Atrial cardiomyopathy — a new concept with a long history

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Atrial cardiomyopathy (ACM) is a relatively common but clinically underestimated disorder, which is characterized by an increased atrial size and dysfunction. Previously, ACM was considered a primary disorder, but in 2016 this concept was revised by European Heart Rhythm Association (EHRA) working group with inclusion of secondary atrial remodeling. The EHRA document details aspects of atrial anatomy and pathophysiology, proposes definitions of ACM, histological classification, outlines the molecular mechanisms of atrial arrhythmia and the problems of personalized treatment and optimization of indications for catheter ablation. Practical application of the proposed ACM classification system, the clinical significance of novel ACM concept and the potential role of this information for a practitioner are presented in this article. Two clinical cases of ACM with “primary” (familial form of ACM due to NPPA gene mutation with primary defect in atrial structure and function) and “secondary” atrial remodeling (ACM caused by a long-term supraventricular tachyarrhythmias due to SCN1B gene mutation).

Key words: atrial remodeling, atrial cardiomyopathy, atrial fibrillation, atrial electromechanical dysfunction, NPPA gene.

Relationships and Activities: none.

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In recent years, the structural and electromechanical atrial abnormalities as markers of unfavorable clinical prognosis in various groups of patients with cardiovascular diseases has been actively studied. The issues of atrial cardiomyopathy are today the subject of scholarly discussion. However, the fact that atrial cardiomyopathy (ACM) is a fairly common, but still clinically underestimated pathology, is beyond doubt by most researchers.

The first report of a familial fibrotic ACM (FACM) was provided by Williams D, et al. (1972) during long-term follow-up of family members with atrial ectopic beats and atrioventricular (AV) block, when three out of five brothers and sisters had progressive symptoms of chrono-, dromo- and inotropic atrial dysfunction [1]. Later, many researchers reported on histopathological changes in the atria (inflammation, interstitial or focal fibrosis) that were observed in patients with atrial fibration (AF) in the absence of structural causes of arrhythmia, such as valvular heart disease or heart failure (HF) [2, 3]. Kottkamp H, et al. (2012) for the first time defined FACM as an independent and progressive ACM with atrial fibrotic lesion, which cannot be caused by age, heart disease, or the presence of atrial fibration [4]. The authors suggested that a specific form of FACM is a common pathological manifestation of all AF types, but is caused by a primary process in atrial myocytes, regardless of arrhythmia. In 2016, experts of the European Heart Rhythm Association (EHRA), the Heart Rhythm Society (HRS), the Asia-Pacific Heart Rhythm Society (APHRS) and the Latin American Society of Cardiac Pacing and Electrophysiology (SOLAECE) proposed new definitions of ACM as any complex of structural, contractile or electrophysiological abnormalities affecting the atria and contributing to the clinically significant manifestations [5]. This definition resembles the concept of arrhythmogenic atrial remodeling, defined as any change in the structure or function of the atria that contributes to atrial arrhythmias [6]. However, a new element of ACM definitions reflects a potentially important position — the adverse consequences of atrial electromechanical disturbances may be completely independent of atrial arrhythmias. This is a very important aspect, emphasizing the fact that the risk of cerebral thromboembolic events (CTEs) in the presence of ACM may not depend on the onset/development of AF. The second difference is that the terminological subtext of atrial remodeling includes the assumption that the atria were normal before they were exposed to any external influences. Thus, ACM can be caused by primary processes in the atria — structural, electrical and functional disorders characteristic of some genetic diseases (for example, due to MYL4 or NPPA gene mutations) [7, 8]), as well as secondary arrhythmogenic changes caused by isolated AF and other risk factors for AF causing structural myocardial remodeling [9, 10].

**ACM — orphan or common disorder?**

It is known that many diseases (hypertension valvular heart disease, heart failure, diabetes, myocarditis) or conditions (aging, smoking, obesity, metabolic disorders) cause or contribute to the development of ACM [11]. However, changes in the atria caused by these diseases are not specific for ACM — the localization, prevalence and degree of pathological atrial remodeling depend on the duration and severity of disease, on the modification of many other concomitant factors that cause significant individual differences. The progression of the remodeling substrate depends on many factors that influence the cardiomyocyte reaction in response to electrical, mechanical, hemodynamic, and metabolic stress. Some components of atrial remodeling are reversible (adaptive), while others are permanent (maladaptive). The progression of atrial injury due to underlying heart disease is a major pathogenic factor. Recent studies have demonstrated the effectiveness of AF prevention by successful management of such modifiable risk factors as obstructive sleep apnea syndrome, obesity, hypertension (HTN), hyperglycemia and dyslipidemia [12-15]. Elimination of these abnormalities contributed to the prevention of further atrial damage, and conversely, additional risk factors was associated with recurrence and persistence of AF with progression of the pathological substrate, which supports the Wijffels-Allessie postulate that AF begets AF [16].

However, in addition to the fact that some pathological processes can affect the atria very selectively (for example, AF-related remodeling), there are other less specific mechanisms that cause changes not only in the atria, but also in the ventricles to a greater or lesser extent (primary cardiomyopathies, HTN, muscular dystrophies (MD), amyloidosis, myocarditis) [17].

Thus, ACM is associated with a variety of causes that contribute to pathological atrial remodeling. The most common causes are isolated AF, HF, HTN, myocarditis, valvular heart disease, diabetes, obesity, amyloidosis, hereditary MD. The main etiological, clinical and morphometric features of atrial remodeling leading to electromechanical dysfunction and ACM are presented in Table 1 [5].

In 2016, experts of the EHRA/HRS/APHRS/SOLAECE working group developed a consensus document with a detailed presentation of atrial anatomy, physiology and pathology, definitions with histological classification of ACM, molecular mechanisms affecting the development of arrhyth-
mias, imaging and mapping methods, where they also identified problematic issues of personalized treatment and optimization of indications for catheter ablation. The authors proposed a histological (pathophysiological) classification using the EHRAS abbreviation (E — EHRA, HR — HRS, A — APHRS, S — SOLEACE) to define 4 classes of ACM [1]: I — primarily cardiomyocyte-dependent; II — primarily fibroblast-dependent; III — mixed cardiomyocyte-fibroblast-dependent; IV — primarily non-collagen deposits (Table 2) [5].

This simple classification reflects the dominant morphological pathology in various clinical and pathophysiological situations. These EHRAS classes correspond to their histopathological characteristics. However, at least two problems limit the application of this classification in clinical practice. First, the system is based on histological interpretation, requiring analysis of atrial tissue samples for verification, which in most cases is technically impossible. Second, there is significant overlap between EHRAS classes within almost every etiological category of ACM (Table 1). For example, the histopathological characterization of valvular heart disease can have features of all four classes; pathomorphological signs of HTN, diabetes and MD will overlap within three classes. Only atrial amyloidosis will be in one class (class IV). While class I is often seen in patients with hereditary AF and diabetes, class II is characteristic of atrial remodeling with aging and smoking (Table 1). In patients with HF, the remodeling type corresponds to class III or II, while class IV is often observed in isolated atrial lesions [5].

**Clinical application of a novel concept with a long history**

At first glance, the ACM classification seems to be not suitable for a practitioner, since for most patients it is impossible to unambiguously determine the EHRAS class without histopathological assessment. But even if the patient’s phenotype is unambiguously assigned to a certain I or IV class, it is not fully clear what to do in the future and how to use this information correctly.

However, considering all of the listed ACM classes have one common feature (electromechanical atrial dysfunction caused by structural, mechanical and electrical remodeling) and these changes most often lead to AF [5-7], which is associated with an increased risk of thromboembolic events (TEE), decompensated HF and mortality due to stroke [11, 13-20], it is quite expected that the analysis of ACM etiology, assessment of atrial hemodynamic parameters (speckle tracking, tissue Doppler imaging), macroscopic determination of atrial fibrosis degree using contract-enhanced magnetic resonance imaging (MRI) and the identification of patient procoagulant status will have important prognostic and therapeutic value.

Figure 1 shows the main thromboembolic risk factors that are used for risk stratification in patients with AF before oral anticoagulant (OAC) therapy.

Today, the CHA2DS2-VASc score is widely used in practice, including predictors (HF, HTN, age from 65 to 74 years, age 75 years and older, female sex, diabetes, prior stroke or transient ischemic attack, TEE, vascular diseases), which determine the decision to use OAC therapy in accordance with generally accepted guidelines [20, 21]. It is known that all these predictors of TEE are also independent risk factors and the main causes of ACM. Logically, clinicians do not make clinical decisions about prescribing OAC therapy on the basis of AF as such, but rather taking into account concomitant conditions and diseases associated, including with ACM.

This hypothesis is supported by the results of studies showing the absence of absolute synchronization of episodes of AF and stroke [21-25]. The authors’ conclusions that ACM is an independent risk factor for cerebral TEE contradict the classical scenario of stroke due to embolization by thrombi from the left atrial (LA) appendage. The ASSERT study revealed that AF were observed within 30 days before stroke in only 8% of patients, and in 16% of patients with cerebral TEE, paroxysmal AF developed after cerebrovascular accident, while in 49%, subclinical episodes of AF were not observed [24, 25]. The absence of a temporal relationship between the AF and cerebral TEE was also demonstrated in the IMPACT study [26]. One of the possible explanations for this phenomenon is the structural mechanisms of atrial remodeling with inotropic and endothelial atrial dysfunction, which increases the risk of stroke even without AF. The well-known diseases with a predominant atrial lesion (cardiac amyloidosis and Fabry disease) associated with an increased risk of TEE, including stroke, which are caused by serious atrial contractile dysfunction, confirm the direct association between ACM and cerebral TEE [27]. Mutations in the MYL4 gene also cause ACM with severe atrial contractile dysfunction [7-9] and a high risk of stroke [8]. ACM with an autosomal recessive inheritance has been well studied in patients with a homozygous NPPA gene mutation (p.Arg150Gln), leading to structural damage to atrial natriuretic peptide (ANP) [28]. The phenotype is characterized by significant bialtrial dilatation, supraventricular arrhythmias with progressive loss of sinus and atrial electrical activity with stable normal left ventricular (LV) contractile function. These patients often require pacemaker implantation and long-term anticoagulant therapy due to the high risk
### Etiology, structure and characteristics of the main ACM phenotypes

| Etiological category of ACM | Clinical and/or morphometric features of atrial remodeling | EHRAS class |
|----------------------------|-------------------------------------------------------------|-------------|
| AF (isolated)              | Atrial morphometry in longstanding persistent AF: cardiomyocyte hypertrophy, myocytolysis, interstitial fibrosis, and decreased expression of connexin-43 | I, II, III |
| Obesity                    | An increase in body mass index per unit is associated with an increased risk of AF by 3,5-5,3% | III, IV |
| HF                         | HF-related phenotype is characterized by the early development of atrial fibrosis. Remodeling components (ionic current changes, connexin), in contrast to AF-induced remodeling, are not accompanied by a decrease in the action potential and slow conduction | II, III, IV |
| Valvular heart disease     | Mitrail stenosis and/or insufficiency, aortic stenosis are associated with structural atrial remodeling and a tendency to AF | I, II, III, IV |
| Myocarditis                | AF in about 30% of cases is part of the clinical picture of myocarditis | III, IV |
| Obstructive sleep apnea    | Adverse effect on conduction (slowing atrial conduction) with increased susceptibility to AF | I, III |
| Diabetes                   | Diabetes is an independent risk factor for the development and progression of AF | I, III, IV |
| HTN                        | HTN is associated with left atrial enlargement and ECG P-wave changes, which are predictors of AF risk | I, II, III |
| Aging                      | Conduction abnormalities, increased refractory period due to atrial fibrosis | II |
| Mutations in the NPPA gene | Phenotype of biatrial dilatation with atrial ectopia and AF (Arg150Gln mutation in the NPPA gene). Association of NPPA variants (S64R and A117V) with AF | I, II, III |
| Isolated atrial amyloidosis | The most common type of age-related amyloidosis, which is limited to atrial involvement | IV |
| Genetic repolarization disorders | Combined heterozygous mutations in the sodium channel protein type 5 subunit alpha (SCN5A) and connexin-40 (GJA5) genes. Mutations in potassium channel subunits (KCNO1, KCNH2, KCND3, and KCNE5) and loss-of-function mutation in the SCN5A gene have been identified in patients with AF. Gain-of-function mutations in the KCNJ8 gene are associated with AF and early repolarization | I |
| Drug-induced atrial fibrillation | — Bisphosphonates (alendronate, zoledronic acid)  
— Inotropic agents (dopamine, dobutamine, dopexamine, arbutamine, enoximone, milrinone, levosimendan)  
— Vasodilators (isosorbide, losartan, flosequinan)  
— Acetylcholine and anticholinergics (atropine)  
— Diuretics (thiazides)  
— Sympathomimetics (pseudoephedrine, albuterol, salbutamol, salmeterol)  
— Xanthines (aminophylline, theophylline)  
— Anticonvulsants (lacosamide, paliperidone)  
— Antidepressants (fluoxetine, tranylcypromine)  
— Anti-migraine drugs (ondansetron, sumatriptan)  
— Antipsychotic agents (clozapine, loxapine, olanzapine)  
— Cholinomimetics (physostigmine, donepezil)  
— Dopamine agonists (apomorphine)  
— Anthracyclines (doxorubicin, mitoxantrone)  
— Antimetabolites (capecitabine, 5-fluorouracil, gemcitabine)  
— Tyrosine kinase (cetuximab, sorafenib, sunitinib) and topoisomerase (amsacrine, etoposide) inhibitors  
— Monoclonal antibodies (alemtuzumab, bevacizumab, rituximab, trastuzumab)  
— Cytokines and immunomodulatory drugs (azathioprine, interferon-gamma, interleukin-2, lenalidomide)  
— Drugs for erectile dysfunction treatment (sildenafil, tadalafil, vardenafil)  
— Anabolic androgenic steroids | I, II, III, IV |
| Hereditary MD               | With hereditary MD, caused by degeneration of myocytes with fatty or fibrous replacement, the heart is involved in the pathological process:  
— Duchenne MD and Becker MD (DCM, dystrophin gene);  
— Type 1 myotonic dystrophy (conduction defects, DMPK gene);  
— Emery-Dreifuss MD (DCM with conduction defects, emerin and lamin A/C genes);  
— Limb-girdle MD (DCM with conduction defects, lamin A/C and sarcoglycan genes) | I, II, III, IV |

**Abbreviations:** DCM — dilated cardiomyopathy, MD — muscular dystrophy, ACM — atrial cardiomyopathy, HF — heart failure, AF — atrial fibrillation, ECG — electrocardiography.
CLINICAL OBSERVATION

EHRAS classification of ACM

| EHRAS classes | Scheme of atrial substrate | Histological characteristics |
|---------------|----------------------------|-----------------------------|
| I. Primarily cardiomyocyte-dependent (AF, diabetes, K- and Na-channel-related genetic disorders). | | Morphological changes in cardiomyocytes (hypertrophy, myocytolysis); without fibrosis and interstitial changes. |
| II. Primarily fibroblast-dependent (aging, smoking). | | Mostly fibrotic changes; cardiomyocytes are not changed. |
| III. Mixed cardiomyocyte-fibroblast-dependent (HF, valve defects). | | Combination of cardiomyocyte (hypertrophy, myocytolysis) and fibrotic changes. |
| IV. Primarily non-collagen deposits (amyloid deposits, glycosphingolipids, granulomas and inflammatory infiltrates). | | Alteration of interstitial matrix without prominent collagen fibre accumulation: IVa — accumulation of amyloid IVf — fatty infiltration IVi — inflammatory cells IVo — other interstitial alterations. |

Abbreviations: ACM — atrial cardiomyopathy, HF — heart failure, AF — atrial fibrillation.

Table 2

Figure 1. Schematic representation of the main risk factors for stroke (risk factors are included in the CHADS2 and CHA2DS2-VASc scores and coincide with risk factors and causes of ACM).

Cardiac examination was initiated by a gynecologist as a search for disorders of the patient’s reproductive system.

As a result of electrocardiography (ECG), the following data were obtained: sinus rhythm with a heart rate (HR) of 73 bpm and first-degree AV
Figure 2. Representative fragments of ECG, HM, pre- and post-contrast MRI, x-ray signs of biatrial cardiomegaly in proband (case 1): 
A) abnormal ECG: wide and biphasic P wave with signs of interatrial block and biatrial dilatation, fragmentated QRS; 
B) speckle-tracking echocardiography of LA; C) signs of a significant decrease in peak atrial longitudinal strain (9.8%); 
D) X-ray signs of biatrial cardiomegaly; 
E) MRI movie in a 4-chamber view along the long axis in late diastolic phase with signs of pronounced biatrial dilatation; 
F) accumulation of contrast agent in the walls of both atria and interatrial septum during the delayed phase of MRI scanning (zones of atrial fibrosis are indicated by arrows); 
G) increased integral area of terminal P wave activity to 0.168 mm*s (negative component of the P wave $\int P-V1=1.4$ mm$\times$0.12 s=0.168 mm*s); 
H) increased duration of the abnormal P wave to 160 ms in III; biphasic P-waves in I, II, III, aVL; duration of 100 ms between two peaks of the biphasic P wave in aVL; 
I) six-axis system (I $-0^\circ$, II $+60^\circ$, aVF $+90^\circ$, aVR $-150^\circ$, aVL $-30^\circ$), representing the normal P wave axis (0-75 $^\circ$); the abnormal P wave axis on the ECG of the proband is equal to $+80^\circ$; 
K) HM fragment with an episode of unstable atrial tachycardia and postectopic depression of the sinus node function with escaping/replacing ectopic atrial rhythm. 

Abbreviations: LV — left ventricle, LA — left atrium, RA — right atrium.
block (PQ interval, 210 ms), signs of biventricular dilatation with third-degree interatrial block (Figure 2 A), counterclockwise rotation of the electrical axis in the frontal plane (qR in I and aVL), signs of incomplete right bundle branch block.

Echocardiography revealed severe biventricular dilatation without a decrease in the ventricular systolic function: LA anteroposterior dimension — 44/68 mm, LA volume indexed to body surface area (BSA) — 73,5 ml/m²; right atrial (RA) anteroposterior dimension — 47/68 mm, RA volume — 129 ml, RA volume index (RAVI) — 74 ml/m²; LV end-diastolic dimension — 42 mm, LV end-systolic dimension — 31 mm, LV end-diastolic volume — 83 ml, LV end-systolic volume — 36 ml, LV ejection fraction (EF) — 56%, LV mass index — 85,7 g/m², LV end-systolic volume — 36 ml, LV ejection fraction (EF) — 56%, LV mass index — 85,7 g/m², grade 1-2 mitral regurgitation; right ventricular fraction (EF) — 56%, LV mass index — 85,7 g/m², LV end-systolic dimension — 31 mm, LV end-diastolic volume — 83 ml, LV ejection fraction (EF) — 56%, LV mass index — 85,7 g/m², grade 1-2 mitral regurgitation; right ventricular (RV) fractional area change — 41%, TAPSE — 14 mm, grade 2 tricuspid regurgitation, volume and gradient of tricuspid regurgitation — 18 ml and 30 mm Hg, respectively; pulmonary artery pressure (mean/systolic) — 32,5/50 mm Hg. The patient had signs of a slight local contractility decrease in the basal and middle anteroseptal LV segments (GLS= -14,9%) and restrictive LV diastolic dysfunction: early diastolic transmitral flow velocity — 0,87 m/s, late diastolic transmitral flow velocity (A) — 0,29 m/s, E/A ratio — 3; deceleration time of early filling (DT) — 105 ms; annular early diastolic velocity (e′) — 12 cm/s; E/e′ ratio — 7,25. To analyze the atrial systolic function using the tissue speckle-tracking echocardiography, a quantitative assessment of longitudinal strain rate and atrial systolic dynamics was carried out. LA peak systolic strain was 9,8% (reference values — 53,1±12,0%), peak systolic strain rate — 0,3 s⁻¹ with reference values of 1,7±0,3 s⁻¹ (Figure 2 B, C).

Signs of biventricular cardiomegaly were revealed by chest x-ray (Figure 2 D). Pronounced atrial dilation with normal ventricular contractile function (LVEF, 72%, RV ejection fraction, 64%) were confirmed by cardiac MRI: longitudinal-transverse dimensions of LA (3,8/3,4 cm/m²) and RA (4,0/3,5 cm/m²) indexed to BSA (Figure 2 E). When assessing the pre- and post-contrast cardiac, no signs of edema were found. In the patient's blood plasma, an increase in the level of myocardial stress biomarker NT-proBNP (N-terminal pro-brain natriuretic peptide) up to 326 pg/ml and a decrease in the level of pro atrial natriuretic peptide — 0,67 nmol/ml.

Taking into account the presence of electro-mechanical dysfunction of significantly dilated atria with signs of ACM (diagnostic diagnosis with restrictive cardiomyopathy) and burdened heredity (recurrent cerebral TEE in the mother from 45 years of age and development of heart failure with AF and fatal stroke at the age of 49), family cascade screening and genetic testing was performed.

Genotyping of proband (II:1) and family members available for examination was carried out in accordance with the Declaration of Helsinki. The patients signed written informed consent. Sequence analysis of 174 genes of the target panel (NGS) in the patient revealed two variants of unknown clinical significance were identified and confirmed by Sanger sequencing: c.G448A (rs762850913) in the 2nd exon of the telethonin gene (TCAP) and c.G455A (rs755829943) in the 3rd exon of the atrial natriuretic peptide (NPPA) gene. Carriage of an identical mutation in the NPPA gene with a similar phenotype of biventricular dilatation and Bayes syndrome was found in the half-brother of the proband — a positive result of the genotype-phenotype segregation. Typical ECG, echocardiography and MRI signs of ACM in the proband’s brother are shown in Figure 3. The family
Figure 3. Representative fragments of ECG, echocardiography and MRI of a relative of proband (case 1), pedigree of family, results of NPPA sequencing, TCAP genes and diagnoses in the MOGE(S) classification: 
A) 12-lead ECG of the proband’s brother with an extended and biphasic P wave in II, III, aVF; 
B) signs of predominant LA dilatation according to echocardiography; 
C) LA according to speckle tracking echocardiography: signs of a slight decrease in peak atrial longitudinal strain (22.4%); 
D) MRI movie in a 4-chamber view along the long axis in late diastolic phase with signs of pronounced LA dilatation; 
E) postcontrast T1-weighted MRI image in a two-chamber view along the short axis demonstrates normal LV and RV dimensions without signs of delayed accumulation of contrast and signs of increased LV trabecularity (without criteria for myocardial non-compaction) in the proband’s brother; 
F) family tree and results of sequencing of NPPA and TCAP genes in family members and diagnoses according to the MOGE(S) classification.

Abbreviations: LV — left ventricle, LA — left atrium, RA — right atrium.
tree, the results of Sequence analysis of the 2nd exon of the TCAP gene, the 3rd exon of NPPA gene in members of the proband’s family and the clinical diagnosis in the MOGE (S) classification are shown in Figure 3 F.

The NPPA gene encodes the synthesis of atrial natriuretic peptide (ANP), which plays a key role in maintaining homeostasis by regulating the natriuresis, diuresis and vasodilation. Along with the regulation of intravascular volume and vascular tone, it takes part in modifying the ion channels and helps prevent atrial electrical remodeling [28]. ANP also participates in the development and onset of pregnancy, promoting trophoblast invasion and remodeling of the uterine spiral artery. NPPA gene mutations, leading to a decrease in the ANP level, disrupt all of these mechanisms. In vivo models (knockout mice) with long-term exposure to low ANP levels resulted in damage to myocytes with the development of extensive fibrotic areas and significant atrial dilatation [30].

In the presented case, the proband had severe manifestations of NPPA mutation — atrial cardiomyopathy with severe dilatation and biatrial fibrosis, SV arrhythmia and reproductive dysfunction (without anatomical, hormonal, immunological, endocrine and other causes). Taking into account the genetic status, low systolic function of significantly dilated atria, endothelial atrial dysfunction with prothrombotic changes (increased von Willebrand factor level) and increased HF signs (mild contractile and severe LV diastolic dysfunction, CHA2DS2-VASc score of 2), the patient was prescribed OACs together with HF therapy.

**Case report 2**

Male patient, born in 1965, without concomitant hypertension, coronary artery disease, diabetes and obesity, without a history of bad habits. From the age of 30, the patient had asymptomatic SV arrhythmias (moderate sinus bradycardia with escape atrial and junctional beats, SV premature beats) and grade 2 mitral valve prolapse. Symptomatic arrhythmias in the form of paroxysmal AF appeared at the age of 30, the patient had asymptomatic SV arrhythmias, LV diastolic dysfunction, CHA2DS2-VASc score of 2, the patient was prescribed OACs together with HF therapy.

The ECG admission showed a sinus rhythm with a heart rate of 82 bpm, first-degree AV block (PQ interval, 240 ms), signs of LA dilation with third-degree interatrial (Figure 4 A) and the biphasic P wave duration in I, II, III, aVF >195 ms, left axis deviation, terminal negative P wave integral in V1 was 0,144 mm*s (P negative amplitude — -1,2 mm, duration — 0,11 s).

Holter monitoring revealed episodes of first-degree AV block and transient right bundle branch block, episodes of stable and unstable junctional rhythm against the background of moderate chronotropic sinus node dysfunction, multifocal atrial ectopic activity (ectopic index — 30-45% per day) — isolated, coupled, and group SV premature beats with episodes of atrial Galavardin’s tachycardia (Figure 4 B) and unstable paroxysmal AF (Figure 4 C).

Echocardiography revealed signs of significant LA dilatation (Figure 4 D): LA anteroposterior dimension — 50/55 mm, LA volume indexed to BSA — 57 ml/m²; RA anteroposterior dimension — 40/47 mm, RAVI — 28 ml/m²; LV end-diastolic dimension — 58 mm, LV end-systolic diameter — 39 mm, LV end-diastolic volume — 156 ml, LV end-systolic volume — 70 ml, LV volume index — 91 ml/m², LV mass index — 98,3 g/m², grade 2 mitral valve prolapse with grade 2-3 mitral regurgitation; RV fractional area change — 47%, TAPSE — 22 mm, grade 1 tricuspid regurgitation; pulmonary artery pressure (mean/systolic) — 17/25 mm Hg; no local and global ventricular myocardial contractility disorders were detected (GLS — -17,6%, LVEF — 56%), moderate LV diastolic dysfunction: E — 0,64 m/s, A — 0,29 m/s, E/A ratio =2,21; DT — 231 ms; e’ — 16 cm/s; E/e’ ratio =4. A quantitative assessment of longitudinal strain and atrial systolic dynamics (Figure 4 D, E, F, G) revealed a decrease in LA contractile function: LA peak systolic strain was 11% (reference values — 53,1±12,0%), peak systolic strain rate — 0,7 s¹.

According to MRI, atrial dilation was revealed, mainly the LA (Figure 4 H, I): longitudinal-transverse dimensions of LA (3,7/3,5 cm/m²) and RA (3,4/2,9 cm/m²) indexed to BSA. No contrast agent accumulation in the ventricles and atria was detected. The myocardial tissue characteristics, local and global ventricular contractility (LVEF, 58%, RVEF, 69%) were normal.

According to selective angiography, atherosclerotic coronary lesions and right coronary artery hypoplasia were not found.

Given the low efficiency of non-invasive interventions to control the rhythm and the presence of structural and electromechanical signs of ACM, endocardial pulmonary vein radiofrequency ablation (RFA) was considered. Before RFA, a transesophageal echocardiography was performed: there were no signs of LA appendage thrombi, but there...
Figure 4. Representative ECG and HM fragments with signs of Bayes syndrome, echocardiographic and MRI features characteristic of ACM in proband (case 2): A) 12-lead ECG with an extended and biphasic P wave in I, II, III, aVF; with an increased terminal negative P wave integral in V1 to 0.144 mm·s; B) HM fragment with recurrent atrial tachycardia; C) HM fragment with paroxysmal AF; (D, E, F, G) signs of predominant LA dilatation with decreased systolic peak longitudinal strain of LA free wall according to speckle-tracking echocardiography; H) MRI movie along the long axis in 4-chamber view in late atrial systolic and atrial diastolic phases (I) with signs of LA dilatation.

Abbreviation: LA — left atrium.

was a pronounced (grade 3) spontaneous contrast-
ing; LA appendage area was 7.8 cm², peak blood flow velocity — 0.47 m/s. Frequency and rhythm control following a successful invasive procedure was achieved with a prophylactic dose of a beta-
blocker. Taking into account the CHA₂DS₂-VASc score of 2 and increased von Willebrand factor, a history of varicose veins and recurrent lower limb
venous thromboembolism, the patient underwent endovenous laser coagulation of great saphenous vein branches and was prescribed prophylactic OAC therapy.

Due to presence of familial ACM with arrhythmia (positive family history: in maternal grandmother, sinus node dysfunction with implantation of pacemaker, AF, LA dilation and dysfunction, arrhythmias and fatal stroke in a grandmother at the age of 50), a family cascade screening and genetic testing were performed.

Genotype test of proband (II: 1) and family members available for examination was carried out in accordance with the Declaration of Helsinki. All patients signed written informed consent. Sequence analysis of 174 genes of the target panel (NGS) in the patient revealed c.C35A variant (p.A12E, NM_001037) in the first exon of the \( \text{SCN1B} \) gene. An identical mutation was found in the mother of the proband. The \( \text{SCN1B} \) gene encodes the sodium channel beta-1 subunit. Mutations in this gene are associated with cardiac arrhythmias (AF that were observed in the family of proband).

Thus, in clinical practice, it is extremely important to take into account the possible etiological factors of ACM, since the causes of ACM can have clear diagnostic, prognostic and therapeutic consequences. For example, mutations in the \( \text{MYL4} \) and \( \text{NPPA} \) genes lead to specific ACM — rapidly progressive, with chrono-, dromo- and inotropic atrial dysfunction, with a high risk of AF, cerebral TEE and the need for OAC therapy or pacing [6–9, 28].

Comparative characteristics of atrial electromechanical dysfunction, parameters of LV diastolic and contractile function, laboratory biomarkers in family members of proband with EHRAS class III ACM (\( \text{NPPA} \) mutation carriers) and a patient with EHRAS class I ACM (\( \text{SCNB1} \) mutation carrier) are presented in Table 3.

| Parameter | Proband N. (\( \text{NPPA} \)) | Family member (\( \text{NPPA} \)) | Proband S. (\( \text{SCNB1} \)) |
|-----------|-------------------------------|-------------------------------|-------------------------------|
| Diastolic echocardiographic parameters of transmitral hemodynamics | | | |
| Early diastolic transmitral flow velocity (E), m/s | 0.87 | 0.72 | 0.64 |
| Late diastolic transmitral flow velocity (A), m/s | 0.29 | 0.37 | 0.24 |
| E/A ratio (normal range <2) | 3 | 1.95 | 2.21 |
| Deceleration time of early filling, ms | 105 | 146 | 231 |
| Septal annular early diastolic velocity (e'), cm/s (normal range <7 cm/s) | 12 | 9 | 16 |
| Lateral annular early diastolic velocity (e'), cm/s (normal range, 10 cm/c) | 14 | 9 | 20 |
| E/e' ratio (normal range <14) | 6.7 | 8 | 4 |
| RA volume index, ml/m² (normal range <34 ml/m²) | 73.5 | 44 | 57 |
| LA volume index, ml/m² (normal range <34 ml/m²) | 74 | 32 | 28 |
| Speckle-tracking echocardiographic data | | | |
| Global longitudinal strain, -% (normal range, -21,5±2,1%) | -14,9 | -172 | -18,1 |
| LA peak systolic strain rate, s-1 (normal range, 1,7±0,3 s-1) | 0,2 | 0,9 | 0,5 |
| LA peak systolic strain, % (normal range 53±12%) | 9,8 | 22,4 | 10,1 |
| ECG signs of LA dilation and interatrial block (Bayes syndrome) | | | |
| PQ interval, ms | 210 | 180 | 240 |
| Biphasic P wave duration P, ms | 180 | 135 | 195 |
| P-wave axis, degree (normal range 0-75') | 80 | -30 | -33 |
| Terminal negative P wave integral, mm*s (normal range ≤0,04 mm*s) | 0,158 | 0,088 | 0,144 |
| Biomarkers of myocardial stress and endothelial dysfunction | | | |
| NT-proBNP, pg/ml (normal range <125 pg/ml) | 326 | 107 | 115 |
| proANP, nmol/ml (normal range, 1,1-2,0 nmol/ml) | 0,67 | 0,84 | 3,13 |
| Von Willebrand factor, IU/dl (50-150 IU/dl) | 165 | - | 179 |
| CHA2DS2-VASc score | 2 | 0 | 2 |

**Abbreviations:** LA — left atrium, RA — right atrium, ECG — electrocardiogram.
The main clinical and prognostic factors of ACM in the presented clinical observations (Table 3) are specified by the severity of mechanical and electrical atrial dysfunction, their structural remodeling (fibrosis), procoagulation status, and atrial endothelial dysfunction. Thus, a more severe ACM phenotype with an early manifestation of the disease was observed in the 1st case with primary atrial remodeling caused by \textit{NPPA} gene mutation. The following were used as a non-invasive clinical tool for assessing ACM: echocardiography with LA function analysis (determination of E/e’, atrial volume indexes, assessment of atrial tissue using speckle tracking echocardiography with determination of peak systolic strain and strain rate), 12-lead surface ECG with analysis of atrial electrical dysfunction markers and MRI (assessment of fibrosis), which have important diagnostic and predictive value for assessing the risk of developing SV arrhythmias, including AF.

Atrial endothelial dysfunction with coagulation system activation and increased synthesis of prothrombotic tissue factors in the LA endocardium (plasminogen activator inhibitor (PAI) 1, von Willebrand factor (vWF), adhesion molecules (ICAM, VCAM, selectins), plasminogen activator inhibitor 1 (PAI-1) and changes in the tumor necrosis factor receptor superfamily such as CD40/CD154, which control interactions between platelets, leukocytes and endothelial cells [31, 32]) are important additional risk factors for ACM-related cerebral TEE.

Thus, Figure 5 shows the main diagnostic elements that can be used in research and practice for verification, classification, treatment and prediction of ACM complications.

As practice shows, a strategically important clinical task in choosing treatment tactics and in determining the prognosis is the etiological verification of ACM. Thus, mutations in the \textit{MYL4} or \textit{NPPA} genes determine severe, rapidly progressive types of ACM with a high risk of AF, HF and cerebral TEE [6-9, 28]; it is also important to take into account/control the toxicity of certain drugs and their adverse effects (Table 1). Treatment of obesity, endocrine disorders (diabetes, hypo- and hyperthyroidism) and infiltrative disorders (amyloidosis) is an equally important factor contributing to an improvement in the ACM prognosis. The beneficial effects of weight loss in

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**Etiological factors**

| Genetic causes (\textit{NPPN}, \textit{MYL4}) | AF-induced remodeling | Ventricular dysfunction (HF, CMP, myocarditis) | Infiltrative diseases (amyloidosis, granulomas) | Endocrine pathology (diabetes, hyperthyrosis) | Valvular heart disease (MV stenosis, AV stenosis) | Drug toxicity (chemotherapy) | Inherited muscular dystrophies | Aging, smoking, obesity, hypertension, obstructive sleep apnea |
|-----------------------------------------------|-----------------------|----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|---------------------------------|---------------------------------|------------------------------------------------------|

**Atrial cardiomyopathy**

- **Mechanical atrial dysfunction:** echocardiography assessment (E/e’, E/A, LA peak systolic strain and strain rate, LAV index and/or RAV index ≥35 ml/m²)

- **Prothrombotic changes—assessment of coagulation biomarkers:** von Willebrand factor, adhesion molecules (ICAM, VCAM, selectins), plasminogen activator inhibitor 1 (PAI-1)

- **Electrical atrial dysfunction (Bayes syndrome):** ECG assessment (heart rate at AF, PQ interval, P wave morphology and axis of, P duration and amplitude, terminal P wave phase in V1; endocardial mapping)

- **Atrial fibrosis:** MRI (atrial LGE, postcontrast assessment T1 and T2 weighted images)

**Prognostic factors**

**AF progression**

**Cerebral TEE**

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**Figure 5.** Etiological, clinical and prognostic factors of ACM. **Abbreviations:** HTN — hypertension, AV — aortic valve, CMP — cardiomyopathy, LA — left atrium, LAV — left atrial volume, MV — mitral valve, MRI — magnetic resonance imaging, RAV — right atrial volume, TEE — thromboembolic events, AF — atrial fibrillation, HF — heart failure, HR — heart rate, ECG — electrocardiography.
obesity and modification of other AF risk factors have been demonstrated in the randomized trials REVERSE-AF and HUNT [33, 34]. Thus, the individual prognosis of a patient with AF is influenced, on the one hand, by the risk factors for TEE, and on the other hand, by factors that cause or maintain an abnormal heart rhythm (Figure 5). The main reason for the progression of AF from paroxysmal to permanent or longstanding persistent is usually the arrhythmia itself. In addition to focal triggers, which are often located at the pulmonary vein orifices, multiple-loop reentry and electrical dissociation between the epicardial and endocardial layers influence the onset and maintenance of AF [35, 36]. The common of these mechanisms is that they depend on electrical and structural atrial changes that are observed in ACM.

Thus, an important clinical, highly sensitive tool for assessing atrial dysfunction is ECG (PQ interval prolongation [37], an increased P wave duration, increased terminal negative P wave in V1, and an abnormal P-wave axis [38]), and also the low voltage in endocardial mapping [39]. Echocardiography is a highly specific method for assessing the atrial structure and function: transmural spectral and tissue Doppler with E/e’ determination, atrial volume indexes, 3D speckle tracking assessment of fibrous tissue with determination of peak systolic strain and strain rate [40]. Non-invasive quantification of atrial fibrosis, which plays an important role in the pathophysiology of AF and is closely associated with recurrent AF, can be performed with contrast-enhanced MRI [41, 42]. In addition to the technique for assessing delayed contrast accumulation to detect replacement fibrosis, pre- and post-contrast T1 mapping can be used to quantify diffuse interstitial fibrosis. Typically, these techniques are widely used for ventricular imaging, while the assessment of thin-walled atria is somewhat limited by technical problems. However, a multicenter study revealed that quantitative MRI assessment of atrial fibrosis can play a key role in the selection of patients for catheter ablation of AF [43-45]. Thus, the risk of recurrent AF increased by 15% in stage I fibrosis (<10% of the atrial wall) and up to 69% in stage IV fibrosis (>30% of the atrial wall) [43].

Discussion

To conduct studies that determine the practical and prognostic value of the ACM concept, highly sensitive and specific clinical tools are in demand today for the early diagnosis of atrial electromechanical dysfunction and the determination of clear prognostic risk factors for cardiovascular events.

If ACM is a significant risk factor for stroke, irrespective of AF, how to identify patients at increased risk of TEE (without history of AF) for OAC therapy? In the study by Wolsk E, et al. (2015), the CHA2DS2-VASc score was defined as an independent risk factor for TEE in the absence of any history of AF in patients with heart failure [46]. Similar results in assessing the predictive value of the CHA2DS2-VASc scale were demonstrated by the studies of Belen E, et al. (2016) when assessing spontaneous LA contrasting in patients with rheumatic mitral stenosis and without AF history, who had a high risk of LA thrombus formation and TEE, despite sinus rhythm [47]. It is known that patients with mechanical valve prostheses and significant mitral stenosis are not adequately protected by a direct OAC and require anticoagulant therapy with warfarin [22]. Could there be other groups of patients who should be given warfarin to prevent TEE when specific signs of ACM are detected? [48]. Is it possible to identify patients who require more aggressive approaches to TEE prevention, such as the combination of an antiplatelet agent with OAC or the use of LA appendage occluders? The study, analysis and potential of using ACM-specific characteristics for assessing the high risk of TEE and OAC therapy in patients with sinus rhythm should be carried out in prospective randomized multicenter studies.

A combined assessment of etiological factors and signs associated with ACM can be useful information in the selection of initial drug therapy, while analysis of fibrosis severity, LA electrical characteristics and function can be critical in choosing invasive interventions. Thus, electromechanical and structural (fibrosis) markers of ACM have demonstrated prognostic value in assessing the risk of AF recurrence after catheter RFA in a number of studies [49-51].

Could these predictors be used to predict outcomes in patients for whom RFA would not be warranted and thereby eliminating the risk of unnecessary procedures? Can the characteristic features of ACM be used to select the optimal catheter ablation technique for a particular patient?

In accordance with current guidelines, RFA is recommended as a second-line treatment for antiarrhythmic drug intolerance or ineffectiveness. As a first-line treatment, indications are limited to paroxysmal AF only. According to these guidelines, RFA is generally considered by clinicians after a longer period of conservative therapy for AF. The development of tools and methods for the identification of ACM markers can allow avoiding the discrepancy between the optimal period for RFA and its time in accordance with a substrate-oriented diagnosis and treatment of AF.

Conclusion

Thus, further randomized prospective studies are required for a comprehensive and individu-
lized approach to treatment, including optimal OAC therapy, ablation (taking into account the type and severity of ACM), and, possibly, genetics-based approaches in the future.

Conceptual reevaluation and classification of ACM are important for predicting and personalizing treatment strategies, taking into account etiology, morphology, pathogenesis, geno- and phenotype. Although the genetic determinants of ACM are poorly understood today, significant efforts have been made in the last decade to identify the genetic causes of AF, which is both a complication of ACM and its common cause. Study of the genetic basis of primary defects in the atrial structure and function, as well as the genetic contribution of other cardiac pathology and concomitant diseases, adverse environmental and lifestyle factors that lead to secondary atrial remodeling, improvement of invasive and non-invasive technologies for visualization of atrial remodeling will contribute to the creation of new risk stratification approaches for complications such as AF, heart failure and TEE.

Relationships and Activities: none.

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