Circulation Reports
Circ Rep 2019; 1: 469–473
doi:10.1253/circrep.CR-19-0088

REVIEW

Hyperuricemia as a Risk Factor for Atrial Fibrillation Due to Soluble and Crystalized Uric Acid

Fikri Taufiq, MD; Peili Li, MD, PhD; Junichiro Miake, MD, PhD; Ichiro Hisatome, MD, PhD

Among the several independent risk factors for atrial fibrillation (AF), hyperuricemia has been widely accepted as associated with the incidence of paroxysmal or persistent AF, as well as with the risk of AF in patients undergoing cardiovascular surgery. The electrophysiological mechanism of AF involves electrical remodeling of the arrhythmogenic substrate and abnormal automaticity as trigger. Both electrical and structural remodeling mediated by oxidative stress derived from either xanthine oxidoreductase (XOR), soluble uric acid (UA) or monosodium urate (MSU) crystals might be plausible explanations for the association of AF with hyperuricemia. XOR generates reactive oxygen species (ROS) that lead to atrial structural remodeling via inflammation. Soluble UA accumulates intracellularly through UA transporters (UAT), shortening the atrial action potential via enhanced expression and activity of Kv1.5 channel proteins. Intracellular accumulation of soluble UA generates ROS in atrial myocytes via nicotinamide adenine dinucleotide phosphate oxidase, which phosphorylates ERK/Akt and heat shock factor 1 (HSF1), thereby increasing transcription and translation of Hsp70, which stabilizes Kv1.5. In macrophages, MSU activates the NLRP3 inflammasome and proteolytic processing mediated by caspase-1 with enhanced interleukin (IL)-1β and IL-18 secretion. Use of an XOR inhibitor, antioxidants, a UAT inhibitor such as a uricosuric agent, and an NLRP3 inflammasome inhibitor, might become a potential strategy to reduce the risk of hyperuricemia-induced AF, and control serum UA level.

Key Words: Atrial fibrillation; Hyperuricemia; Monosodium urate; NLRP3 inflammasome; Oxidative stress; Soluble uric acid; Uric acid transporter; Xanthine oxidoreductase

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial electrical activation. AF is the most common cardiac rhythm abnormality, affecting approximately 33.5 million people worldwide. The high prevalence of AF is probably due to a combination of risk factors such as aging, chronic kidney disease (CKD) or chronic heart disease, and to more frequent diagnosis by way of enhanced monitoring devices.[1–4]

The prevalence of AF is expected to account for an increasing clinical and public health burden.[5] Many epidemiological studies have reported that AF is associated with risk factors such as advanced age, male sex, hypertension, heart failure (HF), coronary artery disease, CKD, sleep apnea, and metabolic factors such as obesity and diabetes mellitus.[6] Although the pathophysiology underlying AF is not well understood, oxidative stress and inflammation are the most likely contributing factors to AF development.

Uric acid (UA) is the end product of purine catabolism in humans. Serum UA (SUA) concentration is significantly higher in humans compared with in other mammals due to loss of uricase activity.[7] Hyperuricemia is defined as serum urate >7.0 mg/dL, regardless of sex and age.[8] Hyperuricemia is usually caused by alterations in the balance between UA synthesis and urinary excretion, although it is predominantly due to impaired renal excretion of urate.[8] Hyperuricemia is an independent risk factor for gout arthritis as well as for nephrolithiasis.[9–11] SUA >6 mg/dL has been reported to contribute to kidney dysfunction.[12]

Among the several independent risk factors for AF, hyperuricemia has been widely accepted as associated with the incidence of paroxysmal or persistent AF, as well as with the risk of AF in patients who have undergone cardiovascular surgery. In the present review, we explain the clinical relevance of hyperuricemia and gout to AF and the electrophysiological and molecular mechanisms of AF underlying the correlation of hyperuricemia with AF.

Received September 19, 2019; accepted September 20, 2019; J-STAGE Advance Publication released online November 1, 2019
Division of Regenerative Medicine and Therapeutics, Department of Genetic Medicine and Regenerative Therapeutics, Institute of Regenerative Medicine and Biofunction, Tottori University Graduate School of Medical Science, Yonago (F.T., P.L., I.H.); Division of Pharmacology, Department of Pathophysiological and Therapeutic Science, Faculty of Medicine, Tottori University, Yonago (J.M.), Japan; and Department of Physiology, Faculty of Medicine Sultan Agung Islamic University, Semarang (F.T.), Indonesia
I.H. is a member of *Circulation Reports*' Editorial Team.
Mailing address: Peili Li, MD, PhD, Division of Regenerative Medicine and Therapeutics, Department of Genetic Medicine and Regenerative Therapeutics, Institute of Regenerative Medicine and Biofunction, Tottori University Graduate School of Medical Science, 36-1 Nishi-cho, Yonago 683-8504, Japan. E-mail: peili-li@med.tottori-u.ac.jp
ISSN-2434-0790

Clinical Significance of Hyperuricemia and SUA in AF

Hyperuricemia is significantly associated with AF.[13,14] Hyperuricemia plays a pivotal role as an independent competing risk factor of AF in apparently healthy people both with and without competing diseases such as hypertension, diabetes mellitus, dyslipidemia, and CKD.[13] Other studies also reported a correlation between hyperuricemia and AF under several clinical conditions such as hypertension, type 2 diabetes mellitus, cardiovascular disease, hemodialysis, HF, and cardiac events.[15]

SUA level also contributes to AF, and patients with elevated SUA frequently develop AF.[16] SUA in men is higher than in women before menopause, although SUA in women increases after menopause. Baseline SUA is associated with an increased risk of future AF in both sexes. Given that the occurrence of AF increases with age in both genders, the fact that SUA in women increases with age may account for the higher risk of AF observed in women than in men.[1–3]

Many studies have established a positive correlation between SUA concentration and AF. A prospective cohort study of 123,238 Chinese patients enrolled from 2006 to 2014 found that high SUA concentration and increases in SUA over time were associated with an increased risk of AF.[16] Furthermore, in another cohort study, gout as a consequence of hyperuricemia was associated with a modestly increased risk of AF.[17]

Electrophysiological Mechanism and Triggers of AF

The electrophysiological mechanism of AF consists of electrical remodeling and abnormal automaticity.

Electrical remodeling of the atrium generates the arrhythmogenic substrate. The properties of transition from paroxysmal AF to sustainable AF are explained by shortening of atrial refractory periods and cycle length, that is, "AF begets AF".[18,19] Repeated excitation physiologically shortens the effective refractory period via intracellular Ca^{2+} overloading, which is followed by progressive pathological shortening of the cardiac refractory period through down-regulation of Ca^{2+} currents and upregulation of inward-rectifier K^+ currents.[20,21] Also, the decrease in Na^+ currents and I_{to} currents results in shortening of the refractory period and reduction of conduction velocity.

The trigger of AF occurs by abnormal automaticity from atrial myocytes or pulmonary veins (PV). Atrial automaticity could be attributable to impaired regulation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$). Impaired $[Ca^{2+}]_i$ induces Ca^{2+} leak from the sarcoplasmic reticulum (SR) during the diastolic phase. Under AF conditions, Ca^{2+}-handling proteins are hyperphosphorylated to increase $[Ca^{2+}]_i$. This induces spontaneous Ca^{2+} release from SR and the increase of inward currents on the cell membrane via activation of the Na^+/Ca^{2+} exchanger to exclude Ca^{2+}, causing delayed after-depolarization[22–26] associated with triggered activity, thereby facilitating the development of AF.[27] Moreover, automaticity through triggered activity in PV becomes a trigger for AF, which sustains the reentry circuit in the boundary between PV and atrial muscles.[28,29]

Molecular Mechanism of AF Associated With Hyperuricemia

Several pathophysiological theories concerning AF induced by UA have been proposed, such as, that elevated SUA concentration may contribute to the pathophysiology of AF via either activation of xanthine oxidoreductase (XOR), intracellular accumulation of soluble UA, or activation of the NLRP3 inflammasome induced by monosodium urate (MSU) crystals.

Oxidative Stress Due to Xanthine Oxidase

XOR is a key enzyme that converts UA precursors into UA. In contrast, XOR can also be a source of reactive oxygen species (ROS). The role of XOR in the pathogenesis of AF has been investigated in several studies.

O_2^- production is enhanced in both the left atrium (LA) and LA appendage (LAA) of patients with AF. Increased activities of both NAD(P)H oxidase and XOR in the LAA contribute to O_2^- production. This increase in O_2^- and its reactive metabolites may exacerbate the pathological consequences of AF, including thrombosis, inflammation, and tissue remodeling.[30] In an in vivo study in dogs, the XOR inhibitor allopurinol prevented AF by atrial pacing-induced left ventricular dysfunction. Treatment with allopurinol for 1 week reduced atrial vulnerability by inhibiting both electrical and structural atrial remodeling.[31]

The relationship between hyperuricemia and changes in cardiac structure has been investigated in mice. The increase in SUA after 16 weeks on a Western diet was accompanied by an increase in XOR activity in cardiac tissue, which showed cardiomyocyte hypertrophy, myocardial oxidative stress, interstitial fibrosis and impaired diastolic relaxation, through activation of the S6 kinase-1 growth pathway, the profibrotic TGF-β1/Smad2/3 signaling pathway, and macrophage pro-inflammatory polarization. Those findings improved after allopurinol treatment.[32] XOR has been shown to play a pivotal role in the generation of superoxide free radicals in the human atria as well.[33,34] Taken together, XOR may produce both UA and ROS, contributing to AF, although, so far, there has been no prospective clinical trial to test whether XOR inhibitors could prevent the onset of AF.

Intracellular Accumulation of UA by UA Transporters

There is growing experimental evidence that intracellular UA activates particular pathways to cause pathological changes in several types of cells, and that UA transporters (UAT) are involved in the intracellular accumulation of UA.

While UAT in renal proximal tubular cells play a pivotal role in the regulation of serum urate level, UAT are expressed not only in renal tubular cells, but also in vascular smooth muscle cells, endothelial cells, adipocytes and pancreatic β-cells.[7]

Mouse atrial myocytes were found to express at least 4 UAT: URATv1/GLUT9, ABCG2, MRP4 and MCT9, as confirmed in human embryonic stem cell-derived cardiomyocytes.[35] Maharani et al observed that UA could stabilize and increase Kv1.5 channel proteins, resulting in increases of the ultra-rapid delayed-rectifier current (I_{Kur}) with shortening of the atrial action potential through UAT in mouse atrial myocytes (HL-1 cells; **Figure 1**).[35] Inhibition of UA-influx UAT by benzbromarone attenuated UA-induced enhancement of Kv1.5 protein expression through

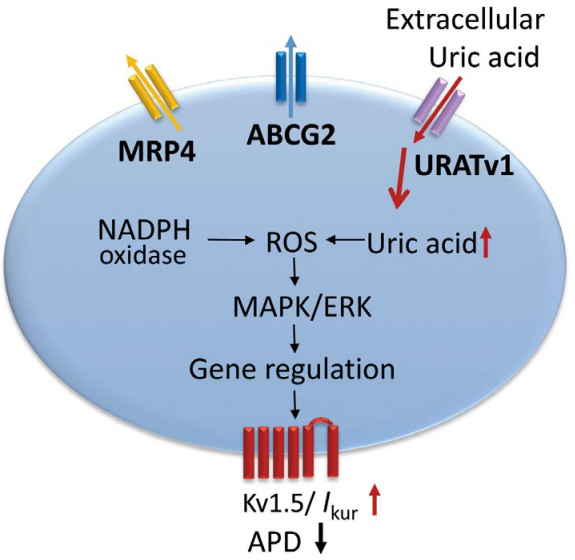

Figure 1. Schematic representation of the mechanisms underlying uric acid-induced enhancement of the Kv1.5 channel protein and function. Accumulation of intracellular uric acid through UAT (URATv1) induces nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase-dependent reactive oxygen species (ROS) production to increase Kv1.5. APD, action potential duration; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; UAT, uric acid transporters.

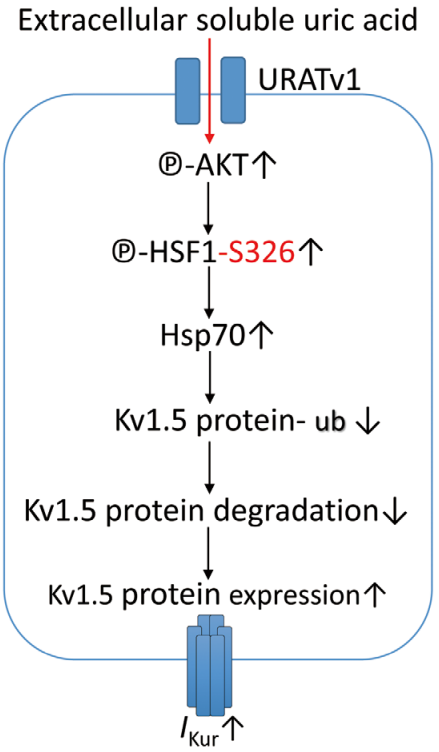

Figure 2. Schematic diagram of possible mechanisms for the uric acid-induced stabilization of Kv1.5 proteins and enhancement of the ultra-rapid delayed-rectifier current (I_{Kur}). AKT, protein kinase B; HSF1-S326, Ser 326 at heat shock factor 1; Hsp70, heat shock protein 70; Kv1.5 protein-ub, ubiquitinated Kv1.5 protein; Ⓟ, Phosphorylated; URATv1, an influx uric acid transporter. Adapted with permission from Taufiq F, et al.[36]

a decrease of intracellular UA. In contrast, inhibition of UA-efflux transporter ABCG2 by KO143 to increase intracellular UA concentration accelerated the UA-induced enhancement of Kv1.5 protein expression. The accumulated intracellular UA caused damage to the cells via an increase of oxidative stress and activation of the ERK1/2 pathway.[35] This effect was oxidative stress dependent, given that the enhancement of Kv1.5 protein expression by UA was abolished by the antioxidant *N*-acetylcysteine and the NADPH-oxidase inhibitor apocynin, suggesting that an antioxidant may be a novel therapeutic approach against AF in hyperuricemic patients.

Activation of Heat Shock Proteins by Intracellular UA Accumulation

Recently, a novel mechanism for UA-induced enhancement of Kv1.5 through UAT was reported.[35,36] Under stress conditions, heat shock protein 70 (Hsp70) prevents misfolding and aggregation of a protein whose expression is regulated by the transcription factor heat shock factor 1 (HSF1). The Hsp70 protein quality control machinery plays pivotal roles in appropriate protein folding, disposal of misfolded proteins and regulation of protein degradation. Activation of HSF1 by phosphorylation and subsequent trimerization and the resultant increase of Hsp70 are critical events by which cells overcome stress and reduce the potential for damage.[37,38] Kv1.5 protein belongs to short-lived proteins whose half-life is regulated by ubiquitin-proteasome systems.[39,40] HSF1 and Hsp70 regulate the expression of Kv1.5, given that HSF1 increases not only SAP97, an anchoring protein of Kv1.5,[41] but also Hsp70, prolonging the half-life of Kv1.5 proteins to enhance Kv1.5 channel currents via increasing the channel density on the cell membrane.[42] Taufiq et al found that intracellular accumulation of UA through UAT increased Kv1.5 proteins through stabilization of Kv1.5 protein without changes in Kv1.5 mRNA.[36] Taufiq et al investigated the mechanism of UA-induced enhancement of the expression of Kv1.5 and demonstrated that intracellular accumulation of UA facilitated phosphorylation of Akt and HSF1 to increase Hsp70, which prolonged the half-life of Kv1.5 proteins.[36] UA-induced facilitation of Akt phosphorylation could enhance expression and phosphorylation of the HSP family to stabilize Kv1.5 proteins, as shown in **Figure 2**. HSF1 is activated by oxidative stress;[43] activation of HSF1 by oxidative stress enhances the expression of HSP.[44,45] We previously reported that activation of HSF1 stabilized Kv1.5 proteins via an increased expression of the anchoring protein SAP97.[41] Whether UA increases SAP97 through phosphorylation of HSF1 should be examined in a future study. Given that UA-induced atrial action potential shortening could facilitate the development of re-entry circuits in the atrium, hyperuricemia may cause atrial arrhythmias including AF. Recently, we reported that hyperuricemia is an independent competing risk factor for AF,[13] which may support the present result suggesting that UA could facilitate the occurrence of reentrant arrhythmias in the atrium. Although further prospective intervention studies are needed to prove whether lowering SUA is effective for preventing AF, inhibition of UAT to lower intracellular

UA may become a novel therapeutic approach against AF in hyperuricemic patients.

NLRP3 Inflammasome Triggered by MSU Crystals

Inflammation plays an important role in inducing and perpetuating AF according to various experimental, epidemiological and cohort observational studies.[46] AF is associated with elevation of the plasma level of several inflammation markers, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP).[47] NLRP3 inflammasome is a multi-proteins complex composed of NLRP3, ASC and pro-caspase-1. Once the three of them assemble, inflammasome triggers formation of bioactive caspase-1, which promotes maturation of the active forms of IL-1β and IL-18.[48] Macrophages and myoblasts secrete these cytokines as components of the inflammatory response.[47]

Although elevation of SUA >7 mg/dL induces the deposition of MSU, MSU directly activates NLRP3 inflammasome. MSU engages caspase-1 via activation of the NLRP3 inflammasome, resulting in the production of IL-1β and IL-18 in the human monocytic cell line THP1. Macrophages obtained from mice deficient in either capase-1, ASC or NLRP3 failed to enhance IL-1β secretion induced by MSU. In an inflammasome-deficient mice model, neutrophil influx induced by MSU was markedly impaired. Moreover, colchicine, a drug able to prevent the initial inflammatory phase of gout, blocks maturation of IL-1β induced by MSU.[49] Except for innate immune cells, NLRP3 inflammasome has been identified in the atrium as a casual factor in the etiology of AF. NLRP3 inflammasome activity was increased in the atrial cardiomyocytes of patients with paroxysmal AF and chronic AF.[50] Levels of NLRP3, ASC and active capase-1 in the right atrium were elevated in patients with persistent AF. In a cardiomyocyte-specific knock-in mouse model expressing constitutively active NLRP3, spontaneous premature atrial contraction and inducible AF developed. MCC950, a selective NLRP3 inflammasome inhibitor, which interrupts assembly of the NLRP3 inflammasome complex, attenuated the induction of AF. Cardiomyocyte-specific activation of NLRP3 inflammasome promotes atrial electrical and structure remodeling, exhibiting abnormal Ca^{2+} release from the SR, atrial effective refractory period shortening, and atrial hypertrophy. In contrast, cardiomyocyte-specific knockdown of NLRP3 suppressed AF induction, and restored normal mRNA levels of Ryr2, Kcna5, Girk1 and Girk4. This evidence clearly demonstrates that MSU activates NLRP3 inflammasome, which is a causal link to AF pathophysiology.

Other cytokines, CRP and TNF-α, have been implicated in the cell signaling activation patterns associated with fibrosis, apoptosis and hypertrophy. The level of TNF-α, an inflammatory mediator, was significantly increased in patients with diastolic HF and a history of AF in a community-based HF cohort.[51] TNF-α altered the expression or distribution of connexin 40 and connexin 43[52] and directly altered Ca^{2+} handling in cardiomyocytes. TNF-α was also found to increase cardiomyocyte apoptosis and myolisis, resulting in atrial dilatation and conduction heterogeneity.[53] The circulating level of CRP is higher in patients with AF compared with those without an AF history. Patients with persistent AF have higher CRP than those with paroxysmal AF.[54]

Conclusions

Hyperuricemia may cause AF either via activation of XOR, intracellular accumulation of soluble UA, or activation of the NLRP3 inflammasome induced by MSU crystals. Thus, use of an XOR inhibitor, antioxidants, a UAT inhibitor such as a uricosuric agent, and inflammasome inhibitors might be a potential strategy to reduce the risk of hyperuricemia-induced AF, and control SUA level.

Disclosures

I.H. has received lecture fees from Teijin Pharma Co. Ltd., Sanwa Kagaku Kenkyusho Co. Ltd., Feizer Co. Ltd., and Fuji Yakuhin Co. Ltd.; and research grants from Daiichi Sankyo Co. Ltd., Bayer Yakuhin, Ltd., Teijin Pharma Co. Ltd., Fuji Yakuhin Co. Ltd. and Sanwa Kagaku Kenkyusho Co. Ltd. I.H. is also a member of *Circulation Reports*' Editorial Team. The other authors declare no conflicts of interest.

References

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: A global burden of disease 2010 study. *Circulation* 2014; **129:** 837–847.
2. Zulkifly H, Lip GYH, Lane DA. Epidemiology of atrial fibrillation. *Int J Clin Pract* 2018; **72:** e13070.
3. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol* 2014; **11:** 639–654.
4. Gehi A, Mounsey J. Atrial fibrillation. *In*: Runge M, Stouffer G, Petterson C, editors. Netter's cardiology, 2nd edn. Philadelphia: Saunders, 2004; 233–239.
5. Ribeiro AL, Otto CM. Heartbeat: The worldwide burden of atrial fibrillation. *Heart* 2018; **104:** 1987–1988.
6. Heijman J, Voigt N, Nattel S, Dobrev D. Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. *Circ Res* 2014; **114:** 1483–1499.
7. Maharani N, Kuwabara M, Hisatome I. Hyperuricemia and atrial fibrillation. *Int Heart J* 2016; **57:** 395–399.
8. Yamanaka H, Japanese Society of Gout and Nucleic Acid Metabolism. Japanese guideline for the management of hyperuricemia and gout: Second edition. *Nucleosides Nucleotides Nucleic Acids* 2011; **30:** 1018–1029.
9. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Impact of gout on the risk of atrial fibrillation. *Rheumatology (Oxford)* 2016; **55:** 721–728.
10. German DC, Holmes EW. Hyperuricemia and gout. *Med Clin North Am* 1986; **70:** 419–436.
11. Kim S, Chang Y, Yun KE, Jung HS, Lee SJ, Shin H, et al. Development of nephrolithiasis in asymptomatic hyperuricemia: A cohort study. *Am J Kidney Dis* 2017; **70:** 173–181.
12. Tseng WC, Chen YT, Lin YP, Ou SM, Yang CY, Lin CH, et al. Hyperuricemia predicts an early decline in renal function among older people: A community-based cohort study. *Sci Rep* 2019; **9:** 980–989.
13. 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:** 137–142.
14. Chen Y, Xia Y, Han X, Yang Y, Yin X, Qiu J, et al. Association between serum uric acid and atrial fibrillation: A cross-sectional community-based study in China. *BMJ Open* 2017; **7:** e019037.
15. Liu Y. Hyperuricemia and risk of atrial fibrillation. *J Atr Fibrillation* 2014; **6:** 967–970.
16. Li S, Cheng J, Cui L, Gurol ME, Bhatt DL, Fonarow GC, et al. Cohort study of repeated measurements of serum urate and risk of incident atrial fibrillation. *J Am Heart Assoc* 2019; **8:** e012020.
17. Kim SC, Liu J, Solomon DH. Risk of incident atrial fibrillation in gout: A cohort study. *Ann Rheum Dis* 2016; **75:** 1473–1478.
18. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: Mechanisms and implications. *Circ Arrhythm Electrophysiol* 2008; **1:** 62–73.
19. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: A study in awake chronically instrumented goats. *Circulation* 1995; **92:** 1954–1968.
20. Dobrev D, Friedrich A, Voigt N, Jost N, Wettwer E, Christ T, et al. The G protein-gated potassium current I(K,ACh) is constitutively active in patients with chronic atrial fibrillation. *Circulation* 2005;

112: 3697–3706.
21. Van Wagoner DR, Pond AL, Lamorgese M, Rossie SS, McCarthy PM, Nerbonne JM. Atrial L-type Ca2+ currents and human atrial fibrillation. *Circ Res* 1999; **85:** 428–436.
22. Nattel S, Dobrev D. The multidimensional role of calcium in atrial fibrillation pathophysiology: Mechanistic insights and therapeutic opportunities. *Eur Heart J* 2012; **33:** 1870–1877.
23. Hove-Madsen L, Llach A, Bayes-Genís A, Roura S, Rodriguez Font E, Arís A, et al. Atrial fibrillation is associated with increased spontaneous calcium release from the sarcoplasmic reticulum in human atrial myocytes. *Circulation* 2004; **110:** 1358–1363.
24. Neef S, Dybkova N, Sossalla S, Ort KR, Fluschnik N, Neumann K, et al. CaMKII-dependent diastolic SR Ca2+ leak and elevated diastolic Ca2+ levels in right atrial myocardium of patients with atrial fibrillation. *Circ Res* 2010; **106:** 1134–1144.
25. Voigt N, Li N, Wang Q, Wang W, Trafford AW, Abu-Taha I, et al. Enhanced sarcoplasmic reticulum Ca2+ leak and increased Na+-Ca2+ exchanger function underlie delayed afterdepolarizations in patients with chronic atrial fibrillation. *Circulation* 2012; **125:** 2059–2070.
26. Vest JA, Wehrens XH, Reiken SR, Lehnart SE, Dobrev D, Chandra P, et al. Defective cardiac ryanodine receptor regulation during atrial fibrillation. *Circulation* 2005; **111:** 2025–2032.
27. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: A translational appraisal. *Physiol Rev* 2011; **91:** 265–325.
28. Atienza F, Almendral J, Moreno J, Vaidyanathan R, Talkachou A, Kalifa J, et al. Activation of inward rectifier potassium channels accelerates atrial fibrillation in humans: Evidence for a reentrant mechanism. *Circulation* 2006; **114:** 2434–2442.
29. Patterson E, Jackman WM, Beckman KJ, Lazzara R, Lockwood D, Scherlag BJ, et al. Spontaneous pulmonary vein firing in man: Relationship to tachycardia-pause early afterdepolarizations and triggered arrhythmia in canine pulmonary veins in vitro. *J Cardiovasc Electrophysiol* 2007; **18:** 1067–1075.
30. Dudley SCJ, Hoch NE, McCann LA, Honeycutt C, Diamandopoulos L, Fukai T, et al. Atrial fibrillation increases production of superoxide by the left atrium and left atrial appendage: Role of the NADPH and xanthine oxidases. *Circulation* 2005; **112:** 1266–1273.
31. Sakabe M, Fujiki A, Sakamoto T, Nakatani Y, Mizumaki K, Inoue H. Xanthine oxidase inhibition prevents atrial fibrillation in a canine model of atrial pacing-induced left ventricular dysfunction. *J Cardiovasc Electrophysiol* 2012; **23:** 1130–1135.
32. Jia G, Habibi J, Bostick BP, Ma L, DeMarco VG, Aroor AR, et al. Uric acid promotes left ventricular diastolic dysfunction in mice fed a Western diet. *Hypertension* 2015; **65:** 531–539.
33. MacGowan SW, Regan MC, Malone C, Sharkey O, Young L, Gorey TF, et al. Superoxide radical and xanthine oxidoreductase activity in the human heart during cardiac operations. *Ann Thorac Surg* 1995; **60:** 1289–1293.
34. Ben Abraham R, Matza M, Marmor S, Rudick V, Frolkis I, Shapira I, et al. Electromechanical impairment of human auricle and rat myocardial strip subjected to exogenous oxidative stress. *Eur J Cardiothorac Surg* 2003; **23:** 66–73.
35. 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* 2015; **79:** 2659–2668.
36. Taufiq F, Maharani N, Li P, Kurata Y, Ikeda N, Kuwabara M, et al. Uric acid-induced enhancements of Kv1.5 protein expression and channel activity via the Akt-HSF1-Hsp70 pathway in HL-1 atrial myocytes. *Circ J* 2019; **83:** 718–726.
37. Vihervaara A, Sistonen L. HSF1 at a glance. *J Cell Sci* 2014; **127:** 261–266.
38. Bironaite D, Brunk U, Venalis A. Protective induction of Hsp70 in heat-stressed primary myoblasts: Involvement of MAPKs. *J Cell Biochem* 2013; **114:** 2024–2031.
39. Li P, Kurata Y, Maharani N, Mahati E, Higaki K, Hasegawa A, et al. E3 ligase CHIP and Hsc70 regulate Kv1.5 protein expression and function in mammalian cells. *J Mol Cell Cardiol* 2015; **86:** 138–146.
40. Kato M, Ogura K, Miake J, Sasaki N, Taniguchi S, Igawa O, et al. Evidence for proteasomal degradation of Kv1.5 channel protein. *Biochem Biophys Res Commun* 2005; **337:** 343–348.
41. Ting YK, Morikawa K, Kurata Y, Li P, Bahrudin U, Mizuta E, et al. Transcriptional activation of the anchoring protein SAP97 by heat shock factor (HSF)-1 stabilizes K(v) 1.5 channels in HL-1 cells. *Br J Pharmacol* 2011; **162:** 1832–1842.
42. Hirota Y, Kurata Y, Kato M, Notsu T, Koshida S, Inoue T, et al. Functional stabilization of Kv1.5 protein by Hsp70 in mammalian cell lines. *Biochem Biophys Res Commun* 2008; **372:** 469–474.
43. Yu MA, Sánchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. *J Hypertens* 2010; **28:** 1234–1242.
44. Ahn SG, Thiele DJ. Redox regulation of mammalian heat shock factor 1 is essential for Hsp gene activation and protection from stress. *Genes Dev* 2003; **17:** 516–528.
45. Niforou K, Cheimonidou C, Trougakos IP. Molecular chaperones and proteostasis regulation during redox imbalance. *Redox Biol* 2014; **2:** 323–332.
46. Giannopoulos G, Cleman MW, Deftereos S. Inflammation fueling atrial fibrillation substrate: Seeking ways to "cool" the heart. *Med Chem* 2014; **10:** 663–671.
47. Bruins P, te Velthuis H, Yazdanbakhsh AP, Jansen PG, van Hardevelt FW, de Beaumont EM, et al. Activation of the complement system during and after cardiopulmonary bypass surgery: Postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. *Circulation* 1997; **96:** 3542–3548.
48. Levy M, Thaiss CA, Elinav E. Taming the inflammasome. *Nat Med* 2015; **21:** 213–215.
49. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* 2006; **440:** 237–241.
50. Yao C, Veleva T, Scott LJ, Cao S, Li L, Chen G, et al. Enhanced cardiomyocyte NLRP3 inflammasome signaling promotes atrial fibrillation. *Circulation* 2018; **138:** 2227–2242.
51. Putko BN, Wang Z, Lo J, Anderson T, Becher H, Dyck JRB, et al. Circulating levels of tumor necrosis factor-alpha receptor 2 are increased in heart failure with preserved ejection fraction relative to heart failure with reduced ejection fraction: Evidence for a divergence in pathophysiology. *PLoS One* 2014; **9:** e99495.
52. Liew R, Khairunnisa K, Gu Y, Tee N, Yin NO, Naylynn TM, et al. Role of tumor necrosis factor-α in the pathogenesis of atrial fibrosis and development of an arrhythmogenic substrate. *Circ J* 2013; **77:** 1171–1179.
53. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol* 2015; **12:** 230–243.
54. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, et al. C-reactive protein elevation in patients with atrial arrhythmias: Inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* 2001; **104:** 2886–2891.