets, according to the methods of variance statistics.

In order to conduct correct comparative analysis with the results of other epidemiological studies, we performed standardization of variables using direct standardization method. To standardize obtained data during analysis we used the age structure of Russian urban population between 25 and 64 years.

The research data for categorical variables are represented in fractions (percent) for eight groups in general for men and women, divided by age, gender and by decades of life. Pearson's chi-squared test was used to determine the statistical significance of the results between different groups. Bonferroni correction was used to eliminate the problem of multiple comparisons, i.e. eliminate type I error (conclusion, that groups have differences, when they actually do not) during paired comparing of average values between four or more independent groups.

Results

There were no statistically significant differences, when answering the question «Do you like your work?» depending on age in men and women of open urban population aged 25–64 years.

Changes in working specialties over the last 12 months were significantly more common in men aged 25–34 and 35–44 years compared to women of the same age groups: 25–34 years (47.7 % — 35.2 %, p<0.05) and 35–44 years (43.4 % — 29.5 %, p<0.01). Statistically significant gender differences were determined in a general population (ASV: 41.2 % — %, p<0.01).

Statistically significant differences in men subpopulation were determined when answering the question «Did your workload change over the last 12 months?». Thus, men aged 55–64 years answered «I started doing additional work» significantly less frequently compared with men of different age groups (25–34 years: 16.4 % — 40.9 % p<0.001), (35–44 years: 16.4 % — 38.3 % p<0.001), (45–54 years: 16.4 % — 32.0 % p<0.001), and with general men subpopulation aged 25–64 years (16.4 % — 31.6 %, p<0.001). Meanwhile, men aged 55–64 years did significantly less additional work compared with women of the same age (16.4 % — 29.0 %, p<0.01). Another answer «I stopped or started doing less additional work» was more common in men aged 55–64 years compared with men of other age groups (25–34 years: 36.9 % — 18.8 % p<0.001), (35–44 years: 36.9 % — 18.5 % p<0.001), (45–54 years: 36.9 % — 11.7 % p<0.001) and with general men subpopulation aged 25–64 years (36.9 % — 21.3 %, p<0.001). Men aged 55–64 years started doing less or stopped doing additional work compared with women of the same age group (36.9 % — 20.1 %, p<0.001). Statistically significant gender differences were determined, when answering the question about changes in workload over the last year in the age group of 45–54 years: 11.7 % — 22.5 %, p <0.01 of men and women, respectively, answered «I started doing less or stopped doing additional work»; and 56.3 % — 40.0 %, p<0.01 answered «It didn't change» (table 1).

Consequently, current study has shown, that changes in working specialties were more common in men aged 25–34 years and 35–44 years compared with women of the same age. Elder men had significantly less side work compared to younger age groups, it is remarkable that men of elder age significantly diminished the amount of side work compared to women of the same age.

Table 1. **Stress at work in open urban population of different age and gender groups**

Question / Attitude	Age groups (years)										
	25–34		35–44		45–54		55–64		25–64		ASV
	Abs	%	Abs	%	Abs	%	Abs	%	Abs	%	%
1. Did your specialty change over the last 12 months?											
Yes	84/43	47.7/35.2*	99/61	43.4/29.5**	81/64	35.1/40.0	77/65	36.0/30.4	341/233	40.2/33.1	41.2/33.8**
No	92/79	52.3/64.8	129/146	56.6/70.5	150/96	64.9/60.0	137/149	64.0/69.6	508/470	59.8/66.9	58.8/66.1
2. Did your workload change over the last12 months?											
I started doing additional work	72/45	…40.9/36.9	87/78	…38.3/37.7	74/60	…32.0/37.5	35/62**	16.4/ 29.0	268/245	…31.6/34.9	34.0/35.6
It didn't change	71/55	40.3/45.1	98/92	43.2/44.4	130/64	56.3/40.0**	100/109	46.7/50.9	399/320	47.0/45.5	47.1/45.0
I stopped or started doing less additional work	33/22	…18.8/18.0	42/37	…18.5/17.9	27/36	…11.7/22.5**	79/43	36.9/ 20.1**	181/138	…21.3/19.6	19.5/19.4

Comment: 1. Significance of differences between men and women is signed with (*) in the upper right corner of the table cell statistically; 2. Significance of differences between men of different age groups and men aged 55–64 years is signed with (*) in the lower left corner of the table cell; * — p <0.05; ** — p <0.01; *** — p <0.001; 3. ASV — age-standardized variable.

Discussion

The problem of stress prevention and management has been studied for more than 40 years in economically developed countries. American researchers were the first ones who noticed the problem of stress. The statistics on how much stress affects American society was published at the end of the last century in the US. They noticed that the reason for chronic colitis in 90% of people was stress. Heart attacks and other cardiovascular diseases, in the development of which stress is the main factor, are the cause death in 50% of cases in the US. The increase of stress pressure has been noticed by the scientists and clinical practitioners of different specialties in Russia and other countries [8, 9, 10]. The influence of social stress factors, including stress at work, on the cardiovascular risk and prognosis was mentioned by the European society of cardiology in 2012 for the first time in their guidelines on CVD prevention in clinical practice, and in 2016 the influence of stress on CVD prevention was reported [11].

The results of the current study are reasonable according to previous data on conventional and non-conventional CVD risk factors in Tyumen population. Thus, open urban male population aged 25–64 years had a decrease of positive attitude to its health, tendency to increase of complaints, and responsibility for maintenance of their health [12, 13], what could be the reason for the tendency of workload decrease in elder men. Furthermore, Tyumen men aged 25–64 years had tendency to increase of personal anxiety, depression, sleep disturbances, hostility and exhaustion with the increase of age, and reached maximum at the age of 55–64 years, that undoubtfully resulted from the stress levels in the studied open population.

According to another study in Tyumen population, senior positions of women and hard physical labor of men and women had the highest impact on cardiovascular mortality [16]. Thus, additional work in women, as the stress manifestation in the workplace, is probably a negative factor, which can influence attributable and relative CVD risk and mortality in women.

Conclusion

The results obtained in this study conducted in unorganized population of Tyumen may be used as the scientific basis for organizing complex socially oriented preventive programs in other moderately urbanized Siberian cities with the main focus on the needs of risk groups — men of young and elder age and women aged 45–54 years.

Conflict of Interest: None declared.

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International Heart and Vascular Disease Journal • Volume 6, № 20, December 2018

Journal of the Cardioprogress Foundation

Results of the most important clinical trials presented at the Congress of the European Society of Cardiology 2018

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A report on all five scientific sessions of the Hot Line sessions of the Congress of the European Society of Cardiology 2018 (Munich, Germany), dedicated to the results of new clinical research in cardiology, is presented.

Keywords: *cardiology, clinical trials, Hot Line sessions.*

Conflicts of interest: nothing to declare.

Received: 05.09.2018 **Accepted:** 26.09.2018

The Congress of the European Society of Cardiology 2018 took place in Munich (Germany) from 25th to 29th of august 2018 with the participation of about 32000 delegates from 156 countries and included 587 scientific sessions. 17 most important clinical trials were selected for 5 Hot Line sessions and were presented for the first time.

Hot Line session I (august 26, 2018)

12019 patients, who were admitted to hospital for 3–10 days with heart failure and ejection fraction of the left ventricle ≤45 %, acute respiratory failure, acute exacerbation of chronic obstructive pulmonary disease, ischemic stroke, infectious or inflammatory disease, including rheumatic diseases, with high risk of venous thromboembolism according to IMPROVE risk assessment model (≥ 4 score or higher or a score of 2 or 3 plus a plasma D-dimer level more than twice upper than normal limit according to the criteria of the local laboratory) took part in double randomized **MARINER** trial [1]. At hospital discharge, patients were randomized to rivaroxaban (n=6007) or placebo

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(n=6012) prescription for 45 days. 10 mg of rivaroxaban was prescribed (with a creatinine clearance ≥50 mL/min) with dose adjusted down to 7.5 mg (in those with a creatinine clearance of 30 to less than 50 mL/min) once a day.

The primary outcomes, symptomatic venous thromboembolism (deep vein thrombosis, pulmonary embolism, death from venous thromboembolism), occurred in 0.83% cases in the rivaroxaban group compared with 1.10% of cases in the placebo group (relative risk — RR 0.76 with 95% confidence interval — CI from 0.52 to 1.09; p = 0.14), and symptomatic non-fatal deep vein thrombosis or non-fatal pulmonary embolism occurred in 0.18% and 0.42% (RR 0.44 with 95% CI from 0.22 to 0.89; p = 0.023) of patients, respectively. Separate evaluation of the results in accordance with the initial kidney function showed, that the efficiencies of low dose of anticoagulant (7.5 mg / day) and placebo (p = 0.994) are equal. Major bleedings occurred in 0.28% of the rivaroxaban group and 0.15% of patients of the placebo group, small clinically significant bleedings were more common during rivaroxaban treatment (1.42% compared with 0.85%, RR 1.66 with 95% CI from 1.17 to 2.35; p = 0.004).

Rivaroxaban 45-day after discharge treatment in patients with severe diseases didn't show any significant risk of symptomatic thromboembolism or death from venous thromboembolism decrease compared with placebo.

The **CAMELIA-TIMI 61** [2] study included overweight or obese patients with atherosclerotic cardiovascular disease or multiple cardiovascular risk factors to receive either 10 mg of lorcaserin twice a day (n=5135) (selective agonist of 5-HT2C receptors of serotonin, which regulates appetite, decrease weight in overweight and obese patients) or placebo (n=5083). At 1 year, weight loss of at least 5% had occurred in 38.7% of patients in the lorcaserin group and in 17.4% of patients in the placebo group (odds ratio, 3.01 with 95% CI from 2.74 to 3.30; p<0.001). However, at the end of the trial an average body weight difference in observed patients from lorcaserin and placebo group was about 1.9 kg.

During a median follow-up of 3.3 years, the primary safety outcome of major cardiovascular events (a composite of cardiovascular death, myocardial infarction, or stroke) was registered with the frequency of 6.1% in lorcaserin group and 6.2% in the placebo group (RR 0.99 with CI from 0.85 to 1.14; p< 0.001 for «not worse»). Lorcaserin caused previously known side effects — dizziness, fatigue, headache, nausea, and also an increase in the number of patients with severe hypoglycaemia (p=0.04) and, furthermore, the decrease of diabetes mellitus risk — 8.5% compared with 10.3% (RR 0.81 CI from 0.66 to 0.99) of cases. The risk of pulmonary hypertension development (1.6% compared with 1.0%; p = 0.26) and valvulopathy (1.8% compared with1.3%; p = 0.24) were not statistically significantly different in the lorcaserin and placebo groups, respectively.

Lorcaserin is the first medication for the reduction in weight with proven efficacy and cardiovascular safety. Lorcaserin contributes to sustained reduction in weight without increasing the incidence of major cardiovascular events compared with placebo in the group of overweight or obese patients with high cardiovascular risk.

Authors of double-blind placebo-controlled multicentral **ARRIVE** [3] trial assessed the efficacy and safety of aspirin among those at moderate estimated risk of a cardiovascular event (20–30% in 10 years) compared with placebo. The investigation included men aged ≥55 years with ≥2 and women aged ≥60 years with ≥3 risk factors, excluding patients with high risk of gastrointestinal and other types of bleedings or with diabetes mellitus. Patients at moderate risk of coronary heart disease were randomized to aspirin with enteric coating 100 mg daily (n = 6.270) or placebo (n = 6.276).

The primary efficacy outcome — time until first adverse event (cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischemic attack) occurred in 4.29% of the aspirin group compared with 4.4% of the placebo group (RR 0.96 with 95% CI from 0.81 to 1.13; p = 0.6038). Gastrointestinal bleeding (the primary safety outcome) occurred in 0.97% of patients of the aspirin group versus 0.46% in the placebo group (RR 2.11 with 95% CI from 1.36 to 3.28; p = 0.0007), but most of them weren't severe.

General frequency of adverse outcomes during the ARRIVE trial was lower than expected, which seems to be associated with effective background control of risk factors, which shifted the risk in the observed cohort from moderate to low, hindering the positive effect of aspirin as a medication of primary prevention. Soon after the ASPREE project demonstrated again negative results on aspirin use for primary prevention in the elderly people [4–6].

Hot Line session II (august 26, 2018)

Randomized **ASCEND** trial [7] aimed to determine whether aspirin administered100 mg daily is effective

for primary prevention of cardiovascular events in 15.480 patients with diabetes (type II in 94 % of cases) compared with placebo.

Primary efficacy outcome (first MI, stroke or transient ischemic attack or vascular death, excluding confirmed intracranial haemorrhage) occurred less frequently in the aspirin group compared with placebo — 8.5 % versus 9.6 % of cases (RR 0.88 with 95 % CI from 0.79 to 0.97; p = 0.01) during extended follow-up of 7.4 years. The key safety outcome (first severe bleeding — intracranial haemorrhage, sight-threatening eye bleeding, gastrointestinal bleeding or any other serious bleeding episode) were more frequent in the aspirin group (4.1 %) compared with placebo (3.2 %) (RR 1.29 with 95 % CI from 1.09 to 1.52; p = 0.003), remarkably, gastrointestinal bleedings were prevalent. There were no significant differences between aspirin group and placebo in accordance to gastrointestinal cancer morbidity (2.0 % versus 2.0 % — RR 0.99 with 95 % CI from 0.80 to 1.24) and other types of cancer (11.6 % and 11.5 %, respectively — RR 1.01 with 95 % CI from 0.92 to 1.11), but in order to confirm / eliminate the preventive effect of aspirin, follow-up will continue for many years.

The use of aspirin prevented serious vascular events in people with diabetes and without obvious cardiovascular diseases, but also caused large bleedings, which counteracted the benefits of therapy.

The second part of **ASCEND** project [8] was to estimate the role of omega-3 fatty acid in primary prevention of cardiovascular events in patients with diabetes. The participants (n = 15 480) of the study were randomized to 1 g of omega- 3 fatty acid (group omega-3 of fatty acid) daily and olive oil (placebo group). During extended follow-up of 7.4 years and adherence rate of 76 % the primary efficacy outcome, major adverse cardiovascular events (vascular death, myocardial infarction, or stroke or transient ischemic attack), occurred in 8.9 % of the omega-3 group compared with 9.2 % of the placebo group (RR 0.97 with 95 % CI from 0.87 to 1.08; p = 0.55). General major adverse cardiovascular event or revascularization of any arteries was 11.4 % versus 11.5 % (RR 1.00 with 95 % CI from 0.91 to 1.09) and all-cause mortality was 9.7 % versus 10.2 % (RR 0.95 with 95 % CI from 0.86 to 1.05) during omega-3 fatty acids intake versus placebo intake, respectively. There were no significant differences between compared groups in accordance to the frequency of serious side effects.

Despite these data, the results of ongoing VITAL and STRENGTH studies, evaluating the efficacy of a high dose of omega-3 fatty acids (4 g / day), are expected to be optimistic, as the REDUCE-IT project with the use of high dose of eicosapentaenoic acid has recently completed with a positive result.

The **ART** trial included 3202 patients, who were randomized to bilateral internal thoracic artery (n = 1.548) and one veins versus single internal thoracic artery and two veins (n = 1.554) bypass grafting. During the follow-up the primary endpoint (survival in 10 years) occurred in 329 cases in the group of single internal thoracic artery and in 315 cases in the group of bilateral internal thoracic artery (RR 0.96 with 95 % CI from 0.82 to 1.12). There were no differences between groups in accordance to severe cardiovascular events occurrence (death, myocardial infarction, stroke) in 10 years. The results of the study were distorted by the fact, that more than one third of the patients underwent the opposite operation to the one, that was initially prescribed. The outcome of coronary artery bypass grafting using two internal thoracic arteries was significantly influenced by the experience of surgeons — a higher experience was associated with decreased mortality.

According to the authors of the study in 80 % of cases coronary artery bypass grafting using two internal thoracic arteries is preferable. However, this technique is associated with high risk of infectious complications in patients with severe obesity or diabetes.

Hot Line session III (august 27, 2018)

The **ATTR-ACT** [9] study estimated the effectiveness and safety of tafamidis, new non-steroidal anti-inflammatory drug, which can inhibit amyloidogenesis in patients with transthyretin amyloid cardiomyopathy. 441 patients with family amyloidosis due to pathogenic mutations, and with wild-type of transthyretin amyloid cardiomyopathy, typical changes during the echocardiography study, transthyretin amyloid detection during biopsy and N-terminal pro brain natriuretic peptide plasma concentration ⩾ 600 mg/mL, 6-minute walk test distance > 100 meters took part in the study. Patients were randomized in the ratio of 2:1:2 to receive 80 mg of tafamidis daily, 20 mg of tafamidis daily or placebo for 30 months. During the follow-up all-cause death and cardiovascular-related hospitalizations (the primary endpoint) was significantly lower in 264 patients of tafamidis groups compared with 177 patients of the placebo group (p <0.001). Tafamidis significantly reduced total mortality (29.5 % versus 42.9 %) compared with placebo group (RR 0.70

with 95% CI from 0.51 to 0.96; p = 0.0259) and the frequency of cardiovascular-related hospitalizations (RR 0.68 with 95% CI from 0.56 to 0.81; p <0.0001). Tafamidis treatment slowed the decrease in the distance of 6-minute walk test (p <0.001) and the quality of life index according to the Kansas City cardiomyopathy Questionnaire (p <0.001). The frequency and side effects types were not significantly different in the group of tafamidis versus placebo group. The advantages of tafamidis did not depend on the aetiology of amyloidosis (hereditary or wild-type) and on the dose (20 or 80 mg), but occurred only at the reversible stage of the disease with I or II functional classes of chronic heart failure according to New York Heart Association Functional Classification.

The authors of **COMMANDER HF** [10] trial assumed that rivaroxaban (inhibitor of Xa factor) can decrease production of thrombin and improve outcomes in patients with an episode of decompensated chronic heart failure and coronary artery disease. Patients with II and III functional classes of chronic heart failure and left ventricular ejection fraction ≥40%, coronary artery disease and elevated plasma natriuretic peptides, without atrial fibrillation were randomized to rivaroxaban 2.5 mg twice daily (n = 2.507) versus placebo (n = 2.515).

During the median follow-up of 21.1 months the primary efficacy outcome (all-cause mortality, myocardial infarction, or stroke) occurred in 25.0% of the rivaroxaban group compared with 26.2% of the placebo group (RR 0.94 with 95% CI from 0.84 to 1.05; p = 0.27). There were no significant differences in all-cause mortality (21.8% versus 22.1%, respectively — RR 0.98 with 95% CI from 0.87 to 1.10) and myocardial infarction risk (RR 0.83 with 95% CI from 0.63 to 1.08), but the frequency of stroke was lower in rivaroxaban group (RR 0.66 with CI from 0.47 to 0.95). The primary safety outcome — fatal bleeding or bleeding into a critical space (intracranial, intraspinal, intraocular, pericardial, intraarticular, retroperitoneal, intramuscular) with potential cause of disability, occurred in 0.7% cases in the rivaroxaban group compared with 0.9% of cases in the placebo group (RR 0.80 with 95% CI from 0.43 to 1.49; p = 0.484), severe bleedings in 3.3% and 2.0% of cases (RR 1.68 with 95% CI from 1.18 to 2.39; p = 0.003), respectively.

Apparently, antithrombotic drugs cannot improve the prognosis in patients with heart failure without atrial fibrillation, who usually die from a critical reduction in heart's pumping function and ventricular arrhythmia.

MITRA.fr [11] trial estimated the hypothesis on the outcomes improvement in patients with reduced left ventricular ejection fraction, severe secondary mitral regurgitation and chronic heart failure by the result of percutaneous mitral valve repair. Patients with severe secondary mitral regurgitation (effective regurgitant orifice >20 mm^2 or regurgitant volume >30 ml per beat), left ventricular ejection fraction of 15–40% and chronic heart failure symptoms were randomized to percutaneous mitral valve repair (n = 152) versus medical therapy (control group) (n = 152).

During 12 months of follow-up, the primary outcome (death or hospitalization for heart failure) occurred in 54.6% and 51.3% of cases (RR 1.16 with 95% CI from 0.73 to 1.84; p = 0.53), all-cause mortality in 24.3% and 22.4% of cases (RR 1.11 with 95% CI from 0.69 to 1.77), hospitalization for heart failure in 48.7% and 47.4% of cases (RR 1.13 with 95% CI from 0.81 to 1.56) in percutaneous mitral valve repair group and control group, respectively.

Despite the neutral results of this work, it is important to mention, that during the latest COAPT study, the incidence of hospitalization for heart failure and the mortality with percutaneous mitral valve repair were significantly reduced in patients with even more pronounced secondary mitral regurgitation.

The **GLOBAL LEADERS** [12] study included patients undergoing percutaneous coronary intervention with a biolimus A9-eluting stent for stable or unstable coronary disease. Patients were randomized to 75–100 mg/day ticagrelor 90 mg 2 times a day for 1 month, followed by ticagrelor for 23 months (experimental group, n = 7.980) versus standard dual antiplatelet therapy for 12 months (75–100 mg/day of aspirin plus 75 mg/day of clopidogrel for stable coronary disease or 75–100 mg/day of aspirin plus 90 mg of ticagrelor 2 times a day for acute coronary syndrome), followed by aspirin monotherapy for 12 months (control group, n = 7.988). During the next two years, the primary efficacy outcome (all-cause mortality or nonfatal Q-wave myocardial infarction) occurred in 3.81% of the experimental group compared with 4.37% of the control group (RR 0.87 with 95% CI from 0.75 to 1.01; p = 0.073), all-cause mortality in 2.81% and 3.17% (RR 0.88 with 95% CI from 0.74 to 1.06; p = 0.18), nonfatal Q-wave myocardial infarction in 1.04% and 1.29% (RR 0.80 with 95% CI from 0.60 to 1.07; p = 0.14) in the experimental and control groups, respectively. The secondary safety outcome (grade 3 or 5 bleeding by the Bleeding Academic Research Consortium criteria) occurred in 2.04% versus 2.12% of cases (RR

0.97 with 95% CI from 0.78 to 1.20; p = 0.77) in the experimental and control groups, respectively.

1 month of ticagrelor and aspirin combination, followed by ticagrelor monotherapy for 23 months was not superior to standard antithrombotic therapy in patients with percutaneous coronary intervention for coronary artery disease.

Hot Line session IV (august 28, 2018)

The epidemiologic **PURE** study included the follow-up of 9.1 years of 138527 participants of the study (aged 35–70 years) from 50 countries, initially without any cardiovascular diseases. Participants were divided into five groups based on the quality of their diet. A PURE Healthy dietary score was developed based on foods associated with a lower risk of death in previous studies (fruit, vegetables, nuts, legumes, fish, dairy products and unprocessed meat). Each diet had its score based on the consumption quintiles of these protective components of the diet from 1 for the lowest quality to 5 for the highest quality food. The total diet score was defined as the summary of the consumption of seven components of the protective nutrition with a minimum score of 7 and a maximum score of 35. Researchers then compared the risks of cardiovascular disease and death in those with the highest quality diet (18 points or more) with the poorest quality diet (11 points or less).

The highest quality diet compared with the poorest quality diet, was associated with significantly lover risk of mortality (RR 0.75 with 95% CI from 0.68 to 0.83, p-trend in accordance to diet category <0.001) and tendency to lowering of the cardiovascular events (RR 0.91 with 95% CI from 0.81 to 1.02; p-trend in accordance to diet category = 0.0413).

Multiple factors have a positive impact on population's health in high-income countries and, consequently, high quality diet is more common in these countries.

The **FREED** study included patients aged 65 years and older with hyperuricaemia from >7 to ⩽ 9 mg/dl and ⩾1 cardiovascular risk factor (arterial hypertension, 2 type diabetes mellitus, glomerular filtration rate 30–60 ml/min/1.73m^2) or resent cardiovascular events. All patients were recommended to change their lifestyle and were randomized to receive oral febuxostat 10 mg/day with possible dose increase to 40 mg (n=533) or allopurinol 100 mg/day (n=537), if serum uric acid was elevated, which lead to more significant decrease of average serum uric acid level in the first group (4.50 mg/dl versus 6.76 mg/dl; p <0.001). During 36 months of therapy, the primary endpoint (death, caused by renal or cardiovascular disease; new or recurrent cerebrovascular event — ischemic or haemorrhagic stroke or transient ischemic attack; new or recurrent non-fatal myocardial infarction, unstable angina; cardiovascular-related hospitalization; atherosclerotic disease, that needs treatment, including aortic aneurism or dissection or arteriosclerosis obliterans; kidney failure, detected by microalbuminuria or moderate proteinuria, progression of albuminuria or proteinuria, a twofold increase of plasma creatinine, development of kidney failure, or kidney death; atrial fibrillation; death from any other cause) occurred with the frequency of 23.3% in the febuxostat group compared with 28.7% in the control group (RR 0.75 with 95% CI from 0.59 to 0.95; p = 0.017), kidney failure occurred in 16.2% compared with 20.5% of cases (RR 0.745 with 95% CI from 0.562 to 0.987; p = 0.04), death, cerebrovascular event or non-fatal coronary event in 4.3% compared with 4.9% of cases (RR 0.861 with 95% CI from 0.492 to 1.506; p = 0.60), respectively.

There was the J-shaped relationship between the development of clinical outcomes and the plasma uric acid level, the lowest risk of the primary endpoint events was observed at the plasma uric acid rate of > 5 to ⩽ 6 mg/dL. Therefore, more pronounced decrease in the uric acid level during the febuxostat treatment compared with allopurinol treatment cannot be considered as an advantage.

The safety and effectiveness of smaller than 3 mm in diameter coronary vessels angioplasty with the balloon, covered by lipophilic medication paclitaxel was estimated during **BASKET-SMALL 2** trial [14]. Patients with prescribed percutaneous coronary intervention were randomized to angioplasty with drug-coated balloons (n=382) or second-generation drug-eluting stents (n=376). Dual antiplatelet therapy was performed in accordance with current guidelines. After 12 months the occurrence of primary endpoint (major adverse cardiac events — death from cardiac events, nonfatal myocardial infarction, and target vessel revascularization) occurred in 7.5% of cases in drug-coated balloons group and in 7.3% of cases in the versus drug-eluting stents group (RR 0.97 with 95% CI from 0.58 to 1.64; p = 0.9180). Probable or definite stent thrombosis occurred in 0.8% versus 1.1% of cases (RR 0.73 with 95% CI from 0.16 to 3.26) and major bleeding occurred in 1.1% versus 2.4% of cases (RR 0.73 with 95% CI from 0.16 to 3.26) in the paclitaxel-coated

balloons group and drug-eluting stents group, respectively.

The results of the study showed, that the use of paclitaxel-coated balloons can be the alternative for second-generation drug-eluting stents in the treatment of blocked arteries with small diameter.

The **VERDICT** trial estimated the hypothesis on the help of early (within 12 hours after first symptoms) invasive therapy and revascularization in patients with non–ST-segment elevation acute coronary syndrome.

Patients with acute coronary syndrome, ischemic changes on the electrocardiogram and biomarkers of myocardium necrosis received dual antiplatelet therapy, fondaparinux, beta-blockers and were randomized to early invasive therapy (n = 1.075) versus standard invasive therapy hours (n = 1.072). 32% of patients did not have coronary artery disease. Over a median follow-up time of 4.3 years, the primary endpoint (all-cause death, non-fatal recurrent myocardial infarction and heart failure or refractory myocardial ischemia) occurred in 27.5% of participants in the early group and 29.5% in the standard care group (RR 0.92 with 95% CI from 0.78 to 1.08; p = 0.29). According to pre-planned subanalysis the reduction in primary endpoint events occurred in a subgroup of patients with a GRACE score >140 (RR 0.81 with 95% CI from 0.67 to 1.00).

Among patients with non–ST-segment elevation acute coronary syndrome, early invasive therapy did not decrease the risk of all-cause death, non-fatal recurrent myocardial infarction and hospitalization for heart failure or refractory myocardial ischemia, however, among high-risk patients with GRACE score >140 early therapy seems to be reasonable.

Hot Line session V (August 28, 2018)

High-sensitivity troponin measurements allow to use lower thresholds of this marker for the diagnosis of myocardial infarction, but it is not known whether it improves clinical outcomes. The **High-STEACS** [15] study included patients presenting to the emergency department with suspected acute coronary syndrome in Scotland. Hospitals were randomized for early (n=5) and 6 month later high-sensitivity troponin test (n=5) together with the gender-specific diagnostic threshold of 99th percentile (34 ng/l for men and 16 ng / l for women) in healthy population.

Among a total of 48.282 of observed patients, 10.360 (21%) had troponin I concentration higher than 99th percentile of diagnostic threshold, identified with standard or high-sensitivity troponin test. 17% of patients were reclassified in the myocardial infarction group by the results of high-sensitivity test, which wasn't diagnosed by standard analysis, and only one-third of reclassified patients were diagnosed with myocardial infarction. The primary outcome (myocardial infarction or cardiovascular death) was registered in 15% of reclassified patients on the stage of test validation and in 12% on the stage of test realization within 1 year (adjusted realization chances ratio against the validation stage 1.10 with 95% CI from 0.75 to 1.61; p = 0.620).

Reclassified patients with high-sensitivity troponin I test after negative results of standard test have the same possibility of myocardial infarction and cardiovascular death during the next year.

Clinically stable patients with infectious endocarditis with aortic and/or mitral valve lesion, caused by streptococcus, *Enterococcus faecalis, Staphylococcus aureus*, or coagulase negative staphylococci, who underwent intravenous antibiotic therapy for more than 10 days, took part in the **POET** trial. Patients with stable condition (absence of fever, normalization of C-reactive protein level, absence of an abscess or other reasons for surgical intervention according to transesophageal echocardiography) were randomized to oral antibiotic therapy (n = 201), in 80% of cases on outpatient basis, with a median duration of 17 days (interquartile range from 14 to 25) or intravenous antibiotic therapy at the hospital (n = 199) with median duration of 19 days (interquartile range from 14 to 25). Patients from the group of oral antibiotic therapy had physical examination every 3–4 days to assess their condition, determine plasma levels of medications. During the follow-up pf 6 months, the primary outcome (all-cause death, unplanned cardiac surgery, embolic events, or relapse of bacteraemia with the primary pathogen) occurred in 9.0% of the oral administration group compared with 12.1% of the intravenous administration group (p = 0.40; satisfying the «not worse» criterion).

Switching to oral antibiotic therapy in stable patients with infective endocarditis can significantly reduce the duration of hospital stay and reduce the risk of new nosocomial infection. To reproduce the results of the POET study in practice, strict adherence of patient selection criteria and monitoring is required.

The slowing of aortic dilation in patients with Marfan syndrome is the important target during beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers treatment. Patients aged from 6 to 40 years, who underwent be-

ta-blockers treatment in case of good tolerance (more than half of the patients), took part in the **AIMS** study. Patients were randomized to 150–300 mg of irbesartan once daily depending on body weight (n=104) or placebo (n=88).

Aortic diameter was assessed using transthoracic echocardiography at baseline and at yearly intervals for up to 5 years. While aortas in both groups continued to enlarge, researchers noted the rate of dilatation was slower in the irbesartan group compared with the placebo group (0.53 mm versus 0.74 mm per year, respectively; p = 0.030). The rate of adverse events, including the need for cardiac surgery to replace the aortic root was similar across the two groups. Irbesartan is well-tolerated by children, which makes it possible to use this medication for potentially delaying the need for elective surgery.

The next Congress of the European Society of Cardiology will be held on August 31st-September 4th 2019 in Paris (France).

Conflict of Interest: None declared.

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International Heart and Vascular Disease Journal • Volume 6, № 20, December 2018
Journal of the Cardioprogress Foundation

EXPERT OPINION

New statement on chronic heart failure in patients with diabetes mellitus of the Heart Failure Association of the European Society of Cardiology: comments of Russian experts

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In 2018 the European Journal of Heart Failure published the new statement on chronic heart failure (CHF) in patients with diabetes mellitus (DM). It contained the data of major clinical trials on CHF prevalence, CHF clinical features and complications, pathophysiological aspects of myocardial dysfunction, CHF treatment in patients with DM, safety and possibility of use of hypoglycemic agents in patients with CHF and DM. The current article presents the comments of the Russian experts on principal positions of this new statement.

Key words: *chronic heart failure, diabetes mellitus, clinical features, treatment, prevention.*

Conflicts of interest: nothing to declare.

Received: 07.10.2018 **Accepted:** 27.10.2018

In 2018 the European Journal of Heart Failure published the new statement on chronic heart failure (CHF) in patients with diabetes mellitus (DM). The document was prepared by the group of international experts (Petar M. Seferović, Mark C. Petrie, Gerasimos S. Filippatos et al., 35 experts in general, including an expert from Russia — professor U.M. Lopatin) [1].

The statement included data of large investigations on the CHF prevalence in patients with diabetes mellitus, CHF clinical features and complications, pathophysiological aspects of myocardial dysfunction, CHF treatment in patients with DM, safety and possibility of use of hypoglycemic agents in patients with CHF and DM.

The comments of the Russian experts on principal positions of this new statement are presented below.

Chromic heart failure prevalence in patients with diabetes mellitus

DM and CHF are serious chronic diseases, which significantly affect the prognosis and life expectancy of the patients. Death, caused by cardiovascular events, is significantly more common in patients with CHF and DM with normal or decreased ejection fraction, compared with patents only with CHF. At the same time, CHF is an independent predictor of fatal and non-fatal complications in patients with type 2 diabetes mellitus (T2DM). The main causes of heart failure in patients with DM are not only coronary artery disease (CAD) and arterial hypertension (AH), but also diabetic cardiomyopathy, which plays significant role in its development [2].

It is known, that T2DM represents about 90–95% of diabetes mellitus cases. The frequency of T2DM has significantly increased during the past years. Its prevalence raised from 4,7% in 1980 to 8,5% in 2014 among people of working age. Average prevalence is about 11,8% (4,7–13,3%) worldwide nowadays [3].

There are few studies on CHF prevalence in patients with DM. According to different data, its prevalence is about 12% and it increases with age approximately to 19% [4–7]. DM is 2–4 times more prevalent (from 24% and higher) in patients with CHF, depending on their region, compared with patients without CHF. According to registries of hospitalized patients with CHF in North America and Europe, the prevalence of DM is 40–45%. According to Swedish CHF registry (68% patients admitted to hospital and 32% outpatient ones), DM was diagnosed in 30% of cases, whereas in patients without CHF, its prevalence was 19%.

According to Kaiser Permanente study, the incidence of DM was significantly higher in patients with HF than without it (13.6 cases of 1000 patients versus 9.2 cases of 1000 patients) over a 5-year follow-up. CHF is the most common CVD in patients with DM in general, compared with myocardial infarction or stroke [8]. According to perspective UKPDS 35 trial, which included newly diagnosed diabetic patients, HF incidence steeply increased with the severity of hyperglycemia (ranging from 2.3 to 11.9/1000 person-years for patients with glycated hemoglobin (HbA1c) < 6% and HbA1c >10%, respectively [9].

The results of the ARIC study showed, that CHF frequency was higher on the stage of early carbohydrate metabolism disturbances (prediabetes) compared with patients with normoglycemia [10].

Obviously, CHF is one of the most frequent macrovascular complication of diabetes. On the other hand, the frequency of carbohydrate metabolism disturbances, including newly diagnosed diabetes, is also very high in patients with CHF. Age and blood glucose levels are important in the development of morbidity and complications.

Type 2 diabetes mellitus and chronic heart failure: clinical presentation and cardiovascular prognosis

The key point in the management and treatment strategy of CHF patients is the identification of the causes of its development. The estimation of the dia-

stolic/ systolic left ventricular dysfunction severity is clinically and prognostically significant [10]. Patients with decreased (low) left ventricular ejection fraction (HFrEF), usually have severe diseases, associated with atherosclerosis, and coronary artery bypass grafting has the same benefit for cardiovascular mortality reduction in patients with or without DM [11].

The diagnosis and treatment of acute and chronic HF working group of European Society of Cardiology (ESC) in 2016 identified the new group of patients with CHF and LV ejection fraction between 40–49 %, named «HF with preserved EF (HFpEF)». The number of patients is increasing in both groups, mostly due to patients with DM without CAD, who has non-ischemic etiology of cardiovascular system lesion: cardiovascular autonomic neuropathy, specific cardiomyocyte damage due to glucose toxicity and oxidative stress, interstitial fibrosis, reduction of coronary reserve due to microangiopathy [12]. That's why the concept of early preventive strategy is very important in patients with DM.

Interestingly, some clinical studies have shown significantly higher risk of diabetes development in patients with CHF, which seems to be associated with insulin sensitivity disturbances: more pronounced insulin resistance leads to more severe CHF manifestation.

In the massive CHARM program 8 % of patients with CHF developed DM over 3 years of follow-up. However, more severe circulatory insufficiency lead to higher possibility of diabetes development [13].

Patients with DM have more severe manifestation of CHF, despite similar parameters of heart's pumping function, compared with patients without DM. They have more chances of death, caused by cardiovascular events with ischemic and non-ischemic etiology [14]. Carbohydrate metabolism decompensation, estimated by HbA1c, also has negative impact on cardiovascular prognosis in patients with CHF and DM.

Observational studies demonstrate, that about 30 % of patients aged over 60 years, have asymptomatic CHF manifestation (22,9 % and 4,8 % of patients with HFpEF and HFrEF, respectively). On the other hand, undiagnosed cases of DM and prediabetes have the same prevalence in the population with CHF [10, 15].

In the PARADIGM-HF trial, 13 % of patients with CHF had undiagnosed DM and 25 % had pre-diabetes [16]. In the CHARM study undiagnosed DM had the same frequency in patients with preserved and decreased left ventricular ejection fraction [17].

There is no doubt, that combination of DM and CHF is a severe comorbid state, and each of its components is associated with an extremely high cardiovascular risk. These patients require early diagnosis of both carbohydrate metabolism disturbances and preclinical manifestation of CHF.

Pathophysiological aspects of myocardial dysfunction in patients with type 2 diabetes mellitus

The combination of T2DM with CAD and AH can lead to CHF development. It is suggested that pathological processes during DM can directly affect heart structure and function [18]. The main factors that cause myocardium dysfunction in patients with DM are insulin resistance and high level of insulin [19]. Their adverse effects are associated with deposition of glycation end products, lipotoxicity and microvascular rarefication [18]. Insulin resistance increases the amount of free fatty acids [20, 21]. The capture of free fatty acids by cardiomyocytes in the amount exceeding the beta-oxidation potential, leads to triglyceride accumulation in the myocardium, which can be manifested by steatosis, which, in turn, can lead to diastolic dysfunction [22]. Insulin resistance is the factor of left ventricular hypertrophy development [23].

Hyperglycemia also affects cardiovascular system by disrupting cardiomyocytes and mitochondria function and activating protein kinase C [24, 25]. In addition, hyperglycemia leads to reactive oxygen species activation, deposition of glycation end products in both endothelium and smooth muscle cells, which leads to concentric myocardial remodeling and an increase in left ventricular diastolic stiffness [25].

Phenotypes of chronic heart failure in patients with diabetes mellitus

Diastolic dysfunction occurs in 75 % of patients with T2DM, and usually develops on early stages of the disease [26, 27], and the severity of diastolic dysfunction correlates with carbohydrate metabolism dysregulation, CHF prevalence and cardiovascular mortality. About half of the patients with T2DM have HFpEF. The main cause of HFrEF development in patients with T2DM is accompanying CAD, the likelihood of which increases in patients with T2DM. HFpEF usually occurs on the early stages of T2DM, whereas HFrEF occurs during more severe T2DM, which means that the severity of hyperglycemia is important for the development of left ventricular dysfunction.

Diabetic cardiomyopathy

In 1954, Lundbaek was the first to propose the existence of a specific diabetic heart muscle disease without involvement of CAD or AH [28]. Two decades later, Rubler et al. [29] described diabetic-related post-mortem findings in patients with DM and HFrEF with normal epicardial coronary arteries and without AH or/and cardiac valves lesions. It is remarkable, that there is no definition of diabetic cardiomyopathy, which makes studies of epidemiology, pathophysiology and clinical course of the disease challenging. The most commonly accepted definition refers to a myocardial dysfunction which occurs in the absence of all other CV disease.

Treatment of heart failure in patients with type 2 diabetes mellitus

According to the results of subanalyses during controlled randomized studies, standard pharmacological therapy of CHF by angiotensin-converting enzyme inhibitors [30], angiotensin II receptor blockers [31], beta-blockers [32], mineralocorticoid receptor antagonists [33], sacubitril / valsartan [34], nitrates and hydralazine [35], ivabradine [36] were similarly effective whether or not patients had DM. Accurate monitoring of blood potassium level is required during angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor antagonists treatment due to frequent renal lesions in patients with Beta-blockers can mask the manifestations of developing hypoglycemia (tachycardia, tremor).

Implantation of cardioverter-defibrillators [37] and cardiac resynchronization therapy [38] were similarly effective whether or not patients had T2DM. The frequency of infectious and other complications, connected with implanted devices, did not depend on the presence of T2DM.

Coronary artery bypass grafting had similar effect on mortality independently on presence of T2DM [39].

The mortality of patients with T2DM after cardiac transplantation was significantly higher due to renal dysfunction, arteries lesions development and infectious complications during immunosuppressive therapy with corticosteroids [40].

Type 2 antidiabetic drugs and the risk of heart failure

The investigations over the past years revealed different effects of several hypoglycemic drugs on the most frequent cardiovascular diseases and its complications, including CHF. The importance of this circumstance was emphasized by the decision of FDA in 2008 on the increase of requirements for hypoglycemic drugs registration, which should not only reduce the level of glycemia, but also have cardiovascular safety profile [41]. However, in modern diabetology, the principles of hypoglycemic drugs use were not clearly formulated, taking into account their impact on the risk of HF development and progression, until recently.

The new position statement of HF Association of the ESC 2018 for patients with CHF and T2DM was a big step forward, which represented the division of the entire arsenal of hypoglycemic drugs, depending on their impact on the risk of CHF development, into four groups for first time.

Drugs that are now known to increase the risk for CHF are hypoglycemic drugs from the group of thiazolidinediones (rosiglitazone, pioglitazone) and a iDPP-4, saxagliptin [43], which increased the rate of CHF hospitalizations in patients with T2DM. Patients at greatest risk were those with a history of CHF, an estimated glomerular filtration rate ⩽60 mL/min, or elevated baseline levels of NT-proBNP, which is a HF marker. On that basis, pioglitazone, rosiglitazone and saxagliptin are contraindicated in patients with T2DM and CHF or at high risk of CHF. At the same time, another drug from iDPP-4 group, sitagliptin, did not have any negative effect on the course of CHF and can be used among this category of patients [44]. Although the increase of the CHF progression risk during alogliptin treatment in patients with T2DM after recent acute coronary syndrome was unreliable [45], iDPP-4 is contraindicated in patients with T2DM and III–IV functional classes of CHF.

Insulin, which causes sodium and water retention and sulphonylurea derivatives as insulin secretagogues are hypoglycemic drugs that might increase the risk of CHF. These drugs can be used only after metformin or other drugs with positive effect on patient's prognosis treatment in patients with CHF.

It has been proposed, that metformin might be safe and efficacious in patients with T2DM and CHF. Previous concerns that metformin may cause metabolic acidosis are no longer justified, and it could be recommended as first-line treatment for patients with T2DM and CHF who have preserved or moderately reduced renal function (i.e. eGFR >30 mL/min) [10]. Glucagon-like peptide 1 receptor agonists, for example liraglutide, exenatide, lixisenatide, semaglutide, are also the drugs with neutral effect on the risk of HF hospitalization [46].

A significant breakthrough in contemporary diabetology was the identification of the hypoglycemic drugs, that lower the risk of CHF progression — sodium–glucose co-transporter type 2 (SGLT2) inhibitors (iSGC2). The use of empagliflozin (EMPA-REG OUTCOME trial, n=7020) [47] and canagliflozin (CANVAS trial, n=10143) [48] was associated with significant lower risk of CHF hospitalizations (35 % and 33 %, respectively).

Considering the numerous mechanisms of the cardiac- and nephroprotective effects of iSGC2, it is assumed, that the drugs of this group may be effective for the treatment of CHF in patients without T2DM. In order to confirm this hypothesis, large randomized placebo-controlled studies of the empagliflozin effect on the CVD associated mortality and CHF hospitalizations in patients with HFrEF were initiated in 2017 (EMPEROR-Reduced, NCT03057977) and with HFpEF (EMPEROR-Preserved, NCT03057951) and of dapagliflozin efficacy in patients with HFrEF (Dapa-HF, NCT03036124).

According to the results of these studies, it can be decided to expand the indications for the use of drugs from iSGC2 group by including the patients without carbohydrate metabolism disturbances.

Conclusion

Consequently, T2DM and CHF are very common. The causes of HF in T2DM are numerous, but CAD and AH are likely the most important contributors to concurrent T2DM and HF, whereas a direct effect of T2DM on the myocardium (diabetic cardiomyopathy) might also play a role. Data from registers and prospective studies indicate that regardless of the etiology and phenotypes, the risk of complications development in patients with T2DM and CHF is high. Some new antidiabetic drugs have a neutral or beneficial effect in reducing CHF hospitalizations in patients with DM.

Conflict of Interest: None declared.

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International Heart and Vascular Disease
Journal • Volume 6, № 20, December 2018

Journal of the Cardioprogress Foundation

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6. Making literary references. Submitted article will not be reviewed until the correction of literary references in accordance with the rules for authors is made. The authors «forget» and somewhere to remove point (such inconsistencies can be corrected in the Revision), but if the design literature is radically different from what is required or present hyperlinks, the Editors will not start with the article to eliminate errors.

7. Keyword. They are written with a small letter, separated by a semicolon. At the end put a point. In

the text of the article the keywords are written separated by commas.

A file is prepared separately in Word, which is then sent as an additional file. The file must contain:

1. Title page of the manuscript. The title of the manuscript is written in capital letters, without hyphenation, in bold. Initials and surnames of authors-Ivanov I. I., Petrov P. p. the full name of organization (s) from which (s) there was a manuscript, the city, the country is Given. Footnotes are in Arabic numerals after the authors ' names and before the names of institutions.

Example of design:

THE PREVALENCE OF RISK FACTORS OF NONCOMMUNICABLE DISEASES IN THE RUSSIAN POPULATION IN 2012–2013. THE RESEARCH RESULTS OF THE ESSE-RF

Muromtseva G. A. [1], Kontsevaya A.V. [1], Konstantinov V. V. [1], Artamonova G. V. [2], Galaganova T. M. [3],...

[1] FGBU State research center of preventive medicine of the Ministry of health of Russia, Moscow;

[2] FGBU Research Institute of complex problems of cardiovascular diseases SB RAMS, Kemerovo;

[3] RD VPO North Ossetian state medical Academy, Vladikavkaz;..., Russia.

2. Information about the authors, where indicated: full name, place of work of all authors, their positions, ORCID; full contact information is required for one (or more) of the author and includes e-mail, available phone number.

All members of the group of authors should meet all four criteria of authorship set forth in the ICMJE recommendations: 1) concept and design development or data analysis and interpretation, and 2) manuscript justification or verification of critical intellectual content, and 3) final approval for publication of the manuscript, and 4) consent to be responsible for all aspects of the work, and assume that issues relating to the thoroughness and diligent execution of any part of the study submitted are duly investigated and resolved. This information should also be contained in the document.

If the submitted material has authors who do not meet the criteria of authorship, but have made some contribution to the work, they should be listed in this document and at the end of the article in the section of Acknowledgements.

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The section contains the disclosure by all authors of possible relations with industrial and financial organizations that may lead to a conflict of interest in connection with the material presented in the manuscript. It is desirable to list the sources of funding for the work. If there is no conflict of interest, it is written: «Conflict of interest is not declared.» Information on the existence of a conflict of interest should also be reflected in the Conflict of interest section at the end of the article.

4. Information about grants. Should be mentioned at the end of the article in the section Acknowledgements and at the end of the section Material and methods — with a full description of the role of the source of funding in the performance of work (design, information collection, analysis, data interpretation, etc.).

5. Information and ethics in the study.

Example of design:

The study was carried out in accordance with the standards of good clinical Practice (Good Clinical Practice) and the principles of the Helsinki Declaration. The study Protocol was approved by the Ethical committees of all participating clinical centers. Prior to being included in the study, written informed consent was obtained from all participants.

This information should also be reflected in the Material and methods section of the article.

All additional information (permits, questionnaires, etc.) can be requested from the authors in addition to the preparation of the work for printing.

6. Information on overlapping publications (if available).

7. Copyright. The use of any material (tables, figures) marked with a copyright icon in the article should be confirmed by a special permission from the author or publisher.

8. Information about the obtained consent in patients for the study.

Obtaining consent from patients for the study should also be reflected in the Material and methods.

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10. The number of words in the article (excluding summaries, sources of literature, figure captions and tables), the number of tables and figures.

The absence of an information file or incomplete text (not containing the above items) is the basis for refusal to accept the manuscript for consideration.

IV. Manusctipt submision check-list

Since the main file of the manuscript is automatically sent to the reviewer for» blind review», it should not contain the names of the authors and institutions. The file contains only the following sections:

1. Article title
2. Summary with key words
3. List of abbreviations
4. Text
5. Acknowledgements (if any)
6. List of references
7. Tables, figures (if they can be embedded in the text of Word format).

The article title is written in capital letters (PREVALENCE of RISK FACTORS...), the end point is not needed. The title should clearly reflect the purpose of the work.

Summary with key words-sections are drawn up each with a separate line, highlighted in bold. The abstract should contain only those sections that are described in the rules for authors. For example, there is no section «Relevance» in the summary. The authors prescribe the relevance of their work in the introductory section of the manuscript.

List of abbreviations — when compiling a list of abbreviations to the article, including text, tables and figures, only those used by the author 3 or more times are included. Usually shrink often used in manuscripts of the terms (e.g., hypertension, CHF FC) and title of clinical trials (SOLVD, TIMI, HOPE).

The first reference to an abbreviation is always accompanied by the full spelling of the abbreviated concept, and the abbreviation is indicated in brackets. For example, blood pressure (BP); heart rate (HR). Capital letters are more often used to denote abbreviations. If abbreviations are used only in tables and figures, and are not used in the text, they should not be included in the list of abbreviations, but should be given a transcript in the note to the table or figure. The summary of the article, as a separate document, is subject to the same rules as the article (abbreviations are made when they are used 3 or more times).

Abbreviations should be generally accepted and understandable to the reader, in accordance with the generally accepted norms in the scientific literature. Undesirable abbreviations that coincide in writing with others that have a different meaning.

Abbreviations in the list of abbreviations are written in alphabetical order, separated by commas, in solid text, using «dash». **Example of design:** BP-blood pressure, HR-heart rate.

Text — the text of the manuscript of the original works should be structured: Introduction, Material and methods, Results, Discussion and Conclusion. The text of reviews and lectures can be unstructured.

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Introduction — it is necessary to describe the context and prerequisites of the work (what is the essence of the problem and its significance). It sets certain goals or describes the object of the study, or a hypothesis that needs to be tested by comparison or observation. Only those sources that directly indicate the problem are cited.

Statistics — all published materials are reviewed by an expert in statistics and must meet «Uniform requirements for manuscripts submitted to biomedical journals» (Uniform Requirements for Manuscripts Submitted to Biomedical Journals, Ann Intern Med 1997, 126: 36–47). In the preparation of the statistical part of the work it is recommended to use special guidelines, for example, the European journal of cardiology: www.oxfordjournals.org/our_journals/eurheartj/for_authors/stat_guide.html

Statistical methods are described in detail in the Material and methods section.

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However, to print in the journal (at the stage of creating a layout) graphics, diagrams and drawings are required in electronic form in the formats «MS Excel», «Adobe Illustrator», «Corel Draw», «MS PowerPoint», photos with a resolution of at least 300 dpi.

The names of the graphs and figures, as well as notes to them should be placed under the figure/graph or placed at the end of the article.

These files are referred to as additional files. Figures should not repeat the materials of the tables.

Tables should contain the compressed, necessary data. Each table is placed at the end of the text (after the list of references) with the number, name and explanation (note, abbreviations).

The tables should clearly indicate the dimension of the indicators and the form of data (M±m; M±SD; Me; Mo; percentiles, etc.). All figures, totals and percentages should be carefully verified, and also correspond to the mention in the text. The explanatory notes are given below the table, if necessary. The footnotes must be in the following order: *, †, §, ||, ¶, #, **, †† etc.

Abbreviations should be listed in a footnote below the table in alphabetical order (for tables its list of abbreviations!).

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Book:

Shlyakhto EV, Konradi AO, Tsyrlin VA. The autonomic nervous system and hypertension. SPb.: Meditsinskoe izdatel'stvo; 2008. (In Russ.) Шляхто Е.В., Конради А.О., Цырлин В.А. Вегетативная нервная система и артериальная гипертензия. СПб.: Медицинское издательство; 2008. ISBN 0000–0000.

Chapter:

Nichols WW, O'Rourke MF. Aging, high blood pressure and disease in humans. In: Arnold E, ed. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 3rd ed. London/Melbourne/Auckland: Lea and Febiger; 1990. p.398–420. ISBN 0000–0000.

Russian chapter:

Diagnostics and treatment of chronic heart failure. In. National clinical guidelines 4th ed. Moscow: Silicea-Polygraf; 2011. pp.203–93. (In Russ.) Диагностика и лечение хронической сердечной недостаточности. В кн: Национальные клинические рекомендации. 4-е издание. М.: Силицея-Полиграф; 2011.сс.203–96. ISBN 0000–0000.

Webpage:

Panteghini M. Recommendations on use of biochemical markers in acute coronary syndrome: IFCC proposals. eJIFCC 14. http://www.ifcc.org/ejifcc/vol14no2/1402062003014n.htm (28 May 2004)

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2. The author is sent a notification letter of receipt of the manuscript with the number (ID), which will be used in subsequent correspondence. The author can track the stages of work on his manuscript through the site. Since the process of bringing the manuscript to the necessary standards takes enough expert time, the payment for the initial review of the article was introduced, which the author (s) are required to carry out after the article is posted on the site.

3. The manuscript must pass the primary selection: the Editorial Board has the right to refuse publication or send comments to the article, which must be corrected by the Author before reviewing.

— checking the completeness of the manuscript: if you do not comply with the requirements of the Rules for the authors to complete the manuscript or its design, the Editors have the right to refuse to publish or in writing to require to send the missing materials or to correct the version already downloaded to the site.

— Manuscripts are checked in the «Antiplagiat» system. The originality of the manuscript should be at least 75 %. We expect manuscripts submitted for publication to be written in an original style that involves new thinking without the use of previously published text. Manuscript with originality below 75 % shall not be admissible.

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7. If the reviewer makes a conclusion about the possibility of publication of the article and does not make significant corrections, the article is given to the expert on statistics and after a positive report is accepted for further work.

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After the decision on the admission of article for publication, the Editorial office inserts the publication of the article in terms of publications. Information about the annual (thematic) plan of publications is placed on the website of the journal.

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1. Information on publication is distributed in the following scientific citation databases: Russian science citation index, CYBERLENINKA and others. The article is assigned a DOI index and the full text is publicly available on the journal's website.

2. Information about the publication of the issue is distributed by mailing of The Cardioprogress Foundation and in social networks.

3. We expect the authors of the articles to actively make efforts to bring the results of their research to the public, namely: to have a personal page on the Internet (personal page), to monitor and update your profile ORCID and RecsearcherID, to involve colleagues in their work through social networks.

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The full text of the journal's policy on Revocation and correction of articles is available in the information section on the website. The editors follow COPE Recommendations issued by the Committee on publishing ethics (COPE) — http://www.publicationethics.org.uk. in cases:

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XIV. Journal subscription

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http://www.heart-vdj.com

On the reception of the articles, making decisions about publication, reviews — mmamedov@mail.ru

On organizational issues (working with the site, subscription) — editor.ihvdj@gmail.com

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ISSN: 2309-0901 (Print)

ISSN: 2311-1631 (Online)

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