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Original article

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Skin autofluorescence as a factor of adverse prognosis in patients with peripheral atherosclerosis

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Abstract:
Objective: to determine the prognostic value of skin autofluorescence (SAF) as a factor of cardiovascular complications and mortality.
Materials and Methods. Our prospective study included 122 patients with peripheral arterial disease (PAD): atherosclerotic stenosis of the brachiocephalic trunk was detected in 95 patient (77.9%), while chronic arterial insufficiency (CAI) of the lower limbs was found in 47 study participants (38.5%). SAF was measured by an original device developed by the authors. Clinical, anthropometric and biochemicalparameters, along with instrumental parameters of the heart and blood vessels, were studied via ultrasound examination. The prospective part of the study (follow-up) was carried out for up to 1,043 (on average, 736) days.
Results.The SAF parameter correlated directly and significantly with scores on the scale of clinical prognostic signs, CAIof the lower limbs, and history of surgeries on the leg arteries. In the course of the follow-up period, there were seven deaths and at least one hospitalization for cardiovascular reasons in 42 patients. The most common were hospitalizations due to conservative treatment of CAI, the need for coronary artery bypass grafting, and coronary stenting. Using the logistic regression method, we determined that the incidence of hospitalization or mortality was associated with SAF values, plasma glucosecontent, and the presence of chronic heart failure above functional class 1. The sensitivity and specificity of the model were 71% and 68%, respectively.
Conclusion.The SAF parameter can be used as an integral independent predictor in patients with multifocal atherosclerosis.

Keywords skin autofluorescence, peripheral atherosclerosis, cardiovascular risk.

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Background

Fighting cardiovascular morbidity and mortality are among keytasks of contemporary medicine. Peripheral arterial disease (PAD), associated with atherosclerosis, is characterized by a grave burden and negative dynamicsof prevalence [1]. E.g., in 2010, over 202 million people had manifestations of PAD, which implied an almost 25% increase since 2000, and two-thirds of them lived in low-income and middle-income countries.The latter is explained by the prevalence of cardiovascular risk factors, especially smoking and diabetes, which are powerful predictors of PAD [2]. PAD is estimated to affect 10–20% of people aged 60 years and older [3].

In recent decades, the search for markers of cardiovascular complications was directed towards advanced glycation end products (AGEs)resulting from non-enzymatic binding of proteins to glucose. Their accumulation in the skin is associated with the mechanism of its aging, and also reflects metabolic stress, which contributes to degenerative processes in vital organs, such as the heart, brain and kidneys [4]. In contrast to the determination of AGEs in the blood via biochemical methods that require blood sampling or expensive gas-liquid chromatography, the use of devices that measureskin autofluorescence (SAF)at the surface of the forearm does not require preliminary preparation, and is absolutely noninvasive, fast, safe, and informative [5]. It is also important that the content of AGEs in the surface layers of the skin is stable and changes slowly, unlike in the blood.

This study tested an easy-to-use original device developed by the authors – a reader thatmeasures the SAF parameter independent of the operator [6].

Objective –to determine the prognostic value of skin autofluorescence as a factor of cardiovascular complications and mortality.

Materials and Methods

The main group of study participants consisted of 122 men 42 to 78 yearsof age admitted to the Department of Vascular Surgery of V.D. Seredavin Clinical Hospital of Samara Oblast. Inclusion criteria encompassed clinical signs of peripheral atherosclerosis in at least one arterial system.

Lack of informed consent, stage 2B or higher of chronic heart failure (CHF), stage 4 or higher of chronic kidney disease, dementia, severe grades of acute and chronic concomitant diseases, along with inability to self-care,constituted the main exclusion criteria.

In the main group, we examined clinical (*Table 1*), anthropometric and biochemical parameters, as well as instrumental parameters of the carotid arteries and heart using ultrasound imaging (*Table 2*). It is necessary to note high prevalence of hypertension (84%) and chronic coronary syndrome (stable angina in 40% of cases and myocardial infarction in 33% of cases) in the study subjects. Among the manifestations of PAD, extracranial artery stenosis and CAI of the lower limbs prevailed in 78% and 38% of patients, correspondingly. Overall, 9% ourstudy subjects underwent surgical revascularization of the lower limb arteries, coronary arteries, and carotid arteriesin 9%, 11.4%, and 5.7%, respectively (Table 1).

The SAF parameter was measured using an original device (reader) developed by the team of the Department of Laser Systems and Bioengineering at Samara National Research University under the leadership of Professor V.P. Zakharov. After placing the forearm inner surface onto the instrument panel, irradiation with a weak luminous flux with a wavelength of 365 nm was carried out for 2 min. During the next 2 min,SAF was measured and computer-based processing took place. Then the procedure was performed two more times on other areas of the skin. The SAF parameter value was determined as the arithmetic mean of three measurements.

The prospective study was conducted for up to 1,043 d (on average, 736 d). Information was obtained via telephone interview directly with the patient or with a family member in 112 of 122 patients. The collected anamneses included hospitalizations, their causes, performedsurgeries if any, dates of hospitalizations, history of COVID-19, and used medications.

A control group was formed comprising 35 apparently healthy men 42 to 68 years of age without clinical signs of diseases caused by atherosclerosis. However, 15 of such study subjectshad hypertension. Of these, 7 were diagnosed with stage 2 of the disease. The group was formed of those who underwent a medical screening, in accordance with the requirements of which total cholesterol and blood glucose content were measured, along with a smoking status and body mass index, and cardiovascular risk stratification was performedsensu SCORE1 (Systematic Coronary Risk Evaluation) scale. SAF values of the main group patients were compared with SAF values of control subjects. Since the participants in the control group were generally younger than the subjects in the main group, 72 age-matched patients were selected from the latter group.

Statistical data processingwas performed using SPSS 25.0 (IBM Corporation, Armonk, NY, USA, license No. 5725-A54). Preliminarily, the shape of the distributions of quantitative parameters was examined graphically and analytically using distribution histograms, Shapiro–Wilk and Kolmogorov–Smirnov criteria with the Lilliefors correction, as well as viathe indicators of asymmetry and kurtosis. The Mann–Whitney test was employed to compare groups. Descriptive statistics are presented in the form of mean and standard deviation (M±SD) or, in the case of a highly skewed distribution, in the form of median (Me) and quartiles (Q25; Q75). Relationships was examined via Spearman's correlation analysis. To assess the impact of various factors on the risk of hospitalizations due to cardiovascular events, logistic regression and Cox regression were used, and ROC curves and Kaplan–Meier curves were constructed. To compare Kaplan–Meier curves, the logrank test and median survival were employed. Odds ratios (OR) and relative risks (RR), along with their 95% confidence intervals (CI), were calculated. The results were considered statistically significant at $p<0.05$.

Results

The parameters of the control group in comparison with similar parameters of the main group subjects that were comparable in terms of their age are shown in *Table 3*. It is worth noting significantly lower SAF value in the control group, in which SAF value correlated with age (r=0.33, p=0.019), total cholesterol content (r=0.40, p=0.008) and risk score in SCORE1 scale (r=0.36, p= 0.019). We found no similar relationships in the main group. To take into account multifocal manifestations of atherosclerosis, concomitant syndromes and diseases, and age, we calculated a cumulative parameter for each patient according to the following criteria:CAI was scored as 1 pt (stage 2A), 2 pts (stage 2B), 3 pts (stages 3-4);previous myocardial infarction, type II diabetes mellitus, history of stroke, angina pectoris, carotid stenosis over 50%, chronic kidney disease (stage 3 and above), and age of 55-65 years were represented by 1 pt each, whereas age over 65 years was scored as 2 pts. The mean score was 7.57±1.85 pts, ranging 4 – 14 pts.

In general, the parameters of the complete blood count in the main group were within the ranges of their normal values (*Table 2*). The cholesterol spectrum implied that the target parameters of low-density lipoprotein cholesterol (LDL) were not achieved in 90% of patients. In 21 subjects, the estimated glomerular filtration rate (GFR) according to CKD-EPI was in the range of 59-35 mL/min, which indicated 17%incidence of stages 3A and 4 of chronic kidney disease.

Table 1.Clinical characteristics of patients with peripheral atherosclerosis (n=122)

Diseases, localization of atherosclerotic lesions	Patients, *n*, (%)
Essential hypertension	103 (84.43%)
Type 2 diabetes mellitus	23 (18.85 %)
Angina pectoris	49 (40.16%)
Previous myocardial infarction	40 (32.79%)
History of stroke	19 (15.57%)
Stages 1A, 1B, 2A, 2B, 3 and 4 chronic arterial insufficiency	47 (38.52%)
Extracranial atherosclerosis	95 (77.87%)
Arterial aneurysm	2 (1.64%)
Renal artery stenosis	3 (2.46%)

Table2. Physiological and biochemical parameters of patients with peripheral atherosclerosis (*n*=122)

Parameters	*M±SD*
Complete blood count	
Red blood cells, 1×10^{12}/L	4.54±0.64
Hemoglobin, g/L	136.91±19.49
Hematocrit, %	40.41±5.92
Platelets, 1×10^{9}/L	218.49±71.51
Leukocytes, 1×10^{9}/L	8.35±2.67
ESR, mm/h*	11.00 (6.00–22.50)
Blood biochemistry	
Troponin I, ng/mL*	0.01 (0.00–1.12)
CK-MB, IU/L*	21.70 (14.43–54.63)
Total CPK, IU/L*	186.00 (103.00–1041.50)
Cholesterol, mmol/L	5.02±1.22
HDL, mmol/L	1.15±0.26
LDL, mmol/L	3.13±0.99
Triglycerides, mmol/L	1.76±0.84
ALT, IU/L*	19.00 (14.10–32.00)
AST, IU/L*	22.10 (15.50–32.00)
Glucose, mmol/L	6.01±2.29
Creatinine, μmol/L	105.99±31.07
Urea, mmol/L	6.49±2.87
GFR, mL/min	69.32±18.15
Instrumental parameters	
SAF, arbitrary units (AU)	6.51±1.24
SBP, mmHg	139.99±19.93
DBP, mmHg	79.36±9.27
Echocardiography	
LVEDD, mm	49.81±5.74
LVESD, mm	32.75±5.38
IVSd, mm	13.96±3.15
PWd,mm	12.01±2.47
FSLV, %	33.30±5.98
LVMI, g/m^2	129.35±32.15
LA,mm	42.68±6.05
Aorta, mm	35.68±5.15
LVEF, %	55.59±8.23
E, m/s	0.67±0.16
A, m/s	0.75±0.18
E/*A*	0.90±0.35
S', m/s	7.86±2.00
E', cm/s	8.84±2.61
A', cm/s	10.59±2.30

ESR, erythrocyte sedimentation rate; CK-MB, MB-fraction of creatine kinase; CPK – creatine phosphokinase; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; ALT, alanine transaminase; AST, aspartate transaminase; GFR, glomerular filtration rate according to CKD-EPI; SAF, skin autofluorescence; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic dimension; IVSd,interventricular septum thickness at end-diastole; PWd,left ventricular posterior wall thickness at end-diastole;FSLV,fractional shortening of the left ventricle; LVMI, left ventricular mass index; LA, left atrium diameter; LVEF, left ventricular ejection fraction; E – early diastolic mitral annular velocity; A – mitral annular systolic velocity; E/A, the ratio of the early to late ventricular filling velocities;S', velocity of mitral annular plane systolic excursion(MAPSE); E',early diastolic velocity of mitral annular plane displacement; A',velocity of mitral annular plane displacement in the phase of atrial systole; *, indicators with a shape of distribution sharply skewed to the right are presented in the form of median and quartiles

Table 3. Main characteristics of the examined groups

Characteristics	Group		Significance level, *p*
	Control (*n*=35) *M±SD*	Main (*n*=72) *M±SD*	
Age, years	56.20±5.73	58.36±4.95	0.064
SAF, AU	4.93±0.98	6.47±1.15	<0.001
SBP, mmHg	131.33±12.91	140.40±19.61	0.036
DBP, mmHg	80.71±8.69	80.44±9.21	0.979
Cholesterol, mmol/L	5.64±1.10	5.05±1.23	0.036
Glucose, mmol/L	5.51±0.88	5.91±1.85	0.947
BMI, kg/m^2	27.86±3.38	28.30±4.74	0.735

Echocardiography parameters (*Table 2*) demonstrated a high prevalence of left ventricular hypertrophy (more than 115 g/m2), as well as the left atrial hypertrophy with signs of diastolic dysfunction, which was confirmed by reduced values of the early diastolic mitral annular velocityEm (normally >10 cm/s), a decrease in E/A ratio, and Em/Amvalues under 1.0. Taking into account the high prevalence of arterial hypertension in examined patients, these data can be explained with high confidence by the presence of a hypertensive heart.

In the main group, the SAF parameter correlated directly and statistically significantly with scores on the scale of clinical prognostic signs (r=0.36, p<0.001), while inverse correlations were observed with hemoglobin content (r=−0.20, p=0.038) and hematocrit (r=−0.25, p=0.008). As for qualitative parameters, SAFexhibitedassociation with CAI (r=0.23, p=0.013), and history of surgeries on the leg arteries (r=0.30, p=0.002).

During the follow-up period, there were seven deaths and at least one hospitalization for cardiovascular reasons in 42 patients (37.5%). Of these, the most common were hospitalizations due to conservative treatment of CAI exacerbation (in 12 patients, or 12%), the need for coronary artery bypass grafting (in 11 subjects, or 10%), and coronary stenting (in 6 study participants, or 5.3%).The need for other operations arose less frequently: aortic bifurcated bypass surgery,amputation, and stenting of the renal arteries were performed in 2 patients (2%), 3 patients (3%), and 3 patients (3%), correspondingly. Two patients (2%) had a stroke.

Using multiple logistic regression, wehave established that both hospitalization and mortality were associated with SAF [OR=1.71 (95% CI: 1.20–2.45), p=0.003] and plasma glucose [OR=1.23 (95% CI: 1.004–1.51), p=0.046]. The predictive quality of the model was as follows: it exhibited the sensitivity of 71%, specificity of 68% with a threshold probability of 0.4, and area under the ROC curve (AUC) of 0.76 (95% CI: 0.68–0.84, p<0.001) (*Figure 1*).

Kaplan–Meier curves, reflecting these events and the time before their onset, were significantly less favorable for an increase in SAFto the level of over 6.4 arbitrary units (AU) (median survival: 1,000 and 716 days), fasting glycemia (median survival: 1,054 and 716 days), the presence of CHFof a functional class above 1 (median survival: 1,000 and 510 days) (*Figures 2 and 3*). All three listed signs were included as independent predictors in multivariate survival analysis, using the technique of Cox regression, with the following relative risks: SAF expressed in AU[RR=1.34 (95% CI: 1.05-1.71), p=0.018], blood glucose expressed in mmol/L[RR=1.13 (95% CI: 1.02-1.25), p=0.016], CHF (functional class 2 vs. 0-1) [RR=2.93 (95% CI: 1.35-6.38), p=0.007].

During the telephone interview, patients were asked about their ongoing medication use. The patient was supposed to name the drugs takenregularly without being asked specificquestions. The most frequently mentioned medicines were acetylsalicylic acid (76%), β-blockers (48%), angiotensin-converting enzyme inhibitors (40%).The frequencies of other groups of medicationswere significantly lower: calcium channel blockers, angiotensin II receptor blockers, antiplatelet agents, and novel oral anticoagulants were mentioned by 22%, 15%, 6%,and 6% of study participants. We should mention low adherence of study subjects (only 50%) to taking statins, which were prescribed to all patients. None of the listed drugs (or groups of drugs) had a statistically significant effect on the prognosis.

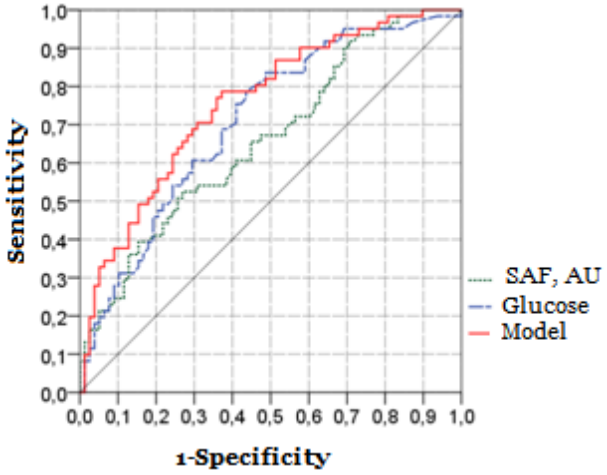

Figure 1. ROC curves for predicting hospitalization for cardiovascular diseases and overall mortality based on skin autofluorescence and serum glucose

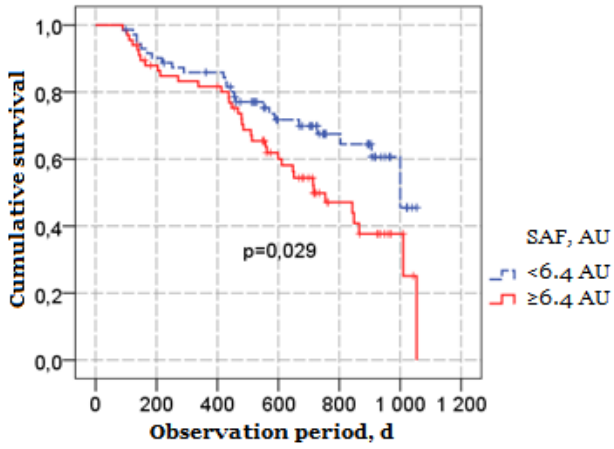

Figure 2. Kaplan–Meier curves for events associated with cardiovascular hospitalization and mortality as a function of skin autofluorescence

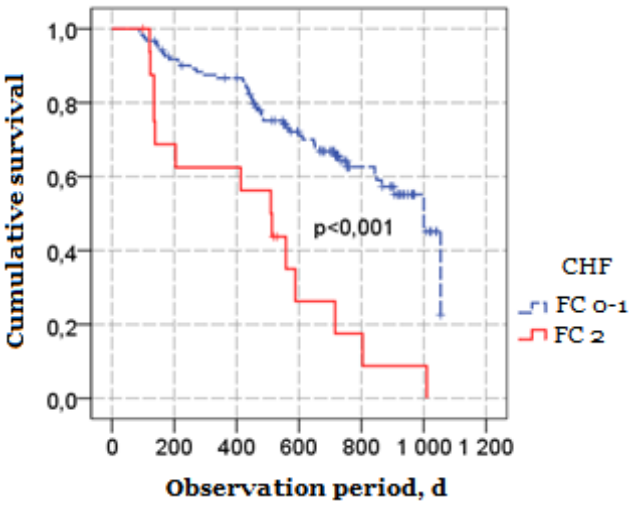

Figure 3. Kaplan–Meier curves for events associated with cardiovascular hospitalization and mortality by functional class of chronic heart failure

Discussion

A special highlight of our study is the inclusion of patients with different localizations of atherosclerotic lesions, all of which together could be classified as PAD. We use this term sensu the 2017 ESC/ESVC guidelines, "...the term peripheral arterial disease covers all arterial lesions other than the coronary arteries and the aorta. In the scientific literature, the term 'peripheral arterial disease' is used for characterizing the diseases of the lower extremities..." [7]. Therefore, two groups are mentioned that are usually considered separately in the scientific literature: patients with hemodynamically significant carotid stenosis and patients with atherosclerosis of the lower limb arteries.

From the standpoint of local clinical consequences, as well as prognostic factors for cardiovascular complications, and from the standpoint of surgical tactics, these two groups aresubstantially different. Moreover, in actual clinical practice, manifestations of these localizations may coexist in the same patient. Furthermore, the clinical manifestations of atherosclerotic lesions in one area may suggest damage to another area, often at a subclinical level detected solely by imaging methods. The ultimate cause of death or disability, regardless of the clinical manifestations of peripheral atherosclerosis, is most often of a cardiac nature (acute myocardial infarction, sudden cardiac death), or else related to stroke.

The REACH (REduction of Atherothrombosis for Continued Health) registry, involving 44 countries, stated that 39% of patients with PAD had a concomitant coronary artery disease, 10% had cerebrovascular disease, and 13% had both ailments in addition to PAD. Less than 40% of patients with PAD did not have concomitant coronary artery disease or cerebrovascular disease [8]. Thus, as stated, a patient with manifestations of one PAD often was a patient with multifocal atherosclerosis. This was also true for the patients included in our study. For example, a history of myocardial infarction,angina pectoris, or stroke was detected in 32.8%, 40%, and 15.6% of cases. Interestingly, patients with an initial diagnosis of coronary artery disease exhibited a much lower likelihood of peripheral atherosclerosis than the likelihood of coronary artery disease in patients with PAD [7].

The inclusion of patients with different varieties of PAD in our study reflects ourperception of atherosclerosis as a systemic lesion of the arterial bed with potentially malignant development. This hypothesis is also confirmed by the significant number of hospitalizations for cardiovascular reasons in the prospective part of our study. Since the main group included subjects with multifocal atherosclerosis, type II diabetes mellitus, arterial hypertension, and chronic coronary artery disease, some of whom underwent various revascularization operations, it was crucial to take into account these important conditions from the standpoint of their prognosis and severity in the form of a cumulative parameter calculated for each patient. In available publications, we did not encounter any examples of an adequate solution in relation to the structure of our patient group. Consequently, we considered the main clinical parameters and events, associated with a negative prognosis of cardiovascular outcomes,based on the published sources [9, 10].

This single-center pilot study examinedSAF in patients with predominantly multifocal peripheral arterial atherosclerosis and the ability of this parameter to reflect cardiovascular remodeling processes and the likelihood of adverse outcomes. Despite the fact that SAF readers have been used abroad over the last two decades to stratify cardiovascular risk, we did not find coverage of this topic in domestic literature.

The inclusion of a control group in our study was necessary to highlight the differences in the SAF parameter, and its dependence on age, cholesterol content and other modifiable risk factors used in the SCORE1 stratification system. Indeed, the relationship of age and total cholesterol withSAF is thoroughly described in the literature [11]. In the main group, such correlations are not observed, sincethe accumulation of AGEs depends more on the activity of the pathological process than on age. SAFis also valuable in screening patients for diabetes, and its role as a predictor of both cardiovascular and disease-specific microvascular complications is well recognized [12]. The SAF method has been validated as a noninvasive method for assessing AGEs in patients with PAD, not only in their skin but in arteries and nerves as well, as shown in patients of our study who underwent lower limb amputation (5 patients with diabetes mellitus and 28 diabetes-free subjects) [13].

In a meta-analysis based on 10 published studies with a total of 4,189 patients at high and very high cardiovascular risk, including patients with PAD, the prognostic role of the SAF parameter was examined. High values of SAF corresponded to an increased risk of death from cardiovascular diseases (RR=2.06; CI 1.58-2.67) and elevated total mortality rate (RR=1.91; CI 1.42-2.56) [14].

A case-control study involving 492 patients with PAD found that their SAF was significantly higher, regardless of known cardiovascular risk factors or comorbidity with diabetes mellitus and chronic kidney disease; furthermore, these conditions were associated with a further increase in the SAF parameter [15]. This study confirmed our results both in terms of elevated SAF, compared with the control, and in the association of SAF with parameters of clinical status and prognosis. Besides, in an observational study of 252 patients with lower limb PAD, a unit increase in SAF value was associated with a 3.05-fold increase in the risk of amputation, regardless of comorbidity with diabetes mellitus or stage of CAI [16]. Independent predictors of events in our study were SAF and fasting blood glucose concentration

(*Figures 1 and 2*). Therefore, glycemic disorders can be explained by type II diabetes mellitus and the phenomenon of elevated fasting glycemia, which implies the presence of prediabetes. According to the published sources, both factors have a significant impact on the prognosis of cardiovascular complications in patients, regardless of clinical manifestations of atherosclerosis, as well as the clinical form of atherosclerosis [17, 18].

Another identified predictor of adverse outcomes was the functional class of CHF (*Figure 3*). Our study excluded patients with CHF above functional class 2 with substantial limitation of exercise tolerance. In a significant proportion of our patients, the following structural changes in the myocardium were identified: hypertrophy of the left heart and functional disorders in the form of diastolic dysfunction, which are considered as essential components of the CHF diagnosis in combination with a complaint on a limited exercise tolerance and a history of arterial hypertension as the main etiological CHF factor. Severe CAI limits manageable walking distance preventing an accurate determination of the CHF severity.

In part, this circumstance can be considered as a limitation of our study significance since it is related to a quarter of patients in the study: stages 3-4 of CAI were detected in 17 patients (17%), while stage 2B of CAI wasfound in 11 subjects (9%). That is why in contemporary studies, biochemical markers of CHF are used in patients with disorders of the lower limbs. For example, in a long-term prospective follow-up study of elderly patients with PAD, cardiac high-sensitivity troponin T and natriuretic peptide precursor, known as a marker of heart failure, were the strongest independent predictors of death vs.conventionalvascular symptoms of atherosclerosis [19]. It is well known that the very fact of CHF occurrence is accompanied by an extremely negative prognosis for the patient's life, including in the elderly, comparable to the prognosis for life in oncological pathology [20].

Conclusion

The results of our study demonstrated thatSAF parameter values were significantly elevated in patients with clinical manifestations of peripheral atherosclerosis. These valueswere proportional to clinical predictors of cardiovascular complications. Hence, the significance of SAF as an integral independent predictor in patients with a wide range of PADs has been confirmed.

Conflict of interest. None declared**.**

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