Novel diagnostic criteria for atrial cardiomyopathy in patients with type 2 diabetes and atrial fibrillation

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Aim. To determine additional diagnostic criteria for atrial cardiomyopathy in patients with type 2 diabetes (T2D) and paroxysmal/persistent atrial fibrillation (AF).

Material and methods. This cross-sectional screening clinical study included 80 patients with AF and T2D, who were divided into 2 groups depending on the left (LAVI) or right atrial volume index (RAVI) according to echocardiography: the first group included 49 patients with increased LAVI, while the second — 31 patients without changes in LAVI and RAVI. Inclusion criteria were presence of paroxysmal or persistent AF, T2D, age up to 65 years. There were following exclusion criteria: current smoking and less than 1 year old, the presence of cardiovascular and pulmonary diseases, heart failure, implanted artificial pacemaker, prior radiofrequency ablation; valvular heart disease and prosthetics; acute myocarditis, infective endocarditis, hypertrophic, dilated, and restrictive cardiomyopathies, storage diseases, severe liver diseases; thyroid disorders; cancer; acute inflammatory and infectious diseases; alcohol abuse, dementia and mental illness.

Results. The groups did not differ significantly in terms of sex, age, cardiovascular risk factors, risk of stroke and bleeding when using anticoagulants, clinical and laboratory parameters, and the structure of drug therapy. The following parameters significant differ between the groups: LAVI (according to study design), mid-regional pro-atrial natriuretic peptide (MR-proANP), glomerular filtration rate (GFR) calculated by creatinine, tissue inhibitor of matrix metalloproteinases 1 (TIMP-1). For MR-proANP, GFR, TIMP-1, ROC curves were created in order to determine its clinical significance and operational characteristics of parameters. GFR, as a diagnostic criterion, showed unsatisfactory clinical significance when constructing the ROC curve: AUC (area under the curve) was 0,38. The MR-proANP of 62,3-85 pmol/L and TIMP-1 of 156 ng/ml and higher allows verification of atrial cardiomyopathy in patients with T2D and AF at AUC of 0,83 (95% confidence interval (CI), 0,73; 0,92) and 0,90 (95% CI, 0,83; 0,98), respectively.

Conclusion. The blood MR-proANP concentration of 62,3-85 pmol/L is diagnostic for atrial cardiomyopathy in patients with T2D and AF with the sensitivity and specificity of 96,8% and 75,5%, respectively, while TIMP-1 values of 156 ng/ml and above had the sensitivity and specificity of 90,3% and 87,8%, respectively.

Keywords: atrial cardiomyopathy, atrial fibrillation, type 2 diabetes.

Relationships and Activities: none.

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In 2016, atrial cardiomyopathy was first presented as any complex of structural, morphological, contractile or electrophysiological changes in the atria that can cause clinically significant manifestations according to the European Consensus of experts [1]. The isolation of this pathology was caused by the fact that there was information on unfavorable prognosis for its development both in relation to chronic heart failure (CHF) and cerebrovascular events, especially at a young age in the presence of genetic diseases [2]. A number of authors suggest that the diagnosis of cardiovascular system pathology at the stage of atrial cardiopathy development will help to see the problem early, which requires the search for therapeutic interventions that can prevent its further progression and adverse outcomes [3, 4].

Experts of the European Consensus distinguish 4 classes of atrial cardiopathy depending on histological changes of the atria and the etiological factor. In patients with isolated form of atrial fibrillation (AF), diabetes mellitus (DM), genetically detected abnormalities, mainly associated with the formation and release of atrial natriuretic peptides (NUP), first-class atrial cardiopathy is isolated [5, 6]. According to the Recommendations of the European Society of Cardiology (2020), the term "isolated AF" is not included in the current classification and is not recommended to use in clinical practice [7]. Experts suggest that at present time, the AF causes in most cases are known and are interrelated with cardiovascular diseases and/or comorbid pathology. At the same time, in the same recommendations, the atrial cardiopathy definition was further developed and discussed. It is noted that atrial cardiopathy at the present stage should be verified on the basis of changes in atrium geometry (dimensions, volume, area).

In addition to atrial imaging techniques, such as speckle tracking during echocardiography (EchoCG), computed tomography and magnetic resonance imaging, inflammation markers (C-reactive protein, cytokines), myocardial stress, adhesion molecules and coagulation factors, as well as collagenolysis system indicators, were studied as potential diagnostic tools of atrial cardiopathy, but mainly separately in individuals with AF or DM [8]. NUPs have been studied primarily in CHF diagnosis, although theoretically their role in atrial cardiopathy detection may be a priority [9]. To verify atrial cardiopathy, many researchers believe that it is necessary to study several biomarkers simultaneously, referring to the multifactorial pathogenesis of its formation [10].

Thus, the identification of new biomarkers of atrial cardiopathy in patients with T2DM and AF, which are likely to take priority of structural changes in the atrium, will allow detecting this pathology at early stage in order to prevent cerebrovascular and cardiovascular complications.

The goal of this study — to detect additional diagnostic criteria for atrial cardiopathy in patients with T2DM and paroxysmal/persistent AF.

Material and methods

A single-stage screening clinical trial was conducted. Within 24 months, the study enrolled 243 consecutive patients admitted to a cardiology hospital due to AF paroxysm. After status stabilization, a cohort of 80 patients with T2DM was identified among them, which were divided into 2 groups depending on indexed volume of left or right atrium (IVLA and IVRA) according to EchoCG data: the first group included 49 patients with an increase in IVLA without an increase in IVRA, the second — 31 patients without changes in IVLA and IVRA. The enrollment criteria were the presence of paroxysmal or persistent AF, T2DM, age up to 65 years. The criteria for non-enrollment were as follows: current and less than 1 year old smoking, presence of cardiovascular and bronchopulmonary diseases, CHF (N-terminal fragment of brain natriuretic peptide (NT-proBNP) >400 pg/ml and/or mid-regional fragment of atrial natriuretic peptide (MR-proANP) >85 pmol/l), implantation of artificial pacemaker, performing radiofrequency ablation in anamnesis; pathology of valves and their prosthetics; acute myocarditis, infectious endocarditis, hypertrophic, dilated cardiomyopathy and restrictive myocardial damages, storage diseases, severe liver diseases; thyroid function abnormalities; oncological diseases; acute inflammatory and infectious diseases; alcohol abuse, dementia and mental diseases that prevent the patient from signing informed consent.

AF was verified by recording a real time 12-channel electrocardiogram. T2DM was detected in accordance with the criteria of the World Health Organization (1999-2013).

EchoCG was performed using a Samsung Accuvix A30 ultrasound scanner (South Korea) in accordance with the recommendations of the American and European Society of Echocardiography. The left ventricular ejection fraction (LV EF) was considered to be preserved by 50% or more, calculated by the Simpsop method. LV diastolic function was assessed by transmitral diastolic blood flow and tissue imaging of diastolic velocities of the mitral annulus. The left ventricular myocardial mass index (LVMMI) was also detected. The criteria for LV hypertrophy were considered to be LVMMI >115 g/m^2 in men and >95 g/m^2 in women, or >50 $g/m^{2,7}$ in men and >47 $g/m^{2,7}$ in women. Atrium enlargement was detected at IVLA >22

Table 1

Clinical and anamnestic characteristics of indicators by examined groups (n=80)

Indicator	Group one (T2DM+AF+IVLA, n=49)	Group two (T2DM+AF, n=31)	P
Age, years	58,2 [46,4; 61,8]	56,9 [43,7; 61,0]	0,238
Women, abs./%	30/61,2	19/61,3	0,819
Men, abs./%	19/38,8	12/38,7	0,819
BMI, kg/m^2	31,2 [27,9; 34,7]	30,2 [27,21; 33,8]	0,341
HR outside of paroxysm in AF, bpm	73,8 [64,5; 79,2]	72,7 [62,6; 80,1]	0,261
SBD, mmHg	131 [116; 145]	130 [111; 142]	0,592
DBP, mmHg	86 [80; 92]	84 [79; 89]	0,620
CHA$_2$DS$_2$VASC scale, score	2,1 [1,2; 3,1]	2,0 [1,5; 3,0]	0,874
HASBLED scale, score	1,5 [1,1; 2,7]	1,7 [1,4; 2,6]	0,832
Total cholesterol, mmol/l	5,6 [4,6; 6,2]	5,5 [4,2; 5,9]	0,774
LDL cholesterol, mmol/l	3,4 [2,4; 3,8]	3,2 [2,2; 3,6]	0,673
TG, mmol/l	2,1 [1,6; 2,5]	2,2 [1,5; 2,6]	0,659
HDL cholesterol, mmol/l	1,1 [0,8; 1,4]	1,2 [0,9; 1,4]	0,831
Fasting plasma glucose, mmol/l	8,5 [6,5; 9,4]	8,1 [6,2; 9,7]	0,173
Glycated hemoglobin, %	7,8 [6,8; 8,0]	7,6 [6,7; 8,0]	0,369
HD, abs./%	47/95,9	28/90,3	0,594
CRD, abs./%	9/18,4	6/19,4	0,855
Antiplatelet agents, abs./%	5/10,2	4/12,9	0,993
Anticoagulants, abs./%	36/73,5	21/67,7	0,766
ACE inhibitors/AIIRA, abs./%	44/89,8	25/80,6	0,410
BB, abs./%	35/71,4	15/48,4	0,067
Statins, abs./%	21/42,9	13/41,9	0,881
Calcium antagonists, abs./%	11/22,4	8/25,8	0,941
Antiarrhythmics constantly, abs./%	5/10,2	1/3,2	0,473
Antihyperglycemic drugs, abs./%	44/89,8	30/96,8	0,473
Metformin, abs./%	32/65,3	24/77,4	0,368
Sulfonylurea medications, abs./%	17/34,7	11/35,5	0,867
DPP4i, abs./%	5/10,2	2/6,4	0,863
SLGT2i, abs./%	8/16,3	4/12,9	0,924
Insulin, abs./%	5/10,2	3/9,7	0,760

Abbreviations: AIIRA — angiotensin II receptor blockers, BB — beta-blockers, HD — hypertensive disease, DBP — diastolic blood pressure, CRD — cardiac rhythm disorders, ACE inhibitors — angiotensin-converting enzyme inhibitors, DPP4i — dipeptidyl peptidase 4 inhibitors, BMI — body mass index, SLGT2i — sodium-glucose co-transporter 2 inhibitors, IVLA — indexed volume of left atrium, SAD — systolic blood pressure, DM — diabetes mellitus, TG — triglycerides, AF — atrial fibrillation, HDL cholesterol — high-density lipoprotein cholesterol, LDL cholesterol — low-density lipoprotein cholesterol, HR — heart rate.

ml/m^2 and IVRA >21 ml/m^2 in accordance with the recommendations of the European Society of Echocardiography (2006).

The NT-proBNP and MR-proANP concentration in blood serum was detected after rhythm recovery by ELISA test on the analyzer Immulite 1000 (DPC, USA) using reagents "Biomedica Group" (Austria). The NT-proBNP concentration in serum >400 pg/ml, and MR-proANP >85 pmol/l were considered as diagnostic criteria for CHF in patients with AF [11].

To assess the collagen matrix state, the concentration of a tissue inhibitor of matrix metalloproteinases type 1 (TIMP-1) in blood serum was detected by ELISA test using reagent Aviscera Bioscience (USA) on analyzer Immulite 1000 (DPC, USA). The reference values of TIMP-1 were 111-138 ng/ml.

Statistical processing was conducted using software STATISTICA 12.0 and online calculator Easy ROC_web-tool for ROC curve analysis (ver. 1.3.1). The critical value of the statistical

Table 2

Structural and functional changes of the heart and target organs by groups of subjects (n=80)

Indicator	Group one (T2DM+AF+IVLA, n=49)	Group two (T2DM+AF, n=31)	P
NT-proBNP, pg/ml	96,7 [14,6; 112,7]	88,5 [16,4; 102,9]	0,089
MR-proANP, pmol/l	78,5 [43,7; 80,1]	56,7 [28,7; 61,4]	0,008
LV EF, %	60,8 [53,1; 65,7]	59,2 [52,9; 64,9]	0,384
LVMMI, g/m^2	105,6 [94,2; 128,4]	100,4 [89,7; 126,9]	0,103
LVMMI, g/m^{2,7}	40,9 [34,5; 56,0]	41,0 [37,7; 52,3]	0,286
IVLA, ml/m^2	34,5 [24,6; 48,2]	19,4 [14,0; 20,4]	<0,001
IVRA, ml/m^2	15,9 [12,3; 20,2]	16,8 [13,9; 20,4]	0,098
E/A	1,1 [0,8; 1,2]	1,0 [0,7; 1,2]	0,748
septale e', m/s	8,0 [6,0; 9,0]	7,0 [5,0; 8,0]	0,176
laterale e', m/s	8,0 [7,0; 10,0]	9,0 [8,0; 10,0]	0,105
E/e' average	14,0 [9,0; 16,0]	14,0 [9,0; 15,0]	0,673
Creatinine, µmol/l	91,6 [77,8; 109,2]	87,3 [71,7; 101,4]	0,093
GFRcre, ml/min/1,73 m^2	59,4 [45,7; 84,1]	64,3 [52,0; 89,4]	0,039
TIMP-1, ng/ml	179,0 [148,0; 205,6]	142,2 [126,4; 187,1]	<0,001

Abbreviations: LVMMI — left ventricular myocardial mass index, IVLA — indexed volume of left atrium, IVRA — indexed volume of right atrium, DM — diabetes mellitus, GFRcre — glomerular filtration rate calculated by creatinine, LV EF — left ventricular ejection fraction, AF — atrial fibrillation, A — maximum rate of late LV filling, MR-proANP — mid-regional fragment of atrial natriuretic peptide, NT-proBNP-N — terminal fragment of brain natriuretic peptide, E — maximum rate of early LV filling, e' — early diastolic rate of fibrous ring movement, TIMP-1 — tissue inhibitor of matrix metalloproteinases.

significance level when testing null hypotheses was taken equal to 0,05. The normality of distribution was checked using the Kolmogorov-Smirnov and Shapiro-Wilk criteria. All quantitative features did not correspond to the law of normal distribution and were presented in the form of median, lower and upper quartiles (Me [25; 75]). For qualitative signs, the absolute frequency of the sign, the sign frequency as a percentage (%) were calculated. For distribution of indicators other than normal, statistical processing was carried out using the Mann-Whitney test — for quantitative indicators; the χ^2 test with the Yates correction or the Fisher test for n≤5 — for qualitative indicators.

The study of relationship between quantitative features was carried out on the basis of Spearman's rank correlation coefficients. Interpretation of the obtained values of statistical relationship test was carried out according to the recommendations of the Rea & Parker. The confidence critical level of null hypotheses in the relationship study was taken as the level of p<0,05.

Detection of the cut-off point corresponding to the optimal value of additional criteria for atrial cardiopathy diagnosis in patients with T2DM and AF was carried out using the method of constructing the ROC curve (receiver operating characteristic), taking into account the Yuden index and detecting the operational characteristics, calculating the
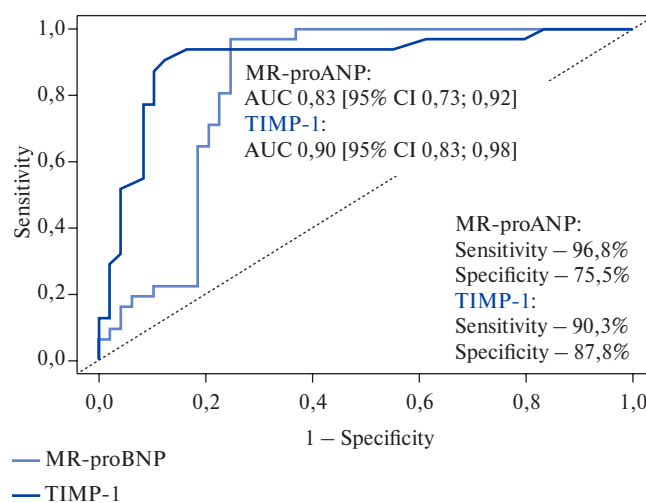

Figure 1. ROC curves for MR-proANP and TIMP-1 in comparison with IVLA as diagnostic criteria for atrial cardiopathy in patients with T2DM and AF (n=80).
Abbreviations: CI — confidence interval, AUC — area under curve, MR-proANP — mid-region fragment of atrial natriuretic peptide, TIMP-1 — tissue inhibitor of matrix metalloproteinases type 1.

quantitative index AUC (Area Under Curve) >0,5 at p<0,05.

The study was controlled by the standards of Good Clinical Practice and the principles of the Helsinki Declaration. The study protocol was promptly appro-

ved by the Ethics Committee. All participants received written informed consent before enrollment.

Results

The clinical and anamnestic characteristics of the enrolled groups of patients are presented in Table 1. The groups did not differ significantly in terms of gender, age, cardiovascular risk factors, risk of stroke and bleeding when using anticoagulants, clinical and laboratory parameters, drug therapy structure.

Structural and functional changes of the heart and target organs by groups of subjects are presented in Table 2.

All patients in the study were found to have preserved LV EF. 51% of patients in the first group and 45,2% of patients in the second group had LV diastolic dysfunction (p=0,779). LV hypertrophy was detected in 40,8% of patients in the first group and in 25,8% of patients in the second group (p=0,259).

Statistically significant differences between the groups were found in the following indicators: IVLA (according to the study design), MR-proANP, glomerular filtration rate (GFR) calculated from creatinine, TIMP-1.

During the correlation analysis, the following data were obtained: direct and inverse relationships of medium and high degree of dependence were revealed, statistically significant relationships between IVLA and MR-proANP (r=0,56; p=0,002), TIMP-1 (r=0,43; p=0,018), GFR (r=-0,37; p=0,012).

ROC curves were constructed for MR-proANP, GFR, TIMP-1 in order to detect the clinical significance and operational characteristics of these biomarkers for atrial cardiopathy diagnosis in patients with T2DM and AF. GFR as a diagnostic criterion demonstrated unsatisfactory clinical significance when ROC curve construction: AUC was 0,38.

When ROC curve construction for all available MR-proANP values up to 85 pmol/l (diagnostic criterion of CHF), a cut-off point of 62,3 pmol/l was obtained. AUC was 0,83 (95% confidence interval (CI) 0,73; 0,92), the standard mean square error of AUC was 0,05 (p<0,001). Therefore, MR-proANP value in the range from 62,3 to 85 pmol/l for the verification of atrial cardiopathy in patients with T2DM and AF allows for diagnostic method sensitivity — 96,8% (95% CI 83,3; 99,9), specificity — 75,5% (95% CI 61,1; 86,7). The ROC analysis for TIMP-1 demonstrated an optimal cut-off point of 156 ng/ml. AUC was 0,90 (95% CI 0,83; 0,98), the standard mean square error of AUC was 0,04 (p<0,001). Therefore, the TIMP-1 value of 156 ng/ml and higher for atrial cardiopathy verification in patients with T2DM and AF allows for diagnostic method sensitivity — 90,3% (95% CI 74,2; 98,0), specificity — 87,8% (95% CI 75,2; 95,4) (Figure 1).

Discussion

In our study, NT-proBNP as an indicator of myocardial stress in heart ventricles was lower than the values corresponding to CHF according to the study design; indicators reflecting LV diastolic dysfunction, LVMMI, did not differ statistically significantly between the groups. Therefore, the value of these indicators as atrial cardiopathy markers in patients with T2DM and AF without CHF is questionable. A number of Russian authors have also demonstrated that NT-proBNP, in contrast to growth differentiation factor-15, is not associated with left atrium fibrosis and its alteration [12]. According to Buttner P, et al. (2018), in 241 patients with AF who underwent catheter ablation, the N-terminal fragment of atrial natriuretic peptide, but not NT-proBNP, was associated with paroxysmal and persistent forms of AF both with an increase in LA diameter and with its normal size (mean values of 15, 20, 19, and 27 ng/ml, respectively, P=0,004) [13]. This is due to the different localization of NUP formation: when the atrial myocardium is stretched, type A NUP is produced, and when the ventricles are stretched, type B NUP is produced.

However, opposite data also exists. Thus, Stanciu AE, et al. (2018) showed that the NT-proBNP concentration increases with increase in left atrium diameter in both paroxysmal and persistent AF [14]. These contradictions are connected to the fact that earlier atrial cardiopathy manifestations without changes in dimetions and volume of the atrium can be electrophysiological atrial disorders detected by voltage mapping in the form of low voltage zones, which reflect the presence of fields of perivascular fibrosis without stretching the myocardial fibers and, accordingly, without increasing the NUP concentration in blood [15]. But even in the range of normal values, as in our study, atrial NPS are statistically significant predictors of atrial fibrosis, detected by voltage mapping [16].

In our study, we obtained a significant prevalence of TIMP-1 in the group of patients with atrial cardiopathy in patients with T2DM and AF. It is well known that both T2DM and AF make a negative contribution to myocardial fibrosis [17]. But in patients with structural remodeling of the left atrium, we obtained higher numbers of TIMP-1, which is an integral indicator of collagen formation in tissues. Similar data were obtained in the study Fragão-Marques M, et al. (2020), which found that patients with AF and aortic stenosis significantly increased

TIMP-1 (p=0,004) in comparison with patients with sinus rhythm [18]. In a large observational study (n=674), it was confirmed that TIMP-1, as well as matrix metalloproteinases, are independent factors of increasing IVLA [19].

The study's limitations are a small sample of patients (n=80), assessment of the predictor value of additional atrial cardiopathy criteria in patients with DM and AF individually, multivariate analysis of biomarkers and instrumental method indicators, such as atrium speckle tracking during EchoCG, voltage mapping during diagnosis of atrial remodeling.

A promising work area should be considered the study of atrial cardiopathy formation not only of the first class, but also in CHF, valvular pathology, amyloidosis and other diseases.

Conclusion

MR-proANP and TIMP-1 as diagnostic methods for detecting atrial cardiopathy in patients with T2DM and AF when constructing the ROC curve showed high clinical significance. MR-proANP concentration in blood in the range from 62,3 to 85 pmol/l for atrial cardiopathy diagnosis in patients with T2DM and AF allows for method sensitivity — 96,8%, specificity — 75,5%, TIMP — 1 156 ng/ml and higher — 90,3% and 87,8%, respectively.

Relationships and Activities: none.

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