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Hyperuricemia and Risk of Atrial Fibrillation

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Abstract

The association between SUA levels and AF is currently poorly known. We reviewed the literature on the association between AF and hyperuricemia.The association between SUA level and AF has been demonstrated. SUA levels are associated with an increased risk for future AF in both sexes. And elevated SUA levels strongly correlate with an increased incidence of AF in patients with type 2 diabetes mellitus. Moreover, hyperuricemia was in connection with endothelial dysfunction, oxidative stress, systemic inflammatory markers, insulin resistance and LA size.

Introduction

Atrial fibrillation (AF) is a clinically common arrhythmia and preferentially afflicts elderly persons.[1] The main risk factors for AF are complicated and multifactorial. A number of clinical risk factors for the development of AF have been confirmed, including old age, male gender, rheumatic heart disease, hypertension, congestive heart failure, hyperthyroidism, chronic kidney disease and diabetes mellitus. Although the pathophysiology of AF remains incompletely understood, accumulative evidences indicated that oxidative stress and inflammation were involved in the process of atrial remodeling which predisposed patients to AF.[2,3] In addition, the consistent relationship between elevated serum uric acid levels and circulating inflammatory markers has been reported. Serum uric acid (SUA) is the breakdown product of purine catabolism. Increased levels are associated with hypertension, kidney disease, obesity, hyperlipidaemia, diabetes, and cardiovascular disease.The association between SUA levels and AF is currently poorly known. In our previous study, the results also showed that low serum albumin and hyperuricemia were independently correlated with the presence of AF compared with the non-AF group.[4] Previous studies also supported the hypothesis that hyperuricemia causes vascular disease via endothelial dysfunction. It is clear that further studies are needed to determine whether the SUA level increases the risk of AF directly or indirectly.[4,5]

Key Words:
Hyperuricemia, Atrial Fibrillation, Oxidative Stress, Inflammatory.

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None.

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Xanthine Oxidase and Serum Uric Acid

SUA derives from the conversion of hypoxanthine to xanthine and of xanthine to SUA,which reactions are catalyzed by xanthine oxidase. Ischemia and cellular damage can promote xanthine accumulation creating a substrate for xanthine oxidase. This enzyme uses molecular oxygen as electron acceptor and leads to the formation of free radical superoxide anion, then promoting oxidative stress. The highest activity of xanthine oxidase is detected in endothelium, intestine, and liver. Among them, endothelial xanthine oxidase plays a crucial role in the cardiovascular oxidative stress. SUA has emerged as a simple and independent marker of morbidity and mortality in a variety of cardiovascular disease states including coronary artery disease,heart failure and AF. In the pathophysiological conditions, SUA reflects upregulated xanthine oxidase activity. Furthermore, SUA may represent an endogenous signal of cell injury activating the cellular immune response. In fact, SUA has been associated with a pro-inflammatory state in human subjects.[6] Masao Sakabe et al. provided experimental evidence that a xanthine oxidase inhibitor, allopurinol, prevents AF associated with congestive heart failure. This results suggest that xanthine oxidase may play an important role in the formation of AF substrates and enhancement of atrial vulnerability, and might be a novel target of AF therapy. The effect of allopurinol to prevent both electrical and structural remodeling, which has different manifestations, is noteworthy.[7]

Hyperuricemia and Atrial Fibrillation

A possible direct link between SUA and AF has barely been addressed.[8]Several studies have reported an association between SUA and AF, which were summarized in Table 1.[7–12] An increasing body of evidence suggests that SUA may represent a marker of AF risk.

Table 1: Summary of the studies investigating the relationship between SUA and AF

Author (year)	Study design	Patient number	Age, years	Main findings
Letsas et al. [9]	Cross-section	Paroxysmal AF: 45 Persistent AF: 41 Non-AF: 86	Paroxysmal AF: 67.4 ± 8.8 Persistent AF: 71.9 ± 9.9 Non-AF: 61.3 ± 14.7	SUA level was associated with permanent AF (OR = 2.712; 95% CI = 1.327–3.555; p = 0.002).
Liu et al. [10]	Cross-section	451 patients with hypertension — AF: 50 Non-AF: 401	AF: 61.8 ± 9.2 Non-AF: 54.9 ± 12.1	Independent association between SUA level and AF was noted (OR = 1.008; 95% CI = 1.003–1.013; p = 0.002).
Tamariz et al. [11]	Longitudinal cohort	15,382 AF-free patients (1085 cases of new-onset AF during the median follow-up duration of 16.8 years)	45–64 years at enrollment	Baseline SUA level was a predictor of AF (HR = 1.16; 95%CI = 1.06–1.26 per 1 standard deviation of increasing SUA level; p< 0.01). Subgroup analyses showed that baseline SUA levels were associated with AF in blacks and women, but not in whites and men.
Suzuki et al. [12]	Cross-section	AF: 1131 Non-AF: 6024	Male: 57.1 ± 13.8 Female: 60.7 ± 15.2	SUA level was associated with permanent AF Adjusted OR for AF was 1.176 (95% CI = 0.935–1.478) in males and 1.888 (95% CI = 1.278–2.790) in females
Tze-Fan Chao et al. [13]	Longitudinal cohort	AF:2339 (1.9%) Non-AF: 120,185	48.8 ± 10.9 years at enrollment	SUA level was associated with permanent AF Adjusted hazard ratio (95% CI) 1.191 (1.098–1.292); p < 0.001
K. Letsas et al[14]	cross-section	Control (n=48) Paroxysmal AF (n=45) Permanent AF (n=41)	Paroxysmal AF: 67.4 ± 8.8 Permanent AF: 71.9 ± 9.9 Control: 61.3 ± 14.7	SUA level was associated with permanent AF Control:5.1 ± 1.3 Paroxysmal AF:5.7 ± 1.1 Permanent AF: 6.7 ± 1.4 p < 0.001

The association between SUA level and AF has been demonstrated. Moreover, Nyrnes A et al. found that serum uric acid levels in men are higher than in women throughout life, although SUA levels increase after menopause, and that baseline SUA was associated with an increased risk for future AF in both sexes. In addition, the occurrence of AF increases with age, and the fact that SUA levels in women, in contrast to men, increase with age may account for the higher risk estimates seen in women.[8] Furthermore, in a small observational study, Letsas et al. showed a stepwise increase of SUA levels in patients with paroxysmal AF and permanent AF compared to control subjects, while after multivariate analysis, SUA was an independent predictor of permanent AF.[9] Also, in a retrospective observational study of hospitalized patients over 40 years an independent association between high SUA levels and AF (paroxysmal or persistent) was evident.[10] In the ARIC study, a large prospective cohort study, elevated SUA was associated with a greater risk of AF development during the follow-up.[11] In the same line, a Japanese hospital-based cohort study demonstrated an independent association between SUA and AF.[12] Another very recent study showed that SUA levels ≥8 mg/dl was an independent predictor of AF while SUA increased significantly between the last year and the year of the first AF detection suggesting a possible involvement in AF development.[6] Besides, Tze-Fan Chao et al. showed that hyperuricemia was associated with a larger left atrial size and may be a novel risk factor for the development of AF.[13] K. Letsas et al. also found an independent association between increased levels of SUA and permanent AF.[14]

To data, there is few information on the relation between elevated SUA and incident AF in patients with type 2 diabetes mellitus. In a recent, Filippo Valbusa et al. reported that in a group of patients with type 2 diabetes mellitus, AF and hyperuricemia are highly prevalent. Their study demonstrated that elevated SUA levels are strongly associated with an increased incidence of AF in patients with type 2 diabetes mellitus even after adjustment for multiple clinical risk factors for AF. Notably, this association was independent of multiple clinical risk factors for AF.[15]

Serum Uric Acid, Systemic Inflammation and Insulin Resistance

SUA, the final product of purine metabolism catalyzed by xanthine oxidase, has been reported to be correlated with the levels of some inflammatory markers, such as c-reactive protein(CRP), interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor-α.[16] The underlying mechanisms of elevated SUA related to risk of AF are still poorly understood.Hyperuricemia was reported to be associated with endothelial dysfunction, oxidative stress, abnormal high levels of systemic inflammatory markers, and insulin resistance.[16–19] Experimental data have shown that when SUA enters cells via specific transporters (including the fructose transporter), it can act as a pro-oxidant, activating the mitogen-activated protein kinase pathway and nuclear factor k-B and inducing the release of a variety of proinflammatory mediators (e.g., IL-6, IL-8, tumor necrosis factor, and monocyte chemoattractant protein-1) and growth factors.[20-24]

Hyperuricemia frequently occurs in obese subjects with insulin resistance, because insulin stimulates sodium and urate reabsorption in the proximal tubule.[24] Moreover, SUA is frequently increased in hypertension, presumably because of the decrease in renal blood flow stimulating urate reabsorption.[25] Recent studies have indicated that SUA has a direct effect on smooth muscle cell proliferation,[26] endothelial dysfunction and decreasing nitric oxide production as well as local activation of the renin-angiotensin system.[27-29] The greater SUA levels could potentially lead to endothelial dysfunction and the activation of the renin-angiotensin system, which could potentially end in AF.[23]

Xanthine oxidoreductase is a major source of reactive oxygen species production, which has been found to be elevated in both animal and human left atria with AF.[3] In a recent experimental study, the enzymatic activity of xanthine oxidase in left atrial appendages was 4.4 times greater in the AF group compared to the control group.[25] Consequently,animal studies have shown that oxidative stress leads to the development of atrial electrical remodeling,[3,30] which in turn results in reentry and a decrease in nitric oxide production leading to S-nitrosylation of ion channels that can shorten the plateau phase of the action potential causing accelerated repolarization and AF.[31,32]

SUA promotes inflammation through the activation of pro-inflammatory cytokines (eg, IL-1β, IL-6, IL-8, tumor necrosis factor, and monocyte chemoattractant protein 1).On the other hand, it has been shown that SUA may exert antioxidant or pro-oxidant effects and stimulate the innate immune response through CD8+

cells. The level of SUA increases with age in both men and women. Women have lower levels of SUA than men, probably because of the uricosuric effect of estrogen.[33]

In animal experiments, hyperuricaemia activates the renin–angiotensin system and reduces nitric oxide. Both superoxide and nitric oxide may modulate cardiac mechanosensitive ion channels.[34] SUA impaired the ion channel expression through uric acid transporter1(URAT1). SUA at 9mg/dl significantly increased the mRNA level and protein level of Nav1.5, Kv1.5 and HERG channels in HL-1 mouse atrial cells. URAT1 inhibitors restored the SUA inducing the increases of both protein and mRNA level of these ion channels, indicating the involvement of URAT1 to facilitate uric acid-induced electrical remodeling, which may cause AF.[35]

Serum Uric Acid and Left Atrium Dimension

Electrical and structural remodeling of left atrium (LA) is an important process involved in the pathogenesis of AF.[36] An enlarged LA size due to structural modeling is a well-known factor that facilitates the initiation and maintenance of AF. Besides, advanced remodeling of LA (enlarged LA size and worsening substrate) was observed in patients with insulin resistance, such as impaired fasting glucose or diabetes.[37] Futhermore, Tze-Fan Chao et al. found that hs-CRP and insulin resistance were higher and LA diameter was larger in patients with a higher SUA level. It indicated that increased inflammation and insulin resistance may be possible explanations for the relationship between the high SUA level and LA size.[13]

In a porcine atrial tachypacing model of AF, LA xanthine oxidase activity was 4.4 times greater in the paced than in the control group. Superoxide production was reduced by 85% after administration of oxypurinol (a xanthine oxidase inhibitor). Of note, in a similar porcine model, it was demonstrated that after 1 week of rapid atrial pacing the detectable xanthine oxidase was decreased in the left but not in the right atrium, suggesting that the oxidative stress was enhanced only in the left atrium. It can therefore be speculated that LA may be preferentially more sensitive to oxidative stress perhaps due to lower metabolic reserve or increased wall stress. In patients with right or left heart failure it has been demonstrated that hyperuricemia is related to elevated right or left atrial filling pressures. Also, SUA levels have been correlated with more impaired right ventricular systolic function and decreased LA work in patients with heart failure. It would therefore be speculated that SUA metabolism is implicated in atrial remodeling, indicating that increased atrial filling pressures cause structural and electrophysiological abnormalities that facilitate the development and perpetuation of AF.[6]Moreover,chronic heart failure is associated with hyperuricemia, increased circulating markers of inflammation, and oxidative stress. This mechanism is also present in pathogenesis of AF.[38]

Conclusions:

SUA has emerged as an independent marker of AF risk. The association between SUA level and AF has been demonstrated. Baseline SUA was associated with an increased risk for future AF in both sexes. Moreover, elevated SUA levels strongly correlate with an increased incidence of AF in patients with type 2 diabetes mellitus.

Hyperuricemia was in connection with endothelial dysfunction, oxidative stress, abnormal high levels of systemic inflammatory markers, and insulin resistance. And increased inflammation and insulin resistance may be possible explanations for the relationship between the high SUA level and LA size.

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