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Gout and arrhythmias: In search for causation beyond association☆

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ABSTRACT

Gout is a systemic disease, characterized by the formation and deposition of crystals in tissues (mainly in and around the joints) of individuals with elevated serum uric acid levels. Lately, a considerable number of reports relating elevated uric acid and/or gout with rhythm disorders, such as atrial fibrillation, have been published. This review summarizes evidence linking common arrhythmias and hyperuricemia/gout and discusses questions or controversies that surround it. Overall, existing evidence may not be overwhelming, but strongly suggests a positive correlation between uric acid levels and common rhythm disorders. Needless to say that such a link – as a univariate association between the two – is to be expected, given the extensive overlap of risk factors and comorbidities of hyperuricemia/gout and arrhythmias. However, the observed associations seem to persist – in most studies – after extensive adjustment for potential confounders. Still, multivariable analyses of epidemiologically collected data cannot substitute for proof coming from basic and clinical studies. There is obviously a need for further basic research to establish a causal relationship between uric acid effects and arrhythmias, as well as translational studies and clinical trials to investigate the therapeutic implications of such a relationship. Simply put, we are fairly certain that there is association, but proof of causation is what we are still in want of.

Introduction

Uric acid is the end product of the metabolic breakdown of purine nucleotides in humans. At the normal arterial pH of 7.40 most uric acid circulates as the urate anion. Hyperuricemia has been defined as the serum urate concentration (6.8 mg/dL) above which monosodium urate crystals form in vitro at physiological pH and temperature. Gout is a systemic disease, characterized by the formation and deposition of crystals in tissues (mainly in and around the joints) of individuals with elevated serum uric acid (SUA) levels [1]. Although both overproduction and under excretion of uric acid can result in hyperuricemia, the primary cause in patients with gout is under excretion (Fig. 1). Gout is recognized as the most common cause of inflammatory arthritis affecting almost 4% of adults in the USA, with epidemiologic studies pointing towards an increase in incidence and prevalence in both developed and developing countries [2,3]. The typical clinical features of the disease occur as a result of the inflammatory response to urate crystal deposition and include episodes of excruciating pain, usually originating from a single peripheral joint, that alternate with symptom-free periods of variable duration.

Apart from these debilitating symptoms and the progressive joint destruction caused by repeated inflammatory insults, hyperuricemia and gout have been associated with a range of conditions, including cardiovascular disease, ultimately leading to increased mortality [4–6]. Lately, the number of reports relating elevated SUA and/or gout with common rhythm disorders, such as atrial fibrillation (AF), has been increasing. In this review we summarize the evidence to date, exploring the potential link between rhythm disturbances and gout and discuss questions and controversies that surround it. Since hyperuricemia is required for the development of symptomatic gout, we also review studies dealing with this topic and discuss the therapeutic implications of this association. Finally, we attempt to make suggestions as to the future directions of research.

Atrial dysrhythmias

Sinus tachycardia

Sinus tachycardia and high resting heart rates have been associated with high levels of SUA [7]. Cicero et al. analyzed the

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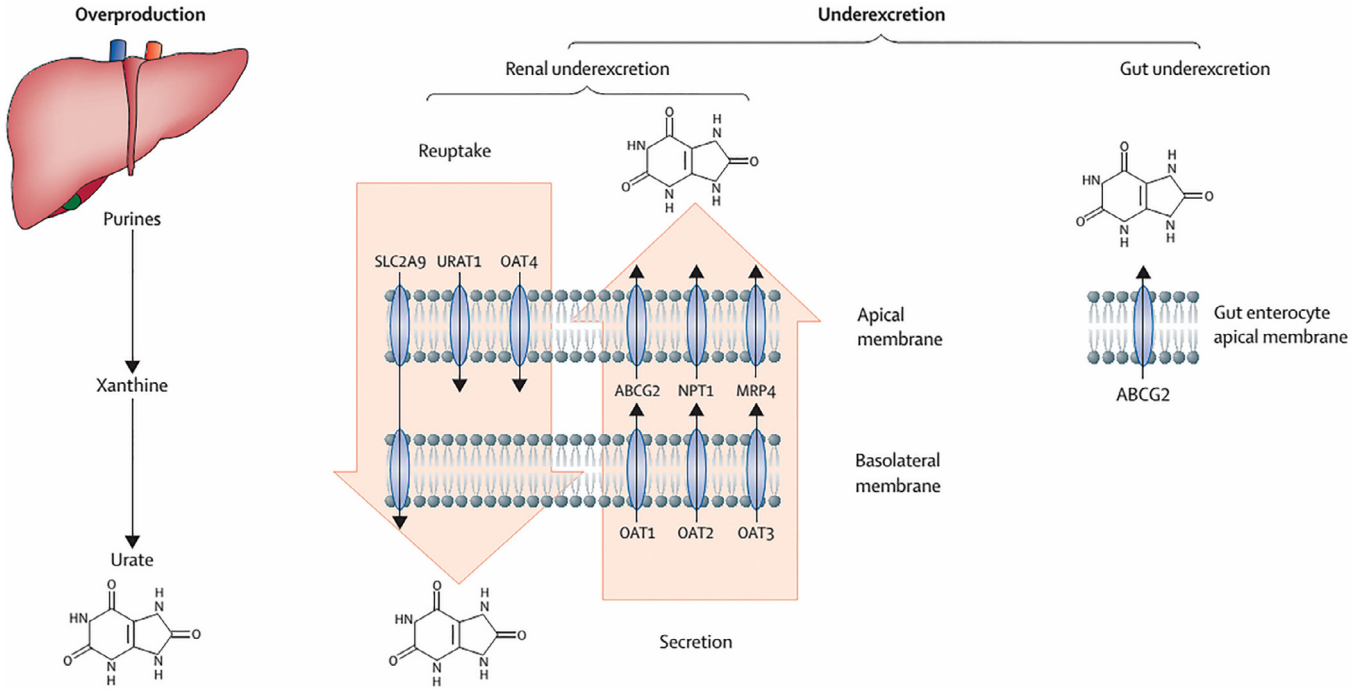

Fig. 1. Mechanisms of hyperuricemia. On the left, overproduction of urate through the purine degradation pathway is a minor contributor to serum urate concentrations. Underexcretion of urate is the dominant cause of hyperuricemia in people with gout. In the center, major components of the renal proximal tubule urate transportasome are clustered according to their role as reuptake transporters of urate from filtered urine or as secretory transporters. On the right, in the gut, variants in ABCG2 with reduced function block excretion and contribute to under-excretion. (From [1], with permission).

data of 1639 individuals that were part of the Brisighella heart study cohort. In the multivariable analysis, after adjustment for various potential confounders, high SUA was independently associated with sinus tachycardia (odds ratio 2.21; 95% confidence interval 1.05–4.16). It should be noted though, that the extensive associations of SUA levels with a range of conditions that might be associated with high heart rates makes it quite difficult to statistically account for all of these potential secondary associations.

Atrial fibrillation

Cross-sectional and case-control studies

One of the first studies reporting an independent association between increased SUA levels and AF came from Letsas et al. [8], who studied 86 consecutive patients with AF (45 with paroxysmal and 41 with permanent AF), seen in an emergency department. The control group consisted of consecutive subjects with no history of arrhythmias that were undergoing a regular routine clinical examination. SUA levels differed significantly between patients with paroxysmal AF, permanent AF and the control group ($P < 0.001$). The multivariable logistic regression analysis showed a significant correlation between SUA and permanent AF, after adjustment for age, gender and statin use (adjusted odds ratio 2.172; 95% confidence interval 1.327–3.555, $P = 0.002$), but not between SUA and paroxysmal AF. Interestingly, this association was independent of C-reactive protein (CRP) levels. Hu et al., while investigating whether the metabolic syndrome is associated with AF and predictors of AF in the elderly hypertensive patients, noticed significantly higher levels of SUA in the AF patients ($P = 0.003$) [9]. However, this association did not persist in the multivariable analysis.

Liu et al. examined this association in patients with essential hypertension but without significant comorbidities or associated conditions that would affect SUA levels [10]. Both in the univariate analysis ($P < 0.001$) and after adjusting for age, hypertension duration, kidney function, interventricular septum thickness and left ventricular posterior wall thickness, SUA was associated with AF (odds ratio 1.008; 95% confidence interval 1.003–1.013, $P = 0.002$).

In 2012 Suzuki et al. reported a gender-specific relationship between AF and SUA [11]. The investigators utilized information from a single hospital database comprising data from 7155 patients and reported that the prevalence of AF significantly increased from the lowest to the highest tertile of SUA in both men and women ($P < 0.001$). After adjustment for several interacting variables including age, renal function, hypertension, heart failure, organic heart disease, stroke and certain medications the association remained independent only in women. Sun et al. explored the relationship between SUA and AF in a larger sample of a rural population in China [12]. Data from 11,338 participants (≥35 years of age) were collected during a single clinic visit that included an echocardiographic evaluation. Hyperuricemia was associated with a significantly higher prevalence of AF (2.4 vs. 1.0%; $P < 0.001$). After adjustment for other cardiovascular and AF risk factors, the association between SUA and AF remained significant (odds ratio = 1.94; 95% confidence interval 1.26–3.00, $P = 0.003$). However (in contrast to the findings of the previous study) when gender was considered the independent association remained significant only in men ($P = 0.003$) and not in women ($P = 0.235$).

Tekin et al. focused on patients with ischemic heart failure and ejection fraction ≤40% [13]. The 363 patients included in the trial were divided in two groups: patients with chronic AF ($n = 78$) and patients with normal sinus rhythm ($n = 285$). Logistic regression analysis showed that SUA was significantly and independently associated with AF (odds ratio 1.27; 95% confidence interval 1.06–1.52, $P = 0.01$). Mantovani et al. studied the relationship between elevated SUA and AF in hospitalized patients with type 2 diabetes [14]. The majority of admissions were for decompensated diabetes, diabetic foot ulcers and infections. Patients with malignancies were excluded. Since the patients were hospitalized, detailed information for several parameters was available (allowing for multiple adjustments for potential confounders). Out of 842 patients,

91 (10.8%) had permanent or persistent AF (none had paroxysmal AF) and 243 (28.9%) had hyperuricemia. In univariable logistic regression analysis, hyperuricemia was associated with a 3.5-fold higher risk of prevalent AF (unadjusted odds ratio 3.41; 95% confidence interval 2.19–5.32, $P < 0.001$). The correlation persisted even after adjustment for multiple AF risk factors and potential confounders. Kuwabara et al. undertook a different approach and attempted to investigate the relationship in an apparently healthy general population [15]. They performed a retrospective cross-sectional study using the data collected from subjects that underwent an annual regular health check-up at St. Luke's International Hospital, in Tokyo, between January 2004 and June 2010. After multiple adjustments, the regression analysis showed that each 1 mg/dl increase in SUA was associated with 35% higher odds for AF (95% confidence interval 22–50%). Interestingly, smoking was not independently associated with AF. After excluding subjects with chronic kidney disease, hypertension, dyslipidemia, diabetes, those on current medication for hyperuricemia and/or gout, as well as those with a history of cardiovascular disease, each 1 mg/dl increase in SUA was associated with 53% higher odds for AF (95% confidence interval 21–92%), following multivariable adjustments. The odds ratio of AF for hyperuricemia was 2.75 (95% confidence interval 2.10–3.60) in all the subjects and 3.19 (95% confidence interval 1.81–5.62) in the subjects of the second cohort.

Another large, single center, cross-sectional trial conducted in Japan included 285,882 individuals that underwent routine screening from January 1979 to December 2013 [16]. Those receiving treatment for hyperuricemia were excluded from analysis. Subjects were stratified into deciles of SUA and AF prevalence was calculated for each decile. Multivariable logistic regression analysis showed that SUA was independently associated with AF in both men and women ($P < 0.001$). As in some of the previous studies, high SUA levels in women showed a stronger association with AF than did in men (adjusted odds ratio 4.71 versus 2.60). The stratification into deciles allowed for the observation that low SUA levels (< 4.3 mg/dl in men and < 3.5 mg/dl in women) were also associated with an increased risk of AF.

Recently, Wakula et al. hypothesized that in patients with paroxysmal AF several biomarkers, including SUA, would be elevated as compared to patients in sinus rhythm [17]. Patients with dual-chamber pacemakers and activated atrial monitoring participated in the study. Depending on the event history of their pacemaker at the date of inclusion two groups were identified. A group with atrial high rate episodes (AHRE) $\geq$6 min in duration and a group with no AHRE. From 49 patients with detected AHRE, 19 with confirmed paroxysmal AF and the highest incidence and longest AHRE episodes were selected and compared with 20 patients with no AHRE and no history of atrial arrhythmias. Univariate analysis showed that levels of SUA were not different in the AHRE and no AHRE subgroups (Wilcoxon test $P = 0.2608$). However, the size of the cohort limits the statistical power of the analysis. In addition, and similar to all case-control design studies, there is always the risk of selection bias. Table 1 summarizes all cross-sectional and case-control studies associating SUA with AF.

Prospective cohort studies

The first prospective study to address this issue was based on a large community cohort of 15,382 AF-free black and white men and women between 45 and 64 years of age sampled from 4 United States communities [18]. The participants were part of the "Atherosclerosis Risk In Communities" (ARIC) study population. The primary outcome was incident AF. The diagnosis was obtained from electrocardiograms (ECGs) during scheduled visits, from hospital discharge records and/or death certificates. During a median follow-up of 16.8 years AF was detected in 1085 participants. Its incidence was positively associated with SUA levels, with an almost threefold risk difference between the lowest and the greatest quartile of SUA (3/1,000 person-years versus 8/1,000 person-years, $P < 0.01$). After multivariable adjustment, SUA remained significantly associated with the risk of incident AF (hazard ratio 1.16; 95% confidence interval 1.06–1.26 per one standard deviation). However, this relation differed by race and gender. Baseline SUA was associated with incident AF in blacks but not in whites and in women but not in men. Censoring the analysis for subjects that developed heart failure and myocardial infarction (MI) before developing AF, attenuated the relation between SUA and AF (hazard ratio 1.07; 95% confidence interval 0.97–1.17 per one standard deviation), and indicated that the association can be, at least partially, explained by the increased risk of other cardiovascular diseases.

In another cohort study, from Taiwan [19], a history of one or more episodes of gouty arthritis, over a mean follow-up of 6.3 years, was associated with higher risk of AF (2.1% versus 1.7% in controls, $P < 0.001$). Adjustments for age and gender did not alter the significant association with new-onset AF (hazard ratio 1.191; 95% confidence interval 1.098–1.292, $P < 0.001$). Of note, however, is the low adherence to evidence-based treatment of symptomatic gout, suggesting that a considerable percentage patients was not treated with uric acid-lowering agents [20]. The same year Valbusa et al. reported that elevated SUA levels were strongly associated with an increased incidence of AF in patients with type 2 diabetes [21]. A random sample of 400 diabetic patients (mean age 65 years), free of atrial flutter/AF at baseline, was followed for 10 years. Hyperuricemia was present in 73 patients. During follow-up 42 cases of AF were recorded. Increased SUA l was associated with an increased risk of incident AF (odds ratio 2.43, 95% confidence interval 1.8–3.4, $P < 0.0001$ per SD increase in SUA level). After adjustments for several cardiovascular and AF risk factors, electrocardiographic features and use of diuretics and allopurinol, the association remained significant (adjusted odds ratio 2.44, 95% confidence interval 1.6 to 3.9, $P < 0.0001$). The results remained largely unchanged even when patients with previous coronary heart disease or heart failure were excluded from the analysis.

Chuang et al. sought to investigate the prospective relationship between hyperuricemia and AF in a cohort of elderly (65 years of age and older) Taiwanese people [22]. Data collected during a nationwide survey from 1485 non-institutionalized individuals, free at AF were analyzed for this purpose. Over a median follow-up of 9.16 years, hyperuricemia was associated with a significantly higher AF incidence rate ($P = 0.049$).

The Tromso study investigated the association between SUA and AF incident in a general population of white north-European descent [23]. Among 6308 participants, AF incidence was 7.26 per 1000 person-years (95% confidence interval 6.36–8.16) in women and 9.60 (95% confidence interval 8.56–10.64) in men. The mean follow-up period was 10.8 years. In the multivariable analysis, one standard deviation of increase in SUA was associated with a risk increment of 17% in men and 40% in women (although the association appeared stronger in women, interaction with gender was not significant, $P = 0.46$). Including C-reactive protein in the covariates did not change the results, implying that the association, at least in the present study, was not driven by inflammatory pathways.

Kuo et al., focused specifically on patients with gout in a study with a mixed design (combining case-control/cross-sectional/cohort studies characteristics) [20]. They used data from the Clinical Practice Research Data-link database in United Kingdom to examine the risk of AF, at the time of first diagnosis of gout, compared with randomly matched controls. A total of 45,328 gout patients and an equal number of controls were entered in the analysis. The proportion of individuals having AF at the time of the index date was significantly higher in gout patients than in controls (7.42% versus 2.83%, $P < 0.001$). After considering several covariates, gout was still associated with increased odds for AF

Table 1
Summary of cross-sectional and case-control studies associating serum uric acid (SUA) with atrial fibrillation (AF).

Author [reference number]	Study design	Population under study	Number of patients with AF	Total population	Main findings
Letsas et al. [8]	Cross-sectional	Paroxysmal and persistent AF	86	130	SUA independent predictor of permanent AF
Hu et al. [9]	Cross-sectional	Metabolic syndrome	125	2055	High SUA was associated with AF
Liu et al. [10]	Cross-sectional	Essential hypertension	50	450	SUA independent predictor of AF
Suzuki et al. [11]	Cross-sectional	Single hospital database	1131	7155	SUA independent predictor of AF in women
Sun et al. [12]	Cross-sectional	Rural population in China	139	11,338	SUA independent predictor of AF in men
Tekin et al. [13]	Cross-sectional	Patients with ischemic heart failure	78	363	SUA independent predictor of AF
Mantovani et al. [14]	Cross-sectional	Hospitalized patients with type 2 diabetes	91	842	SUA independent predictor of AF
Kuwabara et al. [15]	Cross-sectional	Healthy individuals	62	49,294	SUA independent predictor of AF
Kawasoe et al. [16]	Cross-sectional	General population	3430	285,882	SUA independent predictor of AF
Wakula et al. [17]	Case-control	Patients with dual-chamber pacemakers and paroxysmal AF	19	39	SUA not associated with AF

Table 2
Summary of prospective cohort studies associating serum uric acid (SUA) with atrial fibrillation (AF).

Author [reference number]	Population under study	Number of patients with AF	Total population	Mean follow-up (years)	Main findings
Tamariz et al. [18]	General population between 45 and 64 years of age	1083	15,382	16.8	SUA independently associated with AF risk in blacks but not in whites and in women but not in men
Chao et al. [19]	Patients with hyperuricemia	2339	122,524	6.3	Hyperuricemia a significant risk factor for new-onset AF
Valbusa et al. [21]	Patients with type 2 diabetes	42	400	10	SUA independently associated with incident AF
Chuang et al. [22]	Elderly population in Taiwan	90	1485	9.16	Hyperuricemia independently associated with AF
Nyrnes et al. [23]	General population of white north-European descent	572	6308	10.8	SUA independently associated with risk of AF
Kuo et al. [20]	Patients with gout	5856	90,656	9	Gout independently associated with a higher risk of AF
Kim et al. [24]	Patients with gout	3476	280,060	2	Gout independently associated with a modestly increased risk of incident AF

(adjusted odds ratio 1.45; 95% CI 1.29–1.62). During a median follow-up of 9 years, at all times since the index date, the cumulative probability for incident AF was significantly higher in gout patients than in controls (log-rank test $P < 0.001$). The adjusted hazard ratio was 1.09 (95% confidence interval 1.03–1.16). Hazard ratio estimates were similar in both men and women.

The correlation between AF and gout was also studied by Kim et al. [24]. Two different non-gout populations were selected as controls. The primary comparison was made with a population of osteoarthritis patients. Osteoarthritis was selected to minimize confounding by obesity, comorbidities and health care utilization intensity, as these characteristics are similar to those of the gout group. The secondary comparison was made with a group of patients who had no diagnosis of gout at baseline. The same exclusion criteria were applied in both comparison groups. The final study cohort included 70,015 gout and 210,045 osteoarthritis patients. The mean follow-up time was 2.1 years for gout and 2.0 years for osteoarthritis patients. The rate of incident AF was 7.19 per 1,000 person-years in gout and 5.87 per 1,000 person-years in osteoarthritis patients. After adjusting for several variables the hazard ratio of AF associated with gout was 1.13 (95% CI 1.04–1.23). The secondary comparison was made between 91,976 gout patients and 275,928 non-gout patients. After adjusting for more than 35 covariates, the risk of incident AF associated with gout (hazard ratio 1.21, 95% CI 1.11–1.33) remained increased in gout compared to non-gout. The authors concluded that gout was associated with a modestly increased risk of incident AF compared to osteoarthritis and non-gout. Due to the substantial consequences of AF, this association might have an important impact on the gout population. Table 2 summarizes all prospective-cohort studies associating elevated SUA and/or gout with AF.

Meta-analyses

Three meta-analyses have sought to define the relationship between SUA and AF. In 2013 Tamariz et al. searched the MEDLINE database (from 1966–2013) for relevant publications [25]. Six cross-sectional and three cohort studies met their eligibility criteria. . In the cross-sectional studies, 1603 individuals with AF were compared with 6327 individuals without AF. The pooled standardized mean difference of SUA for those with AF was 0.42 (95% CI 0.27–0.58). The three cohort studies included 138,306 individuals without AF at baseline and 3466 individuals that developed AF over a median follow-up of 12 years. The median age of the population was 54 years. The pooled relative risk of incident AF for those with high SUA was 1.67 (95% confidence interval 1.23–2.27). The authors concluded that there is a clear and strong association between AF and elevated SUA. What was not clear is whether SUA represents simply a disease marker or a treatment target.

A few years later, in another meta-analysis, Xu et al. included 7 cohort studies with a total of 146,792 participants [26]. The literature was identified after electronic searches in PubMed, Embase and Web of Science databases. Five studies assessed the impact of hyperuricemia on new-onset AF incidence and two studies assessed the impact of hyperuricemia on AF recurrence in AF patients after catheter ablation. Meta-analysis of all 7 studies showed that hyperuricemia was significantly and independently associated with increased risk of AF (adjusted relative risk 1.80, 95% confidence interval 1.37–2.38, $P < 0.001$). Hyperuricemia showed a significant association with increased risk of both new-onset AF (adjusted relative risk 1.66, 95% confidence interval 1.22–2.26, $P = 0.001$) and AF recurrence (adjusted RR = 2.07, 95%confidence interval 1.61–2.67, $P < 0.001$).

The most recent of the three meta-analyses included only prospective studies [27]. Electronic searches of PubMed and Embase databases and manual searches of selected journals were concluded on October 2016. Six studies involving a total of 426,159 participants were finally selected. The follow-up ranged from 2 to 16.8 years. Hyperuricemia was significantly associated with an increased risk of AF (pooled relative risk 1.49; 95%CI 1.24–1.79, $P < 0.001$). In a sensitivity analysis omitting each study sequentially did not alter the pooled risk estimates in any significant way.

Atrial fibrillation recurrence after ablation procedures

The prognostic significance of increased SUA levels in AF ablation outcomes was only explored in two studies. Another two studies focusing on other parameters presented relative data (baseline SUA values were acquired and analyzed). An initial observation of such an interaction was reported by Letsas et al. [28]. The authors sought to investigate the impact of body mass index on the efficacy and safety of radiofrequency catheter ablation of AF. The data of 226 consecutive patients (183 males) with highly symptomatic, paroxysmal or persistent AF that underwent pulmonary vein isolation (PVI) were retrospectively analyzed. Patients with AF recurrence were more likely to have, among others, increased SUA levels ($P = 0.008$). In univariate Cox regression analysis, SUA was one of the predictors of AF recurrence (hazard ratio 1.194; 95% confidence interval 1.017–1.402, $P = 0.030$). In multivariable Cox regression analysis, fibrinogen and SUA (hazard ratio 1.167; 95% confidence interval 1.000–1.361, $P = 0.05$) were the only independent predictors of AF recurrence. He et al. analyzed data of 330 patients with paroxysmal AF that underwent PVI [29]. Patients were categorized into quartiles on the basis of their pre-operative SUA. From the lowest quartile to the highest quartile, the recurrence rates were 16.0%, 26.4%, 28.3%, and 29.3%, respectively ($P = 0.014$). After adjustments for several factors there was still an increased risk of recurrence of AF in subjects in the highest quartile of SUA compared with subjects in the lowest quartile (hazard ratio 2.804; 95% confidence interval 1.466–5.362, $P = 0.002$). A positive correlation was also reported by Canpolat et al. [30]. A cryoablation procedure was performed on 363 patients with symptomatic paroxysmal atrial fibrillation. Similar to the previous study, they were categorized into quartiles on the basis of their pre-procedural SUA. Recurrence rates from the lowest to the highest quartiles were 2.9%, 7.4%, 11.8%, and 77.9%, respectively ($P < 0.001$). Following multivariable Cox proportional hazard regression analysis, pre-ablation SUA level (hazard ratio 1.96; 95% confidence interval 1.49–2.59, $P < 0.0001$) was among the independent predictors of AF recurrence. On the other hand, Guo et al., who explored the impact of neutrophil/lymphocyte ratio on the prognosis of lone AF patients after catheter ablation, reported that SUA was not correlated with recurrence of the arrhythmia [31].

Ventricular arrhythmias

In terms of the relationship between increased SUA levels and ventricular arrhythmias, the evidence is sparse. From a handful of studies, only one addressed this issue as per protocol with the rest providing indirect evidence of a possible link. As early as 1985, while investigating a potential arrhythmogenic effect of diuretic usage, McDonald et al. noticed a relationship between SUA and ventricular ectopy [32]. The authors speculated that this might be attributed either to the drugs themselves, the comorbidities of the studied population or, alternatively, this could represent a direct causal effect on the ventricular myocardium. Yamada et al. investigated the association between increased SUA levels and the occurrence of ventricular tachycardia (VT) in patients with left ventricular hypertrophy [33]. In this small observational study, 167 individuals with echocardiographic evidence of hypertrophy (interventricular septum and posterior wall thickness >12 mm) were divided in two groups based on whether VT (defined as 5 or more consecutive ventricular beats) was detected or not on a 24 h ECG recording. The multivariable regression analysis showed that SUA was the only independent factor associated with the appearance of VT (odds ratio, 1.61; 95% confidence interval 1.18–2.22; $P < 0.01$). Recently, Singh and Cleveland investigated whether allopurinol use was associated with a reduction in the risk of ventricular arrhythmias [34]. For this purpose a random sample of Medicare beneficiaries was utilized. 28,775 cases of new allopurinol use were studied, with gout as the underlying diagnosis in 74% of cases. Multivariably adjusted analyses revealed that, compared to non-use, allopurinol use was associated with a hazard ratio of ventricular arrhythmia of 0.82 (95% confidence interval 0.76–0.90) and longer use durations were significantly associated with lower multivariate-adjusted hazard ratio [1–180 days, 0.96 (95% confidence interval 0.85–1.08); 181 days to 2 years, 0.76 (95% confidence interval 0.68–0.85); and >2 years, 0.72 (95% confidence interval 0.60–0.87)]. Notably, this was also the case when the analysis was limited to patients not receiving anti-arrhythmic or cardio-protective medications. In fact, for patients without coronary artery disease, the hazard reduction was 38% versus 13% for patients with coronary artery disease. Adjustments for known risk factors produced similar results. It seems that long term allopurinol administration (>6 months) affects pathophysiologic pathways attenuating the vulnerability of the ventricular myocardium to arrhythmia, presumably via a concomitant decrease in SUA and not (at least not only) via an unidentified direct anti-arrhythmic action (in which case the results would have been apparent immediately upon treatment initiation).

Pathophysiologic considerations

Despite the major progress made during the last decade in the understanding of the pathogenesis of gout, it is still unclear (whether and) how uric acid can promote AF induction and its maintenance. Since evidence for this association comes primarily from epidemiologic studies, one can only speculate about the pathophysiologic pathways connecting the two disease states.

Theoretically, both inflammatory-dependent and inflammatory-independent mechanisms might play a role (Fig. 2) [35]. Central to the inflammatory-dependent mechanisms is the activation of the nucleotide-binding domain leucine-rich repeat-containing protein 3 (NLRP3)-inflammasome resulting in the production and release of interleukin-1β (IL-1β). Secreted IL-1β can stimulate the proliferation and differentiation of fibroblasts to myofibroblasts, which in turn release large amount of cytokines, including transforming growth factor β1 (TGF β1) promoting fibrosis. Atrial fibrosis could alternatively (or in parallel) be promoted by the effect of reactive oxygen species on the Ca^{2+}-permeable cation channel TRPM7 [36]. Whatever the case may be, structural remodeling facilitates the development of re-entrant circuits and the perpetuation of the arrhythmia. Inflammation-independent pathways can influence the action potential duration of the atrial cells through up-regulation of Kv1.5 channel proteins, increasing the ultra-rapid delayed rectifier potassium current (I_{Kur}) [37]. In addition IL-1β can directly suppress the L-type Ca^{2+} current ($I_{Ca,L}$) via its action on IL-1 receptors [38]. Both effects (augmented I_{Kur} and reduced $_{ICa,L}$ currents) might result in a shortening of action potential duration providing yet another substrate for maintaining AF.

Electrical remodeling can also be mediated by the interaction between the NLRP3-inflammasome and the sarcoplasmic reticulum Ca^{2+}-ATPase that promotes delayed afterdepolarizations and thus, electrical instability [39,40]. Other possible mechanisms might involve the renin-angiotensin-aldosterone-system [41]. However,

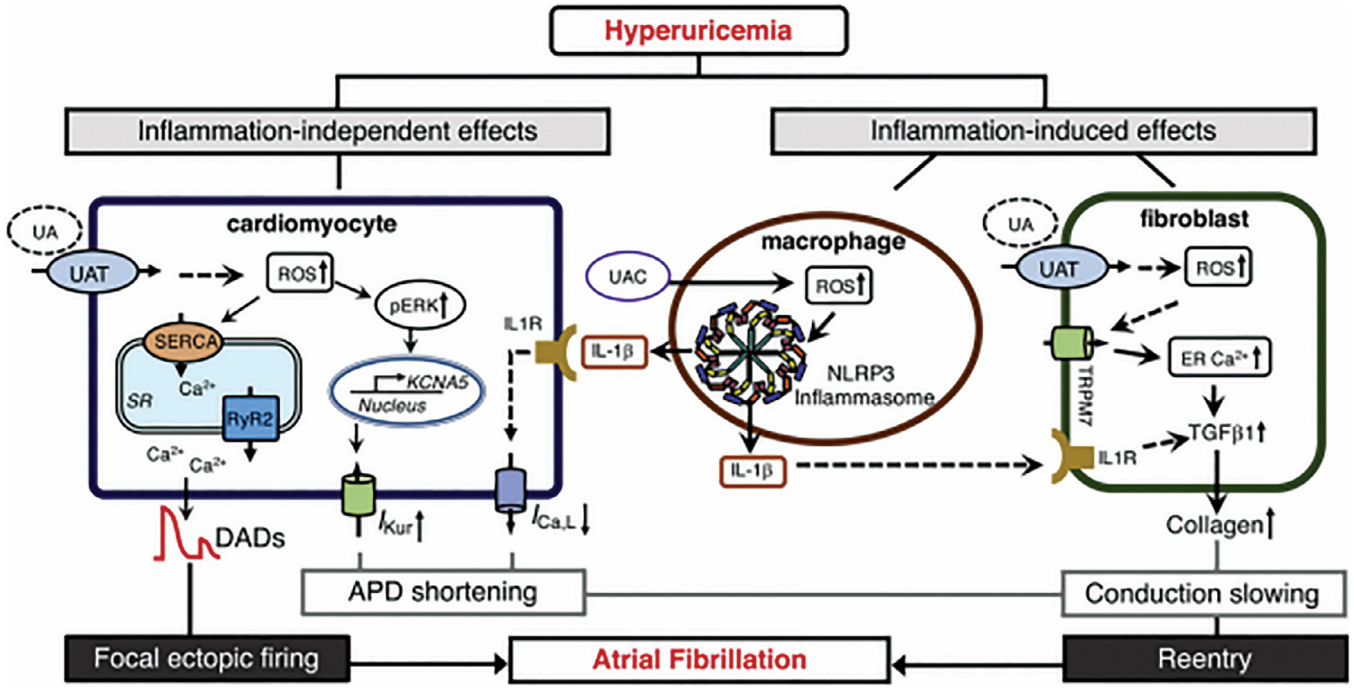

Fig. 2. Putative mechanisms of hyperuricemia-induced atrial fibrillation. APD, action potential duration; DADs, delayed afterdepolarizations; ER, endoplasmic reticulum; I_{Kur}, atrial ultra-rapid delayed rectifier potassium current; $I_{Ca,L}$, L-type Ca^{2+} current; IL-1β, interleukin-1β; ILR, interleukin receptor; KCNA5, gene encoding the voltage-gated potassium channel subfamily A, member 5; NLRP3, nucleotide-binding domain leucine-rich repeat-containing protein 3; RyR2, ryanodine receptor type-2; SERCA, sarcoplasmic reticulum (SR) Ca^{2+}-ATPase; ROS, reactive oxygen species; TGF β1, transforming growth factor β1; pERK, phosphorylated (activated) extracellular signal-regulated kinase; UA, uric acid; UAC, uric acid crystal; UAT, uric acid transporter. Solid lines indicate proven mechanisms, whereas dash lines indicate putative pathways. (Modified from [35], with permission).

one should keep in mind that AF has a complex pathophysiologic background. The discussed pathophysiologic pathways are a conceptual exercise that tries to link the limited available data from animal studies and a hypothesis to an end result.

Therapeutic implications and future perspectives

When considering the presented studies collectively, it becomes apparent that hyperuricemia /gout and cardiovascular disease share several risk factors. Individuals with hyperuricemia/gout should, therefore, be systematically screened for cardiovascular diseases and risk factors, which should be addressed as an important part of their management. Implementation of the current guidelines, with a focus on urate-lowering therapies and close monitoring of treatment targets should help improve outcomes – although this has yet to be persuasively and rigorously shown in clinical studies, especially as far as arrhythmias are concerned. Of note, there is evidence of poor adherence on the part of involved physicians to evidence-based treatment of these conditions [20,42].

Regarding the association between hyperuricemia/gout and arrhythmias, despite the relatively numerous epidemiologic studies addressing the issue, there is a striking paucity of trials of the effects of pharmacologic interventions on clinical outcomes. Consequently, there is an unmet need for new studies, preferably in the form of large randomized control trials, in order to examine the effect of urate-lowering therapies on different arrhythmias, test the hypothesis of a cause-effect relationship between hyperuricemia and rhythm disturbances and elucidate the pathophysiology of a potential beneficial role of such treatments.

Since the bulk of the epidemiologic studies suggest that increased SUA levels are independently associated with the risk of AF, it is conceivable that allopurinol and other urate-lowering agents could be tested for the prevention of incident AF in patients with asymptomatic hyperuricemia and comorbid conditions (including patients after coronary bypass graft surgery) or for prevention of AF recurrence after ablation procedures. Another large patient group where quality data are sparse involves patients with CAD. Ventricular arrhythmias are a major cause of morbidity and mortality in CAD patients and, given the high prevalence of CAD, even modest correlations between SUA levels and ventricular arrhythmias – and, more importantly, similarly modest therapeutic effects – could be of significant clinical impact.

Finally, more data are necessary not only from the bedside but also from the bench. Putative pathways of actions, such as those proposed by Li and Dobrev (Fig. 2) [35] or by Maharani et al. [41], as well as others as yet unknown, should be scrutinized in an effort to discover the molecular mechanisms that could underlie the link between hyperuricemia and arrhythmia, if such mechanisms really do exist.

Conclusion

Existing evidence may not be overwhelming, but strongly suggests a positive correlation between SUA levels and common rhythm disorders. Needless to say that such a link – as a univariate association between the two – is to be expected, given the extensive overlap of risk factors and comorbidities of hyperuricemia/gout and arrhythmias. However, the observed associations seem to persist – in most studies – after extensive adjustment for potential confounders. Still, multivariable analyses of epidemiologically collected data are just mathematical tools and cannot, under any circumstances, substitute proof coming from basic and clinical studies. There is obviously a need for further basic research to establish a causal relationship between uric acid effects and arrhythmias, as well as translational studies and clinical trials to investigate the therapeutic implications of such a relationship.

Simply put, we are fairly certain that there is association, but proof of causation is what we are still in want of.

References

[1] Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet. 2016;388(10055):2039–52.
[2] Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011;63(10):3136–41.
[3] Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol 2015;11(11):649–62.
[4] Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med 2017;15(1):123.
[5] Feig DI, Kang D-H, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359(17):1811–21.
[6] Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation 2007;116(8):894–900.
[7] Cicero AF, Rosticci M, Reggi A, Derosa G, Parini A, Grandi E, et al. Relationship between serum uric acid and electrocardiographic alterations in a large sample of general population: data from the Brisighella heart study. High Blood Press Cardiovasc Prev 2015;22(2):129–34.
[8] Letsas KP, Korantzopoulos P, Filippatos GS, Mihas CC, Markou V, Gavrielatos G, et al. Uric acid elevation in atrial fibrillation. Hellenic J Cardiol 2010;51(3):209–13.
[9] Hu YF, Chen SA, Yeh HI. Metabolic syndrome does not impose greater atrial fibrillation risk in elderly hypertensive patients. Acta Cardiol 2010;65(6):653–9.
[10] Liu T, Zhang X, Korantzopoulos P, Wang S, Li G. Uric acid levels and atrial fibrillation in hypertensive patients. Intern Med 2011;50(8):799–803.
[11] Suzuki S, Sagara K, Otsuka T, Matsuno S, Funada R, Uejima T, et al. Gender-specific relationship between serum uric acid level and atrial fibrillation prevalence. Circ J 2012;76(3):607–11.
[12] Sun GZ, Guo L, Wang J, Ye N, Wang XZ, Sun YX. Association between hyperuricemia and atrial fibrillation in rural China: a cross-sectional study. BMC Cardiovasc Disord 2015;15:98.
[13] Tekin G, Tekin YK, Erbay AR, Turhan H, Yetkin E. Serum uric acid levels are associated with atrial fibrillation in patients with ischemic heart failure. Angiology 2013;64(4):300–3.
[14] Mantovani A, Rigolon R, Pichiri I, Pernigo M, Bergamini C, Zoppini G, et al. Hyperuricemia is associated with an increased prevalence of atrial fibrillation in hospitalized patients with type 2 diabetes. J Endocrinol Invest 2016;39(2):159–67.
[15] Kuwabara M, Niwa K, Nishihara S, Nishi Y, Takahashi O, Kario K, et al. Hyperuricemia is an independent competing risk factor for atrial fibrillation. Int J Cardiol 2017;231:137–42.
[16] Kawasoe S, Kubozono T, Yoshifuku S, Ojima S, Oketani N, Miyata M, et al. Uric acid level and prevalence of atrial fibrillation in a Japanese general population of 285,882. Circ J 2016;80(12):2453–9.
[17] Wakula P, Neumann B, Kienemund J, Thon-Gutschi E, Stojakovic T, Manninger M, et al. CHA2DS2-VASc score and blood biomarkers to identify patients with atrial high-rate episodes and paroxysmal atrial fibrillation. Europace 2017;19(4):544–51.
[18] Tamariz L, Agarwal S, Soliman EZ, Chamberlain AM, Prineas R, Folsom AR, et al. Association of serum uric acid with incident atrial fibrillation (from the Atherosclerosis Risk in Communities [ARIC] study). Am J Cardiol 2011;108(9):1272–6.
[19] Chao TF, Hung CL, Chen SJ, Wang KL, Chen TJ, Lin YJ, et al. The association between hyperuricemia, left atrial size and new-onset atrial fibrillation. Int J Cardiol 2013;168(4):4027–32.
[20] Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Impact of gout on the risk of atrial fibrillation. Rheumatology (Oxford) 2016;55(4):721–8.
[21] Valbusa F, Bertolini L, Bonapace S, Zenari L, Zoppini G, Arcaro G, et al. Relation of elevated serum uric acid levels to incidence of atrial fibrillation in patients with type 2 diabetes mellitus. Am J Cardiol 2013;112(4):499–504.
[22] Chuang SY, Wu CC, Hsu PF, Chia-Yu Chen R, Liu WL, Hsu YY, et al. Hyperuricemia and incident atrial fibrillation in a normotensive elderly population in Taiwan. Nutr Metab Cardiovasc Dis: NMCD 2014;24(9):1020–6.
[23] Nyrnes A, Toft I, Njolstad I, Mathiesen EB, Wilsgaard T, Hansen JB, et al. Uric acid is associated with future atrial fibrillation: an 11-year follow-up of 6308 men and women–the Tromso Study. Europace 2014;16(3):320–6.
[24] Kim SC, Liu J, Solomon DH. Risk of incident atrial fibrillation in gout: a cohort study. Ann Rheum Dis 2016;75(8):1473–8.
[25] Tamariz L, Hernandez F, Bush A, Palacio A, Hare JM. Association between serum uric acid and atrial fibrillation: a systematic review and meta-analysis. Heart Rhythm 2014;11(7):1102–8.
[26] Xu X, Du N, Wang R, Wang Y, Cai S. Hyperuricemia is independently associated with increased risk of atrial fibrillation: a meta-analysis of cohort studies. Int J Cardiol 2015;184:699–702.
[27] Zhang CH, Huang DS, Shen D, Zhang LW, Ma YJ, Wang YM, et al. Association between serum uric acid levels and atrial fibrillation risk. Cell Physiol Biochem 2016;38(4):1589–95.
[28] Letsas KP, Siklody CH, Korantzopoulos P, Weber R, Burkle G, Mihas CC, et al. The impact of body mass index on the efficacy and safety of catheter ablation of atrial fibrillation. Int J Cardiol 2013;164(1):94–8.
[29] He XN, Li SN, Zhan JL, Xie SL, Zhang ZJ, Dong JZ, et al. Serum uric acid levels correlate with recurrence of paroxysmal atrial fibrillation after catheter ablation. Chin Med J 2013;126(5):860–4.
[30] Canpolat U, Aytemir K, Yorgun H, Sahiner L, Kaya EB, Cay S, et al. Usefulness of serum uric acid level to predict atrial fibrillation recurrence after cryoballoon-based catheter ablation. Europace 2014;16(12):1731–7.
[31] Guo X, Zhang S, Yan X, Chen Y, Yu R, Long D, et al. Postablation neutrophil/lymphocyte ratio correlates with arrhythmia recurrence after catheter ablation of lone atrial fibrillation. Chin Med J 2014;127(6):1033–8.
[32] McDonald CJ, Hui SL, Tierney WM. Diuretic-induced laboratory abnormalities that predict ventricular ectopy. J Chronic Dis 1986;39(2):127–35.
[33] Yamada S, Suzuki H, Kamioka M, Kamiyama Y, Saitoh S, Takeishi Y. Uric acid increases the incidence of ventricular arrhythmia in patients with left ventricular hypertrophy. Fukushima J Med Sci 2012;58(2):101–6.
[34] Singh JA, Cleveland J. Allopurinol and the risk of ventricular arrhythmias in the elderly: a study using US Medicare data. BMC Med 2017;15(1):59.
[35] Li N, Dobrev D. Hyperuricemia: a causal player or a bystander linking inflammatory signaling and atrial fibrillation? Int J Cardiol 2017;231:177–8.
[36] Du J, Xie J, Zhang Z, Tsujikawa H, Fusco D, Silverman D, et al. TRPM7-mediated Ca(2+) signals confer fibrogenesis in human atrial fibrillation. Circ Res 2010;106(5):992–1003.
[37] Maharani N, Ting YK, Cheng J, Hasegawa A, Kurata Y, Li P, et al. Molecular mechanisms underlying urate-induced enhancement of Kv1.5 channel expression in HL-1 atrial myocytes. Circ J: Off J Jpn Circ Soc 2015;79(12):2659–68.
[38] El Khoury N, Mathieu S, Fiset C. Interleukin-1beta reduces L-type Ca2+ current through protein kinase C activation in mouse heart. J Biol Chem 2014;289(32):21896–908.
[39] Yao C, Scott L, Wehrens X, Dobrev D, Li N. Abstract 14531: activation of NLRP3 inflammasome promotes atrial fibrillation. Circulation 2016;134(Suppl 1) A14531-A.
[40] Mitrokhin VM, Mladenov MI, Kamkin AG. IL-1 provokes electrical abnormalities in rat atrial myocardium. Int Immunopharmacol 2015;28(1):780–4.
[41] Maharani N, Kuwabara M, Hisatome I. Hyperuricemia and atrial fibrillation. Int Heart J 2016;57(4):395–9.
[42] Aung T, Myung G, FitzGerald JD. Treatment approaches and adherence to urate-lowering therapy for patients with gout. Patient Prefer Adherence 2017;11:795–800.