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Ventricular late potentials in patients with chronic rheumatic heart disease

Predicting renal dysfunction in patients with chronic heart failure

Acute Pulmonary Embolism Hemorrhagic Pulmonary Infarction and Ischemic Myocardial Infarction – A Case Report

**International Heart and Vascular Disease Journal**
**Journal of the Cardioprogress Foundation**

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## Contents

# Editor's Welcome

Dear colleagues!

In the 29th issue of the International Heart and Vascular Disease Journal, there are the leading article, original and review articles, as well as clinical case report.

The leading article section presents the original work of the Russian author who aimed to evaluate ventricular late potentials (VLPs), its significance and relationship with survival rate of patients with rheumatic heart disease. The study included 260 patients with mitral stenosis, 103 with aortic stenosis and 81 with mitral valve regurgitation. Patients showed deterioration of VLPs parameters during ten years of observation. At the same time LVPs did not differ between groups with various types of valvular heart disease.

The journal traditionally publishes the results of large epidemiological studies on the prevalence and features of the risk factors. According to the results of Siberian researches the prevalence of smoking is 24,8% among people aged 45–69 years. There was no difference in the amount of smoking depending on the levels of family-related stress. At the same time, there were twice as many smokers among the participants with high level of work-related stress compared with those with low work-related stress. The participants with high level of family-related stress tend to quit smoking more often compared with those with the same level of work-related stress. Another study from Uzbekistan included 325 patients with coronary heart disease (CHD) and various functional classes of chronic heart failure (CHF). Along with the gold standard – the estimation of eGFR, they assessed pulsative and resistant indices at the level of renal arteries and albumin/creatinine ratio that can be also considered as informative methods for the assessment of renal functional state in patients with CHF.

The review article section included two works on the comorbidity of cardiovascular and renal diseases. Authors demonstrate their stage-based treatment approach and principles of prevention as well as nephroprotective and cardioprotective regimens and anticoagulation for the prevention of disease progression on the example of a long-term management of an actual patient with arterial hypertension, atrial fibrillation and CKD. The second article is dedicated to the risk factors of acute myocardial infarction development in patients with end-stage chronic kidney disease including patients on hemodialysis. The role of hyperphosphatemia, hyperuricemia, anemia, oxidative stress, inflammation and endothelial dysfunction in the occurrence of cardiac events is considered. The attention is focused on the assessment of cardiac troponin I level in the diagnosis of acute myocardial infarction in hemodialysis patients.

Deep vein thrombosis of the lower extremities often leads to one of the most life-threatening complications such as thromboembolism of the branches of the pulmonary artery. The care report is dedicated to the analysis of the development of acute pulmonary embolism with myocardial and lung infarction with a premorbid background after traumatic injury to the deep veins of the left leg.

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.

**Mekhman N. Mamedov**
Editor-in-Chief
President of the "Cardioprogress" Foundation

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Journal of the Cardioprogress Foundation

LEADING ARTICLE

# Ventricular late potentials in patients with rheumatic heart disease

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**Abstract**

**Objective.** *The evaluation of ventricular late potentials (VLPs), its significance and relationship with survival of patients with rheumatic heart disease (RHD).*

**Materials and Methods.** *The study included 260 patients with mitral stenosis, 103 with aortic stenosis and 81 with mitral valve regurgitation. Patients were followed up for 10 years. Echocardiography was performed on a Philips Affinity 50 apparatus, 24-hour ECG monitoring was performed on a Cardiotechnika-04–3P (M) monitor with an assessment of VLPs: TotQRSF, LAS40, RMS40.*

**Results.** *The parameters of VLPs significantly changed in patients with RHD during 10-year observation: RMS40 decreased by 9.85 (5.72;13.98) ms and LAS40 increased by 2.83 (5.01;0.65) ms. However, RMS40 and LAS40 did not differ between groups with different types and severity of valvular heart diseases. Patients with prosthetic heart valves had higher LAS40 values of 34.39±15.97 ms and TotQRSF of 94.43±19.64 ms compared with patients who did not underwent surgery: LAS40 of 34.39±15.97 ms and TotQRSF of 87.62±14.76 ms, respectively. The characteristics of LVPs significantly differed between survivors (TotQRSF 88.98±16.59 ms, RMS40 40.67±22.83 ms, LAS40 31.40±12.62 ms) and those who died (TotQRSF 97.00±12.67 ms, RMS40 27.43±15.19 ms, LAS40 36.57±15.25 ms). Increased TotQRS in patients with RHD increased mortality — odds ratio (OR) — 1.026 (1.007;1.046).*

**Conclusion.** *Patients with RHD showed deterioration of VLP parameters during ten years of observation. Deceased subjects with RHD had more pronounced VLP and increased TotQRSF. VLPs did not differ between groups with various types of valvular heart disease.*

**Keywords:** *rheumatic heart disease, ventricular late potentials, mitral stenosis.*

**Conflicts of interest:** none declared.

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## Introduction

High-resolution electrocardiography (ECG) with the help of computer processing of the ECG signal detects very low amplitude signals in the ventricles. A standard electrocardiogram that is routinely used to diagnose cardiac arrhythmias cannot detect these signals [1, 2]. Ventricular late potentials (VLPs) are thought to result from fragmentation of electromotive forces in abnormal areas of ventricular myocardium, where activation is delayed by slow conduction, and are considered as independent predictor for the development of life-threatening arrhythmias that lead to sudden cardiac death [3]. VLPs are discussed in the literature from the perspective of patients with chronic heart failure (CHF) with preserved left ventricular ejection fraction (LVEF), since they are associated with diastolic dysfunction. The dysfunction is associated with decreased elasticity of the myocardium due to hypertrophy, fibrosis or sclerosis [4]. VLPs occur in areas with slow conduction of excitation through the myocardium that causes the development of arrhythmogenic zones and contributes to the occurrence of malignant ventricular arrhythmias [5]. The method of VLPs registration is based on the identification of high-frequency (over 20–50 Hz) and low-amplitude (less than 20 μV) signals that occur at the end of the QRS complex [6].

The development of VLPs is associated with slow conduction in abnormal areas of ventricular myocardium. Healthy cardiomyocytes alternate with areas of necrosis and fibrosis or with ischemic areas. This alternation of zones with normal and slow conduction in the myocardium causes the formation of the re-entry phenomenon [7]. The fragmentation of electromotive forces appears is areas with reduced blood supply or small focal necrosis. After the stabilization of patient's condition, for example, in case of unstable angina pectoris, the VLPs parameters improve and they disappear in one third of patients [8]. However, in patients with stable angina pectoris, antianginal pharmacotherapy and angioplasty do not improve the rate of VLPs [8].

In recently published literature, the data on VLPs are contradictory. The value of high-resolution ECG for the assessment of the risk of sudden cardiac death ranges from 7 to 40 %, and the negative predictive value exceeds 95 % [9]. In patients with myocardial infarction (MI), the TotQRSF values are considered to be the most significant for the assessment of the prognosis. The MUSTT study included 1268 patients with LVEF<40 % and unstable ventricular tachycardia and showed that the QRS duration> 114 m/s was associated with higher risk of arrhythmic events during 5-year follow-up in 28 % of cases (compared with 17 % risk in the rest of patients) [10]. However, the results of recent studies bring into question on the value of VLPs [11]. In 968 of patients with MI and percutaneous revascularization [12], VLPs did not have a predictive value for the development of life-threatening arrhythmias or sudden cardiac death [12]. However, even though VLPs cannot be considered as traditional risk factor [13,14], it can have high negative predictive value. This can be useful for the identification of patients with low risk, including patients with chronic rheumatic heart disease (RHD) that can be considered a model of slowly progressive CHF. There are only a few works that studied LVPs in patients with heart valve stenosis, the main focus in the literature is on mitral valve prolapse or the assessment of VLPs after surgery, but the studied samples are small. Therefore, it is interesting to study VLPs in patients with RHD and to assess the changes of its parameters during a long period of time.

## Objective

The evaluation of VLPs, its significance and relationship with survival rate of patients with RHD.

## Materials and methods

The study included 444 patients (17.12 % — men, 82.88 % — women) with average age of 58.06±9.65 years who were diagnosed with RDH and signed written informed consent. After the analysis of medical records, we identified 260 patients (from RDH group) with mitral stenosis (191 patients) and combined mitral and aortic stenosis (69 patients), 103 with aortic stenosis and 81 with mitral regurgitation. According to current guidelines on the management of valvular heart disease, acute rheumatic fever is the main cause of mitral or combined mitral and aortic stenosis; aortic — calcific aortic stenosis; mitral valve regurgitation — degenerative disease. The exclusion criteria were: decompensation of CHF at the time of inclusion and severe concomitant pathology that potentially negatively affects life expectancy; life-threatening arrhythmias. Patients were followed up for ten years. The incidence of concomitant diseases at the time of inclusion: arterial hypertension — 44.6 %, atrial fibrillation — 49.1 %, angina pectoris — 17.3 %. The frequency of prescribed drug therapy: ACE inhibitors / sartans — 86.7 %, β-blockers — 57.7 %, spironolactone — 80.3 %. The groups were comparable

by the frequency of prescribed pharmacotherapy for CHF and concomitant cardiovascular diseases.

All the patients underwent echocardiography on the Philips Affinity 50 apparatus. Holter ECG monitoring with the assessment of VLPs was performed on the cardiorespiratory monitor «Cardiotekhnika-04–3R (M)» by "Inkart" company. The ECG signal was processed and filtered between 40–250 Hz in order to obtain the resulting filtered QRS complex [15]. The program calculated the duration of the filtered QRS complex on the vectorcardiography (TotQRSF), the mean square amplitude of the last 40 m / s of the QRS complex on the vectorcardiography (RMS40); the duration of the section from the end of the QRS complex on the vectorcardiography (points S) to the beginning of the QRS complex over 40 μV (LAS40). The following values were considered as pathology: TotQRSF> 114–120 m/s, LAS40> 38 m / s, RMS40<20 μV [9].

The statistical analysis of the obtained data was performed in the IBM SPSS Statistics 23.0 software. The assessment of the normality of the distribution of quantitative variables was carried out using the Shapiro-Wilk test. We also performed logistic regression analysis with the assessment of the odds ratio (OR) and linear regression analysis with the estimation of the regression coefficient — B, and the coefficient of determination — R2. The t-test was for paired samples was performed. We calculated mean (M); confidence interval (CI) was set up as 95% for the mean; standard deviation (SD); the level of significance (p). The differences were considered statistically significant with p<0.05.

## Results

When we compared the results of high-resolution ECG parameters (Table 1) during 10-year follow-up, we have found that TotQRSF increased by 1.33 m/s; LAS40 by 2.83 m/s, and RMS40 decreased by 9.85 μV, however, only the change of the last two indicators were statistically significant.

Due to the fact that many participants with RHD had aortic stenosis, we assessed the effect of VLPs parameters of combined mitral and aortic stenosis. The difference was significant for the TotQRSF parameter (p=0.001): in patients with mitral stenosis — 88.84 (87.73; 90.25) m/s; in patients with combined mitral and aortic stenosis — 97.64 (94.27; 101.02) m/s. The groups did not differ by the RMS40 and LAS40 parameters. The comparison of patients with RHD and patients only with aortic stenosis also revealed significant difference (p= 0.001) in TotQRSF by 91.13±17.55 m/s (aortic stenosis — 100.33± 25.19 m/s). As well as the comparison with patients with only mitral regurgitation (p= 0.001): TotQRSF 86.35± 10.72. The values of RMS40 and LAS40 parameters in patients with RHD, mitral regurgitation and isolated aortic stenosis did not differ significantly. We also assessed the effect of VLPs on the severity of mitral stenosis. Patients were divided into two groups depending on the area of the mitral valve orifice: less than 1.5 $cm^2$ and over 1.5 $cm^2$, that is the criterion for surgical treatment of the defect. However, these groups of patients with RHD did not differ by the VLPs parameters: TotQRSF 88.82 (87.20; 90.44) m/s (SMo<1.5 $cm^2$ – 89.96 (87.95; 91.97) m/s); RMS40 44.65 (41.17; 48.12) μV (SMo<1.5 $cm^2$–41.63 (38.58; 44.68) μV); LAS40 32.23 (31.06; 33.39) m s (SMo<1.5$cm^2$ – 30.49 (29.20; 31.78) m/s).

Initially, participants with RHD were divided into two groups depending on the presence of pulmonary hypertension (Table 2). The group with pulmonary hypertension showed the decrease of the following indicators: RMS40 (B= –5.288 (–9.731; –0.845), p=0.020, R2–0.009); TotQRSF (B= –2.266 (–4.411; –0.122), p= 0.038, R2–0.007) and almost significant change of LAS40 (B= –2.767 (–5.535; 0.002), p= 0.050, R2–0.006).

The total number of patients with mitral stenosis was 260 and 83 patients underwent valve surgery, the time after the intervention before VLPs was 4.95± 2.24 years. The analysis of the VLPs in the group of

Table 1. **The dynamics of VLPs parameters**

| ECG paramters | Initial M±SD | After 10-year follow-up M±SD | The difference between parameters M (95% CI) | p |
|---|---|---|---|---|
| TotQRSF, m/s | 88.13±11.35 | 89.46±16.14 | 1.33 (–3.54; 0.89) | 0.237 |
| RMS40, μV | 47.81±27.37 | 37.96±21.49 | 9.85 (5.72; 13.98) | 0.001 |
| LAS40, m/s | 29.89±9.26 | 32.72±14.76 | 2.83 (5.01; 0.65) | 0.012 |

Table 2. **VLPs parameters in patients with pulmonary hypertension**

| ECG parameters | RHD without pulmonary hypertension; M (95% CI) | RHD with pulmonary hypertension; M (95% CI) | p |
|---|---|---|---|
| TotQRSF, m/s | 92.66 (89.99;95.32) | 89.89 (88.54; 91.24) | 0.050 |
| RMS40, μV | 45.62 (42.06;49.18) | 40.33 (37.55; 43.11) | 0.020 |
| LAS40, m/s | 33.75 (31.82;35.68) | 31.48 (30.32; 32.65) | 0.038 |

patients with RHD who underwent surgical treatment of the defect showed that the frequency of VLPs significantly increased in the operated group (Table 3): TotQRSF up to 94.43± 1.79 m/s (OR 1.088 (1.038; 1.139), p= 0.001) and LAS40 up to 34.39± 1.43 m/s (OR 1.127 (1.038; 1.224), p= 0.004). There were no differences in RMS40 between the groups, however, OR was 1.041 (1.012; 1.070), p= 0.005.

During the follow-up period 30 patients died out of 260 patients with RHD, the main cause of death was RHD. The comparison VLP parameters in deceased and survived patients is presented in table 4. Deceased patients had significantly higher TotQRSF 97.00± 12.67 m/s (p= 0.008, OR 1.026 (1.007; 1.046)) and LAS40 indices 36.57±15.25 m/s (p= 0.029, OR 0.964 (0.933; 0.996)), and showed significant decrease of RMS40 to 27.43±15.19 μV (p=0.439, OR 0.995 (0.982; 1.008)).

## Discussion

VLPs that are known to reflect electrical and anatomical heterogeneity of the myocardium with the development of zones with normal and delayed conduction [7], changed in patients with RHD during ten-year follow-up — the RMS40 decreased and LAS40 increased. These changes reflect the processes in ventricular myocardium in patients with RHD. However, the influence of valvular heart disease: mitral and aortic stenosis, mitral regurgitation, combined mitral and aortic stenosis, on VLPs parameters (RMS40 and LAS40) has not been shown previously. This may be partly explained by the absence differences in the number of foci with delayed fragmented activity [3] in patients with various valvular heart diseases. The exception was significant change of TotQRSF parameter in these groups of patients. This may indicate higher number of zones with slow conduction of excitation and increased risk of life-threatening arrhythmias according to the TotQRSF parameter in patients with valve stenosis and lower number — with mitral valve regurgitation. The results were similar in patients with different severity of mitral stenosis.

However, in patients with pulmonary hypertension, the changes were less severe (according to TotQRSF and LAS40 parameters). Although patients with pulmonary hypertension are expected to have higher number of zones with electrical heterogeneity in the myocardium. The obtained results may be explained by the fact that most changes on echocardiography in patients with mitral stenosis appear in the right ventricle and atrium, while there were no significant differences of the parameters in the left cavities and ventricular hypertrophy between groups. In the group of patients who underwent surgery, we expected the decrease of VLPs parameters due to the improvement of hemodynamics; however, in patients with prosthetic valves, these parameters were significantly higher. The reason for such results may be postoperative changes in the myocardium [4] or initially high VLPs parameters in these patients.

One of the most significant results was obtained in this study when comparing VLPs parameters in deceased and survived patients. It has been shown not only significant change of all VLPs parameters in deceased patients, but also the influence of these indicators on the outcome [8] in patients with RHD. Therefore, the dynamics of VLP parameters determines the need for its further investigation and control in patients with RHD.

## Conclusion

Therefore, patients with RHD showed the deterioration of VLP parameters with the severity of valvular heart disease, and deceased subjects with RHD had more pronounced VLP and increased TotQRSF. VLPs did not differ between groups with various types of valvular heart disease.

**Conflict of interest:** none declared

Table 3. **VLPs in participants with and without surgery**

| ECG parameters | Patients with RHD after surgery M±SD | Patients with RHD without surgery M±SD | p |
|---|---|---|---|
| TotQRSF, m/s | 87.62±14.76 | 94.43±19.64 | 0.001 |
| RMS40, μV | 40.05±20.89 | 39.55±26.74 | 0.856 |
| LAS40, m/s | 30.70±11.28 | 34.39±15.97 | 0.023 |

Table 4. **VLPs in deceased and survived patients with RHD**

| ECG parameters | Survived patients with RHD M±SD | Deceased patients with RHD M±SD | p |
|---|---|---|---|
| TotQRSF, m/s | 88.98±16.59 | 97.00±12.67 | 0.013 |
| RMS40, μV | 40.67±22.83 | 27.43±15.19 | 0.001 |
| LAS40, m/s | 31.40±12.62 | 36.57±15.25 | 0.041 |

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# Smoking, work and family stress in an open population aged 45–69 years in Siberia, Russia

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**Abstract**

**Objective.** *To study the association between smoking and work and family stress in an open population aged 45–69 years in Novosibirsk, Russia.*

**Materials and methods.** *This prospective cohort study HAPIEE (№ AAAA-A17–117112850280-2) was carried out in 2013–2016 and included a random representative cohort of 4171 Novosibirsk citizens aged 25–69 years. Of those, 1770 (42.4 %) were men and 2401 (57.6 %) were women who lived in Novosibirsk permanently. We used*

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*the WHO questionnaires "Knowledge and Attitude towards Health" to assess attitude towards smoking. The level of work-related and family-related stress was assessed with the Karasek scale. The scales were adjusted during the large epidemiological study that was conducted as a part of the WHO-MONICA psychosocial program in 1988–1994.*

**Results.** *Among people aged 45–69 25% were smokers (53% men and 17% women). Men made more attempts to quit smoking compared with women. Smoking prevalence is lower among older adults. Of all the participants, 14% indicated that they had high levels of family-related stress (11.8% men and 15.9% women). The level of family-related stress was not associated with age. 16.4% of respondents indicated that they had high levels of work-related stress (15.8 men and 16.8 women). The level of work-related stress was higher in the younger age groups both in men and women. Among people with low level of family-related stress 22.1% are smokers and among those with high level of family-related stress — 22.7%. Of those with high level of work-related stress 26.7% are smokers and with low levels of work-related stress — 12.4%. Individuals who indicated that they had low level of work-related stress tend to quit smoking more often and those who have high level of work-related stress try to change their attitude towards smoking more often. The participants with high level of family-related stress tend to quit smoking or change their attitude more often.*

**Conclusion.** *Our study showed that the prevalence of smoking among people aged 45–69 years was 24.8%. There was no difference in the amount of smoking depending on the levels of family-related stress. At the same time, there were twice as many smokers among the participants with high level of work-related stress compared with those with low work-related stress. The participants with high level of family-related stress tend to quit smoking more often compared with those with the same level of work-related stress. The results of our study indicate that the preventive measures are needed in order to lower the prevalence of smoking and the levels of stress in people aged 45–69 years.*

**Keywords***: epidemiology, work-related stress, family-related stress, smoking.*

**Conflicts of interest:** none declared.

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## Introduction

The major health risk factors in Russia are psychosocial and behavioral factors. They play a major role in the development of cardiovascular disease (CVD) and mortality rate. Smoking is one of the most important behavioral factors [1, 2]. According to the World Health Organization (WHO) report on the global tobacco epidemic 2009, tobacco is one of the leading causes of preventable death cases and annually causes deaths of more than 5 million people worldwide. Tobacco smoking causes lung cancer and CVD that eventually lead to death. These cases are mostly seen in the middle- and low-income countries. If the smoking rate stays the same, then by 2030 over 8 million people will be dying from smoking-associated diseases annually and by the end of the decade smoking will cause up to 1 billion deaths worldwide [3, 4]. People with psychosocial and behavioral risk factors have the highest risk of CVD (arterial hypertension, myocardial infarction, stroke) development [5].

As such, the objective of this study was to evaluate the association between smoking and work and family stress in an open population aged 45–69 years in Novosibirsk, Russia.

## Materials and methods

The HAPIEE (Health, Alcohol and Psychosocial Factors In Eastern Europe) [6] study was carried out in 2003–2005 and included a random representative cohort of Novosibirsk citizens aged 45–69 years (n=4171). Of those, 1770 (42.4%) were men and 2401 (57.6%) were women who lived in two districts of Novosibirsk permanently. The mean age was 56.5± 7.01 years in men and 56.3± 7.07 years in women. The response rate was 61%. We used the WHO questionnaires "Knowledge and Attitude towards Health" to assess attitude towards smoking. The level of work-related and family-related stress was assessed with the Karasek scale. The scales were adjusted during the large epidemiological study that was conducted as a part of the WHO "MONICA" (Multinational Monitoring of Trends and Determinants of Cardiovascular Disease) study and MONICA-Psychosocial Optional Study (MOPSY) in 1988–1994 [7–11]. The questionaries were filled in by

the participants. Statistical analysis was performed using IBM SPSS Statistics version 11.5. Kruskal-Wallis One Way Analysis of Variance, Kruskal-Wallis H — equivalent to Chi square were used to assess the difference between groups. p≤ 0.05 was considered statistically significant.

The study was approved by the local biomedical ethics committee (Protocol № 4, 15.10.2009).

## Results

Smoking rate among young people aged 25–44 was 31.8%, among people aged 45–69 years — 24.7%. Of those, 27.3% and 20.2% respectively would like to change their attitude towards smoking, quit smoking or decrease the amount of cigarettes they smoke ($\chi^2$=53.953 df=5; p<0.001).

Both in the younger age group (25–44 years) and in the older age group (45–69 years) most people face family conflicts (35.3% and 45.2% ($\chi^2$=42.412 df=3; p<0.001)), death or disease of a close relative (23.1% and 38.9% ($\chi^2$= 81.592 df=3 p<0.001)), and changes in the family status (20.5% and 21% ($\chi^2$=6.363 df=2 p<0.05)), respectively.

The most common workplace-associated stressful situations in the two age groups are listed in the Table 3 and are, as follows: high level of responsibility at work — 60.1% and 42.5% ($\chi^2$=92.559 df=2; p<0.001), inability to relax after work — 34.3% and 41.4% ($\chi^2$=58.901 df=4; p<0.001), change of specialty — 47% and 38.9% ($\chi^2$=20.538 df=1; p<0.001), increased workload — 36.6% and 30.2%($\chi^2$=23.832 df=2; p<0.001), unsatisfying job — 8.1 and 14.9% ($\chi^2$=79.406 df=4; p<0.001), respectively.

We also assessed attitude towards smoking in people aged 25–69 years depending on sex. In the younger age group 43.7% of men and 22.8% of women are smokers. More men than women tried to change their smoking status (11.7% vs 4%, respectively). In the older age group 35% and 17.2% of women are smokers, and more men than women never tried to quit smoking (6.6% vs 3%, respectively). It is clear that in the both age groups there are more male smokers than female; however, there are more smokers among younger people (25–44 years) compared with older people (45–69 years) ($\chi^2$=481.543 df=15; p<0.001(total); $\chi^2$=16.682 df=5; p<0.001 (men); $\chi^2$=46.674 df=5; p<0.001 (women)).

Moreover, we assessed attitude towards smoking in three additional subgroups divided by age: 1st group (45–54 years), 2nd group (55–64 years) and 3d group (65–69 years). There are 29.2% of smokers in the 1st age group, 23.2% of smoker in the 2nd age group and 16% in the 3d age group. More individuals in the 1st and 2nd age groups tried to quit smoking compared with the participants from the 3d group. The number of participants who never tried to change their attitude towards smoking decreases by half with age. In the older age groups there were statistically significantly more non-smokers (Kruskal-Wallis One Way Analysis of Variance Kruskal-Wallis H (equivalent to Chi square)= 54.389, Degrees of freedom= 5, P value= 0.00000).

When we analyzed attitude towards smoking among men of different age, we determined that in the 1st age group 43% of men are smokers, in the 2nd group — 33% and in the 3d group — 21%. Compared with the 3d group, more men in the 1st and 2nd age groups wanted to quit smoking (34% and 27% vs 18%). The proportion of men who smoke and have never tried to quit is three times smaller in the 3d age group — 2.2% compared with 8.6% in the 1st age group ((Kruskal-Wallis One Way Analysis of Variance Kruskal-Wallis H (equivalent to Chi square)= 49.515, Degrees of freedom= 5, P value= 0.0000000).

We also analyzed attitude towards smoking among women of different age and determined that in the 1st age group 30% of women are smokers, in the 2nd group — 26% and in the 3d group — 21%. More women in the 1st (16%) and 2nd (14%) age group were interested in quitting smoking than in the 3d age group (10%). The proportion of women who smoke and have never tried to quit is higher in the 1st age group compared with the 2nd and 3d groups (Kruskal-Wallis One Way Analysis of Variance Kruskal-Wallis H (equivalent to Chi square)= 16.736, Degrees of freedom= 5, P value= 0.0050281).

*Table 1.* **Stress levels distribution in Novosibirsk population aged 45–69 years**

| | Men | | Women | | Both | |
|---|---|---|---|---|---|---|
| Family-related stress | N | % | N | % | N | % |
| Low | 108 | 6,1 | 141 | 5,9 | 249 | 6,0 |
| Medium | 1453 | 82,1 | 1879 | 78,3 | 3332 | 79,9 |
| High | 209 | 11,8 | 381 | 15,9 | 590 | 14,1 |
| Total | 1770 | 100,0 | 2401 | 100 | 4171 | 100,0 |

Family stress levels are similar among participants of all ages. High family stress level varies from 14 to 14.7%. As such, it can be assumed that family stress level in people aged 45–69 years is not associated with age (Kruskal-Wallis One Way Analysis of Variance Kruskal-Wallis H (equivalent to Chi square)= 0.385, Degrees of freedom=2, P value=0.824968).

Family stress level distribution in male participants is similar in all age groups and reaches maximal levels in the 2nd age group (12.5%), but these results don't reach statistical significance (Kruskal-Wallis One Way Analysis of Variance Kruskal-Wallis H (equivalent to Chi square)= 0.640, Degrees of freedom= 2, P value= 0.726310).

Family stress level distribution in female participants is also similar in all age groups — 15.7% in the 1st age group and 17.7% in the 3d age group (Kruskal-Wallis One Way Analysis of Variance Kruskal-Wallis H (equivalent to Chi square)= 0.126, Degrees of freedom= 2, P value= 0.938927).

High workplace-associated stress levels were noted in 16.4% of all the participants. Stress levels were statistically significantly higher in women compared with men (16.8% vs 15.8% respectively). The proportion of individuals with medium workplace-associated stress levels was higher in men (69.4%) than in women (65.2%).

We also analyzed workplace-stress level among both men and women of the three age groups and the analysis showed that there were more individuals with high workplace-associated stress levels in the 1st age group (18.3%) compared with the 3d age group (12.3%). At the same time, the proportion of individuals with low workplace-associated stress was higher in the 3d age group — 22.3% compared with the 1st age group (12.2%) ((Kruskal-Wallis One Way Analysis of Variance Kruskal-Wallis H (equivalent to Chi square)= 46.622, Degrees of freedom= 2, P value= 0.00000).

Analysis of workplace-associated stress distribution in male participants showed that men in the 1st and 2nd age groups had higher levels of stress (17% and 16.7%) compared with the participants in the 3d group (11.3%), and the differences are statistically significant. There were more men with low workplace-associated stress levels in the 3d group (19.2%) compared with the 1st group (11%) (Kruskal-Wallis One Way Analysis of Variance Kruskal-Wallis H (equivalent to Chi square)= 13.712, Degrees of freedom= 2, P value= 0.001053).

Analysis of workplace-associated stress distribution in female participants showed that the proportion of women with high stress level was higher in the 1st age group (19.5%) compared with the 3d age group (13.1%). The proportion of women with low workplace-associated stress level was higher in the 3d group (24.6%) compared with the 1st age group (13.2%) (Kruskal-Wallis One Way Analysis of Variance Kruskal-Wallis H (equivalent to Chi square)= 34.910, Degrees of freedom= 2, P value= 0.00000).

Among the participants with high family-related stress level 22.7% are smokers and with low family-related stress level — 22.1% (Table 2). The participants with high family-related stress more often were able to successfully quit smoking (23.1% vs 10.8%) or reduce the number of cigarettes they smoke daily. The participants with medium family stress level were usually unsuccessful in quitting smoking. Almost

*Table 2.* **Family-related stress levels distribution in Novosibirsk population aged 45–69 years depending on attitude towards smoking**

| Attitude towards smoking | Stress level (men and women 45–69 years) | | | | | |
|---|---|---|---|---|---|---|
| | Low | | Medium | | High | |
| | N | % | N | % | N | % |
| Have you ever tried to change your attitude towards smoking? | | | | | | |
| 1. I have never smoked | 167 | 67,1 | 1715 | 51,5 | 302 | 51,2 |
| 2. I have stopped smoking | 27 | 10,8 | 772 | 23,2 | 154 | 26,1 |
| 3. I have reduced the number of cigarettes I smoke | 6 | 2,4 | 214 | 6,4 | 49 | 8,3 |
| 4. I have stopped smoking for some time, but now I smoke again | 21 | 8,4 | 227 | 6,8 | 47 | 8,0 |
| 5. I tried to quit smoking, but failed | 9 | 3,6 | 247 | 7,4 | 25 | 4,2 |
| 6. I smoke and I have never tried quitting | 19 | 7,6 | 157 | 4,7 | 13 | 2,2 |
| Total | 249 | 100% | 3332 | 100% | 590 | 100% |

twice as many participants with high family stress level tried to change their attitude towards smoking (20.5 %) as with low family stress (14.5 %).

Analysis of family stress distribution in male participants depending on the attitude towards smoking showed that more men with high family stress level were smokers (35.9 %) than with low family stress (33.4 %). Among men with high family stress only 31.1 % never smoked, anf among men with low family stress — 51 %. More men with high family stress used to smoke, but quit (33 %), compared with men with low family stress (14.8 %). More men with low family stress currently smoke and have never tried to quit (10.2 %) compared with those with high family stress — 2.4 % (Kruskal-Wallis One Way Analysis of Variance Kruskal-Wallis H (equivalent to Chi square)= 26.845, Degrees of freedom= 5, Pvalue= 0.000061).

Analysis of family stress distribution in female participants depending on the attitude towards smoking showed that 14.2% of women with low family stress and 15.5% of women with high family stress are smokers. 22.3 % of women with high family stress were able to quit smoking compared with women with low family stress (6.4 %). More women with low family stress never smoked (79.4 %) compared with women with high family stress (62.2 %). At the same time, more women with low family stress smoke and never tried to quit — 5.7 % compared with 2.1 % (Kruskal-Wallis One Way Analysis of Variance Kruskal-Wallis H (equivalent to Chi square)= 20.550, Degrees of freedom= 5, P value=0.000985).

Currently, 26.7 % of the participants with high workplace-related stress and 12.4 % of the participants with low workplace-related stress smoke (Table 3). More individuals with low workplace-related stress used to smoke but were able to quit compared with individuals with high workplace-related stress. Also, more individuals with low workplace-related stress smoke less than they used to, quit smoking for some time or tried to change their attitude towards smoking but didn't succeed.

Analysis of workplace stress distribution in male participants depending on the attitude towards smoking showed that 36.8% of men with high workplace stress and 26.1 % of men with low workplace stress. At the same time, more men with high level of workplace related stress (40 %) compared with men with low level of workplace stress (26.8 %) have never smoked. More men with low workplace-related stress used to smoke but were able to quit (47.1 %) compared with men with high workplace-related stress (23.2 %). More men with low workplace-related stress smoke and have never tried to quit (8.8 %) compared with those with high workplace-related stress level (5.4 %). More men with high workplace-related stress smoke less than they used to, quit smoking for some time or tried to change their attitude towards smoking but didn't succeed. (Kruskal-Wallis One Way Analysis of Variance Kruskal-Wallis H (equivalent to Chi square)= 44.518 Degrees of freedom= 5, P value= 0.00000).

Analysis of workplace stress distribution in female participants depending on the attitude towards smoking showed that 19.6% of women with high workplace stress and only 4.2% of women with low workplace stress. More women with low workplace stress (47.9 %) compared with women with high workplace stress (13.4 %) used to smoke but were able to quit. More women with high workplace stress (17.4 %) compared with women with low workplace stress (3.7 %)

*Table 3.* **Workplace-related stress levels distribution in Novosibirsk population aged 45–69 years depending on attitude towards smoking**

| Attitude towards smoking | Stress level (men and women 45–69 years) | | | | | |
|---|---|---|---|---|---|---|
| | Low | | Medium | | High | |
| | N | % | N | % | N | % |
| **Have you ever tried to change your attitude towards smoking?** | | | | | | |
| 1. I have never smoked | 277 | 40,0 | 1525 | 54,6 | 382 | 55,9 |
| 2. I have stopped smoking | 330 | 47,6 | 504 | 18,0 | 119 | 17,4 |
| 3. I have reduced the number of cigarettes I smoke | 28 | 4,0 | 187 | 6,7 | 54 | 7,9 |
| 4. I have stopped smoking for some time, but now I smoke again | 19 | 2,7 | 207 | 7,4 | 69 | 10,1 |
| 5. I tried to quit smoking, but failed | 14 | 2,0 | 232 | 8,3 | 35 | 5,1 |
| 6. I smoke and I have never tried quitting | 25 | 3,6 | 140 | 5,0 | 24 | 3,5 |
| Total | 693 | 100 | 2795 | 100,0 | 683 | 100,0 |

smoke less than they used to, quit smoking for some time or tried to change their attitude towards smoking but didn't succeed (Kruskal-Wallis One Way Analysis of Variance Kruskal-Wallis H (equivalent to Chi square)= 195.047, Degrees of freedom= 5, P value= 0.00000).

## Discussion

According to the Tobacco Research and Intervention Program everyone gets exposed to some kind of stress during their life and cope with it differently. Many people believe that stress can be reduced by smoking a cigarette. There are several reasons why people use smoking as a coping mechanism: they can relax and socialize during smoking and later helps to manage symptoms of nicotine withdrawal symptoms [14].

However, there are no evidence that nicotine helps to relieve stress and at the same time, there are no studies that showed that smokers have higher levels pf stress compared to non-smokers [15–17].

During the observation period in 1984–2003 in Novosibirsk we have carried out four population screenings in 1984, 1988, 1994 (25–64 years) and 2003–2005 (45–69 years) and studied attitude towards smoking. According to the results of these screening programs, the number of smokers has increased, especially among women. In 1984–1989 55% of men and 4% of women smoked, and by 1994 the number of smokers increased — 61% of men and 11% of women [18–21]. The problem of smoking control has only worsened over the described period of time, as the prevalence of tobacco use has increased [2]. The results of the current study are similar to the previous findings and tendencies. We analyzed the prevalence of family stress, workplace-associated stress and their association with smoking in men and women aged 45–69 years. According to our results, 35% of men and 17% of women smoke (24.8% of all population). There are many people who wish to change their attitude towards smoking and quit or reduce smoking (72%). There are more male smokers than female smokers; men tended to change their attitude towards smoking more often compared with women, but at the same time, there are more individuals who never tried to quit among men compared with women. Prevalence of smokers decrease with age.

Analysis of workplace stress in different age groups showed that the level of stress is similar among people of different age both in men and in women and, therefore, is not associated with age.

Analysis of family stress in different age groups showed that individuals with high level of family stress usually tended to quit smoking or change their attitude towards smoking more often compared with individuals with low level of family stress.

There were more smokers and those who were able to quit smoking among men and women with high level of family stress. Men and women with low level of family stress have even never smoked or are smokers who are not ready to change their attitude towards tobacco use.

Analysis of workplace-related stress showed that people with low level of workplace-related stress tended to quit smoking more often, and those with high level of workplace-related stress tended to change their attitude towards smoking more often.

Men and women with high workplace-related stress smoke more often but also try to change their attitude towards smoking more often. Men and women with low workplace-related stress quit smoking more often, but at the same time the proportion of individuals who smoke and have never tried to quit is higher in this cohort.

It can be assumed that stimulation and relaxation is often needed at the workplace, and according to some studies, adult smokers have periods of high stress between smoking and only smoking can relieve this stress [22–24]. However, when some time passes, people develop stress associated with nicotine withdrawal and need to smoke again. We agree with the authors who state that smoking doesn't relieve stress and can only cause its development [24].

## Conclusion

1. Our study showed that the prevalence of smoking among people aged 45–69 years was 24.8% (35% men and 17% women). There are many people who wish to change their attitude towards smoking and quit or reduce smoking (72%). Men tended to change their attitude towards smoking more often compared with women.

2. There was no difference in the amount of smoking depending on the levels of family-related stress. Both men and women with high level of family-related stress are often smokers but try to quit more often. Men and women with low level of family stress have even never smoked or are smokers who are not ready to change their attitude towards tobacco use.

3. There were twice as many smokers among the participants with high level of work-related stress as among those with low work-related stress. The participants with high level of workplace-related stress tend to quit smoking more often and the

participants with low levels of workplace-related stress try to change their attitude towards smoking more often.

4. The participants with high level of family-related stress tend to quit smoking more often compared with those with the same level of work-related stress.

**Conflict of interest**: none declared

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# Predicting renal dysfunction in patients with chronic heart failure

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**Abstract**

**Objective.** *To determine informative methods for the identification of renal dysfunction (RD) in patients with chronic heart failure (CHF).*

**Materials and methods.** *The study included 325 patients with coronary heart disease (CHD) with I (n= 92), II (n= 140) and III (n= 93) functional class (FC) of CHF. All patients underwent clinical examination, 6-minute walk test (6MWT), echocardiography (EchoCG), doppler ultrasound of renal blood flow of the right and left renal artery (RA); serum creatinine assessment (Cr), glomerular filtration rate (GFR) was estimated by the CKD-EPI formula (eGFR). All the patients were divided into 3 groups according to eGFR: group 1 with eGFR⩽ 60 (eGFR= 30–60) ml / min / 1.73 m² (n= 92), group 2 with eGFR= 60–90 ml / min / 1.73 m² (n= 158), group 3 with eGFR⩾90 ml / min / 1.73 m² (n= 69).*

**Results.** *Patients with CHF had subclinical impairment of renal function: 30.1 % of examined patients with I–III FC of CHF had eGFR below 60 ml / min / 1.73 m², 44.6 % had microalbuminuria (n= 145). The level of microalbuminuria and albumine / creatinione ratio were significantly higher in patients with CHF compared with the control group. Patients with I–III FC of CHF showed significant increase in resistant and pulsative indicators of the right and left RA, and decreased linear blood flow.*

**Conclusion.** *All the studied methods, including eGFR identification as the gold standard, as well as the assessment of the pulsative and resistant indices of RA, albumine / creatinine ratio, and microalbuminuria can be considered informative for the assessment of renal functional state in patients with CHF.*

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**Key words:** *chronic heart failure, renal dysfunction, glomerular filtration rate, microalbuminuria, renal blood flow.*

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## Introduction

Chronic heart failure (CHF) is one of the most urgent medical and social issues of increased concern worldwide. The prevalence and unfavorable prognosis of CHF is constantly increasing [1]. The development of renal dysfunction (RD) in patients with CHF can be explained by neurohumoral imbalance that leads to excessive sodium and water retention, as well as the progression of CHF [2]. It has been found that impaired renal function is an independent risk factor for heart failure that progressively aggravates the course of CHF and complicates the treatment of such patients [3]. According to some reports, impaired renal function have more pronounced effect on clinical course and mortality of patients with CHF compared with functional class (FC) of heart failure and left ventricular ejection fraction [4]. The CHARM study found that the presence of microalbuminuria (MAU) in patients with CHF increases the risk of adverse clinical events [5]. Currently, MAU is considered as one of the most significant predictors for the development of cardiovascular complications and can be used for the diagnosis of RD in patients with CHF [6]. Data of most clinical trials, large retrospective analyzes from the PRIME II and SOLVD Prevention and Treatment studies, and the meta-analysis of publications for over 60 years indicates that RD negatively affects outcomes, length of stay in a hospital and overall mortality in patients with CHF [3,7]. However, the results of these studies are based on the evaluation of blood creatinine, MAU and glomerular filtration rate (GFR), when the state of renal hemodynamics and its association with GFR in patients with CHF remains unknown. In connection with the above, it is essential to optimize the early diagnosis of kidney damage in patients with CHF with the identification of RD predictors [8, 9, 10]. Therefore, we decided to assess renal function in patients with CHF and without primary renal and / or endocrine pathology and to determine the most significant methods for early diagnosis of RD in patients with CHF.

## Objective

To identify the most informative methods for the diagnosis of RD in patients with CHF.

## Materials and methods

The study included 325 patients with coronary heart disease (CHD) and with I (n=92), II (n=140) and III (n=93) FC of CHF. Average age of study participants was 62,5±8,14 years. The control group included 20 healthy participants. Clinical characteristics of included patients is presented in table 1.

All the patients underwent general clinical examination including: 6-minute walk test (6MWT), echocardiography (EchoCG), doppler ultrasound of renal blood flow with color doppler mapping with the assessment of peak systolic velocity (PSV), end-diastolic velocity (EDV), time-averaged velocity (TAV), resistance index (RI), pulsatile index (PI) of the right and left renal artery (RA) [7].

The state of renal filtration function was estimated by serum creatinine assessment (Cr), glomerular filtration rate (GFR) was estimated by the CKD-EPI formula (eGFR) [10], albumin/ creatinine ratio (Al/Cr) (mg/mmol) in morning urine. Albumin excretion in urine was determined by enzyme-linked immunosorbent assay (ELISA) by Al /Cr ratio (mg/g), MAU was determined if this ratio was over 20 mg/g, high normal level of albuminuria — over 10 mg/g [4]. All the patients were divided into 3 groups according to eGFR: group 1 with eGFR⩽ 60 (eGFR= 30–60) ml/min/1.73 $m^2$ (n=92), group 2 with eGFR= 60–90 ml/min/1.73 $m^2$ (n=158), group 3 with eGFR⩾90 ml/min/1.73 $m^2$ (n=69).

The study was performed in accordance with the standards of Good Clinical Practice and the principles

Table 1. **Clinical characteristics of included patients**

| Parameter | Total | Men | Women | I FC of CHF | II FC of CHF | III FC of CHF | Arterial hypertension (AH) | Postinfarction cardiosclerosis (PICS) |
|---|---|---|---|---|---|---|---|---|
| n (number of patients) | 325 | 205 | 120 | 92 | 140 | 93 | 298 | 166 |

of Helsinki Declaration. The study protocol was approved by Ethical Committees of all clinical centers. Written informed consent was received from all the participants prior to the study.

Statistical analysis was performed using Microsoft Office Excel-2013 and STATISTICA-6,0 software. Methods of parametric and non-parametric statistics were used with the estimation of means (M), standard deviation (SD), standard error of the mean (m) and relative values (frequency, %). Differences between groups were compared with Student t-test (t) with the calculation of error probability (p). Kurtosis value was used to determine whether the data set was modeled for normal distribution. p<0,05 was set as the level of significance.

## Results and discussion

The analysis of Cr level and eGFR showed that 98 patients (30.1%) with I–III FC of CHF had eGFR<60 ml/min/1.73 m$^2$, 227 patients (69.9%) — over 60 ml/min/1.73 m$^2$, of which 158 patients had eGFR over 60 ml/min/1.73 m$^2$, but under 90 ml/min/1.73 m$^2$ that corresponds to stage II CKD and 69 patients had eGFR≥90 ml/mi/1.73 m$^2$. Patients with I FC of CHF had Cr and eGFR of 86.5±15.35 mcmol/L and 74.5±15.1 ml/in/1.73 m$^2$, respectively, patients with FC II — 93.1±20, 4 mcmol/L and 72.7±16.1 ml/min/1.73 m$^2$, respectively; and with III FC of CHF –103.6±22.2 mcmol/L and 60.4±16.2 ml/min/1.73 m$^2$, respectively. Patients with III FC of CHF had significantly higher Cr level and lower eGFR — 16.5% (p<0.05) and 18.9% (p<0.05), respectively, compared with I FC of CHF. 38 (40.1%) patients with significant GFR decrease (<60 ml/min/1.73 m$^2$) had III FC of CHF.

Albumin excretion (AE) in morning urine was determined by Al /Cr ratio. MAU was determined in 44,6% (n=145) patients. High normal level of albuminuria (HNLA) was determined in 11,4% (n=37) patients. AE was associated with GFR level (r= –0,32, p= 0,01). As it can be seen from table 2, MAU level was significantly higher in I–III FC of CHF compared with the control group.

The state of renal hemodynamics and its relationship with the severity of clinical symptoms and prognosis is worth further investigation. Therefore, the parameters of renal blood flow of the right and left RA were investigated. Patients with I FC of CHF at the level of the right and left RA had increased PI — by 29.1% (p<0.001) and 23.8% (p<0.001), RI — by 6.8% (p<0.001) and 1% (p>0.05), decreased TAV — by 40.9% (p<0.001) and 35.5% (p<0.001), decreased EDV — by 21.4% (p<0.005) and 3% (p>0.05) cm/s, respectively, compared with the control group (Table 3). Patients with II FC of CHF had increased PI — by 30.2% (p<0.001) and 24.6% (p<0.001) and RI — by 7.6% (p<0.001) and 1% (p>0.05), decreased TAV — by 56.9% (p<0.001) and 56.2% (p<0.001), EDV — by 35.2% (p<0.001) and 19,7% (p<0.001), PSV — by 15.8% (p<0.001) and 15.6% (p<0.001), re-

Table 3. **Renal blood flow parameters of the left and right RA in patients with I–III FC of CHF (M±SD)**

| Parameter | Right renal artery | | | | Left renal artery | | | |
|---|---|---|---|---|---|---|---|---|
| | Control group | I FC | II FC | III FC | Control group | I FC | II FC | III FC |
| PSV, sm/sec | 59.57± 1.95 | 57.52±14.77 | 51.42±13.11^ | 49.42±14.51^ | 59.64±3.34 | 57.33±13.08 | 51.58±12.93^ | 50.1±13.27^ |
| RI | 0.669± 0.016 | 0.718±0.030^ | 0.724±0.046^ | 0.718±0.036^ | 0.710±0.01 | 0.716±0.052 | 0.716±0.092 | 0.712±0.054 |
| EDV sm/sec | 19.72± 0.52 | 16.25±4.27**** | 14.59±4.9^ | 14.38±4.76^ | 17.24±0.866 | 16.78±3.6 | 14.4±4.69^ | 14.49±4.21^ |
| TAV sm/sec | 39.64±0.924 | 28.14±4.85^ | 25.27±4.75^ | 24.53±5.52^ | 38.44±2.032 | 28.36±4.09^ | 24, 6±4.93^ | 24.77±4.58^ |
| PI | 1.00± 0.036 | 1.42±0.222^ | 1.44±0.255^ | 1.43±0.262^ | 1.1±0.024 | 1.45±0.277^ | 1.46±0.291^ | 1.41±0.282^ |

**Footnote.** * — the result is significant with p<0,05; ** — the result is significant with p<0,02; *** — the result is significant with p<0,01; **** — the result is significant with p<0,005; ^ — the result is significant with p<0,001 compared with the control group.

Table 2. **Renal function parameters in patients with I–III FC of CHF (M±SD)**

| № п/п | Parameter | Control group (n=20) | I FC of CHF (n=92) | II FC of CHF (n=140) | III FC of CHF (n=93) |
|---|---|---|---|---|---|
| 1 | Cr, mcmol/l | 53.8±12.4 | 86.5±15.4 | 93.1±20.4 | 103.6±22.2 |
| 2 | eGFR, ml/min/1.73 m$^2$ | 126.5±5.5 | 74.5±15.1 | 72.7±16.1 | 60.4±16.2 |
| 6 | Al/Cr in the morning urine (mg/mmol) | - | 10.1±3.2 | 10.3±8.7 | 12.8±4.4 |

Table 4. **RD criteria in patients with CHF (M±SD)**

| Parameter | Patients with I–III FC of CHF | | | | | |
|---|---|---|---|---|---|---|
| | group 1 (eGFR≤60 ml/min/1.73 m²) | p (group 1 vs. group 2) | group2 (eGFR=60–90 ml/min/1.73 m²) | p (group 1 vs. group 3) | group3 (eGFR>90 ml/min/1.73 m²) | p (group 2 vs. group 3) |
| Cr, mcmol/l | 120.7±27.0 | p<0.001 | 88.2±11.5 | p<0.001 | 63.4±11.9 | p<0.05 |
| eGFR, ml/min/1.73 m² | 50.7±8.5 | p<0.01 | 75.0±8.6 | p<0.005 | 96.7±6.2 | p<0.05 |
| Al/Cr in the morning urine (mg/mmol) | 37.3±9.7 | p<0.05 | 10.3±5.7 | p<0.001 | 2.8±4.4 | p>0.05 |
| PSV, right RA/ left RA sm/sec | 50.4±6.9/ 49.5±6.8 | p>0.05 | 53.84±9.08/ 52.77±9.51 | p>0.05 | 54.4±6.2/ 55.25±5.5 | p>0.05 |
| EDV, right RA/ left RA sm/sec | 14.5±2.9/13.9±3.5 | p>0.05 | 15.98±3.88/ 15.8±3.38 | p>0.05 | 15.3±2.8/ 16.0±2.6 | p>0.05 |
| RI, right RA/ left RA sm/sec | 0.86±0.055/ 0.81±0.066 | p<0.05 | 0.751±0.042/ 0.752±0.056 | p<0.05 | 0.688±0.047/ 0.677±0.066 | p>0.05 |
| PI, right RA/ left RA sm/sec | 1.477±0.229/ 1.465±0.256 | p<0.05 | 1.27±0.13/ 1.26±0.11 | p<0.05 | 1.156±0.175/ 1.18±0.18 | p>0.05 |

spectively, compared with the control group. Patients with III FC had increased PI — by 29.9 % (p<0.001) and 21.9 % (p<0.001), decreased TAV — by 61.6 % (p<0.001) and 55.2 % (p<0.001), EDV- by 37.1 % (p<0.001) and 19 % (p<0.001), PSV — by 20.5 % (p<0.001) and 19 % (p<0.001), respectively, compared with the control group. Renal blood flow parameters in patients with CHF are presented in Table 3.

Linear velocities of blood flow (EDV, PSV) were lower in most patients with CHF, and resistance and pulsatile indices were higher compared with healthy controls (p<0,05). Similar blood flow parameters (linear and volumetric) correlated between right and left RA that indicates the absence of renal stenosis of only one artery in included patients (r=0,85, p<0,001).

eGFR reduced to the level of stage 3 CKD in 30 % of patients with CHF and without renal pathology, 58 % of patients with CHF had eGFR over 60 ml/min/1.73 m², but under 90 ml/min/1.73 m² that corresponds to the 2nd stage of CKD. Table 4 presents renal function parameters in patients with eGFR<60 ml/min/1.73 m², eGFR=60–90 ml/min/1.73 m² and eGFR≥90 ml/min/1.73 m² including eGFR, renal blood flow parameters and albuminuria level (Al/Cr).

Patients with various stages of RD had significant differences in parameters: group with eGFR≤60 ml/min/1.73 m² compared with eGFR=60–90 ml/min/1.73 m² and eGFR>90 ml/min/1.73 m² had 3,6 and 13,3 higher level of Al/Cr in the morning urine (p<0,05), respectively, RI at the level of the RA increased by 12,7 % and 30,2 %, respectively, and PI — by 14 % and 21,7 %. At the same time linear parameters of renal blood flow (PSV and EDV) did not differ significantly between groups.

The search for new biological markers of RD in patients with cardiorenal syndrome is worth further investigation [4,11]. The importance of MAU as an isolated precursor of chronic kidney disease (CKD) and cardiovascular mortality has been noted in many prospective and epidemiological studies, especially in patients with diabetes mellitus and arterial hypertension [12,13]. It is known that MAU is associated with atherosclerosis and CKD. It also remarkable that MAU affects mortality in the entire population, and can be used as the indicator of generalized endothelial damage [1,5].

In our opinion even "isolated" CHF can lead to the functional impairment of kidneys [2]. We have assessed the parameters of kidneys functional state in patients with CHF with minimal number of additional factors that can lead to kidney damage. Even in such sample, 30.1 % of patients showed decreased eGFR below 60 ml/min/1.73 m², MAU was detected in 44.6 % (n=145) of patients with CHF. MAU that was established by Al/Cr ratio in patients with I–III FC of CHF was higher compared with the control group an increased with the degree of RD. Patients with I–III FC of CHF showed significant decrease in linear blood flow, an increase of RI and PI as indicators of vascular resistance compared with the control group; as well as significant increase of RI and PI with the degree of RD at the level of the right and left RA. Patients with CHF showed subclinical impairment of renal function, characterized by decreased GFR, MAU, decreased velocity parameters and increased pulsative and resistant indices in the study, which indicate RD and, therefore, can be considered as reliable tool for the identification of RD in these patients. The determination of eGFR, Al/Cr ratio and renal hemodynamics in patients with CHF can be used for the early diagnosis of RD.

Most patients with CHF showed subclinical renal dysfunction [3]. It is known that RD in patients with CHF is associated with decreased ejection fraction followed by renal hypoperfusion and increased renal vascular resistance [7]. The involvement of kidneys is one of the key points in the progression of CHF and, therefore, preservation of renal function is essential in secondary prevention of CHF [2]. Today it is well-known that many risk factors that are associated with the development of CHF are also considered general cardiovascular risk factors. The problem of the association between heart and kidneys is described from two points of view: for one hand, the primary myocardial damage causes the impairment of renal function and central hemodynamics, circulatory hypoxia and humoral changes, for the other hand, renal dysfunction leads to the development and progression of cardiovascular pathology and aggravates disease prognosis [4, 13].

## Conclusion

Patients with CHF showed subclinical renal function impairment: 30,1 % of included patients with I–III FC of CHF had decreased eGFR below 60 ml/min/1.73 $m^2$, 44,6 % (n=145) had MAU.

Patients with I–III FC of CHF showed increased MAU and Al/Cr ratio, increased resistance and pulsative indices and decreased linear blood flow parameters compared with the control group. Increased pulsative and resistance indices of the RA, MAU were associated with GFR decrease, and these parameters can be considered as early predictors of renal function impairment in patients with CHF.

**Conflict of interest:** none declared.

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# Managing patients with chronic kidney disease and cardiovascular comorbidities in primary care

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**Abstract**

*This paper discusses the ambulatory care approaches to patients with co-existing chronic kidney disease (CKD) and cardiovascular disease (CVD). We provide diagnostic algorithm and evaluation principles in this group of patients. We demonstrate our stage-based treatment approach and principles of prevention on the example of a long-term management of an actual patient with arterial hypertension, atrial fibrillation and CKD. We also discuss nephroprotective and cardioprotective regimens and anticoagulation for the prevention of disease progression.*

**Key words:** *atrial fibrillation, comorbidities, chronic kidney disease, polycystic kidney disease, nephroprotection, albuminuria, cardiorenal syndrome*

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## Introduction

Chronic kidney disease (CKD) is a serious medical, social and economic challenge in health care due to the growing prevalence worldwide and close association with chronic disease development, primarily, cardiovascular diseases that lead to worsening of life

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quality, increased mortality and need for dialysis in the majority of patients [1].

Currently the pathogenesis of cardiac and kidney remodeling and early biomarkers of kidney damage and CKD progression are being actively studied. Early biomarkers of kidney damage and CKD progression include NGAL (Neutrophil Gelatinase-Associated Lipocalin), kidney injury molecule-1, liver fatty acid binding protein, fibroblast growth factor 23 and Klotho [2, 3, 4]. Kidney and cardiac remodeling is caused by myofibroblast development and angiofibrogenesis, which is, in turn, is induced by angiotensin II, transforming growth factor beta 1, plasminogen activator inhibitor-1, vascular endothelial growth factor, matrix metalloproteinase and other factors that cause structural and functional changes and heart and kidney fibrosis in CKD patients [5].

The prevalence of CKD varies from 7% to 12.5% according to a number of different sources [6–9]. The National Guidelines "Chronic Kidney Disease: screening, diagnosis, prevention and management" state that CKD is as highly prevalent as hypertension (HTN), diabetes mellitus (DM), obesity and metabolic syndrome [6, 10, 11]. As for 2019, around 30 thousand individuals have stage V CKD and are treated with renal replacement therapy and up to 20 million people have stage I–IV CKD. Moreover, up to 60 million people are currently at risk of CKD. These are the patients with DM, HTN, obesity and heart failure (HF) [12, 13].

## CKD risk factors

In order to identify the patients who are at high risk of CKD, the primary physician should be well aware of CKD risk factors [8].

Individuals with coexistent chronic diseases, that affect kidneys such as HTN, DM, congestive heart failure (CHF), connective tissue diseases are at the highest risk of CKD. Clinical guidelines in endocrinology, cardiology and rheumatology recommend routine control of creatinine level.

Moreover, CKD risk increases with age. Individuals over 50 years of age are at high risk of CKD development.

Another group of patients with high risk of CKD development are individuals with harmful exogenous effects on kidneys, such as:

a. Nephrotoxic medications and nutritional supplements, such as nonsteroidal anti-inflammatory drugs (NSAIDs);

b. Occupational hazards (organic solvents, heavy metals, insecticides, etc.)

c. Diets too low or high in protein, such as sport diet.

Patients with a history of acute kidney injury are also at high risk of CKD.

## CKD and other chronic non-communicable diseases

CKD not only worsens the patient's prognosis and quality of life but also influences other co-existent chronic diseases and may cause their progression. The high prevalence of both CKD and cardiovascular disease (CVD) in the population led to the introduction of the term "cardiorenal syndrome" [14]. The common mechanisms of these diseases like chronic systemic inflammation and endothelial dysfunction cause the development and progression of cardiovascular and renal dysfunction. Furthermore, kidney disease cause anemia, volume overload and calcium and phosphate metabolic disorders that negatively affect CVD [11, 15]. All patients with stage I and II CKD and A2-A3 albuminuria or with stage III CKD are at a very high cardiovascular risk [6, 9].

According to the PREVEND study, albuminuria, which is one of the CKD markers, is an independent risk factor of CVD mortality [3]. CKD also plays an important role is the development of left ventricle diastolic dysfunction in patients with congestive heart failure (CHF) [16].

The ARIC (Atherosclerosis Riskin Communities Study) study showed that the incidence of cardiovascular complications is twice as high in patients with stage III–IV CKD compared with stage II CKD [17].

Arterial hypertension, which is one of the most prevalent chronic noncommunicable diseases, is also closely connected with CKD. The multicenter, observational study CHRONOGRAPH analyzed 1600 patients with HTN. Of those, CKD markers (decreased glomerular filtration rate (GFR)< 60 ml/min/1.73 $m^2$ and/or urine albumin/creatinine ratio> 30 mg/g) were identified in 49.4% [18].

One of the most important problems in daily clinical practice is a combination of CKD and atrial fibrillation (AF). Both diseases are highly prevalent, especially in older patients. Around 15–20% of CKD patients have one of the forms of AF [19–20].

The connection between these two diseases can be explained by the pathogenesis of their development — atherosclerosis, chronic inflammation, hypertension, diabetes, obesity. CKD is also an important predictor of atrial fibrillation (AF) relapse after catheter ablation in patients with unstable AF [19]. It is crucial to detect CKD in AF patients, determine its stage and monitor its development, because the worsening of

kidney function affects pharmacodynamics of the most drugs. CKD stage determines the possibility to use the renin-angiotensin-aldosterone system (RAAS) blockers and the dosing of anticoagulants.

Along with CVD, DM is an important cause of CKD. According to the Russian National DM registry (2013–2016), CKD is highly prevalent in this group of individuals. At the same time, the majority of patients with DM had stage I and II CKD, meaning that most care provides follow DM guidelines and diagnose DM early due to annual RFG and albuminuria control [22].

Timely diagnosis and appropriate management of CKD in elderly patients are important goals of outpatient care. Being over the age of 50 is an unmodifiable CKD risk factor and most elderly patients have multiple comorbidities, in particular, HTN, atherosclerosis and DM that increase the risk of kidney damage. Uncontrolled NSAIDs use is another major reason of CKD development in this group of patients [23].

## CKD diagnosis

CKD is diagnosed based on the following criteria [11]:

- Laboratory changes over the past 3 months;
- Histological changes in the kidney;
- Structural changes seen in visualization;
- History of kidney transplantation.

As such, the presence of structural changes (nephrolithiasis, multiple cysts, hydronephrosis, etc.), renal disease based on the laboratory changes (pyelonephritis), histological changes on biopsy (glomerulonephritis) or persistent signs of renal dysfunction verify the diagnosis of CKD. The markers of renal dysfunction include:

- Albuminuria (⩾ 30 mg/24 h)
- Albumin/creatinine ratio⩾ 30 mg/g (⩾3 mg/mmol)
- GFR<60 ml/min/1,73 $m^2$.

Screening of high-risk patients is crucial for prompt diagnosis of CKD at early stages, when preventive measures are most effective. Besides from blood creatinine and GFR, albuminuria is another essential marker for CKD.

In routine outpatient care the presence of excessive protein in urine is assessed with urine dipstick test strips but this diagnostic tool can determine only major proteinuria. In case of severe proteinuria, the level of albuminuria can be determined in the single portion of urine. Albuminuria test is a simple and highly sensitive method that can be used to identify CKD early and, therefore, should be used as a screening tool [5, 16]. It can be used in the following cases:

- Qualitative test is positive;
- Patient is at high risk of CKD;
- Patient has stage I–III CKD but no evident proteinuria.

In patients with CKD, the screening frequency is determined by disease severity and rate of progression. According to the European guidelines on CKD, GFR and albuminuria should be evaluated at least once a year. More frequent control of GFR and albuminuria is recommended in patients at high risk of disease progression and/or when these test results are needed to guide management [25].

Russian clinical guidelines provide the frequency of patient evaluation depending on the GFR and the presence of proteinuria [2]. Evaluation frequency is presented in Table 1.

Table 1. **Evaluation frequency of patients with CKD**

| Evaluation frequency | CKD stage |
|---|---|
| Annually | C1–2, A0-A2 |
| Every 6 months | C 1–2 A3<br>C 3A-3B A0-A3 |
| Every 3 months | C 4 A0-A2 |
| Every 6 weeks | C 4 A4, C 5 |

The frequency can be corrected depending on the disease progression rate, presence of co-existent diseases, etc. In case of the secondary CKD, management decisions should be based on existent clinical guidelines on the specific disease, like HTN or systemic diseases [7].

## Prevention of CKD progression

Multiple studies have shown that various renoprotective measures slow the rate of the decline in GFR in patients with CKD. These measures include:

- Reaching blood pressure goals;
- Proteinuria reduction;
- Uric acid level reduction;
- Hypercalcemia and hyperphosphatemia management;
- Normalization of hemoglobin level.

Hypertension and proteinuria management with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) improve the prognosis in patients CKD [26]. This is due to the fact that proteinuria is common in early stages of CKD; HTN is usually a cause of kidney dysfunction or accompanies it. Anemia and disturbances in calcium and phosphate homeostasis are usually present in the later stages of CKD, when preventive measures are no more crucial. Therefore, early use of nephropro-

tective agents can improve patient prognosis [18]. It is still unknown if renin-angiotensin-aldosterone system (RAAS) inhibitors are beneficial in patients with stage VI–V CKD. According to the European guidelines on CKD, there is no need to stop these medications if GFR declines to≤ 30 ml/min as they still provide nephroprotection [25]. At the same time, Russian clinical guidelines state that in elderly patients with the late-stage renal disease there is an increased risk of GFR decline and hyperkalemia [23]. Therefore, each case of further ACEIs/ARBs use should be decided individually based on the changes in biochemical markers of kidney function.

Normalization of lipid levels is another important nephroprotective measure. Statins are usually used but the higher the CKD stage is, the lower their effectiveness becomes. Early lipid lowering therapy provides the best prophylactic effect. In stages VI–V, statins do not provide significant improvement in mortality or risk of CVD development [10].

Although these protective measures have proven to be effective, target lipid levels and blood pressure levels are still rarely reached. According to the 2001–2010 NHANES study, blood pressure levels≤130/80 mmHg and low-density lipoprotein (LDL) levels< 100 mg/dl were attained only in 19.5% of cases [8]. Therefore, for effective CKD prevention, clinicians have to follow the specific algorithm.

1. Identify patients at high CKD risk.

2. Regularly evaluate albuminuria and plasma creatinine and calculate GFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and also perform urinalysis with albumin/creatinine ratio measurement.

3. The stage of CKD and albuminuria level should be included when indicating the final diagnosis.

4. In patients with HTN, blood pressure goals should be attained with antihypertensive therapy. A required component of this therapy is either an ACEi or an ARB in case of ACEi intolerance. In most cases, antihypertensive therapy should combine several medications including dihydropyridine calcium channel blockers.

5. All patients with stage III CKD independently of the presence of HTN, should receive ACEIs (ARBs) in order to decrease proteinuria. ACEIs (ARBs) should also be given to patients with stage I–II CKD and albuminuria> 30 mg/24 h. In patients with stage VI–V CKD, ACEIs (ARBS) should be cancelled in case of decreasing GFR. ACEIs (ARBs) have similar effects on the level of proteinuria and CKD progression. BRAs cause less side effects such as dry cough, angioedema and hyperkalemia. Some BRAs, however, have some specific features. For instance, only losartan reduces serum uric acid levels and that makes it a preferred choice in patients with HTN and hyperuricemia. Moreover, telmisartan reduces lipoprotein and triglyceride levels and irbesartan is the only ARB that was proven to be effective in all CKD stages [12].

6. The stage of CKD and the presence of other co-existent disease should be taken into account when calculating the cardiovascular risk and lipid goals. Statins should be used if lipid levels are high.

7. Dietary recommendations should be developed based on the patient's specific characteristics such as the stage of CKD, body mass index (BMI) and blood pressure level. The optimal daily salt and protein amount should be determined.

These are some dietary recommendations for patients with CKD:

- Limit the amount of salt to<5 g per day;
- Limit the amount of daily protein depending on the CKD stage: 1.0–1.2 g/kg in CKD stage I–II, 0.6–0.9 g/kg in CKD stage III, 0.3–0.6 g/kg in CKD stage IV.

Multiple studies suggest that limiting protein intake slows the progression of CKD. Low protein diet reduces proteinuria, improves renal perfusion and purine metabolism and increases the efficacy of antihypertensive treatment and corrects hyperkalemia and hyperphosphatemia. On the other hand, low protein diet has some negative effects as well — it leads to the development of protein-energy malnutrition, and, therefore, the diet should be picked based on the CKD etiology and co-existent diseases.

8. It is important to evaluate all the medications that the patient might be taking for other co-existent diseases and to exclude the nephrotoxic drugs. In patients with CKD, preference should be given to medications that are eliminated not only by the kidneys.

## Clinical case

In order to illustrate the clinical effectiveness of nephroprotective therapy in a patient with co-existent cardiovascular (AH and AF) diseases and CKD we would like to present a clinical case.

Patient K., 78 y.o. The patient has been visiting our clinic for regular follow ups since 2005. She first came to the clinic due to a history of uncontrolled hypertension (200–210/110–120 mmHg). Before that the patient was regularly seen in another ambulatory clinic. Her medical problems include coronary artery disease (CAD), stable atrial fibrillation (AF),

stage III HTN. Her calculated cardiovascular risk is very high. She also had cerebrovascular disease and had a stroke in 2001. The patient was regularly taking enalapril (20 mg twice daily), nifedipine (20 mg twice daily), bisoprolol (5 mg/daily), acetylsalicylic acid (100 mg/daily). Complete blood count and urinalysis were normal. 24-hour urine collection revealed proteinuria — 250 mg/24 hour. The ECG showed fibrillation and diffuse left ventricular hypertrophy. Lipid panel: total cholesterol 7.8 mmol/l, LDL cholesterol 4.5 mmol/l. Other labs included creatinine 98.7 μmol/l, uric acid 243 μmol/l, iron 17.8 μmol/l, potassium 4.3 mmol/l. Chest x-ray showed no abnormalities. Echocardiography: moderate left atrial dilation, left ventricular hypertrophy, ejection fraction 61%. Renal ultrasound: left kidney 14.2×7.8 cm, right kidney 14.5×7.0 cm., multiple anechogenic round and oval structures, up to 4.1×3.5 cm in both kidneys.

The patient didn't recall if renal ultrasound was ever performed before. Nothing was indicated in the patient's medical records.

As such, according to the results of all tests, we diagnosed the patient with stage 3aA2 CKD, polycystic kidney disease, stage III hypertension, CAD, stable AF, and cerebrovascular disease. She also had a stroke in 2001. We started pharmacologic treatment with perindopril, amlodipine, hydrochlorothiazide, bisoprolol, atorvastatin and warfarin. However, blood pressure goals (130/90 mmHg) weren't attained, and we decided to start a fixed-dose combination of valsartan, amlodipine and hydrochlorothiazide. Target blood pressure level was reached and stabilized at 130–140/80 mmHg. We also managed to reach target total cholesterol and LDL levels in this patient. The patient continued to have stable disease for 11 years. Elevations in blood pressure were rare and were successfully managed by captopril (25 mg). Blood tests were performed twice per year and lipid and creatinine levels were stable. Stable disease in this patient with significant multimorbidity (CAD, AF, history of stroke, stage III HTN, stage 3aA2 CKD) indicates high efficacy of renoprotective therapy. In 2017, at the age of 75 y.o., the patient started to feel fatigued and short of breath after usual activities. Evaluation showed creatinine 215 μmol/l, urea 15.9 mmol/l, potassium 5.6 mmol/l, uric acid 508. Nephrologist was consulted. Due to the CKD progression to stage C4, it was decided to stop valsartan and hydrochlorothiazide. After these medications were cancelled, blood pressure increased and a third additional antihypertensive agent without negative effects on kidneys was added. Although torasimide and moxonidine were both the potential choices, we decided to stop on moxonidine (2 μg) as the patient had no edema and significant CHF symptoms and was reluctant to take diuretics. Moxonidine is an imidazoline receptor agonist in the medulla and doesn't have proven renoprotective activity but it also doesn't have negative on renal function. Some studies suggest that moxonidine decreases sympathetic activity and therefore has some renoprotective effect. Minoxidine is also well-tolerated in elderly patients [27]. As such, it is possible to use it in patients with CKD if there is a need for a tighter blood pressure control.

We also added allopurinol (100 mg) to reduce plasma uric acid levels. Although the prognostic effect of allopurinol on CKD progression prevention is still unknown, positive prognostic effect on normalizing uric acid levels in CKD was shown empirically [17].

We recommended diet low in protein and potassium. Considering that the patient's BMI was in normal range (22 kg/m$^2$) and she had normal carbohydrate metabolism, we didn't recommend the reduction in fat and carbohydrates in order to satisfy the patient's energy needs. In 2019 the patient was hospitalized for an episode of hemoptysis. She was diagnosed with mild community-acquired pneumonia and received appropriate treatment. Fibrobronchoscopy was performed and showed no pathological findings. The patient recovered and was discharged. Later, she refused to take warfarin because of the hemoptysis episode and was started on apixaban. As such, currently the patient is taking amlodipine 10 mg, minoxidil 2 μg, bisoprolol 5 mg, apixaban 5 mg, atorvastatin 20 mg, allopurinol 100 mg. The patient is stable. In 2019 her laboratory findings were: creatinine 175 μmol/l, uric acid 243 μmol/l. Liver function enzymes were normal throughout all observation period. In 2019 hemoglobin decreased to 108 g/l which corresponds to mild anemia. Serum iron level is normal and anemia treatment was no indicated.

This patient's strong treatment adherence played the major role in the CKD progression slowing. It was achieved by regular follow-ups, patient education and patient's trust. The patient has multiple significant comorbidities and nevertheless she had good quality of life. She lives unassisted and performs all her household chores. Moreover, she has an energy consuming hobby — she enjoys gardening. She works in the garden several hours a day from April to October, watering and planting flowers, pulling out weeds.

Still having the ability to enjoy the activities she likes significantly improves her quality of life.

The patient has two 42-year-old twin daughters. They were evaluated and both were found to have polycystic kidney disease, stage I hypertension and dyslipidemia. Both were educated on their disease, the importance of regular follow-ups and on the renoprotective therapy principles. We provided dietary counselling and explained the need of optimizing their physical activity in detail, determined the right dosages of perindopril and atorvastatin, target blood pressure and lipid levels.

Polycystic kidney disease (PKD) is a genetically determined pathological process that is associated with the formation and progression of multiple kidney cysts that are formed from the tubules and collecting ducts. There are two main types of polycystic kidney disease: autosomal dominant PKD and autosomal recessive PKD.

ADPKD is one of the most common kidney genetic disorder the average prevalence of which is about 1 in 400–1000 newborns.

ARPKD is less prevalent and is diagnosed in 1 in 10000–20000 newborns. PKD causes around 8–10% of all end-stage renal disease that require renal replacement therapy. It is the fourth leading cause of kidney failure after diabetic nephropathy, chronic glomerulonephritis and arterial hypertension.

Currently a number of new treatment approaches that could slow PKD progression is being developed. Tolvaptan, a V2 receptor antagonist, is one of the most promising of them. In two small studies (CRISP — The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; n=202; observation period — 11 years and MDRD — Modification of Diet in Renal Disease) tolvaptan successfully slowed the cyst development and GFR reduction. Moreover, some preliminary trials showed that somatostatin and its analogs as well as mTOR (mammaliantargetofrapamycin — one of the signal pathways that mediates the control of cell growth and proliferation and the protection from apoptosis) inhibitors can also be beneficial in patients with PKD [28, 29].

The case that we presented illustrates two main aspects of primary care physician's work. Firstly, individual approach to each patient based on the latest clinical guidelines should be used. It is also important to provide constant patient education, develop dietary modifications and choose the most appropriate amount of physical activity. Secondly, patients at high risk such as the relatives of patients with CKD should be evaluated for the early signs of kidney dysfunction in order to start preventive measures in advance.

## Conclusion

In ambulatory care, patients with chronic kidney disease and co-existent CVD should be managed by a multidisciplinary team that includes a nephrologist and an endocrinologist, cardiologist or rheumatologist depending on underlying disease. Still, the primary care physician should take the leading role in managing these patients. Therefore, the primary practitioner should be well familiar with the assessment algorithm, the principles of dietary modification and stage-wise pharmacologic treatment approaches. The correct choice of medications is also crucial in a comorbid patient. Agents with proven cardio- and nephroprotective effects should be preferred and the dosing should be adjusted according to the kidney function. The primary care provides are responsible for improving the patient's adherence to treatment. Another important component of primary care is screening of individuals at high risk of kidney disease.

**Conflict of interest**: none declared.

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REVIEW ARTICE

# Myocardial infarction in hemodialysis patients

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**Abstract**

*The review provides data on risk factors of the development of acute myocardial infarction in patients with end-stage chronic kidney disease, including hemodialysis patients. The role of traditional, specific "renal" and dialysis-related risk factors for the development of acute myocardial infarction in patients undergoing hemodialysis is discussed. The role of hyperphosphatemia, hyperuricemia, anemia, oxidative stress, inflammation and endothelial dysfunction in the occurrence of cardiac events is also considered. The clinical significance of intra-and interdialytic hypotension as potential factor predisposing for the development of acute myocardial infarction is highlighted. We also focused attention on the assessment of cardiac troponin I level in the diagnosis of acute myocardial infarction in hemodialysis patients.*

**Key words:** *myocardial infarction, hemodialysis, intradialytic hypotension, troponin I.*

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In 2002 the research group led by Andrew S. Levey presented clinical guidelines for the treatment of chronic kidney disease (CKD in the American Journal of Kidney Diseases) [1]. CKD is defined as kidney damage and / or impaired kidney function for over three months, regardless of origin [1]. Markers of kidney damage include albuminuria / proteinuria, erythrocyturia, and decreased glomerular filtration rate (GFR)<60 ml/min/1.73 $m^2$ is considered as indicator of decreased renal function [1]. The division of CKD into five stages is based on the degree of GFR reduction, where the fifth corresponds to the terminal stage of CKD [2]. The international guidelines from 2014 emphasize the division of CKD stage 3 into 2 substages by GFR value — 3A (GFR from 59 to 45 ml/min/1.73 $m^2$) and 3B (GFR from 44 to 30 ml/min/1.73 $m^2$) [3]. Authors claim that renal and cardiovascular prognosis are different in these subgroups [3]. Thus, patients with stage 3A CKD have high cardiovascular risk and moderate rates of CKD progression, and patients with stage 3B CKD have higher risk of end-stage renal failure compared with fatal cardiovascular complications (CVC) [3]. On the other hand, patients with CKD, regardless of the stage of pathological process, belong to the group with high cardiovascular risk [3].

In recent years, the relevance of the studies on CVC in patients with CKD has increased due to higher incidence, severity of the course, the presence of complications and disability. According to A.G. Strokova et al. (2017) approximately 80 % of patients with end-stage CKD are on programmed hemodialysis (HD) [4]. In Kyrgyzstan, the population of patients with stage 5 "D" of CKD is over half thousand people [5]. Many studies have noted that in patients with end-stage CKD, cardiovascular complications account for at least one third of all admissions and about 43–50 % of all deaths [6]. 20 % of all deaths in patients with end-stage CKD cis caused by acute myocardial infarction (AMI) [7]. Recent publications report that by the start of renal replacement therapy (RRT), coronary heart disease is detected in about 40 % of patients [8]. C.A. Herzog et al. (2007) showed that AMI develops by the end of the first year of RRT in 30 % of patients, and by the end of the second year — in 52 % [7]. This study also showed that during the first year, the mortality rate from AMI in patients with end-stage CKD reaches 59 %, by the end of the second year — 74 % [6]. In CKD, regardless of the GFR value, the risk of AMI development increases, but it is even higher in patients on programmed HD [3]. It is important to emphasize the fact that in-hospital mortality from AMI among patients on HD is 30 %, and in patients with normal renal function — 2 % [9]. Therefore, in patients with unstable hemodynamics and multiple lesions of the coronary arteries, myocardial revascularization is highly recommended. It should be noted that X-ray imaging is an important step in the diagnosis and treatment of such patients [7].

## Risk factors for the development of acute myocardial infarction in patients on programmed hemodialysis

As indicated above, patients on programmed HD have a high risk of AMI [3]. Similar to other countries [1,3], in Russia most patients with type 2 diabetes mellitus and arterial hypertension are undergoing HD [5]. In most cases these patients belong to older age group. At the same time, the incidence of comorbidities increases with age, and atherosclerosis of coronary arteries is observed more frequently in older patients. It is also remarkable that the duration of HD therapy not only accelerates systemic atherosclerosis, but also causes structural changes in blood vessels. In addition, specific "renal" risk factors for CVC become more pronounced in patients with CKD during HD (Table 1).

## Hyperphosphatemia

Patients on HD have consistently high blood phosphorus levels (over 1.45 mmol/L) that increases the fre-

*Table 1.* **Risk factors for acute myocardial infarction development in patients on HD**

| Traditional risk factors | Specific "renal" risk factors | Factors associated with dialysis therapy |
|---|---|---|
| Age, smoking, arterial hypertension, hypercholesterolemia, dyslipidemia, obesity, diabetes mellitus, hereditary predisposition, etc. | Decreased glomerular filtration rate, hyperphosphatemia, anemia, hyperuricemia, inflammation, oxidative stress, endothelial dysfunction. | The duration of dialysis therapy, intra- and interdialytic arterial hypotension. |

quency of CVC [10]. Hyperphosphatemia accelerates the calcification of coronary arteries, causes systemic inflammation, oxidative stress, and promotes vascular calcification of the media in patients undergoing programmed HD [11]. M. Tagawa et al. (2014) studied the association between phosphate, calcium, intact parathyroid hormone and composite cardiovascular endpoints, including AMI [12]. The authors of the Japan Renal Data Registry included 65,849 patients on programmed HD in the study. The endpoint was the first episode of AMI or cerebral stroke during 1-year follow-up [12]. AMI was recorded in 1048 patients with end-stage CKD who underwent programmed HD [12]. The frequency of hemorrhagic and ischemic strokes was 651 and 2089 cases, respectively. The risk of AMI development was associated with phosphate level≥6.5 mg/dL (odds ratio, 1.49; CI, 1.23–1.80) [12]. Another study noted that the increased of blood phosphorus for every 1 mg/dL increases the mortality by 18% [13]. Hyperphosphatemia in patients on programmed HD impairs the compliance and increases stiffness of the arteries. Data on the association between hyperphosphatemia and calcification of coronary arteries were obtained in two large population studies [14,15]. The MESA study (MultiEthnic Study of Atherosclerosis) showed the association between hyperphosphatemia and calcification of coronary arteries in young and middle-aged patients with CKD with normal renal function. For every 1 mg/dL increase of serum phosphorus, the risk of coronary arteries calcification increased by 21% [15]. Impaired phosphorus-calcium metabolism causes endothelial dysfunction accompanied by increased lipid peroxidation and oxidative stress that increases the risk of AMI. The accumulation of calcium in smooth muscle cells and subsequent calcification of coronary arteries in patients undergoing programmed HD is considered one of the most significant factors in the pathogenesis of CVC [14].

## Hyperuricemia

The increase of blood uric acid>0.42 mmol/L in men and>0.36 mmol/L in women is an independent risk factor of CVC in patients on programmed HD [1]. Persistent hyperuricemia in patients with CKD can be a predictor of myocardial ischemia and increases the risk of AMI by 4% [16]. The concentration of uric acid increases in coronary arteries during hypoxia due to temporary occlusion of the vessel [17]. Hyperuricemia in patients on programmed HD together with other factors enhances chronic inflammation, athero- and thrombogenesis. Nowadays the role of hyperuricemia in the development of CVC in patients on programmed HD is controversial [18], although elevated uric acid levels in CKD are also associated with other cardiovascular risk factors. The British Regional Heart Study included 7688 people aged from 40 to 59 years, and showed the association between elevated uric acid levels and fatal and non-fatal manifestations of coronary heart disease [19]. With every 1 mg/dL increase of uric acid level, the risk coefficient of coronary heart disease mortality in women increased up to 1.48 mg/dL [20]. According to other data, the difference of uric acid level of 1.45 mg/dL increases the risk of CVC by 22% [21].

## Anemia and oxidative stress

Anemia is a common complication of CKD that can develop in patient with all types of HD. Thus, in the absence of treatment, the level of hemoglobin less than 100 g/l is observed in over 90% of patients [22]. Low hemoglobin level can serve as extracardiac factor that increases myocardial ischemia. Hypoxic vasodilation increases the activity of the sympathetic nervous system and causes tachycardia and increases venous return that can lead to a matched increase in cardiac output [22]. At the same time anemia is associated with high fibrinogen and C-reactive protein blood levels. Persistent anemia increases oxidative stress that also negatively affects the state of the cardiovascular system [22]. It is also remarkable that low hemoglobin level decreases coronary flow reserve [23]. In patients on HD, anemia increases arterial blood flow velocities, leads to the thickening of large arteries walls and decreased arterial compliance, increases peak systolic blood pressure (BP), stroke volume and cardiac output and, therefore, contributes to the development of AMI [22]. The results of researches have shown that the decrease in hemoglobin level of 4–5 g/l affects the prognosis of CVC and, therefore, requires correction [23].

Many researchers note that the HD session is associated with the development of oxidative stress, because during the contact with the dialysis membrane, leukocytes (neutrophils, monocytes) activates and lead to excessive production of reactive oxygen species, such as superoxide radical anion ($O_2$), $H_2O_2$, hydroxyl radical through complement-dependent and complement-independent mechanisms [24]. The severity of oxidative stress is influenced by the biocompatibility of the dialysis membrane [25]. During the uremia, the antioxidant reserve is reduced,

which, in particular, is expressed as increased ratio of oxidized glutathione / reduced glutathione in blood plasma [25]. When patient additionally have anemia, it initiates oxidative modification of low-density lipoproteins, proteins, activates phospholipases and oxidative stress is aggravated that contributes to destabilization of atherosclerotic plaques and the development of AMI. Moreover, even a single HD session enhances lipid peroxidation and reduces the level of antioxidants [25].

## Inflammation and endothelial dysfunction

The association between endothelial dysfunction and inflammation manifests by both general triggering stimuli and complex of cellular and humoral factors that mediate their pathogenesis and also serve as markers of these conditions, factors for further damage of endothelium and the development of endothelial dysfunction [26]. A number of authors noted the association between systemic inflammation and the level of nitric oxide. Other factors also play an important role in the pathogenesis of coronary atherosclerosis: impaired coronary autoregulation with atherosclerosis and calcification of the arterial endothelium, anemia, oxidative stress, dyslipidemia, and increased levels of C-reactive protein [27]. The development of AMI in patients with CKD who are on programmed HD is associated not only with the destabilization of atherosclerotic plaque and thrombus formation, but also with the inflammation of vessel's wall [3]. Patients with anemia and end-stage CKD more frequently have increased C-reactive protein compared with patients without CKD. Moreover, almost all dialysis-dependent patients who had AMI, showed increased level of C-reactive protein [25]. In addition, programmed HD activates lipid peroxidation processes that damaged membrane lipids, inactivates SH-groups of proteins, impairs cell division and phagocytosis, and, therefore, leads to change in the structural and functional organization of membranes [25,26].

## Intra- and interdialytic arterial hypotension

Decreased BP induced by HD increases the risk of AMI through the activation of sympathetic nervous system, increases or decreases heart rate, which, in case of severe calcification of coronary arteries, leads to myocardial hypoxia, as well as complications from permanent vascular access — arteriovenous fistula thrombosis [28,29]. The prevalence of intradialytic arterial hypotension ranges from 10 to 50%, and mortality rate due to decreased blood pressure during the HD procedure can reach 10–15% per year [30]. The meta-analysis by J. Kuipers et al. (2019) showed that the prevalence of HD sessions complicated by intradialytic arterial hypotension does not exceed 12% [31]. The main risk factors associated with intradialytic arterial hypotension in different studies included diabetes mellitus, high weight gain, female sex and low body weight [31]. It is assumed that the level of calcium in coronary arteries is associated with decreased blood pressure during the HD procedure in patients with end-stage CKD [28,29]. Many patients on HD with prolonged intradialytic arterial hypotension develop silent myocardial ischemia, which increases the risk of AMI and life-threatening cardiac arrhythmias [28,29].

## The diagnosis of AMI in patients on hemodialysis

According to A.Yu. Nikolaev, the diagnosis of painless and arrhythmic forms of AMI causes certain difficulties in patients on HD, especially among people with diabetic nephropathy and autonomic neuropathy [32]. Patients on HD often have stenosis of the proximal coronary arteries that causes AMI [32]. F.I. Belyalov points out that patients with end-stage CKD less often have AMI that manifest with pain in the chest, arm and neck, elevation of the ST segment on the electrocardiogram (ECG), and more often — shortness of breath and symptoms of heart failure. The absence of pain syndrome can be explained by decreased threshold of pain receptors, increased left ventricular myocardial mass, and imbalanced autonomic regulation of cardiac activity. In addition, it should also be noted that electrolyte imbalance, especially during HD sessions, can lead to changes in the terminal portion of the QRS complex that can reduce the diagnostic value of ECG studies in this category of patients [33]. Therefore, echocardiographic study in patients on programmed HD have high diagnostic value. Thus, the detection of hypo- and akinetic zones of ventricular myocardium in the absence of bundle branch block and atrial fibrillation in patients on programmed HD can be interpreted as AMI [34].

The important step is the identification of highly sensitive troponin I, since it rarely rises even in patients with end-stage CKD without myocardial ischemia. Due to kinetics, troponin T and troponin I respond differently to renal function changes [35,36]. The level of troponin T in patients with renal failure

can increase up to 17–53 %, troponin I — up to 7 %. After the HD session, the troponin T level increases in 86 % of cases, when the troponin I level decreases [6]. In patients on programmed HD, the diagnosis of AMI should be based on all classical criteria — clinical, ECG and laboratory biomarkers. The high incidence of atypical AMI manifestations in these patients leads to underdiagnosis and inappropriate treatment. In patients on programmed HD AMI often manifests as shortness of breath that can be interpreted as volume overload. The M.Yu. Gilyarova (2019) showed that in patients with AMI symptoms, the level of troponin should be assessed within 3–6 hours [8]. The researchers point out that the level of troponin above the 99$^{th}$ percentile and its change by over 20 % is the criterion for the diagnosis of AMI in patients with CKD. It should also be noted that HD affects the level of cardiac biomarkers. Their level may increase due to hemoconcentration or decrease due to clearance or binding to the dialysis membrane. The assessment of dynamic changes of troponin levels increases the diagnostic accuracy. Meanwhile, if relying only on the level of troponin, up to 12 % of cases of ST segment elevation AMI can be skipped [8].

## Conclusion

Thus, the presented data indicate hyperphosphatemia, hyperuricemia, anemia and oxidative stress, inflammation, and endothelial dysfunction play a pivotal role in the development of AMI in patients undergoing programmed HD. An additional risk factor for AMI is frequent and prolonged episodes of intradialytic arterial hypotension. The diagnosis of AMI in patients with the terminal stage of CKD and on programmed HD is based on the dynamic assessment of ECG parameters and the levels of cardiac troponins. Many issues of pathogenesis and treatment of AMI in patients with CKD on programmed HD need further clarification.

**Conflict of interest**: none declared.

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CASE REPORT

# Acute Pulmonary Embolism, Hemorrhagic Pulmonary Infarction and Ischemic Myocardial Infarction — A Case Report

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**Abstract**

*Deep vein thrombosis (DVT) of the lower extremities often leads to one of the most life-threatening complications such as thromboembolism of the branches of the pulmonary artery. The article describes a clinical case of acute pulmonary embolism with myocardial and lung infarction with a premorbid background after traumatic injury to the deep veins of the left leg. A 57-year-old patient was admitted to our hospital with chest pain that was not relieved by nitrates for 24 hours. The patient was regularly followed by her general practitioner for coronary artery disease and arterial hypertension. The patient had a traumatic injury of the left lower limb about three weeks ago. Later, a trophic ulcer developed at the site of the injury. Death occurred one hour after admission. Dense, easily crumbling blood clots were visualized in the deep veins of the left leg. Numerous thrombi sized from 0.3 to 1.5 cm and up to 2.1 cm long were found in the large, lobar and segmental branches of the pulmonary artery. Microscopic*

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*signs of acute transmural myocardial infarction of the anterior left ventricular wall were detected with areas of necrotized cardiomyocytes with a demarcation zone of inflammation and undulating deformation of cardiomyocytes. Histological examination revealed necrotic areas of lung tissue impregnated with erythrocytes in the lungs. Such a combined pathology is extremely rare. A sequence of changes is traced not only in the vessels, but also in organs with the development of different types of infarction. This combination of different types of infarction was probably associated with pulmonary hypertension and concomitant diseases such as coronary artery disease, arterial hypertension and atherosclerosis.*

**Key words:** *veins, thrombosytes, thrombotic embolism, pulmonary infarction, myocardial infarction.*

**Conflict of interests:** none declared.

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## Introduction

Lower extremity deep vein thrombosis (DVT) is still one of the major challenges of modern medicine as it is associated with high levels of mortality and disability. According to Russian Phlebology Association and Russian Association of Surgeons DVT cases occur for the first time in 50–70 per 100 000 each year. In 32–45 % of cases, lower extremity DVT is complicated by massive pulmonary embolism (PE) that is fatal in 17 % of patients [1]. Deep vein thrombosis develops when fibrin clots accumulate in the areas where the vessels are damaged and the coagulation cascade activation begins. Activity of antithrombotic proteins such as thrombomodulin and endothelial cell protein C receptor is suppressed and the thrombus is formed [2, 3, 4, 5]. Poor outcomes are associated with co-existent diseases such as coronary artery disease (CAD), arterial hypertension (AH), atherosclerosis as they lead to hypoxic cell injury [6]. Hypoxia can also activate procoagulant factors such as tissue factor (TF) and P-selectin (adhesion molecule) expressed in endothelial cells and lead to leukocyte recruitment. TF initiates coagulation together with P-selectin and are the important components of thrombosis [7–9].

Despite the amount of information we have about thrombosis and its complications, clinical features and pathogenesis, the descriptions of pathomorphological changes are quite limited. Therefore, **the objective** of this paper was to describe the case of DVT with acute pulmonary embolism hemorrhagic pulmonary infarction and ischemic myocardial infarction in a patient with co-existent CAD and after traumatic vessel damage.

## Materials and methods

We analyzed the available medical records and clinical and morphological characteristics using the histological techniques (hematoxylin and eosin staining).

## Results

A 57-year-old patient was admitted to our hospital with chest pain that was not relieved by nitrates for 24 hours. The patient was regularly followed by her general practitioner for coronary artery disease and arterial hypertension. The patient had a traumatic injury of the left lower limb about three weeks ago. Later, a trophic ulcer developed at the site of the injury. The patients didn't seek medical help and tried to relieve her condition with nonsteroidal anti-inflammatory drugs (NSAIDs).

## Objective and instrumental findings

Electrocardiography (ECG) results: sinus rhythm, heart rate — 63 beats per minutes, left axis deviation. ST elevation for 5 mm in leads V3 through V6. Signs of acute transmural anterolateral myocardial infarction. **Troponin test:** positive.

Complete blood count: see Table 1 and 2.

C-reactive protein — 100 mg/l (0–5 vg.l). Coagulation studies: fibrinogen 15.6 mmol/l (5.9–11.7 mmol/l), prothrombin index — 186.1 % (80.0–125.0)%, D-dimer — 2297 ng/ml (<250 ng/ml). Alanine aminotransferase — 68 U/L (1.0–45.0) U/L; aspar-

Table 1. **Complete blood count**

| Values | Leucocytes | Erythrocytes | Hemoglobin | Thrombocutes | Erythrocyte sedimentation rate |
|---|---|---|---|---|---|
| Patient | 19×10×9/l | 8.64×10×9/l | 101 g/l | 254×10×9/l | 20 mm/h |
| Reference range | 3.80–8.76 | 4.54–6.00 | 120–147 | 173–360 | 2–8 |

Table 2. **Leukocyte count and differential**

| Values | Segmented neutrophils | Band forms | Neutrophils | Lymphocytes |
|---|---|---|---|---|
| Patients | 77 % | 18 % | 62.0 % | 26.0 % |
| Reference range | 47–72 | 1–6 | 40.1–67.0 | 23.6–48.0 |

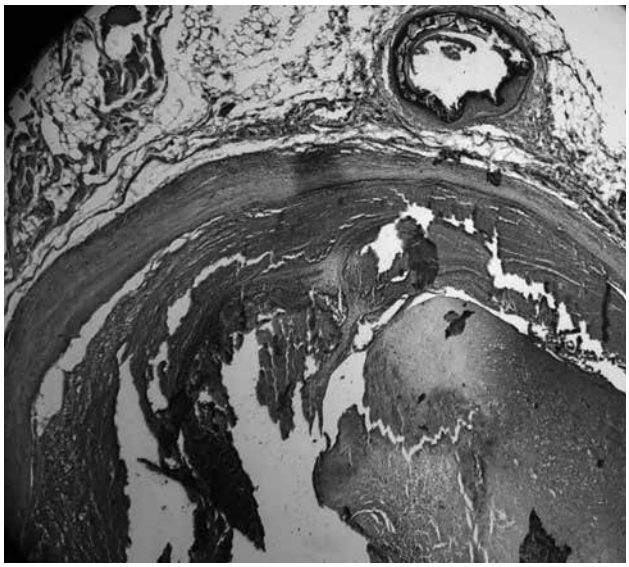
tate aminotransferase — 57 U/L (1.0–35.0) U/L, urea 9.6 (2.8–8.3) mmol/l, creatinine — 94 μmol/l (53–97) μmol /l, glucose 4.86 mmol/l (4.0–5.9 mmol/l), cholesterol — 9 mmol/l (3.1–5 mmol/l).

One hour later the patient acutely deteriorated and died. Post-mortem analysis with pathomorphological evaluation was later performed.

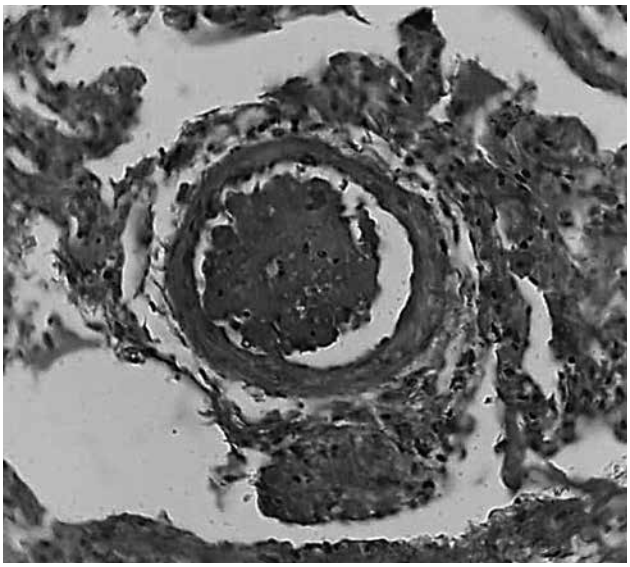
An ulcer 3.2×2.1 cm was found on the anterior surface of the patient's left shin. Atrophic and sclerotic changes were found in the dermal layer.

Deep veins of the left shin were full of blood, with multiple fibrotic changes and round cell infiltration with surface injury and fibrin deposition in the intima. Dense, easily crumbling dark-red and mixed blood clots with uneven surface were visualized in the deep veins of the left shin (Picture 1).

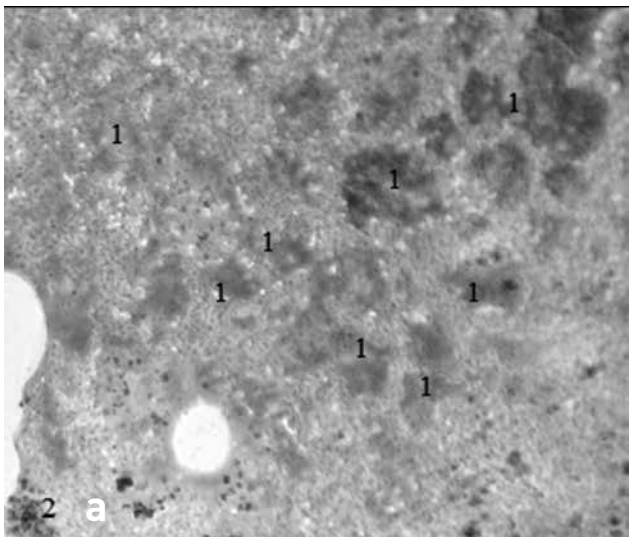
Numerous thrombi sized from 0.3 to 1.5 cm and up to 2.1 cm long that could be easily squeezed out from blood vesseld were found in the large, lobar and segmental branches of the pulmonary artery (Picture 2). Histological examination of the lungs revealed necrotic areas of lung tissue impregnated with erythrocytes (Picture 3). Erythrocytes, macrophages and fluid was found in the alveoli. The capillaries in the

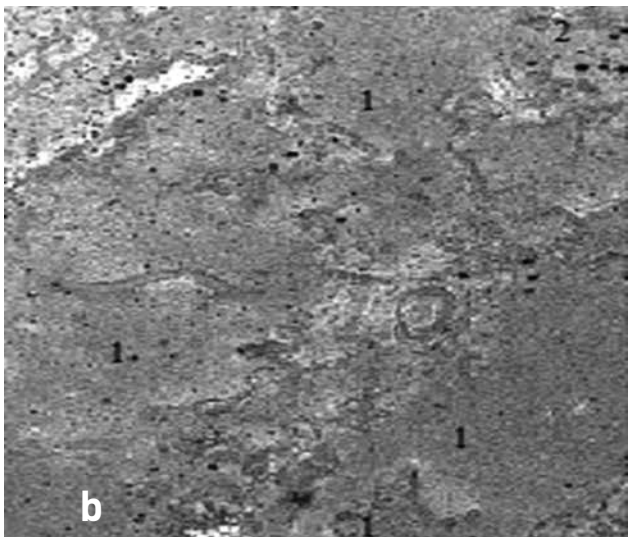


**Picture 1.** Thrombus in the deep vein of the left sheen. Hematoxylin & Eosin, × 400



**Picture 2.** Thrombus in the pulmonary artery. Hematoxylin & Eosin × 400




**Picture 3.** a-b. Microscopy of hemorrhagic infarction of the lung: 1 - necrotic areas of lung tissue impregnated with erythrocytes. Alveoli filled with erythrocytes. 2 - Areas of hemosiderin. Hematoxylin & Eosin × 400

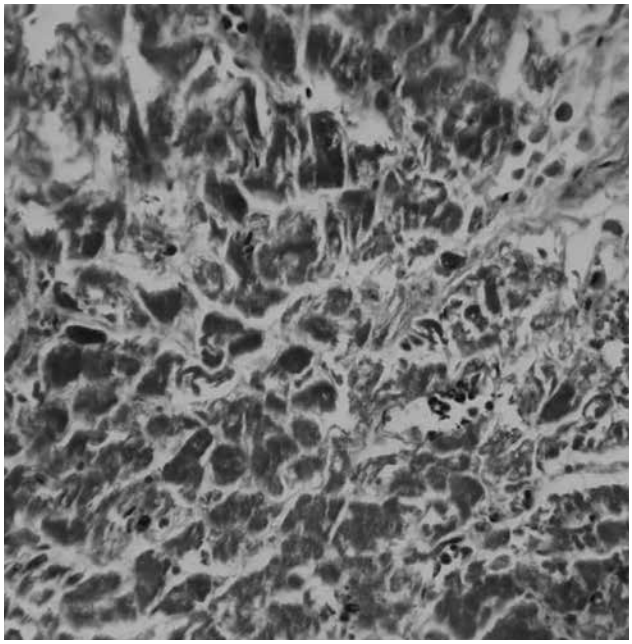
lung tissue in the area of the vessel occlusion are full of blood and there are intraalveolar hemorrhages.

Microscopic signs of acute transmural myocardial infarction of the anterior left ventricular wall were detected with areas of necrotized cardiomyocytes with a demarcation zone of inflammation and undulating deformation of cardiomyocytes (Picture 4). The nuclei became homogenous, partly fragmentated. Stromal tissue became metachromatic. Fibrotic changes were noted in the blood vessel walls and the lumen was filled with a mass of disintegrated erythrocytes. Necrotic areas were demarcated by leucocytes. Apart from them, hypertrophied LV cardiomyocytes sized up to 1.9 cm were noted, heart mass — 350 grams. Histologic evaluation showed areas of fragmentation, hypertrophied cardiomyocytes and perivascular connective tissue (Picture 5). Coronary arteries with atherosclerotic changes, fibrotic plaques and calcinosis (9/4 mm). Left coronary artery is filled with dark-red microthrombi that are tightly attached to vessel walls.

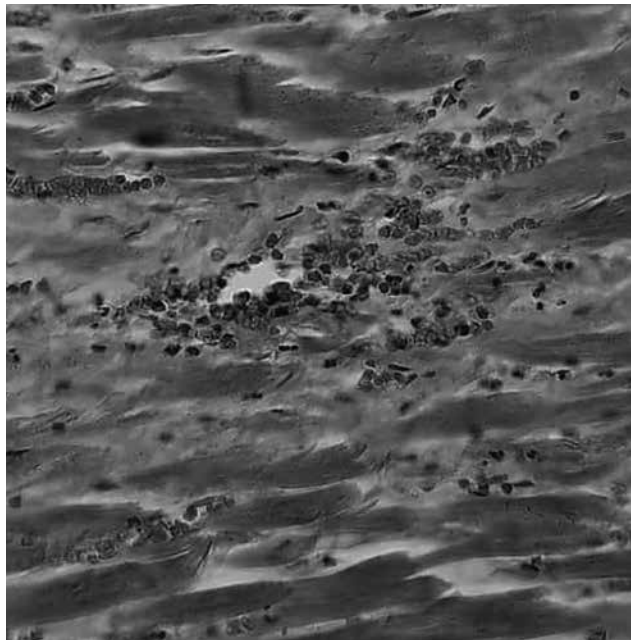
A pathology report contained the following: Deep vein thrombosis of the left shin. Acute pulmonary embolism. Hemorrhagic pulmonary infarction. Acute transmural myocardial infarction. Pulmonary edema. Acute respiratory and cardiac failure. Left knee joint posttraumatic arthritis. Atherosclerosis. Arterial hypertension, left ventricular hypertrophy (1.9 cm), diffuse perivascular cardiac sclerosis.

Discussion. Despite the fact that this patient had poor prognosis due to the signs and symptoms of cardiovascular decompensation associated with various CAD forms, understanding the pathomorphological features of thrombosis development associated with progressive thrombophlebitis and deep vein thrombosis is important and extremely relevant [1]. The presented clinical case shows the effects of traumatic vessel injury, as well as the existing coronary atherosclerosis that causes subendothelial thrombi formation in the area of the damaged atherosclerotic plaque and leads to the development of myocardial ischemia, PE with complications and hemorrhagic lung infarction. PE is associated with two pathological processes: mechanical vessel obstruction and humoral changes. Major thromboembolic lung vessel obstruction (reduction of the total arterial lumen by 40–50 % that corresponds to the obstruction of 2–3 branches of pulmonary artery) increases total pulmonary vessel resistance. This, in turn, obstructs blood flow from the right ventricle, decreases the filling of left ventricle and, eventually, leads to the reduction of cardiac output and arterial pressure [4, 6, 7, 8].

Such a combined pathology is extremely rare. Therefore, the described case is unique and important. A sequence of changes is traced not only in the vessels, but also in organs with the development of different types of infarction. Obviously, ischemic myocardial infarction caused by thrombosis developed first, and led to the reduction of functional myocardium mass, ventricular dilation, changes in the neurohumoral regulation of heart function and vessel tone, changes in the intracardiac and central haemodynamics and PE and hemorrhagic pulmonary infarc-



**Picture 4.** Microscopy of fragmented hypertrophied cardiomyocytes, cardiac sclerosis. Hematoxylin & Eosin, × 400



**Picture 5.** Microscopy of acute transmural infarction: areas of necrotic cardiomyocytes with cardiolysis. Hematoxylin & Eosin, × 900

tion due to the obstruction of major lobar branches of the pulmonary artery [2, 3, 5, 7, 8]. This combination of different types of infarction was probably associated with pulmonary hypertension and concomitant diseases such as coronary artery disease, arterial hypertension and atherosclerosis. The clinical case described in this report shows that PE can develop without the classic mechanism — pulmonocoronary reflex.

Conclusion. The described clinical case proves the key role of CAD complicated by chronic cardiac failure, traumatic limb injury in the development and progression of DVT. Pre-existing heart disease reduces compensatory functions of cardio-vascular system and worsen prognosis.

**Conflict of interest:** none declared.

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# Author Guidelines

## *MANUSCRIPT PUBLICATION RULES IN THE INTERNATIONAL HEART AND VASCULAR DISEASE JOURNAL*

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1) *Original papers* present the results of clinical studies. The word limit is 3.000 (including references, tables, and figure legends). The maximal number of references is 15. The structured abstract should contain 5 sections (**Aim, Material and Methods, Results, Conclusion**, and **Key words**), and be no longer than 300 words.

2) *Lectures*, or clinically oriented reviews, are written by experts in broader areas of medicine. Lectures could be focused on epidemiology, pathophysiology, diagnostics, treatment, and prevention. The word limit is 5.000 (including references, tables, and figure legends). The maximal reference number is 80. The unstructured abstract is no longer than 150 words.

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The "letter of direction (accompanying)" should be made out on one or two sheets. Using the form of the official institution-at the choice of the author's team. In the address: "to The chief editor of the Russian cardiology journal, academician of RAS, Professor Oganov R. G.". The signatures of **all authors** should be placed at the bottom.

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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.

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**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],...

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

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*Book:*

Shlyakhto EV, Konradi AO, Tsyrlin VA. The autonomic nervous system and hypertension. SPb.: Meditsinskoe izdatel'stvo; 2008. Russian. 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. Russian 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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