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Review

Further Advances in Atrial Fibrillation Research: A Metabolomic Perspective

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Abstract: Atrial fibrillation involves an important type of heart arrhythmia caused by a lack of control in the electrical signals that arrive in the heart, produce an irregular auricular contraction, and induce blood clotting, which finally can lead to stroke. Atrial fibrillation presents some specific characteristics, but it has been treated and prevented using conventional methods similar to those applied to other cardiovascular diseases. However, due to the influence of this pathology on the mortality caused by cerebrovascular accidents, further studies on the molecular mechanism of atrial fibrillation are required. Our aim here is provide a compressive review of the use of metabolomics on this condition, from the study of the metabolic profile of plasma to the development of animal models. In summary, most of the reported studies highlighted alterations in the energetic pathways related to the development of the condition.

Keywords: atrial fibrillation; heart arrhythmia; metabolomics; metabolic profile

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1. Introduction

Atrial fibrillation (AF) is one of the most common types of arrhythmia [1,2]. In this pathology, the electric signals that come from the atria (two small chambers of the heart) are sent in a very fast and uncontrolled way, which produces vibration in the atria instead of contraction, and the electric signals reach to the ventricles irregularly (Figure 1) [3]. When the contract of the auricles is not effective, blood can accumulate or clot. If one of these clots is placed in a cerebral artery, it can lead to stroke [4].

This is a pathology with a substantial effect on the morbidity and mortality of the patients with cardiovascular conditions (around 15% of strokes occur in people with AF). It has a prevalence of 0.7% in patients between 55 and 59 years old, and its incidence increases to 17.8% after 85 years old [5,6].

For the treatment of AF drugs such as aspirine, warfarine and other medicines for the heart may be used [7]. However, over the last several decades, it has been proved that traditional cardiovascular disease risk control does not seem to reduce AF in a significant way due to a series of specific factors that influence it, such as age, high blood pressure, congenital heart failure, stroke, obesity, and diabetes [8].

One of the proposed approaches to know the factors that affect AF and reduce its prevalence is the application of metabolomics, the systematic study of the chemical process involving metabolites in a particular tissue or biofluid [9]. Metabolites are the small molecule

intermediates and products of cell metabolism. However, up to now metabolomics research about heart arrythmias, specifically on AF, has been limited. Most published studies have examined the metabolic profile of auricular tissue from AF patients or from animal models, such as a canine model. Despite this, as far as we know, no prospective evaluations of the metabolomic profile associated with risk of AF have been published. To address this gap, it was proposed to explore the association of molecules identified through indirected metabolomic associated with newly diagnosed AF risk in a subset of participants in the Atherosclerosis Risk in Communities (ARIC) study [10,11].

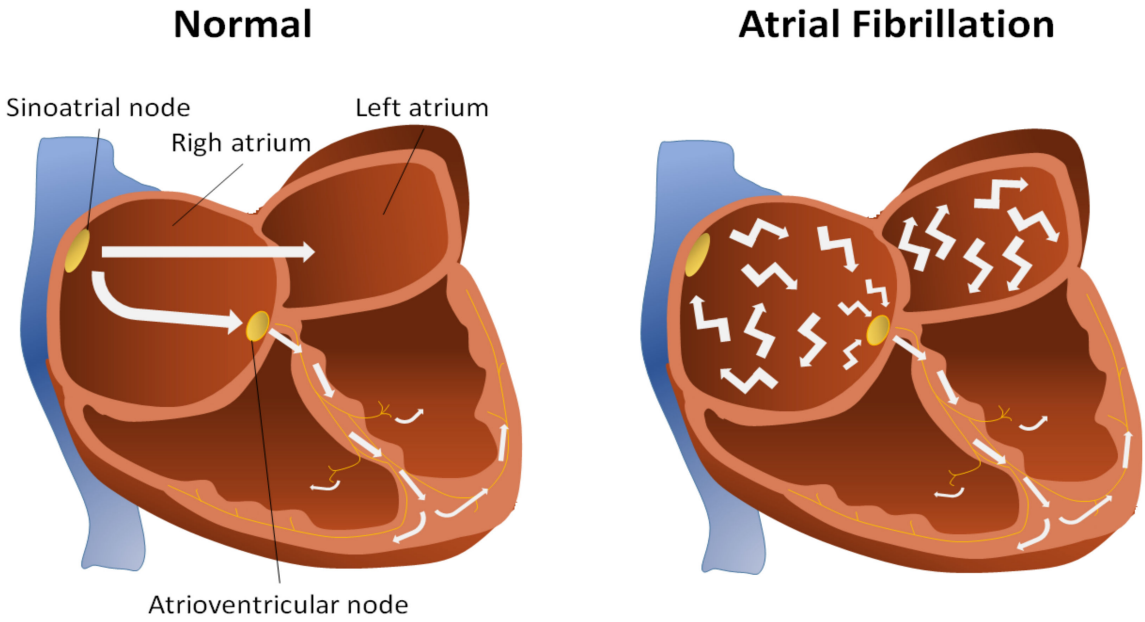

Figure 1. Cardiac electric signals in normal and AF heart.

Thus, the application of metabolomics in the study of AF has so far been limited. Phenotypic changes in AF seem to point to changes in metabolites induced by environmental factors [6]. Therefore, understanding and defining all the molecules involved in these processes and their interactions is one of the great current challenges. Compared to genomics and proteomics, metabolomics are more closely related to phenotypic expression and influential environmental factors and therefore can better reflect the state of the human body and help to achieve a better understanding of AF. In this review, our aim is to compile and summarize the studies carried out so far to identify new biomarkers of AF (Table 1), focusing on the two most used metabolomic: Nuclear Magnetic Resonance (NMR) and Mass Spectrometry (MS).

Table 1. Proposed metabolic biomarkers for AF in human patients and animal models.

Study	Objective	Biological System	Sample	Metabolic Biomarkers
Lai et al. [12]	AF diagnosis or prediction	Human	Atrial appendage and plasma	Betaine, choline, creatinine, D-glutamic acid, glycerophosphocholine, hypoxanthine, L-valine, and niacinamide
Mayr et al. [13]	Metabolic adaptation to persistent AF	Human	Atrial appendages	Beta-hydroxybutyrate, tyrosine, and glycine

Table 1. *Cont.*

Study	Objective	Biological System	Sample	Metabolic Biomarkers
She et al. [14]	Identify metabolic alterations correlated to the occurrence of AF	Human	Plasma	L-threonine, hypotaurine, L-leucine, L-3-amino-isobutyric acid, L-lysine, L-arginine, L-asparagine, β-alanine, L-kynurenine, L-glutamic acid, saccharopine, L-methionine, 4-hydroxy pyrrolidine-2-carboxylic, and L-homoserine and L-histidine
Zhou et al. [15]	Identify biomarkers for AF screening	Human	Plasma	2-Methylbenzothiazole, 4-hydroxybenzoic acid, acetylcholine, adenine, adenosine 3′-monophosphate, adenosine-diphosphate, AMP, citrulline, cysteine, D-arabinose-5-phosphate disodium salt, DL-beta-hydroxybutyric acid, gamma-linolenic acid, guanosine 5′-monophosphate, hypoxanthine, inosine, isoleucine, O-acetyl-L-carnitine, oxidized glutathione, para-aminobenzoic acid, proline, trigonelline, umbelliferone, uridine 5′-diphosphate, and uridine 5′-monophosphate
Jing Li et al. [16]	Predictive model for AF recurrence	Human	Serum and faecal samples	LysoPC(15:0), lysoPE(0:0/16:0), chenodeoxycholic acid, sebacic acid, lysoPE(0:0/20:0), corticosterone, α-linolenic acid, and uracil
Ming-Yang Li et al. [17]	Biomarkers for chronic AF in mitral valve disease	Human	Plasma	Sucrose, cellobiose, lactose, raffinose, galactinol, arachidonic acid, palmitic acid, and linoleic acid
De Souza et al. [6]	Biomarkers for congestive heart failure induce AF	Dog	Left atrium	Alanine, glucose, glutamine, glutamate, taurine, α-ketoacid, and α-ketoisovale
Jie et al. [18]	Characterize the remodeling of energy metabolism during persistent AF	Sheep	Left atrium	Citrate, pyroglutamic acid, methionine, glycine, glutamic acid, proline, tyrosine, arginine, pyruvate, lactate, glycogen, and glucisamine

2. Application of Metabolomics in Atrial Fibrillation

2.1. Blood-Derived and Heart Tissue Biomarkers Analysis in Atrial Fibrillation

After years of research and therapeutic interventions related to AF, scientists are still struggling to understand the causes and mechanisms of this condition. Blood-derived biomarkers, such as clotting markers, kidney function, inflammation, myocardial injury, and cardiovascular stress, have been associated with clinical events [19]. In this context, Lai et al. [13] demonstrated the feasibility to use plasma metabolomics analysis to predict AF. They also found metabolic alterations in atrial appendage samples that allow the discrimination between patients with and without AF. They reported a combination of D-glutamic acid, creatinine, and choline as a potential biomarker for AF prediction. However, they recognized that is necessary to reproduce their results with a larger sample size, to validate their findings.

Along with development and progression of AF, metabolite biomarkers could reflect its pathophysiological mechanisms. Mayr et al. [14] carried out a nondirected metabolomic analysis NMR to verify whether both β-hidroxibutirate and its ketogenic aminoacid, as well as glycine, were increased in myocardial blood samples of patients with persistent AF.

In another study carried out by She et al. [15], the plasma amino acid metabolic profile was analyzed in elderly patients, admitted to the cardiology unit of Xi'an Jiaotong University Affiliated Hospital, who were diagnosed with AF. Fasting venous blood collections were performed over 23 selected patients and 37 healthy controls, separating the plasma by centrifugation, and the amino acid profile was evaluated by GC/MS [15]. Quantification of 61 serum amino acids was performed, and the results were compared between groups. It was observed that amino acid metabolism was altered in patients with AF, indicating that amino acid levels could be a potential diagnostic marker of AF. In addition, the association between the amino acids measured and the clinical characteristics shown by the patients was evaluated. The results showed a significant correlation between amino acids and cholesterol levels or coagulation in some patients. Furthermore, the circulating level of 4-hydroxypyrrolidin-2-carboxylic acid decreased in the presence of persistent AF. All of this indicates the importance of the metabolic profile in AF, suggesting a therapeutic strategy of amino acid supplementation as a potential treatment for the disease.

Zhou et al. [16] performed a combination of metabolomics and proteomic analyses to identify potential biomarkers and related metabolic networks in AF. They found that 24 metabolites, 16 lipids, and 16 proteins were significantly dysregulated in AF patients. Specifically, purine metabolic pathway and fatty acid metabolism were perturbed by AF onset.

Jing Li et al. [17] studied the shifts in gut microbiome and metabolome associated with risk of recurrent AF after percutaneous radiofrequency catheter ablation, which represents an important treatment strategy for AF patients. Compared with non-AF controls, gut microbiota composition and metabolomic profile from serum and feces samples were significantly altered between patients with recurrent AF and non-recurrent AF group.

Finally, a multiomics study was performed by Ming-Yang Li et al. [18] to identify potential biomarkes for chronic AF in mitral valve disease. They found 57 proteins and 55 metabolites differentially expressed between AF and sinus rhythm patients. The authors conclude that some identified proteins and metabolites may be futher developed as biomarkers for mitral valve disease-associated AF.

2.2. Metabolomic Study of Atrial Fibrillation in an Animal Model

Additionally, for the identification in human samples of specific markers for an accurate and effective diagnosis of AF, animal models have been used to improve our understanding of the pathology. For example, a big animal model of ventricular tachycardia was developed by De Souza et al. [6], to study AF caused by heart failure in dogs. In this study, metabolic changes in cardiomyocytes of left atrium were analyzed. They observed several metabolites changes that suggested an increase in metabolomic stress along with poor energetic management and a shift from glycolysis to ketoacid metabolism. This study focused on metabolomics of heart tissue affected by AF, without directly addressing the association between circulating metabolites and the risk of developing the disease [6,10]. They used Nuclear Magnetic Resonance (NMR) and found important time-dependent alterations in protein levels involved in cardiac oxidative injury, including metabolic enzymes, heat shock proteins, and antioxidant and contractile filament proteins. The metabolomic analysis they carried out showed consistent results with these disturbances. This study was the first one using an animal model to analyze changes to protein and metabolite expression and point out the importance of these alterations to the development of AF [6].

A nonsustained atrial pacing sheep model was developed by Jie et al. [19] to study energy metabolism remodeling during persistent AF. Metabolomic analysis found an up-regulation of glucose metabolism and a down-regulation of lipid metabolic pathways.

2.3. Metabolomic Analysis of Liver Markers with Atrial Fibrillation

Several studies have linked higher circulating levels of liver enzymes, which are markers of liver damage, with an increased risk of AF [11,20–24]. However, the mechanism that relates high levels of bile acids and the risk of AF is not very clear yet. The reason

is that both glycolithocholate sulfate and glycocholenate sulfate can be found at elevated levels in the context of liver diseases [20,21]. However, Alonso et al. [11] found that markers of liver damage and function are independent from associating the two bile acids with a higher risk of AF. Thus, this suggests that there might be different pathways under this association [10].

The aforementioned studies are reinforced by previous assays performed in mice's ventricular muscle [10,11] that had evidenced the occurrence of arrhythmias in relation to abnormal levels of bile acids due to negative inotropic effects. Moreover, other studies in neonatal rat cardiomyocite culture have observed the same effect, where bradycardia and a loss of synchronous beats are caused by the conjugation of bile acids with taurine [22,23].

In addition, intrahepatic cholestasis of pregnancy, characterized by elevated maternal serum bile acid levels, has been associated with the appearance of fetal cardiac arrhythmias [24]. Rainer et al. [25] studied possible arrhythmogenic effects of bile acids in the adult human heart. They deduced that increasing concentrations of bile acids conjugated with taurine and glycine are responsible for increased extra-arrhythmic contractions in the myocardium.

2.4. Energy Metabolism and Its Influence on Atrial Fibrillation

Cardiac tissue can use different sources for energy production. However, after a meal, 60% to 70% of ATP production in myocardial tissue is due to beta-oxidation of fatty acids. Thus, fatty acids play a vital role in the energy balance of the heart [26]. In this context, two medium-chain fatty acids, e.g., decanylcarnitine and octanoylcarnitine, have been associated with cardioembolic stroke, mainly caused by AF [26], as we explained before. Decenylcarnitine and other fatty acids have also been linked to impaired glucose tolerance in previous studies [27].

Glucose metabolism also plays a very important role in energetic requirement of heart tissue. A recent microarray analysis form transmural ventricle tissue in patients with permanent AF revealed ventricularization of gene expression and up-regulation of transcripts involved in metabolic activities, including several enzymes related to glucose metabolism, suggesting a link between a change in glucose metabolism and AF [28].

Among these enzymes, we can find triose phosphate isomerase and glyceraldehyde-3-phosphate dehydrogenase. These two glycolytic enzymes perform a positive regulation as part of the reprogramming of the human atrial transcriptome in permanent AF [14].

3. Discussion

As discussed in this scientific review on AF and the use of metabolomics, we have found several studies in which metabolomics analysis arises as a powerful ally to provide a novel molecular approach in AF research. Specifically, metabolomics analysis allows us a better understanding of the AF and the mechanisms underlying them, the identification of new biomarkers for the diagnosis and/or prognosis of this condition, and even the identification of the different factors that indirectly promote their appearance under certain circumstances.

However, all the summarized studies present certain limitations. It should be noted the size of the population analyzed is one of the most recurring limitations. In many cases, the patients were volunteers, so there may be a possible selection and observation bias. Further validation of markers in larger independent data sets are needed [13–17], especially in human studies, where highlighted plasma biomarkers may not reflect changes in heart tissue with enough confidence to be used in patient stratification yet [13,15,16,18] and further research in this field is needed to define sensitive predictive or diagnostic biomarkers for AF. Besides that, proposed metabolic biomarkers were analyzed only in certain metabolic pathways, although the participation in more complex processes is well known [13,14,16]. The assay technique used in present pilot studies may be limiting if it is not complemented by other techniques that allow for the analysis of all biomarkers, as is the case of NMR [14], which presents lower sensitivity and lower analytical resolution than

mass spectrometry, or undirected metabolomic methods [15], which restrict the accurate valuations. After the bioinformatic analysis, it was observed that some of the molecules found as possible biomarkers have not yet been described, thus their clinical impact is unknown [18]. Likewise, it is possible that there are still undiscovered markers that can be used for patient stratification [6,13–19].

Strategies such as proteomics and metabolomics have been shown to be powerful tools for biomarker identification and pathological studies [6,13–19]. This technology is becoming a powerful ally in overcoming the current challenges of achieving a better understanding of proteins and molecules as well as the metabolic pathways and processes in which they participate [6]. This will allow us to understand how their alterations are related to different pathologies, as in the case of AF. We are only at the tip of the iceberg of the possibilities that these tools can offer, so there is a clear need for much more research for the development and improvement of these techniques in AF research. In this way, we will be able to continue making progress; achieve a better understanding of the diseases that, successfully treated, could translate into better quality of life for people who are affected by AF; and help people who present abnormal values of these biomarkers even though they have not developed the disease yet. The key risk factors are increasing age, miocardial infarction, valvular heart disease, and hypertension. To avoid the development of AF, a healthy lifestyle that contributes to normalizing biomarkers values should be followed [5].

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