The Role of Hyperuricemia in the Development of Atrial Fibrillation

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Atrial fibrillation (AF) is one of the most common cardiac arrhythmias. We have discussed the role of hyperuricemia as a predisposing factor for the onset of AF. Numerous clinical and experimental investigators demonstrated the correlation between serum uric acid (SUA) level and arrhythmia development and its complications. The development and progression of AF are connected to a complex of changes in atrial cardiac muscle tissue. The electrical, structural, contractile remodeling, neurohumoral systems, inflammation, fibrosis, oxidative stress, endothelial dysfunction, activation of NLRP3 inflammasome induced by crystals of monosodium urate (MSU), heat shock proteins (HSP), cytokines – all have a role in the development of this process. Furthermore, the role of xanthine oxidase (XO) is considered in the pathogenesis of AF through activation of systemic inflammation and oxidative stress, preparing that substrate for AF. The overwhelming data suggest a direct pathophysiological role of the increased SUA and XO activity as risk factors for AF. This article offers a comprehensive review of investigations that shows the interrelation between hyperuricemia and the risk of AF.

Keywords: atrial fibrillation; uric acid; hyperuricemia; myocardial remodeling; oxidative stress; xanthine oxidase; uric acid transporters; heat shock proteins (HSP); NLRP3 inflammasome; cytokines.

Роль гиперурикемии в развитии фибрилляции предсердий

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Фибрилляция предсердий (ФП) — одно из наиболее распространенных нарушений сердечного ритма. В настоящее время обсуждается роль гиперурикемии как одного из предрасполагающих факторов возникновения ФП. Результаты многочисленных клинических и экспериментальных исследований продемонстрировали взаимосвязь повышения уровня мочевой кислоты (МК) относительно развития аритмии и ее осложнений. Развитие и прогрессирование ФП связаны с комплексом изменений ткани миокарда предсердий — электрическим, структурным, сократительным ремоделированием, известна роль нейрогуморальных систем, воспаления, фиброза, оксидативного стресса, эндотелиальной дисфункции, активации инфламмасомы NLRP3, индуцированной кристаллами моноурата натрия (МУН), белков теплового шока (HSP), цитокинов в развитии данного процесса. Накопленные данные позволяют предположить существование прямой патофизиологической роли повышенного уровня МК в сыворотке крови и активности ксантиноксидазы с риском ФП. Роль ксантиноксидазы в патогенезе ФП рассматривается через активацию системного воспаления и оксидативного стресса, формируя тем самым субстрат для ФП. Настоящая статья посвящена обзору исследований о взаимосвязи гиперурикемии с риском развития ФП.

Ключевые слова: фибрилляция предсердий; мочевая кислота; гиперурикемия; ремоделирование миокарда; оксидативный стресс; ксантиноксидаза; переносчики уратов; белки теплового шока (HSP); инфламмасома NLRP3; цитокины.

ЭКО • ВЕКТОР

Atrial fibrillation (AF) is a supraventricular tachycardia characterized by uncoordinated electrical atrial activity [1]. This is one of the most widespread heart arrhythmias and causes about 80% of paroxysmal supraventricular tachycardia cases. The occurrence of AF in the general population reaches 2% and continues to increase [2]. AF morbidity is expected to double in the next 50 years. This increase is directly associated with an aging population, an increase of congestive heart failure prevalence, and improvements in diagnostics of this kind of arrhythmia disease [3]. In addition, AF deteriorates a patient's quality of life and increases the risk of lethal cardiovascular complications [4]. AF is prognostically unfavorable because it is followed by a growth of overall mortality and, in particular, cardiovascular mortality. The mortality rate is higher in AF patients than in patients with sinus rhythm. It also can be associated with a large number of thromboembolic complications [5].

Many epidemiological studies report that hyperuricemia is considered to be a significant AF risk factor as well as age, male sex, inheritance, obesity, hypercholesterolemia, tobacco smoking, strenuous physical activity, arterial hypertension, valvular heart disease, coronary heart disease, heart failure, and diabetes mellitus [6].

The role of uric acid (UA) in developing the most widespread cardiovascular diseases was first reported in the 1950s. Nowadays, the interest in studying purine metabolism and UA as its end-product is increasing. This is associated with an observable growth of both asymptomatic and clinically manifested hyperuricemia [7–10].

For the last decades, the spread of hyperuricemia has been considerably increasing worldwide. The data show a verifiable growth of hyperuricemia prevalence in the U.S. over the past decade from 19.1% to 21.4% [11]. A meta-analysis published by B. Liu et al. reported that the overall prevalence of hyperuricemia made up 21.6% for males and 8.6% for females, according to 59 Chinese studies sampled for meta-analysis, which were performed over the recent years [12]. It was demonstrated that the risk of hyperuricemia was increased among males in the age above 30 and females in the age above 50. The predominance of hyperuricemia prevalence among males was observed in other studies as well [13]. In the aforementioned Chinese study, it has been revealed that hyperuricemia among males has been found four times more often than among females [12]. Furthermore, a distinct age range of hyperuricemia prevalence: from 14.7% at a young age to 20.5% at the age of 55–64 was observed [14].

Hyperuricemia increases the UA concentration in the blood serum above 360 μmol/L for females and 400 μmol/L for males. However, these values could be subjected to various factors, such as race, sex, regular consumption of certain food products (red meat, seafood, alcohol) [15–17]. 5%–8% of the population has an asymptomatic increase in UA level, and only 5%–20% of them suffer from gout [18]. UA is a weak organic acid generated
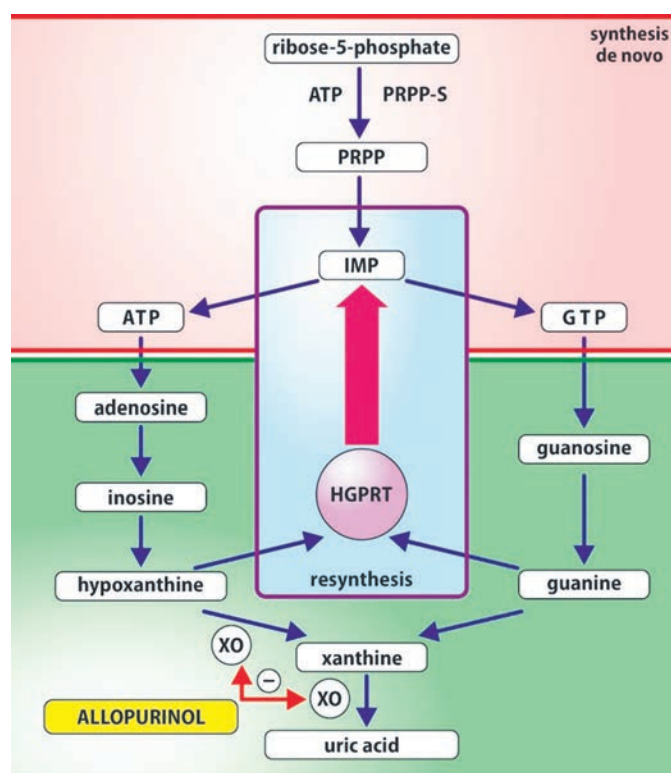
Fig. 1. De novo purine synthesis. Phosphoribosyl pyrophosphate synthetase (PRPP-S), adenosine triphosphate (ATP), phosphoribosyl pyrophosphate (PRPP), inosine monophosphate (IMP), guanosine triphosphate (GTP), hypoxanthine-guanine phosphoribosyltransferase (HGPRT), xanthine oxidase (XO).

during the elimination of purine metabolism wastes. The key enzyme is phosphoribosyl pyrophosphate synthetase (PRPP-S). It launches several stages through which inosine monophosphate (IMP) produces adenosine triphosphate (ATP) and guanosine triphosphate (GTP). While performing their functions, ATP and GTP undergo a disintegration process which results in hypoxanthine, produced as a result of ATP degradation, and guanine made as a result of GTP degradation. Thus, they act as UA metabolic predecessors. These nitrogenous bases are oxidizing to xanthine, which in turn undergo oxidative transformation to the UA. The critical enzyme at this stage is the enzyme of xanthine oxidase (XO) (Fig. 1) [6].

Recent studies have confirmed a XO activity in the human heart (MacGowan et al., 1995) [19] and its allocation in microvascular endothelial cells, macrophages, and mast cells. The highest activity of XO becomes apparent in the endothelium. Endothelial XO plays a crucial role in vascular oxidative stress, which contributes to the development of AF [20]. The accumulated data allow us to propose a direct pathophysiological role of the increased UA concentration in the blood serum and XO activity with a risk of AF [21].

Ischemia and cellular damage facilitate to accumulation of xanthine, creating a substrate for XO. This enzyme participates in the purine degradation of the UA that is a source of superoxide radicals. This enzyme uses molecular oxygen as an electron acceptor and leads to the superoxide anion free radicals, thus contributing to oxidative stress. Superoxide anion can create hydrogen peroxide through the activity of superoxide dismutase, if Ferrum is present, it is a hydroxyl radical.

Moreover, the superoxide anion interacts with nitric oxide (NO) and composes a toxic molecule of peroxynitrite. Together, hydroxyl radicals and peroxynitrite induce cellular reactions ranging from subtle changes of cell functions to severe oxidative damage to affected macromolecules, leading to necrosis and apoptosis. Thus, XO is an inductor of oxidative stress, and emerging free radicals directly damage cardiomyocytes [20].

The development and progression of AF are connected to a complex of changes in atrial cardiac muscle tissue: electrical, structural, contractile remodeling, including secondary cardiovascular alterations in the left atrium due to remodeling of the left ventricle as a result of a pressure overload [22].

Structural remodeling during AF is characterized by atrial dilation and fibrosis, massive connective tissue accumulation, and individual myocytes' disruption. Fibrosis is a substrate of the micro-reentry mechanism, the circular movement of the excitation wave in the atrial cardiac muscle [23].

The electrophysiological mechanism of AF consists of electrical remodeling and abnormal automaticity, characterized by reduction of the cardiac action potential duration and effective refractory period. The autonomic dysfunction and the direct tachycardia influence on functions of ion channels are determined as possible sources of changes in atrial electrophysiological properties. Atrial automaticity can be associated with dysregulation of the intracellular Ca^{2+} concentration. Dysregulation of Ca^{2+} causes its release from the sarcoplasmic reticulum (SR) during the diastole periods and increases inward currents in cell membrane due to Na^+/Ca^{2+} exchange activation, which in turn induce afterdepolarization associated with triggered activity, thus facilitating aggravation of AF [24]. In addition, automaticity through triggered activity in the pulmonary veins (PV) becomes a trigger to AF, supporting the reentry mechanism at the boundaries between PV and the atrium [25]. As well as ischemia, fast atrial contraction can lead to a shortening of the refractory period due to high-energy phosphate depletion and activation of ATP-sensitive K^+ channels, as well as to Ca^{2+} atrial cardiac muscle overload [26]. Furthermore, decreasing Na^+ currents and transient outward potassium current (/to) reduces the refractory period and decreases cardiac conduction [27]. Together, these mechanisms facilitate the generation of multiple excitation waves in the atria, frequent activation of the atria, and refractory dispersion [28].

The role of neurohumoral systems, in particular, renin-angiotensin-aldosterone system, inflammation, fibrosis oxidative stress, and endothelial dysfunction (for example, through a decrease of the NO production by endothelium), activation of the NLRP3 inflammasome, induced by monosodium urate (MSU) crystals, was revealed in the development of that process [26].

The link between hyperuricemia and changes in cardiac structure was examined in mice. The increase of the UA was followed by increased XO activity in cardiac tissue, which caused cardiomyocyte hypertrophy, myocardial oxidative stress, interstitial fibrosis, and disturbance of diastole relaxation due to activation of S6 kinase beta-1, profibrotic TGF-β1/Smad2/3 signaling. These results improved after the allopurinol administration. Thus, XO may facilitate an aggravation of AF. However, no prospective clinical studies have yet been performed to test the possibility of xanthine oxidase inhibitor's ability to prevent a genesis of AF [29].

Mouse cardiomyocytes were found to express at least 4 UA transporters (UAT): URATv1/GLUT9, ABCG2, MRP4, and MCT9. According to Maharani et al., urate transporters help activate a protein in voltage-dependent Kv1.5 potassium channels. This results in an inducement of ultrarapid delayed rectifier current (/Kur) with the decrease of atrial action potential and, in this way, influencing the development of arrhythmogenic substrate [30].

The inhibition of the UA-influx by a UAT with benzbromarone attenuated the enhancement of Kv1.5 protein expression by decreasing intracellular UA. In contrast, inhibition of ABCG2, the UA-efflux transporter, accelerated an expression of Kv1.5 protein. Accumulated intracellular UA induced cellular damage due to oxidative stress. Blocking the enhanced Kv1.5 protein expression was abolished by the *N*-acetylcysteine antioxidant and apocynin, the inhibitor

of NADPH oxidase. This makes it possible to assume that antioxidants may be a new therapeutical approach in the AF treatment in patients with hyperuricemia [30].

One of the promising approaches in modern-day cardiology is the study of the impact of heat shock proteins (HSP) on the state of the cardiovascular system. HSP is synthesized in all nucleus cells, and its expression is increased during any stressful exposure (inflammation, hypoxia, intoxication). In stressful conditions, heat shock protein 70 (Hsp70) prevents the protein misfolding and the Kv1.5 protein aggregation, which expression is regulated by heat shock factor 1 (HSF1). HSF1 activation and Hsp70 associated increase are crucial factors that help cells overcome stress and reduce the risk of damage [29]. Taufiq et al. researched a UA inducement mechanism for boosting a Kv1.5 expression and revealed how intracellular accumulation of the UA facilitates HSF1 activation and Hsp70 increase. HSF1 is activated by oxidative stress, and HSF1 activation increases HSP expression. It has been proved that an inducement of HSP synthesis could be observed during hyperuricemia [31].

According to various experimental, epidemiological, and cohort observational studies, inflammation plays a vital role in the AF onset and preservation [32, 33]. AF is associated with an elevation of several inflammatory markers in the blood plasma, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP). NLRP3 inflammasome is a multi-protein complex, which consists of NLRP3, ASC, and procaspase-1 enzymes. In addition, NLRP3 inflammasome launches the production of bioactive caspase-1, which contributes to the maturation of active IL-1β and IL-18 [34]. Macrophages and myoblasts release these cytokines as components of the inflammatory response [35].

An increased UA level (more than 400 μmol/L) in the blood serum induces the concretion of monosodium urate (MSU) crystals and directly activates the NLRP3 inflammasome. MSU utilizes caspase-1 by activating the NLRP3 inflammasome, resulting in IL-1β and IL-18 output in the human monocytic cell line (THP1). In an inflammasome-deficient mice model, neutrophil influx induced by MSU was markedly impaired. Moreover, colchicine, the medicine used to prevent the first stage of gout inflammation, can block IL-1β maturation caused by MSU. NLRP3 inflammasome activity was increased in atrial cardiomyocytes of patients with paroxysmal and permanent AF. In addition, NLRP3 and caspase-1 levels in the right atrium were increased in patients with permanent AF [36].

An AF inducement has been demonstrated in a knock-in mouse model, which constantly expressed active NLRP3. MCC950, a selective inhibitor of the NLRP3 inflammasome, interrupts the NLRP3 inflammasome complex assembly and suppresses AF induction. The activation of the NLRP3 inflammasome, specific to cardiomyocytes, induces electrical and structural remodeling of atria, exhibiting abnormal release of Ca^{2+} from the SR, efficient contraction of the atrial effective refractory period, and atrial enlargement. On the contrary, NLRP3 knockdown suppressed the AF induction and restored the normal levels of mRNA, Ryr2, Kcna5, Girk1, and Girk4. This data demonstrates that MSU activates the NLRP3 inflammasome, associated with AF pathophysiology [37].

CRP and TNF-α proinflammatory cytokines participate in cellular signal activation and are associated with fibrosis, apoptosis, and hypertrophy. The level of TNF-α, an inflammatory mediator, was considerably increased in patients with a history of diastolic heart failure (DHF) and AF in a cohort of patients with DHF [37]. TNF-α changed the expression or distribution of connexin 40 and connexin 43 and directly changed the Ca^{2+} processing in cardiomyocytes [38]. Also, it has been revealed that TNF-α increases the apoptosis of cardiomyocytes and myolysis. This leads to the dilation of atria and conduction heterogeneity [39]. The level of circulating CRP is higher in patients with a history of AF than in patients without AF. For patients with permanent AF, the CRP level is higher compared to patients with paroxysmal AF [40]

Performed experimental and clinical studies prove the negative effect of proinflammatory cytokines on AF aggravation. The study showed that mice with increased TNF-α expression had an increased risk of AF aggravation. Furthermore, the influence of proinflammatory cytokines on AF aggravation was estimated in an experiment in dogs. It was concluded that the growth of IL and TNF-α concentrations in plasma significantly increases the risk of AF aggravation and prescription of infliximab, a TNF-α inhibitor, prevents the onset of arrhythmia [4].

Data collected for the last several years indicate thin most cases of hyperuricemia associated with gout are more likely connected with acid underexcretion than overproduction. In total, 300–600 mg (1.8–3.6 mmol) of the UA is excreted in 24 hours. Approximately 95% of the UA is excreted in urine as a result of glomerular filtration. However, almost all UA later undergo subsequent reabsorption of underexposed urate transporters (URAT-1) and organic anion transporters in proximal tubules. After that, it is again secreted in the distal tubules in urine, and later 80 % of the acid is completely reabsorbed into the blood, and 20 % is excreted in the urine. An increase in the UA level in the blood serum influences endothelial cells and vascular smooth muscles, resulting in microvascular kidney damage. As a result, kidneys may have a crucial role in the UA inadequate excretion and thus become a reason for hyperuricemia [6].

Hyperuricemia is significantly associated with AF. In addition, the results of numerous clinical and experimental studies demonstrated an interlink between an increase of UA and the development of arrhythmia with complications [41].

A retrospective study of 49,292 medical records, completed by Japanese scientists Kuwabara M. et al. in 2016 revealed that hyperuricemia is a significant independent and competing risk factor of AF in a healthy person, as well as old age, male sex, high body mass index, low FEV1/FVC ratio, and increased hemoglobin levels [42].

Lots of studies have found a positive correlation between the UA concentration and AF. For example, a prospective cohort study of 123,238 Chinese patients enrolled in the study from 2006 to 2014 showed that high UA concentration and its increase with time was associated with an increased risk of AF. Furthermore, in another cohort study, gout resulting from hyperuricemia was associated with a moderately increased risk of AF [1].

According to the meta-analysis of clinical studies performed by Chinese scientists Chun-Hong Zhang et al. in 2015, the UA increased level in the blood serum was associated with the risk of paroxysmal and persistent AF occurrence in the general population and also in patients subjected to coronary artery bypass surgery. This connection can be explained by the influence of oxidative stress and activation of the systemic inflammatory response [43].

A study of 140 patients, performed by Deshko M.S. et al. in 2015, demonstrated the connection of the higher level of UA in the blood serum in patients with permanent AF, regardless of whether they have AHT and/or CAD, compared with those without arrhythmia. Furthermore, an increase of XO activity facilitated the increase in the UA level, xanthine dehydrogenase conversion in XO (boosting the velocity of synthesis), adenosine triphosphate degradation to adenosine and hypoxanthine (boosting the quantity of substrate), and

also a competitive decrease of the UA excretion in the kidney proximal tubules due to lactic acid increased production [44, 45]. A high level of UA may be an AF predictor. This is confirmed by a large-scale cohort study of 6,308 people in the general population of Norway (Nyrnes A. et al., 2014) [46].

To this date, the treatment of AF appears to be one of the most significant challenges for public health. The results of numerous clinical and experimental studies demonstrated the prognostic significance of the UA level increase to the development of arrhythmia and its complications. Hence, it is necessary to focus on monitoring the UA level in the blood serum in rheumatic patients and decreasing cardiovascular and kidney disease risks. Furthermore, assessing the patient's clinical status and understanding of subtle mechanisms of arrhythmogenesis make it possible to discuss specific treatment courses aligned with a current view of precision medicine.

ADDITIONAL INFORMATION

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