

## Review article

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### SERUM FATTY ACID BINDING PROTEINS AS A POTENTIAL BIOMARKER IN ATRIAL FIBRILLATION

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Atrial fibrillation (AF) is a commonly occurring arrhythmia which significantly reduces patients' quality of life and substantially shortens life expectancy. Although long chain fatty acids (LCFAs) are the basic energy substrates for myocardial metabolism, their excess can result in lipotoxicity, which increases the risk of arrhythmia. Intracellularly, LCFAs are bound by fatty acid binding proteins (FABPs) and this results in low level of free LCFAs in the cytoplasm. Based on this principle, FABPs are considered "safeguards" against overwhelming accumulation of esterified into different bioactive lipid fractions (*e.g.* ceramide, diacylglycerols) LCFAs. So far, several FABPs have been discovered in humans. Currently, in relation to cardiovascular diseases heart-type fatty acid binding protein (H-FABP) and adipocyte fatty acid binding protein (A-FABP) play significant roles. Nowadays, A-FABP is of great interest for research related with obesity, diabetes and coexisting disorders including cardiovascular diseases. Concomitantly, H-FABP is already well-established marker in the early diagnosis of myocardial infarction. Moreover, FABPs were assigned as a potential biomarker of AF in patients with *de novo* diagnosed arrhythmia, chronic heart failure (CHF), and in patients undergoing cardiac surgery. Another group of studies where the concentrations of plasma FABPs were analyzed are patients subjected to electrical cardioversion (ECV) and radio-catheter ablation therapy (RFA). It is worth mentioning that, in addition to traditional anti-arrhythmic drugs (AADs) or ECV, ablation techniques are used with good effects. Even though the treatment of arrhythmias is constantly developing, the maintenance of the sinus rhythm (SR) is still a serious problem. Therefore, it is worth looking for a biomarker which is suitable for the patient's treatment qualifications as well as assessing its effectiveness. Thus, the aim of this work is to present current data on the clinical significance of FABPs in terms of the development and treatment of AF.

**Key words:** *atrial fibrillation, heart-type fatty acid binding protein, adipocyte fatty acid binding protein, chronic heart failure, post-operative atrial fibrillation, electrical cardioversion, radio-catheter ablation*

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#### INTRODUCTION

Atrial fibrillation (AF) is the most common supraventricular arrhythmia, which is characterized by rapid and irregular activation of the atria without P waves discrete on the electrocardiogram surface. Its prevalence ranges from 0.4% to 2%, therefore, it affects over 30 million people in the world (1). Moreover, it is predicted that the number of people will double within next 10 years. AF is associated with a high risk of stroke and, in consequence, hospitalization and reduced quality of life (2). This type of arrhythmia is independently related with a 2-fold and 1.5-fold increase in general mortality in women and in men, respectively (3). Pathophysiology of AF is complex and includes different mechanisms (4), which was shown in *Table 1*. Besides, hyperventilation syndrome (hypocapnia with hypokalaemia and hypomagnesaemia) which can be induced by spontaneous hyperventilation or mechanical ventilation is one of the risk factors of the severe proarrhythmic event (5).

Metabolism of the heart is mainly based on  $\beta$ -oxidation of LCFAs (70% of the obtained ATP), which are transported to the cardiomyocytes by passive and/or facilitated diffusion. The transport is carried out with the participation of plasma membrane fatty acid transporters, *i.e.* fatty acid translocase (FAT/CD36), plasma membrane associated fatty acid binding protein (FABPpm) and fatty acid transport proteins (FATP1-6) (6). Upon entering cardiac myocytes LCFAs are immediately either activated, forming LCFA-acyl-CoAs, or combined with cytosolic fatty acid binding proteins (FABPs). Subsequently, both forms of LCFAs are transported into the mitochondria, the place of their oxidation, or serve as substrates for esterification to lipid fractions. Regulation of plasmalemmal expression of LCFAs protein transporters as well as cytosolic FABPs availability changes intracellular fatty acids fate. A favorable mechanism increases LCFA's utilization *via*  $\beta$ -oxidation as a protective mechanism against toxic accumulation of different lipid species in the cytoplasm. Nevertheless, increased LCFAs oxidation level is associated with greater myocardial oxygen

Table 1. Pathophysiological changes in the atrial tissue associated with atrial fibrillation, their mechanisms and biomarkers.

| Pathophysiological change                                               | Proarrhythmic mechanisms                                                                            | Biomarker                   | References       |
|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------|------------------|
| <b>Changes in the extracellular matrix, fibroblasts and fat cells</b>   |                                                                                                     |                             |                  |
| Interstitial fibrosis and replacement myocardium through fibrous tissue | Electrical distraction, conduction block                                                            | MMPs, TIMP                  | (65), (66)       |
| Inflammation                                                            | Reactions favoring fibrosis                                                                         | CRP, IL-6, IL-2, OPG        | (67), (68), (69) |
| Infiltration by adipose tissue                                          | Reactions conducive to fibrosis/inflammation, local conduction block                                | Activin A                   | (70)             |
| Deposition of amyloid                                                   | Conduction disorders                                                                                | ANP                         | (7)              |
| <b>Ion channels dysregulation</b>                                       |                                                                                                     |                             |                  |
| Ion channels reconstruction                                             | Increased heterogeneity of atrial repolarization                                                    | GIRK                        | (71)             |
| Ca <sup>2+</sup> economy instability                                    | Increased inclination to ectopic                                                                    | SERCA2                      | (72)             |
| Slot connections redistribution                                         | Conduction disorders                                                                                | Cx40, Cx43                  | (73)             |
| <b>Changes in cardiomyocytes</b>                                        |                                                                                                     |                             |                  |
| Apoptosis and necrosis                                                  | Muscle replacement through fibrous tissue                                                           | CASP-3, BCL-2               | (74)             |
| Myocytes hyperplasia                                                    | Intensification of conduction disorders                                                             | β-adrenoceptors, G proteins | (33)             |
| <b>Endothelial and vascular changes</b>                                 |                                                                                                     |                             |                  |
| Changes in microcirculation vessels                                     | Intensification of atrial ischemia, inhomogeneity of electrical activity, structural reconstruction | VCAM-1                      | (75)             |
| Endocardium reconstruction                                              | Risk of thrombus formation                                                                          | VWF, ADAMTS13, TM, PAI-1    | (75), (76), (77) |
| <b>The autonomic nervous system disturbances</b>                        |                                                                                                     |                             |                  |
| Increase in sympathetic innervation                                     | Increased inclination to ectopic                                                                    | NGF                         | (78)             |

**Abbreviations:** ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ANP, atrial natriuretic peptide; BCL-2, B-cell lymphoma 2; CASP-3, caspase-3; CRP, C-reactive protein; Cx40, connexin40; Cx43, connexin43; GIRK, G protein-gated potassium current I; IL-2, interleukin-2; IL-6, interleukin-6; MMPs, matrix metalloproteinases; NGF, nerve growth factor; OPG, osteoprotegerin; PAI-1, plasminogen activator inhibitor-1; SERCA2, sarco/endoplasmic reticulum Ca<sup>2+</sup> ATPase; TIM, tissue inhibitor of metalloproteinase; TM, thrombomodulin; VCAM-1, vascular cell adhesion molecule 1; VWF, von Willebrand factor.

consumption, which may lead to hypoxia and consequently cardiomyocyte necrosis, which in turn triggers arrhythmia.

There are also studies presenting a strong relationship between the abundance of epicardial adipose tissue - EAT (an increased bioavailability of LCFAs in a close adjacent to myocardium) and the risk of cardiovascular diseases including AF. The amount of EAT that accumulates around the atria is related to the risk, persistence, and severity of AF. Moreover, EAT is a major source of adipokines, inflammatory cytokines, reactive oxidative species, growth factors, or MMPs, which can contribute to the fibrotic remodelling of the atrial myocardium. Fibro-fatty infiltrations of the subepicardium can be the cause of disorganization of both the atrial myocardium and depolarization wave front (favouring micro re-entry circuits) as well as a local conduction block. Activin A, a member of the transforming growth factor beta (TGF-β) superfamily which is mainly produced by EAT, exhibits a marked fibrotic effect on the atrial myocardium. What is more, matrix metalloproteinases (MMPs)

are key regulators of extracellular matrix homeostasis, including different types of collagen fibers and basement membrane components. During AF, it has been demonstrated that up-regulated activity of several MMPs, notably MMP2 and 7, contributes to the increased interstitial fibrosis. It has been proved that inflammation is an important determinant of the pathogenesis of AF. Inflammatory factors: C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor alpha (TNF-α) production and secretion by EAT is pronounced, notably during ischaemic cardiopathy, obesity, or diabetes (7, 8). Furthermore, absence of IL-6 triggers an increase in cardiac susceptibility to lipid deposition as well as reduction in myocardial oxidative capacity under the condition of excessive lipid delivery (9). Mysliwiec *et al.* observed an accumulation of triacylglycerols in the cardiomyocytes in mice fed high fat diet and deprived of IL-6 compared to wild-type mice (10). Moreover, EAT contains progenitor cells which can serve as a source of myofibroblasts producing extracellular matrix. In opposite, AF

itself is the source of hemodynamic disturbances of the myocardium, which leads to ischemia and necrosis of the cardiomyocytes and, in turn, may increase the concentrations of cytoplasmic fatty acid binding proteins in the plasma.

## FATTY ACID BINDING PROTEINS

FABPs are small cytoplasmic proteins with molecular mass of 14 – 15 kDa, which are able to bind and transfer LCFAs to different intracellular destinations. Furthermore, FABPs are considered a harmless sink for LCFAs protecting cells against damaging by excessive lipid accumulation (11, 12). As lipid chaperones, FABPs may actively facilitate the transport of LCFAs to the specific compartments in the cell, *i.e.* to the lipid droplets for storage, endoplasmic reticulum for signalling, trafficking and membrane synthesis, to mitochondria or peroxisomes for oxidation, enzymes for regulation of their activity, nucleus for lipid-mediated transcriptional regulation, or even outside the cell for autocrine or paracrine signalling (13). The functional diversity of FABPs is generated via lipid interactions with these chaperone proteins to support systemic homeostatic networks by facilitating signalling within and between the cells as well as communication between organs (14). So far, several FABPs isoforms have been described depending on the place of their highest expression and tissue specificity, for instance: liver (L-FABP), heart (H-FABP), intestine (I-FABP), brain (B-FABP), epidermis (E-FABP) and adipocytes (A-FABP) (15). Among them, heart and adipocyte FABPs are highly involved in the cardiovascular diseases development and/or diagnosis.

### HEART-TYPE FATTY ACID BINDING PROTEIN AND ADIPOCYTE FATTY ACID BINDING PROTEIN: FUNCTIONS AND APPLICATION IN CARDIOLOGY

H-FABP, which is encoded by the H-FABP gene, is abundant in the cytosol of the cardiomyocytes, where it transports long chain fatty acids (15). Physiological function of H-FABP is to transport LCFAs from the cell membrane to the intracellular depots of the mitochondrial utilization, by means of which fatty acids join the citric acid cycle (16). Thus, H-FABP is a powerful regulator of the LCFAs mitochondrial  $\beta$ -oxidative system in the heart (15). Recently, it has been shown that H-FABP is a sensitive biomarker for myocardial infarction and can be detected in the blood within one to three hours after the pain appeared (17). When H-FABP is measured together with troponin, its sensitivity exceeds the troponin's sensitivity up to 20.6% at 3 – 6 hour following the chest pain onset (18). Analyzing only patients with STEMI (ST elevation myocardial infarction), an increased concentration of H-FABP can be detected as early as 30 minutes in the circulation. Combining blood measurements of H-FABP with the available markers like creatine kinase isoenzyme MB (CK-MB) and cardiac Troponin I (cTnI), H-FABP can provide a relevant diagnostic value (19). Therefore, a quantitative plate test has been used for the determination of H-FABP in myocardial infarction diagnosis. Additionally, H-FABP is increased in patients with hypertrophic and dilated cardiomyopathy, heart failure, stroke, obstructive sleep apnea, and pulmonary embolism (20).

A-FABP is also called fatty acid binding protein 4 or aP2. It is present mainly in adipose tissue and macrophages (21) and plays an important role in the development of insulin resistance and atherosclerosis in relation to low grade chronic inflammation. In adipocytes A-FABP accounts for almost 1% of the total cytosol protein content (22). Recent studies have shown that the elevated

level of circulating A-FABP is closely related to metabolic impairments in such conditions as obesity, insulin resistance, diabetes mellitus and cardiovascular diseases (hypertension, atherosclerosis and cardiac dysfunction) by inducing inflammation, inhibiting cholesterol efflux or mediating lipid-induced endoplasmic reticulum (ER) stress in macrophages (23). Latest research revealed that A-FABP acts as a negative regulator of lipid-induced autophagy by inhibiting the Janus kinase 2 (JAK2) signalling pathway. Impairment of JAK2-dependent autophagy further instigates ER stress, thereby leading to the exaggeration of inflammatory responses in macrophages (24). Furthermore, ER stress and inflammation regulate and interplay with each other in obesity and A-FABP is substantially involved in both pathomechanisms. Inhibition of A-FABP and induction of autophagic flux may be the potential therapeutic strategies for the treatment of obesity-related inflammatory complications (24, 25). Metabolic and cardiovascular diseases mediated activation of the sympathetic nerve system and/or induction of inflammatory cytokines may increase lipolysis in adipocytes, resulting in a vicious circle of additional production and secretion of A-FABP. Increased levels of A-FABP have been shown to have a negative inotropic effect on cardiomyocytes (23). Djousse *et al.* proved that an elevated plasma concentration of A-FABP was associated with a modestly higher risk of heart failure in older adults in the USA after adjustment for confounding factors (26). It was also shown that, inhibition or neutralization of secreted A-FABP may represent an effective therapeutic strategy against metabolic and cardiovascular diseases (27, 28).

### A-FABP PLASMA LEVEL AS A POTENTIAL BIOMARKER OF ATRIAL FIBRILLATION

In 2017, Lind *et al.* published a study summarizing the use of a novel, specially engineered proteomic chip to discover new prognostic biomarkers for the risk of AF (29). The research was carried out on the inhabitants of Uppsala in Sweden. The first cohort of patients were members of the PIVUS register (Prospective Investigation of the Vasculature in Uppsala Seniors) in the number  $n = 978$  and the second member of the ULSAM register (Uppsala Longitudinal Study of Adult Men) in the number  $n = 725$ . The first group in 50% consisted of women of the average age of 70.1 years, and the median follow-up time was 10.0 years. The ULSAM registry consisted of men only, where the average age was 77.5 years, and the average follow-up time was 7.9 years. In this study, ninety-two plasma proteins were evaluated at the starting point using a proximity microprocessor (PEA).

The report showed that there were 148 AF events in the PIVUS group and 123 arrhythmia in the ULSAM group during follow-up. The carried out analyzes confirmed the previously described relationship between N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP), fibroblast growth factor 23 (FGF-23), growth/differentiation factor 15 (GDF-15) and random AF (29). Moreover, they discovered that four proteins: A-FABPs, IL-6, T-cell immunoglobulin and mucin domain 1 (TIM-1) and adrenomedullin (AM) could also be of importance in the development of AF (29).

### H-FABP LEVEL AS A POTENTIAL BIOMARKER OF ATRIAL FIBRILLATION IN PATIENTS WITH HEART FAILURE

CHF has been reported to be a risk factor for the new onset of AF due to atrial dilatation, local conduction disturbances, atrial fibrosis and atrial volume overload (30). On the other

hand, it is known that AF deteriorates cardiac functions by inducing tachycardia and atrial contractile dysfunction as well as reducing ventricular filling (31).

Otaki *et al.*, basing on plasma H-FABP and troponin measurements, assessed whether myocardial damage is associated with AF (32). Moreover, in this study it was determined whether the above markers predict subsequent cardiovascular events in patients with atrial arrhythmia. The research was performed on 201 CHF patients with atrial fibrillation (CHF-AF) and 201 CHF patients with sinus rhythm (CHF-SR). Patients with diagnosed acute coronary syndrome within three months prior to admission were excluded. The analysis showed that the CHF-AF patients had higher plasma H-FABP and troponin T (TnT) levels than the CHF-SR individuals. At the same time it should be emphasized that there were no significant differences in age, gender, NYHA (New York Heart Association) functional classification, prevalence of hypertension and diabetes mellitus, CHF etiology, heart rate, estimated glomerular filtration rate (eGFR), BNP, left ventricular end-diastolic diameter, left ventricular ejection fraction and drugs usage, *i.e.* angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers,  $\beta$ -blockers or calcium channel blockers between the CHF-AF and CHF-SR subjects (32). Furthermore, a multivariate analysis revealed that the H-FABP and TnT concentrations were independent predictors for cardiovascular events after adjusting for age and the NYHA functional classification, eGFR and left atrial (LA) dimension in CHF-AF patients. Moreover, according to the univariate analysis in CHF-SR patients, the level of H-FABP, but not TnT (as well as age, NYHA functional classification, eGFR and BNP) was significantly associated with cardiovascular events. In addition, the cut-off values for the levels of H-FABP and TnT were higher in the CHF-AF patients than in the CHF-SR patients (33). These results suggest that the presence of AF may increase areas of myocardial necrosis, which is related to an increase in H-FABP secretion to the plasma. Another conclusion from this study is the fact that the H-FABP plasma levels can be used to stratify the risk of cardiovascular events in CHF-AF and CHF-SR patients.

#### POST-OPERATIVE ATRIAL FIBRILLATION AND H-FABP LEVEL

Post-operative atrial fibrillation (POAF) often occurs after cardiac surgery and can induce thromboembolic events and heart failure as well as prolong hospitalization, which altogether leads to poor prognosis (34). The incidence of POAF is as high as 20 – 30%, even with the use of beta-blockers, which are the only recommended prophylactic medication for POAF (35). Furthermore, the mechanisms of POAF have not been fully elucidated. Structural and electrical remodelling are the two elements proposed in the possible mechanisms of POAF. Structural remodelling includes the pre-operative atrial damage associated with heart disease (atrial dilatation and fibrosis), which leads to changes in the mechanical function (36) and conduction properties of the heart. Therefore, it contributes to the formation of the new re-entry foci (37). On the other hand, electrical remodeling involves electrophysiological changes such as shortening of the refractory period and calcium overload (38). Moreover, in cardiac surgery, ischemic myocardial damage due to inadequate cardioprotection, traumatic pericarditis and myocarditis, along with an increase in adrenergic tone, may contribute to electrical remodelling. Additionally, it has been suggested that the occurrence of increased LCFA metabolism during stress in patients with dilated cardiomyopathy (DCM) contributes to the progression of the left ventricle (LV)

hypertrophy and remodelling as well as CHF (39). In addition, various types of arrhythmia, including atrial tachycardia, are observed at higher rates in children with inherited fatty acids oxidation deficiencies (40). Therefore, POAF might be attributable to impaired fatty acids metabolism in the atrium.

In the recent study published by Shingu *et al.* (41) in patients who underwent cardiovascular surgery between 2013 and 2015, right atrial myocardial tissue (10 mm × 10 mm) has been excised from the insertion point of a two-staged drainage cannula before the establishment of cardiopulmonary bypass. Analyses were performed for the following genes related to the atrial myocardium energy homeostasis: glucose transporter type 4 (GLUT4), peroxisome proliferator-activated receptor- $\alpha$  (PPAR $\alpha$ ), FAT/CD36, carnitine palmitoyltransferase I (CPT I) and H-FABP. The analyzed in this study POAF, which was defined as AF lasting at least 5 min within 7 days after the surgery, was observed in 18/38 (47%) patients. POAF recurrence was also observed in 7/18 (39%) patients but all the 18 POAF patients were discharged home with SR. The gene expression analysis showed that H-FABP expression was significantly reduced in the POAF group compared to the non-POAF control group. The multivariate analysis of pre-operative parameters for the prediction of POAF evinced that reduced H-FABP expression was an arrhythmia predictor of POAF, regardless of age and LA diameter (41).

In 2013 Rader *et al.* published the study regarding perioperative plasma H-FABP levels in AF after a cardiac surgery (42). The POAF was observed most often on the second and the third day after the surgery in 55% of the participants. Furthermore, in the above patients AF was relevantly combined with Coronary Artery Bypass Grafting (CABG) and valve surgery (altogether 11 events, 79%), followed by isolated valve surgery (9 events, 64%), while patients undergoing isolated CABG had the least number of AF incidences (14 events, 42%) (42). In age- and CABG-adjusted joint regression it was revealed that the last plasma H-FABP measurement before the development of AF was significantly higher in patients with AF compared to the subjects without AF. A summary of plasma H-FABP concentration in CHF-AF patients and cardiac perioperative phase is provided in *Table 2*. Interestingly, preoperative plasma H-FABP content was not associated with POAF, suggesting that ischemic injury during or just after the surgery, but not preoperative ischemia, determined arrhythmic risk (42).

#### ELECTRICAL CARDIOVERSION AND PLASMA H-FABP LEVEL

Electrical cardioversion (ECV) is a choice method in patients with recent-onset AF and severe haemodynamic disturbances (43). The advantages of ECV are associated with a high initial success rate (68% – 98%) (44). However, this treatment requires sedation or general anesthesia and long-term maintenance of SR is not reliably achieved (45). In addition, following ECV atrial fibrillation relapse is associated with increased mortality (46, 47), thus highlighting the importance of identifying the appropriate patients group for cardioversion and, where possible, addressing reversible factors related with poorer outcomes (48).

Sbarouni *et al.* sought to investigate whether plasma H-FABP content, a new marker of myocardial necrosis, increases in relation to ECV of atrial fibrillation (49). In this study 25 patients admitted to the hospital in Athens for ECV of atrial fibrillation have been examined. Peripheral venous blood samples were taken immediately before electrical cardioversion, 1 h and 24 h after the procedure and assayed for H-FABP

Table 2. The importance of H-FABP level in CHF-AF patients and in cardiac perioperative phase.

|                                                            | H-FABP analyses                                                                                                                                                                           | Reference |
|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>Predicting cardiovascular events in CHF-AF patients</b> | H-FABP concentration is significantly associated with cardiovascular events.                                                                                                              | (32)      |
|                                                            | H-FABP is an independent predictor of cardiovascular events after adjusting for age, NYHA functional classification, eGFR and LA dimension                                                | (32)      |
| <b>New onset of AF in cardiac perioperative phase</b>      | H-FABP atrial expression is significantly reduced in the POAF group compared to the non-POAF group.                                                                                       | (41)      |
|                                                            | Pre-operative gene expression of H-FABP was not different between the POAF-recurrence group and the non-POAF-recurrence group.                                                            | (41)      |
|                                                            | Reduced atrial H-FABP expression was a predictor of POAF, independent of age and LA diameter.                                                                                             | (41)      |
|                                                            | In age- and CABG-adjusted joint regression, the last H-FABP level before development of AF was significantly higher in patients with AF compared to H-FABP levels in patients without AF. | (42)      |
|                                                            | Patients with developed POAF had similar preoperative, but higher postoperative H-FABP level compared to the subjects who remained in normal sinus rhythm.                                | (42)      |

*Abbreviations:* AF, atrial fibrillation; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; H-FABP, heart-type fatty acid binding protein; LA, left atrial; NYHA, New York Heart Association; POAF, post-operative atrial fibrillation.

Table 3. Biomarkers in electrical cardioversion and radio-catheter ablation therapy.

| Author          | References | Year | Research design                                                                                                                                                                                                                        | Significant change                                                             | Not significant change                                                                                  |
|-----------------|------------|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| Sbarouni E.     | (63)       | 2011 | ✓ Myocardial necrosis does not occur during ECV.                                                                                                                                                                                       |                                                                                | ↓ H-FABP                                                                                                |
| Iakobishvili Z. | (64)       | 2015 | ✓ Patients with persistent AF have initially elevated biomarkers levels.<br><br>✓ After ECV, there is a gradual non-significant decrease of biomarkers.                                                                                |                                                                                | <u>Before:</u><br>↑ hs-cTnT<br>↑ BNP<br>↑ hs-CRP<br><br><u>After:</u><br>↓ hs-cTnT<br>↓ BNP<br>↓ hs-CRP |
| Pudil R.        | (70)       | 2008 | ✓ Myocardial injury induced by RFA can be detected by a biomarker.<br><br>✓ Biomarker levels in patients with AF compared to patients with AVNRT.<br><br>✓ The increase in biomarker levels correlates with the total duration of RFA. | ↑ GPBB<br>↑ cTnI,<br>↑ CK-MB<br>↑ H-FABP<br><br>↑ cTnI,<br>↑ CK-MB<br>↑ H-FABP | ↑ GPBB<br>↑ cTnI,<br>↑ CK-MB                                                                            |

*Abbreviations:* AF, atrial fibrillation; AVNRT, atrioventricular nodal re-entry tachycardia; BNP, brain natriuretic peptide; CK-MB, creatine kinase MB isoenzyme; cTnI, cardiac troponin I; hs-CRP, high sensitivity C-reactive protein; ECV, electrical cardioversion; GPBB, glycogen phosphorylase isoenzyme BB; hs-cTnT, high sensitivity cardiac troponin T; H-FABP, heart-type fatty acid binding protein; RFA, radio-catheter ablation therapy.

concentration. Successful cardioversion and sinus rhythm restoration were achieved in 18 patients (72%). Plasma concentration of H-FABP did not change in relation to the

procedure at a baseline, 1 h and 24 h post cardioversion or to the success of the procedure either (46). Recently, also Iakobishvili *et al.* have analyzed serum biomarkers content (high-sensitivity

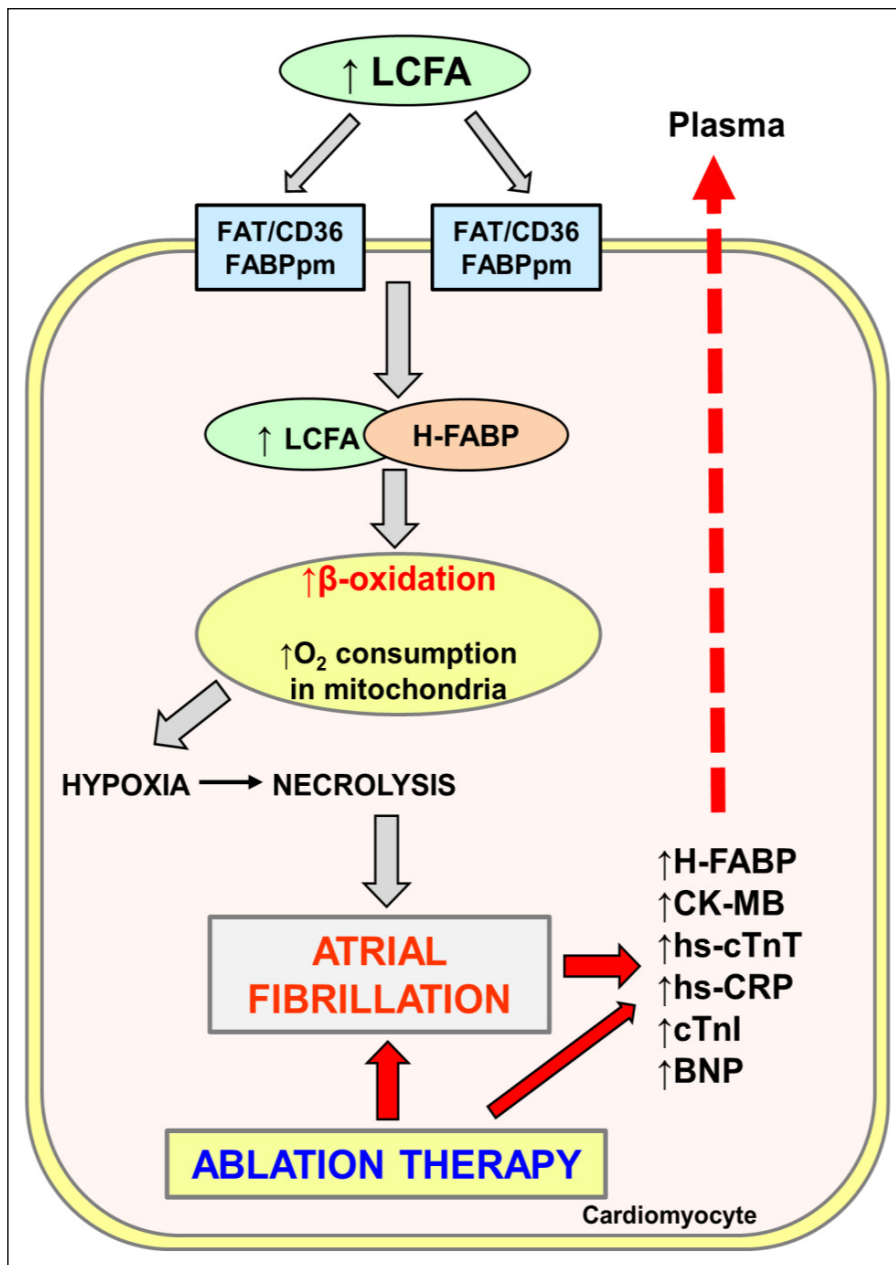


Fig. 1. Increased availability of long chain fatty acids and its connection with atrial fibrillation induction in cardiac muscle. Abbreviations: BNP, brain natriuretic peptide; CK-MB, creatine kinase MB isoenzyme; cTnI, cardiac troponin I; hs-CRP, high sensitivity C-reactive protein; FABPpm, plasma membrane fatty acid binding protein; FAT/CD36, fatty acid translocase; hs-cTnT, high sensitivity cardiac troponin T; H-FABP, heart-type fatty acid binding protein; LCFA, long chain fatty acid.

cTnT and CRP as well as BNP) after ECV (50). This study proved that patients with persistent atrial fibrillation have elevated hs-cTnT levels, as part of a general rise in biomarkers such as BNP and hs-CRP, without a further rise after cardioversion.

In connection with the above, it can be argued that myocardial necrosis does not occur during cardioversion and the level of H-FABP and hs-cTnT cannot be used as an effective determinant of ECV efficacy.

#### RADIO-CATHETER ABLATION THERAPY AND H-FABP CONTENT

According to the latest 2016 European Society of Cardiology guidelines for the treatment of AF, radio-catheter ablation therapy (RFA) may be the first line for treating this kind of arrhythmia (51). RFA is particularly recommended for

patients with ineffectiveness of paroxysmal and persistent AF pharmacological treatment, and in turn shows higher efficacy in maintaining the SR in relation to anti-arrhythmic therapy (43).

Recently, the results of the CABANA trial (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) have been published (52). This multicenter study included 2204 participants from ten countries and after 48 months of observations, the analysis revealed the following remarks:

1. ablation significantly reduced mortality or cardiovascular hospitalization by 17% compared to the drug therapy;
2. ablation significantly (by 47%) decreased AF recurrent compared to the drug therapy;
3. ablation is an acceptable treatment strategy for AF with low side effect rates, even in patients with higher risk (66).

As demonstrated by numerous studies, both techniques (high frequency - RF or cryoballoon) display similar efficacy (53-55). In 2008, Pudil *et al.* analyzed in a prospective study plasma markers

Table 4. Anti-arrhythmic drugs used for maintaining sinus rhythm after cardioversion.

| Drug               | Treatment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | References       |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| <b>Amiodarone</b>  | <ul style="list-style-type: none"> <li>✓ Caution when using concomitant therapy with QT-prolonging drugs and in patients with SAN or conduction impairments.</li> <li>✓ The conversion rate of amiodarone in comparison to placebo was variable and was not always consistently superior to the placebo in the placebo controlled studies.</li> <li>✓ Amiodarone reduced the SCD by 26% and CV deaths by 18% but did not reduce the overall mortality.</li> </ul>                                                                                                                          | (79), (80), (81) |
| <b>Dronedarone</b> | <ul style="list-style-type: none"> <li>✓ Dronedarone is a suitable choice for maintaining SR, especially in young patients, and eliminating the non-cardiac toxic effect seen with amiodarone.</li> <li>✓ It is preferred treatment in hemodynamically stable patients and those with NYHA class I-II heart failure.</li> <li>✓ Contra-indicated in NYHA Class III or IV or unstable heart failure, during concomitant therapy with QT-prolonging drugs, or powerful CYP3A4 inhibitors (e.g. verapamil, diltiazem, azole antifungal agents), as well as when CrCl&lt;30 ml/min.</li> </ul> | (82), (83)       |
| <b>Flecainide</b>  | <ul style="list-style-type: none"> <li>✓ Flecainide is recommended as one of the first line therapy for rhythm control in patients with recurrent PAF particularly young age patients and patients with structurally normal heart with normal ventricular function.</li> <li>✓ Contra-indicated if CrCl is less than 50 mg/mL, liver disease, IHD or reduced LV ejection fraction.</li> <li>✓ Acute treatment with flecainide was associated with the conversion rates between 52% and 95%.</li> </ul>                                                                                     | (84), (85)       |
| <b>Propafenone</b> | <ul style="list-style-type: none"> <li>✓ It is as effective as flecainide treatment, though flecainide is faster in conversion and both are having the same incidence of side effects and negligible pro-arrhythmic potential for malignant arrhythmias especially in structurally normal heart.</li> <li>✓ Contra-indicated in IHD or reduced LV ejection fraction.</li> </ul>                                                                                                                                                                                                            | (86)             |
| <b>d,l Sotalol</b> | <ul style="list-style-type: none"> <li>✓ Sotalol has a relevant risk of torsades de pointes.</li> <li>✓ Contra-indicated when significant LV hypertrophy, systolic heart failure, asthma, pre-existing QT prolongation, hypokalaemia or CrCl&lt;50 mg/mL are present.</li> </ul>                                                                                                                                                                                                                                                                                                           | (87), (88)       |
| <b>Ibutilide</b>   | <ul style="list-style-type: none"> <li>✓ Not included in European Society of Cardiology Guidelines.</li> <li>✓ Ibutilide is not superior to amiodarone and flecainide in conversion of AF.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                      | (89)             |
| <b>Dofetilide</b>  | <ul style="list-style-type: none"> <li>✓ Dofetilide restores and maintains SR in heart failure patients and occasionally in patients re-fractory to other antiarrhythmic drugs.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                 | (90), (91)       |
| <b>Vernakalant</b> | <ul style="list-style-type: none"> <li>✓ Oral vernakalant administration in maintaining SR after cardioversion of sustained AF was superior to placebo in sustaining SR over a 28-day treatment.</li> <li>✓ ACT 5 study assessing the safety of I.V. vernakalant in acute conversion of the new onset AF was terminated prematurely by the cosponsors as requested by the FDA due to reported severe hypotension and bradycardia with one fatal cardiogenic shock case.</li> </ul>                                                                                                         | (92), (93)       |
| <b>Ranolazine</b>  | <ul style="list-style-type: none"> <li>✓ No significant randomized trials done on the efficacy of ranolazine in AF.</li> <li>✓ Ranolazine was independently associated with a reduction of AF compared to the amiodarone administration after CABG, with no difference in the incidence of adverse events.</li> </ul>                                                                                                                                                                                                                                                                      | (94)             |
| <b>Antazoline</b>  | <ul style="list-style-type: none"> <li>✓ Intravenous antazoline injections were effective and safe in the rapid conversion of non-valvular paroxysmal AF to SR in patients without heart failure.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                               | (95)             |

*Abbreviations:* ACT, Arrhythmia Conversion Trial; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CrCl, creatinine clearance; CV, cardiovascular; CYP, cytochrome P; FDA, Food and Drug Administration; IHD, ischaemic heart disease; PAF, paroxysmal atrial fibrillation; SAN, sinus advanced node; SCD, sudden cardiac death; SR, sinus rhythm.

of myocardial damage induced by RFA using the protein biochip microarray system (56). The study involved 32 subjects with

atrioventricular nodal re-entry tachycardia (AVNRT), right atrial flutter (AFL) and AF. In this study cTnI, CK-MB, H-FABP and

GPBB (glycogen phosphorylase isoenzyme BB) were measured, applying the biochip array technology at a baseline and 24 hours after RFA. Analyses have shown that myocardial injury induced by RFA can be detected with cTnI, CK-MB, H-FABP and GPBB measurements. Furthermore, plasma cTnI, CK-MB and H-FABP levels increased considerably in the patients with AFL and AF compared to the AVNRT patients, suggesting greater myocardial damage during ablation or more viable atrial myocardium (Fig. 1) (56). Similar conclusions can be drawn by analyzing results of Martinez-Comendador *et al.* study (57). It was shown that the modified Cox-Maze (CM) lesion caused greater elevation of plasma biomarker (CK-MB and cTnI) concentrations than the isolated LA procedure. Moreover, in CM using cryoablation caused greater elevation of plasma biomarkers than CM using RF. The increase does not seem to have an adverse effect on sinus rhythm or overall outcome (58). Yoshihara *et al.* showed that in patients with AF after Maze procedure and bilateral appendectomy, ANP level was decreased, which was consistent with the reduction in ANP release after removal of the left atrial appendage (LAA) (58). This is in agreement with final reduction in ANP and BNP release after percutaneous endocardial LAA occlusion using WATCHMAN and LARIAT device (59). These procedure leads to ischemic necrosis resulting in degranulation and ANP release from atrial tissue and consequently massive natriuresis and hyponatremia. As the acute LAA necrosis changes to fibrosis, the ANP secretion from the LAA declines and probably the right atrium takes over the ANP secretory function (59). On the other hand, Ad *et al.* (60) proved that CM with cryoablation was only reported to exhibit better clinical outcomes in comparison with combination of cryoablation and RF. This suggests that greater myocardial damage can evoke arrhythmia. A summary of biomarkers level after ECV and RFA is provided in Table 3.

Recurrence of AF after ablation (the most effective treatment method) is generally classified into three types according to the phase after ablation in which they appear: (1) early recurrence (within 3 months) is observed at least in 50% of patients or more; (2) late recurrence (from 3 months to 1 year) which occurs in 25 – 40% of cases; and (3) very late recurrence (more than 1 year) (61). Therefore, it is worth determining the safe level of biomarkers, including H-FABP, in order to increase the treatment effectiveness and reduce the recurrence of arrhythmia.

## CARDIOVERSION - WHAT'S NOW?

### PHARMACOLOGY USED FOR MAINTAINING SINUS RHYTHM

Anti-arrhythmic drugs (AADs) for AF have been available for a long time and used for different indications, for instance in cardioversion to maintain sinus rhythm and prevent recurrence or control ventricular rate. However, there are some limitations of their usage, *i.e.* potential proarrhythmic cardiovascular and non-cardiovascular toxicity as well as a little impact on SR maintaining (62). The decision to choose rhythm or rate control strategies should be individualized and depends on the expected benefit of restoring SR, chance on failure to maintain SR in the long-term, and the likelihood of adverse drug effects. Rhythm control remains the first choice for patients with the first episode or highly symptomatic episodes of AF and for patients who have AF caused by a reversible cause (*e.g.* hyperthyroidism, postcardiac surgery) or who have a high chance of remaining in long-term SR (young patients, no hypertension, normal left atrium size, short preceding AF duration). Also patients with symptomatic AF who are suitable for the ablation therapy (*e.g.* focal AF, class IC flutter), restoration and maintenance of SR

would be the first choice (63). AADs are classified broadly in four major groups according to their electrophysiological properties. Recently it has been shown that SR achieved after conversion of AF may be prolonged by certain non-antiarrhythmic drugs such as angiotensin - converting enzyme inhibitors (ACEIs), corticosteroids, aldosterone antagonists, statins, and omega 3-PUFA (64). The most important information about ADDs can be found in Table 4.

## Conclusions

Atrial fibrillation, despite its prevalence rate, still holds many secrets about its pathophysiology, course, and treatment efficacy. New markers that can be used to predict arrhythmia as well as treatment effects are still being sought. Despite the achievement of advanced treatment techniques such as ablation, we are still dissatisfied with recurrent disease. Therefore, it is right to conduct new research on biomarker that monitor the effects of treatment or qualifying patients for the chosen treatment method. The results of research on FABPs confirm the participation of these proteins in AF, however, to demonstrate their usefulness further studies are needed.

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