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LEFT ATRIAL FIBROSIS AS AN ELECTROANATOMIC SUBSTRATE OF ATRIAL FIBRILLATION: POSSIBILITIES FOR QUANTITATIVE ASSESSMENT

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The article focuses on the role of left atrial (LA) fibrosis as the basis of the electroanatomic substrate in atrial fibrillation (AF), which determines not only the stability of AF but also the success of catheter ablation (CA). In the article the molecular and cellular aspects of LA fibrosis formation and possible mechanisms of arrhythmogenic effects of fibrotic tissue are considered in details, the methods of estimation of LA fibrosis size determining the effectiveness of CA in patients with AF are demonstrated. Current data on the possibilities of using circulating fibrosis biomarkers as predictors of fibrosis severity and recurrence of AF after CA are presented.

Key words: atrial fibrillation; left atrial fibrosis; catheter ablation; circulating biomarkers

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Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with an increased risk of stroke and heart failure, as well as increased mortality. The incidence of AF increases with age, and it is estimated that the number of adult patients with AF will more than double by 2050 [1].

Atrial fibrosis has been found to be a key pathogenetic factor in the development and progression of AF [2], being a driver for the maintenance and progression of AF [3, 4]. It has been demonstrated that the efficacy of catheter ablation (CA) for AF is influenced by the extent of fibrous substrate present in the left atrium (LA) [5, 6]. Consequently, accurately predicting the severity of the electroanatomic substrate is a critical issue when selecting patients for CA.

LA FIBROSIS AS THE BASIS OF ELECTROANATOMICAL SUBSTRATE OF AF

It has been demonstrated that the efficacy of CA for AF is influenced by the extent of fibrous substrate present in the LA [5, 6]. Consequently, accurately predicting the severity of the electroanatomic substrate is a critical issue when selecting patients for CA. Newly formed connective tissue fibers replace damaged myocardial cells, altering tissue hemostasis by promoting excessive accumulation of VM proteins. This subsequently leads to a disruption of the architectural integrity of the heart, thereby promoting atrial remodeling and dysfunction.

Modern etiopathologic classification distinguishes two types of fibrosis: reactive and reparative (replacement). Reactive fibrosis is characterized by the accumulation of collagen components within the connective tissue space, both interstitially (between cells) and in the perivascular space, as well as in the perimysium. This accumulation results in the thickening of fibrous connective tissue surrounding muscle bundles, effectively isolating them from one another (Fig. 1). Interstitial fibrosis develops in the context of chronic damage, such as pressure overload (e.g., valve defects, hypertension), cardiac inflammation

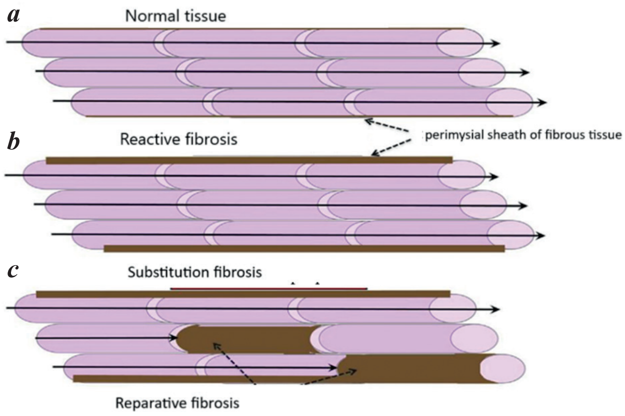

Fig. 1. Types of myocardial tissue fibrosis (modified from Nattel S. [8]): a - normal bundle of cardiac tissue consisting of longitudinally arranged cardiomyocytes surrounded by a perimysial sheath of fibrous tissue; b - reactive (interstitial) fibrosis increases the amount of perimysial fibrous tissue surrounding muscle bundles; c - replacement (reparative) fibrosis replaces dead cardiomyocytes and may interfere with longitudinal conduction. Arrows indicate longitudinal conductivity.

(e.g., myocarditis), and metabolic disorders (e.g., obesity, diabetes mellitus), as well as the natural aging process. Interstitial fibrosis can accelerate longitudinal conduction in the myocardium, which is associated with the development of more resistant forms of AF [7].

Reparative or replacement fibrosis is initiated following the necrosis and apoptosis of cardiomyocytes, transforming necrotic regions of the myocardium into fibrotic scar tissue, which is predominantly composed of type I collagen (Fig. 1). The resulting areas of fibrosis disrupt the longitudinal bundles, creating distinct longitudinal conduction barriers. These areas are significantly more impaired in terms of electrical conduction and are more irreversible compared to reactive fibrosis.

Depending on the structure, size and distribution of fibrous tissue histologically the following types of fibrosis are distinguished: interstitial, in the form of thickening and expansion of VM; compact, consisting of dense areas of collagen; diffuse, characterized by mixed areas of myocardial and collagen fibers; patchy with the presence of areas of collagen bundles and long collagen strands.

Different patterns and types of fibrosis can coexist within a single atrium, and the distribution of fibrotic tissue significantly influences the electrical processes in the atrial myocardium (Fig. 2). For example, areas of fibrosis that separate myocardial muscle bundles from each other and impede normal conduction can promote impulse re-entry by causing slowed or «zigzag» conduction and the formation of unidirectional conduction blocks. The increased number of fibroblasts alters cardiomyocyte properties such as conduction, resting potential, repolarization and excitability due to newly formed heterocellular junctions. In addition, fibroblasts can exert a proarrhythmic effect on cardiomyocytes «at a distance», through the secretion of paracrine factors, which leads to conduction slowing and changes in refractoriness [9].

Electrophysiological prerequisites for the occurrence of AF are mechanisms of abnormal pulse formation, such as automatism or trigger activity, arising due to spontaneous diastolic depolarization against the background of suprathreshold inward current of Na^+ and Ca^{2+} ions in the 4th phase of the action potential (AP), shortening of the refractory period due to excessive release of K^+ ions. Triggers originating in the atria at the pulmonary vein orifices become chaotic as they collide with sites with different conduction velocities and refractory periods and form one or more macroscopic circles of re-entry in one or both atria, leading to the onset of AF. During this process, myocardial cells undergo shortening of AP and refractory period due to decrease of depolarizing current of Ca^{2+} ions through L-type channels and increase of repolarizing current of K^+ ions. The longer the atrium is in the state of fibrillation, the more pronounced are the processes of electrical remodeling in it, which can maintain AF.

According to the spiral wave or rotor model, a re-entry wave has a resemblance to a spiral that rotates long and fast around a central core. The stability of this mechanism is attributed to high cellular excitability and a short period of atrial refractoriness. The developmental features and stability of AF have been found to depend on the structure, size, and distribution of fibrous tissue. For example, the compact type of fibrosis is less arrhythmogenic compared to other forms of fibrosis and promotes organized rotation (flutter) of impulses around the area of fibrosis due to unidirectional re-entry type blockade [10]. Diffuse fibrosis contributes to the maintenance of AF due to a decrease in atrial conduction velocity, leading to spiral wave formation [11].

J.M. De Bakker et al. found that patchy fibrosis is arrhythmogenic due to the development of zigzag electrical conduction between different bundles and long tracts [12]. Interstitial fibrosis impairs transverse conduction by dividing myocardial bundles, while not affecting longitudinal conduction. It is this arrangement of thick interstitial collagen filaments that is closely associated with persistent and more persistent forms of AF [7, 13].

A significant contribution to understanding the pathophysiology of the relationship between atrial fibrosis and arrhythmogenesis was made by S.P.Krul et al. [14]. Their study highlighted the importance of the quality, rather than the quantity, of fibrous tissue in the pathogenesis of arrhythmogenic substrate formation by re-entry mechanisms, which contributes to the maintenance of AF.

B.J. Hansen et al. conducted simultaneous mapping of subendocardial and subepi-

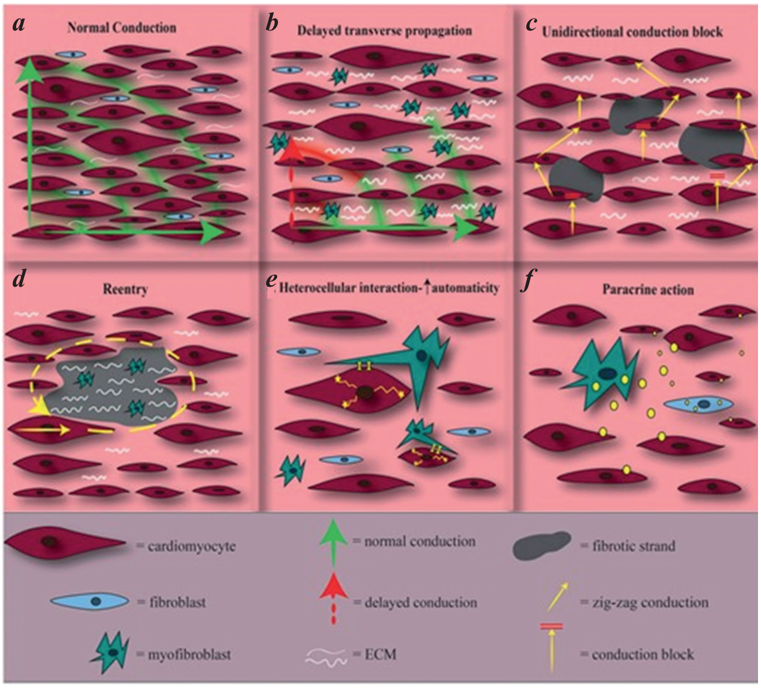

Fig. 2. Realization of proarrhythmogenic effects of fibrous tissue (adapted from Xintarakou A. [9]), where a - unaltered cardiac tissue with normal wavefront propagation; b - slowed propagation of the transverse wavefront due to interstitial collagen filaments that disrupt intercellular connections of myocytes; c - slowing of zigzag conduction and blockade of unidirectional conduction due to «spotty» fibrous barriers; d - fibrosis contributing to the re-entry mechanism; e - heterocellular gap junctions between myofibroblasts and cardiomyocytes leading to increased automaticity; f - paracrine action of fibroblasts/myofibroblasts.

cardial atrial activation areas and subsequently compared these activation patterns with a magnetic resonance imaging (MRI) model of the atria. Researchers have confirmed that fibrosis disrupts myocardial structure, creating obstacles to both longitudinal and transverse conduction, thereby establishing an anatomical substrate conducive to the maintenance of AF [15]. Thus, an understanding of the role of fibrosis as a maintenance substrate of AF has now been developed.

CELLULAR AND PARACRINE MECHANISMS OF FIBROSIS FORMATION

Cardiomyocyte death is often the initial event responsible for activation of fibrotic processes in the myocardium. In other cases, damaging stimuli (such as pressure overload or myocardial inflammation) may activate profibrotic pathways in the absence of cell death. Several cell types are involved in the fibrotic remodeling of the heart; however, in all conditions associated with cardiac fibrosis, a key cellular event is the transdifferentiation of fibroblasts into secretory and contractile cells known as myofibroblasts.

Myofibroblasts, arising from fibroblasts and other epitheliocytes by epithelial-mesenchymal transition, have high sensitivity to profibrogenic and proinflammatory mediators, and are capable of secreting specialized VM proteins: fibronectin, periostin, collagens of type I and III (these types are characteristic exclusively for cardiac fibrosis). Additionally, myofibroblasts have contractile activity due to the presence of smooth muscle actin α (α-SMA) and mechanically act on intercellular matter.

Monocytes, macrophages and mast cells are able to produce and secrete a large number of proinflammatory mediators such as cytokines (interleukin-1 [IL-1β], tumor necrosis factor [TNF-α], and interleukin-6 [IL-6]) and profibrotic growth factors such as transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), thereby participating in the inflammatory and reparative response after myocardial injury (Fig. 3). Increased levels of mast cell-derived chymase, tryptase, and histamine also stimulate fibroblast proliferation and collagen synthesis, and enhance connective tissue growth factor (CTGF) synthesis. Macrophages produce renin and angiotensin-converting enzyme, molecules that promote the production of angiotensin II (ATII), in large quantities. It has been observed that patients with AF have increased infiltration of left atrial auricular macrophages compared to patients with sinus rhythm [16]. In the study of C.H.Liao et al. it was shown that the accumulation of mast cells in the atria is pathogenetically associated with atrial fibrosis through the expression of growth factor PDGF-A and increases myocardial susceptibility to AF [17].

T cells located in the myocardium have different functions: for example, Th1 and CD8+ cells have antifibrotic functions because they release mediators that inhibit the action of the profibrotic TGF-β (Fig. 3). Cytotoxic T cells, Th2 exhibit significant profibrotic activity by secreting IL-4 and IL-13, molecules that directly stimulate collagen secretion, or by activating TFG-β. Endothelial cells may undergo endothelial to mesenchymal transition, directly contributing to the expansion of the fibroblast pool in the fibrotic heart, with the potential for perivascular fibrosis.

Several studies suggest that under conditions of stress, viable cardiomyocytes may also contribute to the development of interstitial fibrosis by activating interstitial fibroblasts: with adenosine triphosphate release being one of the early signals that activate fibroblast responses after cardiac injury.

Among the various growth factors, TGFβ, FGF, and PDGF have been best studied. Elucidating their role and associated biomarkers involved in signaling pathways is an important goal to identify the mechanisms causing cardiac fibrosis.

TGF-β is a key regulator of the fibrotic process. TGF-β is found in three isoforms (TGF-β1, 2 and 3) encoded by three different genes. Of greatest interest is TGF-ß1, a proinflammatory cytokine that plays a central role in the transformation of fibroblasts into myofibroblasts. TGF-β1 induces the expression of myofibroblast markers and profibrotic growth factors (such as CTGF, FGF). Moreover, TGF-β1 regulates VM remodeling by promoting an imbalance between profibrotic and fibrotic matrix metalloproteinase (MMP/TIMP) enzymes. The enhancing effect of TGF-β occurs when reactive oxygen species (ROS) are released in a positive feedback type [19].

Proinflammatory cytokines such as tumor necrosis factor α (TNF-α, IL-1β, and IL-6) act on cardiac fibroblasts to enhance proinflammatory cytokine production

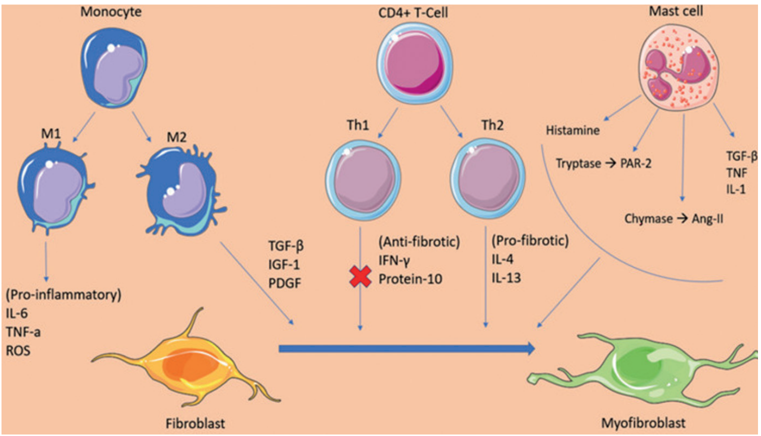

Fig. 3. Cellular mediators of atrial fibrosis (adapted from Sagris M. [18]). Immune cells such as monocytes, CD4+ T cells and mast cells contribute to tissue fibrosis by secreting profibrotic factors and regulatory molecules that enhance the activation and differentiation of fibroblasts into myofibroblasts. Antifibrotic mediators secreted by Th1 cells that are gradually replaced by the products of profibrotic Th2 cells have been shown. TGFβ, transforming growth factor beta; TNFα, tumor necrosis factor alpha; PDGF, platelet-derived growth factor; IL-1, interleukin 1; IL-4, interleukin 4; IL-6, interleukin 6; IL-10, interleukin 10; ROS - reactive oxygen species; IFNy - interferon gamma; IGF-1 - insulin-like growth factor 1; Th1 - T helper type 1; Th2 - T helper type 2; PAR-2 - protease-activated receptor 2; Ang-II - angiotensin.

and indirectly promote VM accumulation by regulating CTGF production. Interleukin-33 (IL-33), a member of the interleukin-1 family, realizes its effects through IL-1R4 (ST2) receptors. IL-33 is released from damaged cardiac cells and binds to the transmembrane receptor ST2L, preventing cardiomyocyte death. In response to injury, cardiac fibroblasts and cardiomyocytes produce a soluble form of the IL-33 receptor called sST2 in large quantities. When sST2 levels are elevated, due to obstruction of signaling through the IL-33/ST2L receptor system, the cardioprotective effects of IL-33 are attenuated and the profibrotic response is enhanced.

The renin-angiotensin-aldosterone system, catecholamines, and endothelin-1 stimulate fibrosis in a variety of ways, both related to TGF-β and independent of it. In the classical pathway of angiotensinogen conversion to angiotensin I by renin, further conversion to ATII by angiotensin-converting enzyme or chymase follows. ATII via type 1 receptor increases the secretion of proinflammatory cytokines (IL-6, TNFα), free radical oxidation, promotes fibroblast proliferation and their collagen synthetic activity through AT1-receptor-dependent interactions, through the production of TGF-β, PDGF. Aldosterone also increases the synthesis of pro-inflammatory, pro-oxidant molecules, TGF-β.

Reactive oxygen species (ROS) are involved in the profibrotic differentiation of fibroblasts into myofibroblasts by regulating collagen synthesis and matrix metalloproteinase (MMPs) activity, the main enzymes of BM degradation. Increased oxidative stress activates MMPs and reduces fibrillar collagen synthesis in cardiac fibroblasts [8].

Fibroblasts that have been activated by angiotensin-II, PDGF, TGF-β, and CTGF synthesize and release profibrotic mediators such as PDGF, TGF-β, independently maintaining and potentiating the fibrotic process. In this process, the ATII/TGFβ/CTGF-based triad enhances cardiac fibroblast activation [20].

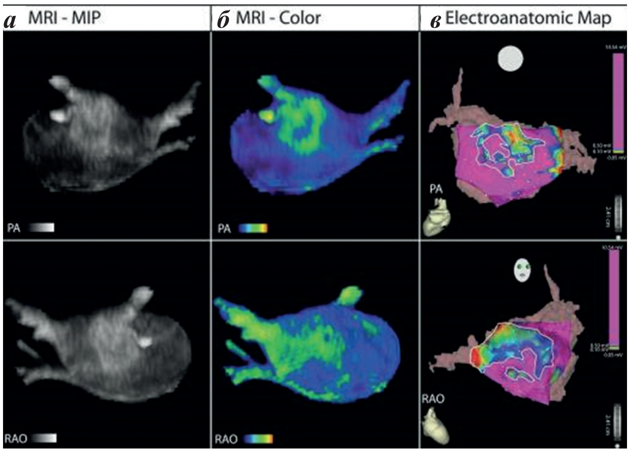

Fig. 4. Relationship between magnetic resonance imaging and electroanatomic mapping data of the left atrium in posterior (PA) and right anterior oblique (RAO) projections. Segmented MRI (a) reveals distinct areas of enhancement in the posterior wall of the LA and interatrial septum. The color 3D model (b) of the LA allows for a clearer delineation of contrast enhancement zones. Low-voltage areas (delineated by white lines) detected during electroanatomic mapping (c), in the region of the posterior wall of the LA and septum, correlate with areas of contrast enhancement detected during MRI. Adapted from Oakes R.S. et al [23].

It seems that basic research aimed at studying the pathogenesis of atrial fibrosis formation may help to develop new diagnostic approaches and therapeutic targets in patients with AF.

WAYS TO ASSESS THE SEVERITY OF ATRIAL FIBROSIS

Magnetic resonance imaging with delayed gadolinium contrast is an established volumetric analysis and imaging modality for the assessment of LA remodeling and allows identification and quantification of atrial fibrosis. Contrast enhancement is due to delayed washout of gadolinium from damaged tissue with disruption of structure, as opposed to normal atrial tissue.

To date, an MRI protocol for visualization of LA fibrosis has been developed. The DECAAF study used Corview image processing and analysis software developed and patented at UTAH [6]. This software allows a complete process of segmentation of the LA wall, identification of fibrosis and export of the final 3D models, manually tracking the blood pool in the pulmonary veins in each slice of the MRI volume and defining endocardial and epicardial boundaries. To assess fibrosis, the algorithm automatically selects intensity thresholds, offering Gaussian intensity distributions for fibrotic tissue (enhanced voxels) and healthy myocardium. The typical threshold value is in the range of 2 to 4 SD.

For three-dimensional visualization of LA fibrosis, color coding is more commonly used, with blue representing healthy tissue and green and yellow representing contrast-enhanced (i.e., fibrotic) tissue (Figure 5). The group of N.F.Marrouche et al. proposed the UTAH classification for quantitative analysis of fibrosis by stages, based on the increase of fibrosis content in the LA wall as a percentage of the total area of the LA wall: stage I is defined as <10%, stage II - from 10 to 20%, stage III - from 20 to 30% and stage IV - >30% [6]. The severity stage of LA fibrosis has been shown to correlate with the results of catheter ablation of AF, regardless of the presence of other comorbidities or the nature of AF [21].

Three-dimensional electroanatomic mapping (EAM), including activation and bipolar (voltage) mapping, allows to assess, in addition to anatomy, the heterogeneity of electrophysiologic properties of atrial myocardium relevant to arrhythmias, i.e., to detect arrhythmogenic electroanatomic substrate. Bipolar mapping is actively used to identify low-voltage zones (LVZs) and scar areas as surrogate markers of atrial fibrosis in AF [22]. It has been observed that LVZs are associated with fragmented electrical impulse transmission and slowed conduction, which may contribute to the formation of a re-entry mechanism. Improvements in mapping with the advent of multipole mapping electrodes and additional modules in navigation systems have contributed to the wider application of this method.

R.S.Oakes et al. revealed that the LVZs recorded in bipolar EAM of the LA correlate closely with the areas retaining contrast during MRI and the severity of LA fibrosis (Fig. 4) [23]. L.C.Malcolme-Lawes et al. when comparing

MRI with EAM data in 50 patients with AF, also found an association between areas with increased gadolinium accumulation and LVZ in the LA [24].

Most current studies use regions with reduced voltagecontrast characteristics as a surrogate marker of arrhythmogenic fibrotic substrate of AF [6, 21, 25, 27]. A.Verma et al. in a study of 700 patients found that the presence of extensive scar areas, registered during EAM in the form of no voltage or bipolar signal amplitude ≤0.05 mV, and low voltage areas with signal amplitude ≤0.5 mV, are independent predictors of AF recurrence after performed CA [26].

Z.Liu et al. found that a higher level of total LVZ as a % of LA area is a major risk factor for the development of long-period persistent AF, and indicates that LVZ is associated with the persistence and maintenance of AF [27]. The distribution of LVZs differed at different stages of AF, with predominant localization along the anterior wall in paroxysmal AF, with further spread to the septum in persistent AF, and transition to the posterior wall and the bottom of the LA in long-term persistent and permanent forms of AF, which may be of importance for CA [27].

Endomyocardial biopsy is the most reliable method of detecting and clarifying the degree of LA fibrosis, but given its invasive nature and high risk of complications, this diagnostic method is not used in routine practice. In the HEAL-AF and HEAL-AF2 studies, Y. Takahashi et al. found an association between atrial structural remodeling detected histologically by atrial biopsy and the presence of LVZs detected by EAM [28]. Such histologic factors as diffuse interstitial fibrosis without signs of replacement fibrosis, increased intercellular space, and loss of myofibrils were significantly associated with decreased electroanatomic characteristics (decreased voltage, signal fractionation, and slowed conduction). Additionally, it was found that the percentage increase in LA fibrosis, increased intercellular space and decreased cardiomyocyte nuclear density were more pronounced in the persistent form of AF, compared to the paroxysmal form [28]. Thus, instrumental imaging techniques have great diagnostic value but are invasive, time-consuming, and difficult to reproduce, making the search for more accessible markers of atrial fibrosis an important challenge.

EVALUATION OF FIBROSIS ZONE SIZE IN PREDICTING RECURRENCE AFTER CA

Several models have been developed to predict the efficacy of catheter ablation in patients with AF. In a prospective multicenter study, J. Kosiuk et al. developed the DR-FLASH prognostic model, including the following factors for recurrent AF after CA: diabetes mellitus, renal dysfunction, persistent form of AF, LA diameter >45 mm, age >65 years, female gender, arterial hypertension. The DR-FLASH model was also effective in predicting the presence of areas of LA fibrosis: with each score, the probability of having areas of LA fibrosis increased 2.2-fold. In addition, the risk of recurrent AF after pulmonary vein orifice isolation increased 1.3-fold with each score and was almost 2-fold higher in patients with a DR-FLASH score >3 points [29].

N.F.Marrouche et al. are one of the first researchers who proved the relationship between the recurrence of AF after CA and the severity of LA fibrosis detected by cardiac MRI: a direct correlation between the area of LA fibrosis and the probability of AF recurrence was obtained; moreover, the relationship was significantly stronger at a lower stage of fibrosis (<10%) than at a higher one (>30%) [6]. Similar results were obtained by Akoum et al. who found that patients with a higher degree of fibrosis assessed before CA had a higher chance of developing a recurrence of AF after ablation [5].

A group of Russian investigators in a prospective observational study on 181 patients demonstrated that an increase in % electroanatomic substrate area was shown to be the only independent predictor of recurrence of AF after both primary radiofrequency ablation of pulmonary vein orifices and after repeated procedures. In addition to substrate area, duration of history of AF and LA size were independent predictors of recurrence after repeat CA [30]. The results of a prospective study by E.V. Dedukh et al. of 64 patients after primary pulmonary vein aperture isolation showed that the presence of LVZ >20% was an independent predictor of AF recurrence [31].

G.A.Begg et al. studied the role of circulating biomarkers as predictors of recurrent AF after CA, along with LVZ, clinical and echocardiographic parameters. Of the factors studied, LVZ area greater than 30% was the only independent variable predicting recurrent AF after performed CA [32].

T.Yamaguchi et al. also confirmed the significance of increased LVZ as a predictor of recurrence of persistent AF; moreover, recurrence of persistent AF was more frequent in patients with UTAH stage IV fibrosis compared to stages I-III. The authors attributed the higher rate of AF recurrence in stage IV fibrosis to more pronounced residual fibrosis, which acts as an anatomical substrate of AF [33].

POSSIBILITIES OF CIRCULATING BIOMARKERS AS PREDICTORS OF LA FIBROSIS AND CA RECURRENCE

The concept of molecular biomarkers in risk stratification of patients with AF has been widely developed in the last decade [34], yet the use of circulating fibrosis markers as possible predictors of fibrosis size and CA efficacy is poorly understood and seems promising.

A meta-analysis by Hui Jiang et al. included 36 studies that summarized data on 11 blood markers. Some biomarkers have convincingly demonstrated their association with recurrences of AF after CA [35]. Baseline elevated levels of biomarkers such as atrial natriuretic peptide (ANP) (but only in the absence of structural heart pathology), brain natriuretic peptide (BNP), N-terminal brain natriuretic propeptide (NT-pro-BNP), interleukin-6 (IL-6), C-reactive protein (only in Asian studies), low-density lipoprotein (LDL), tissue inhibitor of metalloproteinase 2 (TIMP-2) were associated with an increased risk of recurrent AF after CA [35].

Natriuretic peptides (NUPs) comprise a class of proteins with diuretic and natriuretic actions, and ANP and BNP are two common NUPs in clinical practice. Volume expansion or pressure overload initiates the production of NT-proBNP, it has a longer half-life 6 times that of BNP, making it easier to detect in the blood. BNP and NT-proBNP are the best prognostic indicators to assess prognosis and monitor heart failure (HF) and complement clinical risk factors to assess a patient's risk of developing AF.

Large cohort studies (Cardiovascular Health Study, and the CHARGE-AF Consortium) have confirmed the association between NT-proBNP concentration and the development of AF [36, 37]. Y.Yuan et al. found a significant relationship between the initial level of NT-proBNP and the recurrence of AF after ablation [38].G.A.Begg et al. in a prospective study did not confirm the prognostic role of circulating fibrosis biomarkers (N-terminal propeptide of procollagen type III, PIIINP, galectin-3, fibroblast growth factor 23, FGF-23, and C-terminal telopeptide of collagen type I, ICTP) as predictors of AF recurrence after AF ablation, in contrast to NT-proBNP area [32].

The most studied biomarkers in chronic HF patients with preserved left ventricular ejection fraction in recent decades are the inflammatory and fibrosis biomarkers sST2 and GDF-15.

ST2 (Growth STimulation expressed gene 2, stimulating growth factor expressed gene 2, also known as IL1RL1 and Supression of tumorigenicity 2) is a member of the interleukin-1 (IL-1) receptor family that plays a central role in the regulation of immune and anti-inflammatory responses [39]. ST2 exists in two forms: a transmembrane receptor (ST2L), and a soluble form of sST2 that circulates freely in the blood. ST2L is a membrane-bound receptor for which IL-33 is a functional ligand. IL-33 can act as both a pro-inflammatory and anti-inflammatory cytokine. With respect to the heart, IL-33 is thought to exert cardioprotective effects by reducing fibrosis and manifestations of hypertrophy in mechanically stressed tissues. The soluble form of ST2L, sST2, is released into the blood and acts as a trap receptor for IL-33, inhibiting the effects of IL-33/ST2L signaling. Elevated concentrations of sST2 freely circulating in the bloodstream attenuate the systemic biological effects of IL-33, thus excess sST2 leads to cardiac fibrosis. There are only sporadic reports on the association of sST2 concentration with LA fibrosis and CA outcomes in AF.

The aim of the study conducted by Z.Wang et al. was to investigate the potential of serum sST2 levels in predicting the extent of LVZ [40]. The results showed that sST2 with a threshold value of 26.65 ng/mL was the only independent predictor of LVZ area >20%. In addition, patients with sST2 levels <26.65 ng/mL were significantly less likely to have a recurrence of AF after 12 months of follow-up, which, according to the authors, can be used as a predictor of recurrent AF after CA [40].

H.Liu et al. in 2020 published the results of a prospective study that evaluated the role of sST2 in predicting the recurrence of AF in a group of 258 patients after CA. Preoperative sST2 levels were found to be significantly higher in patients with recurrence than in patients without recurrence (31.3 ng/mL vs. 20.3 ng/mL, $p < 0.001$). Some of the patients in the study underwent repeat CA, with newly performed endocardial mapping. Finally, it was obtained that sST2 level >26.9 ng/mL was a predictor of recurrent AF with «new abnormalities» in endocardial mapping with a sensitivity of 100% and specificity of 75.9% [41].

Growth differentiation factor-15 (GDF-15, MIC-1) is a member of the transforming growth factor β superfamily. GDF-15 is produced by cardiomyocytes, adipocytes, macrophages, and endothelial cells, and expression is regulated by proinflammatory cytokines including (TNF)-α, interleukin (IL)-1β, and IL-6. GDF-15 exerts anti-inflammatory effects, leading to inhibition of lipopolysaccharide-stimulated TNF-α secretion by macrophages. Increased GDF-15 levels have been found to be associated with increased mortality and incidence of cardiovascular events in patients with acute coronary syndrome, coronary heart disease, and HG [42]. In the large multicenter ARISTOTLE and RE-LY trials, GDF-15 has shown to be a risk factor for major bleeding, mortality, and stroke in AF [43]. It is suggested that GDF-15 may be involved in atrial structural remodeling by enhancing collagen synthesis and transformation, and fibroblast proliferation.

Our research group found a direct correlation of GDF-15 level with LVZ area and LA volume index. It was also obtained that GDF-15 levels above a threshold level of 840 pg/mL may be an independent predictor of LVZ area >30%, which is associated with severe fibrosis and expected poor CA performance [44]. Y.Wei et al. studied the relationship of GDF-15 level with CA outcomes: it was found that the initial elevated level of GDF-15 before CA correlated with the degree of LA remodeling and was associated with an increased risk of AF recurrence [45].

V.A.Ionin et al. studied in patients with AF and metabolic syndrome the association of profibrogenic biomarkers galectin-3 and GDF-15 with the risk of AF recurrence within 12 months after radiofrequency ablation. Epicardial fat thickness, the degree of left atrial fibrosis, and galectin-3 and GDF-15 concentrations have been identified as independent predictors of recurrent AF after ablation [46].

Thus, the available data suggest the feasibility of further studies to investigate the role of proinflammatory and profibrotic biomarkers as predictors of fibrosis severity in patients with AF referred for CA.

CONCLUSION

A personalized approach based on quantifying or predicting the severity of the electroanatomic substrate of atrial fibrillation is warranted in selecting the optimal treatment strategy for patients. Currently, the application of circulating proinflammatory and profibrotic biomarkers signaling specific pathogenetic mechanisms at different stages of the atrial fibrillation continuum is promising and requires further investigation.

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