

## · 高尿酸血症/痛风相关代谢性疾病专栏 ·

## 高尿酸血症与心房颤动的关系

刘彤 杨亚娟

**【摘要】** 心房颤动是临床上最常见的持续性心律失常,可能导致心力衰竭、血栓栓塞等并发症。心房颤动的发生、发展可能与心房重构、炎性反应及氧化应激有关。人体内血尿酸不仅与心房氧化应激程度密切相关,还与炎性标志物水平相关,因此血尿酸水平与多种心血管疾病密切相关。近年来,越来越多的研究表明,血尿酸水平升高和心房颤动的发生风险密切相关,其可能机制一方面是高尿酸血症可以使高血压、肾功能衰竭等疾病发生风险增加,而后者是心房颤动发生的重要危险因素;另一方面氧化应激和炎性反应参与了心房颤动的发生,这可能是高尿酸血症和心房颤动联系的中间环节。

**【关键词】** 高尿酸血症;尿酸;黄嘌呤氧化酶;心房颤动

**基金项目:**国家自然科学基金资助项目(81270245, 81570298)

**Relationship between hyperuricemia and atrial fibrillation** Liu Tong, Yang Yajuan. Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin 300211, China  
Corresponding author: Liu Tong, Email:liutongdoc@126.com

**【Abstract】** As the most common sustained arrhythmia, atrial fibrillation (AF) can lead to complications such as heart failure, thromboembolism. Atrial electrical and structural remodeling, inflammatory reaction and oxidative stress may play important roles in the occurrence and progress of AF. Uric acid is closely related to not only the degree of oxidative stress, but also the level of inflammatory markers, which contributes to the relationship between uric acid and cardiovascular diseases. In recent years, more and more studies confirmed that hyperuricemia can increase the risk of AF. On the one hand, elevated level of serum uric acid increases the risk of hypertension and renal failure, which are the risk factors of AF. On the other hand, oxidative stress and inflammatory reaction process are involved in the occurrence of AF, which may be a hub for the relationship between hyperuricemia and AF.

**【Key words】** Hyperuricemia; Uric acid; Xanthine oxidase; Atrial fibrillation

**Fund program:** National Natural Science Foundation of China(81270245, 81570298)

心房颤动是临床上最常见的持续性心律失常,可引起心力衰竭、血栓栓塞等严重并发症,已经成为全球重要的公共卫生问题<sup>[1]</sup>。心房颤动发生的具体病理生理机制尚不完全清楚,心房电重构、结构重构、炎性反应和氧化应激激活都参与了心房颤动的发生和发展过程<sup>[2-7]</sup>。在心脏手术后发生心房颤动患者的心房肌组织中可发现炎性细胞浸润及心房间质纤维化<sup>[8]</sup>。另一项研究发现,C反应蛋白及其他促炎性细胞因子浓度升高可以预测心房颤动的发生风险及心房颤动复律后的复发<sup>[5,9]</sup>。此外,氧化应

激也可能是心房颤动发生的重要机制之一。研究表明,黄嘌呤氧化酶激活可导致体内活性氧簇产生增加,参与心房重构和心房颤动的发生、发展。在快速心房起搏猪的模型中,心房快速起搏可导致左心耳NADPH氧化酶及黄嘌呤氧化酶活性升高,应用黄嘌呤氧化酶抑制剂后过氧化物产生显著减少<sup>[10]</sup>。

### 1 高尿酸血症与心血管疾病

血清中的尿酸是黄嘌呤经过黄嘌呤脱氢酶和黄嘌呤氧化酶的降解最终形成的代谢产物,而这个过程受黄嘌呤氧化酶调节。黄嘌呤氧化酶是人体内活性氧簇产生的一个关键酶,可以反映体内氧化应激水平<sup>[11-12]</sup>。因此,尿酸水平升高反映黄嘌呤氧化酶活性增加,可能与心房氧化应激程度密切相关。另一方面,血清尿酸水平与多种炎性标志物呈正相关,这些炎性标志物包括高敏C反应蛋白、白细胞介素-1、

白细胞介素-6、肿瘤坏死因子- $\alpha$  等。尿酸还可以通过激活促炎性细胞因子或局部组织血管紧张素-醛固酮系统来促进炎症反应。

大量证据表明,血清尿酸水平与多种心血管疾病密切相关。Krishnan 等<sup>[13]</sup>研究显示,高尿酸血症是急性心肌梗死发生的独立预测因素。Choi 和 Curhan<sup>[14]</sup>报道,有痛风病史患者发生心血管事件风险和总死亡率明显升高。另外,多项研究表明高尿酸血症是高血压的一个独立危险因素,且尿酸水平与新发高血压关系更为密切<sup>[12]</sup>。除此之外,高尿酸血症与冠心病有密切联系,尤其是在心血管疾病风险较高的人群及女性人群中两者联系更加显著<sup>[15]</sup>。

## 2 高尿酸血症与心房颤动

近年来,越来越多的研究证实血尿酸水平升高和心房颤动的发生风险密切相关<sup>[16]</sup>。Suzuki 等<sup>[17]</sup>发现,心房颤动患者血尿酸水平明显高于非心房颤动患者,表明高尿酸血症是心房颤动发生的一个重要危险因素。另外,研究者还发现在调整协变量后,血尿酸水平在女性人群中仍是心房颤动的一个独立危险因素( $OR = 1.888$ , 95%  $CI$ : 1.278 ~ 2.790),然而在男性人群中血尿酸水平无法预测心房颤动的发生风险( $OR = 1.176$ , 95%  $CI$ : 0.935 ~ 1.478),提示高尿酸血症对心房颤动的预测价值可能存在性别差异。Tamariz 等<sup>[18]</sup>入选 15 382 名无心房颤动病史的普通人群进行前瞻性队列研究,以新发心房颤动为主要研究终点,在调整了年龄、性别、种族等因素后,研究者发现血尿酸水平可以预测心房颤动的发生( $HR = 1.16$ , 95%  $CI$ : 1.06 ~ 1.26),且两者间的关系与性别和种族相关(在黑种人及女性人群中两者相关性更明显)。然而,另一些研究未能显示高尿酸血症与心房颤动的关系存在性别差异。中国台湾的一项研究提示,高尿酸血症预测心房颤动发生的风险比在男性(1.288)和女性(1.115)相似<sup>[19]</sup>。同样,Nyrnes 等<sup>[20]</sup>的研究中也提出无论是在男性人群还是女性人群中,血尿酸水平升高都是发生心房颤动的一个独立危险因素。因此,尿酸与心房颤动的关系是否受性别影响还需要更多的研究来进一步证实。

多项研究在不同人群中评价高尿酸血症与心房颤动发生的关系。笔者的研究入选了 451 例原发性高血压患者,将其分为心房颤动组和非心房颤动组,多元回归分析显示,尿酸水平是心房颤动发生的独立预测因素( $OR = 1.008$ , 95%  $CI$ : 1.003 ~ 1.013,  $P = 0.002$ )<sup>[21]</sup>。Chuang 等<sup>[22]</sup>发现,在非高血压的老年人群( $\geq 65$ 岁)中高尿酸血症与心房颤动之间有

密切关系( $HR = 3.78$ , 95%  $CI$ : 1.24 ~ 11.59),但是在合并高血压的老年人群中并未发现两者间的联系( $HR = 1.20$ , 95%  $CI$ : 0.74 ~ 1.94)。Valbusa 等<sup>[23]</sup>的前瞻性队列研究入选了 400 例无心房颤动病史的糖尿病患者并对其进行了 10 年随访,结果发现血尿酸水平升高可增加心房颤动的发生风险( $OR = 2.44$ , 95%  $CI$ : 1.6 ~ 3.9,  $P < 0.0001$ )。此外,Memetoglu 等<sup>[24]</sup>发现,在拟行冠状动脉搭桥术的患者中,术后发生心房颤动患者的术前血尿酸水平明显高于没有发生心房颤动的患者[( $7.8 \pm 1.1$ ) mg/dl vs. ( $5 \pm 0.9$ ) mg/dl,  $P < 0.05$ ],多元回归分析显示,术前高尿酸血症是发生术后心房颤动的独立危险因素( $OR = 3.137$ , 95%  $CI$ : 1.873 ~ 5.256,  $P < 0.001$ )。Chao 等<sup>[19]</sup>发现,高尿酸血症与左心房直径密切相关,并可以增加新发心房颤动的发生风险( $HR = 1.191$ , 95%  $CI$ : 1.098 ~ 1.292,  $P < 0.001$ )。最新 1 篇荟萃分析入选了 9 篇有关血尿酸水平与心房颤动关系的相关研究,横断面研究结果显示,心房颤动患者较非心房颤动患者血尿酸水平显著升高,前瞻性队列研究的荟萃分析提示,高尿酸血症可增加心房颤动风险 1.67 倍<sup>[25]</sup>。

Canpolat 等<sup>[26]</sup>发现,血尿酸水平升高是心房颤动射频消融术后复发的一个独立危险因素( $HR = 1.96$ , 95%  $CI$ : 1.49 ~ 2.59,  $P < 0.001$ )。然而,不同研究间结果有所差异,笔者刚刚发表的一项荟萃分析入选 4 项相关研究并未发现血清高尿酸是导管消融术后心房颤动复发的一个独立危险因素( $OR = 1.37$ , 95%  $CI$ : 0.98 ~ 1.93,  $P = 0.07$ )<sup>[27]</sup>。

综上所述,血尿酸水平升高导致心房颤动发生的机制尚不十分清楚,主要推测与以下因素有关。首先,血尿酸水平升高可导致平滑肌细胞增生,内皮细胞功能紊乱,一氧化氮合成减少及局部组织肾素-血管紧张素-醛固酮系统激活,增加高血压、肾功能衰竭的发生风险;而高血压、肾功能衰竭可增加心房颤动的发生风险<sup>[28-30]</sup>。另外,已有许多研究表明血尿酸水平与体内炎症反应和氧化应激标志物呈正相关,且血尿酸水平可以反映心房组织水平黄嘌呤氧化酶激活和活性氧簇水平升高,而炎症和氧化应激是心房颤动发生、发展的重要机制,因此炎症反应和氧化应激激活可能是两者相关的核心环节。临床上抑制黄嘌呤氧化酶活性的药物如别嘌呤醇可以显著降低血尿酸水平,有望成为心房颤动上游治疗的药物选择之一。

## 参 考 文 献

- [1] Ferrari R, Bertini M, Blomstrom-Lundqvist C, et al. An update on atrial fibrillation in 2014: from pathophysiology to treatment [J]. *Int J Cardiol*, 2016, 203: 22-29. DOI: 10.1016/j.ijcard.2015.10.089.
- [2] Harada M, Van Wagoner DR, Nattel S. Role of inflammation in atrial fibrillation pathophysiology and management [J]. *Circ J*, 2015, 79(3): 495-502. DOI: 10.1253/circj.CJ-15-0138.
- [3] Hu YF, Chen YJ, Lin YJ, et al. Inflammation and the pathogenesis of atrial fibrillation [J]. *Nat Rev Cardiol*, 2015, 12(4): 230-243. DOI: 10.1038/nrcardio.2015.2.
- [4] Watson T, Kakar P, Lip GY. Cardioversion for atrial fibrillation: does inflammation matter [J]. *Am J Cardiol*, 2007, 99(11): 1617-1618.
- [5] Liu T, Li G, Li L, et al. Association between C-reactive protein and recurrence of atrial fibrillation after successful electrical cardioversion: a meta-analysis [J]. *J Am Coll Cardiol*, 2007, 49(15): 1642-1648.
- [6] Korantzopoulos P, Kolettis TM, Kountouris E, et al. Oral vitamin C administration reduces early recurrence rates after electrical cardioversion of persistent atrial fibrillation and attenuates associated inflammation [J]. *Int J Cardiol*, 2005, 102(2): 321-326.
- [7] Korantzopoulos P, Kolettis TM, Galaris D, et al. The role of oxidative stress in the pathogenesis and perpetuation of atrial fibrillation [J]. *Int J Cardiol*, 2007, 115(2): 135-143.
- [8] Bruins P, te Velthuis H, Yazdanbakhsh AP, 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 [J]. *Circulation*, 1997, 96(10): 3542-3548.
- [9] Liu T, Li L, Korantzopoulos P, et al. Meta-analysis of association between C-reactive protein and immediate success of electrical cardioversion in persistent atrial fibrillation [J]. *Am J Cardiol*, 2008, 101(12): 1749-1752. DOI: 10.1016/j.amjcard.2008.02.066.
- [10] Dudley SC Jr, Hoch NE, McCann LA, et al. Atrial fibrillation increases production of superoxide by the left atrium and left atrial appendage: role of the NADPH and xanthine oxidases [J]. *Circulation*, 2005, 112(9): 1266-1273.
- [11] Baker JF, Krishnan E, Chen L, et al. Serum uric acid and cardiovascular disease: recent developments, and where do they leave us [J]. *Am J Med*, 2005, 118(8): 816-826.
- [12] Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk [J]. *N Engl J Med*, 2008, 359(17): 1811-1821. DOI: 10.1056/NEJMr0800885.
- [13] Krishnan E, Svendsen K, Neaton JD, et al. Long-term cardiovascular mortality among middle-aged men with gout [J]. *Arch Intern Med*, 2008, 168(10): 1104-1110. DOI: 10.1001/archinte.168.10.1104.
- [14] Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease [J]. *Circulation*, 2007, 116(8): 894-900.
- [15] Borghi C, Verardi FM, Pareo I, et al. Hyperuricemia and cardiovascular disease risk [J]. *Expert Rev Cardiovasc Ther*, 2014, 12(10): 1219-1225. DOI: 10.1586/14779072.2014.957675.
- [16] 马进才, 邵清森, 刘彤. 高尿酸血症与心房颤动相关性的研究现状 [J]. *中国心血管杂志*, 2014, 19(4): 314-316. DOI: 10.3969/j.issn.1007-5410.2014.04.29.
- [17] Suzuki S, Sagara K, Otsuka T, et al. Gender-specific relationship between serum uric acid level and atrial fibrillation prevalence [J]. *Circ J*, 2012, 76(3): 607-611.
- [18] Tamariz L, Agarwal S, Soliman EZ, et al. Association of serum uric acid with incident atrial fibrillation (from the Atherosclerosis Risk in Communities [ARIC] study) [J]. *Am J Cardiol*, 2011, 108(9): 1272-1276. DOI: 10.1016/j.amjcard.2011.06.043.
- [19] Chao TF, Hung CL, Chen SJ, et al. The association between hyperuricemia, left atrial size and new-onset atrial fibrillation [J]. *Int J Cardiol*, 2013, 168(4): 4027-4032. DOI: 10.1016/j.ijcard.2013.06.067.
- [20] Nyrnes A, Toft I, Njølstad I, et al. Uric acid is associated with future atrial fibrillation: an 11-year follow-up of 6308 men and women—the Tromsø Study [J]. *Europace*, 2014, 16(3): 320-326. DOI: 10.1093/europace/eut260.
- [21] Liu T, Zhang X, Korantzopoulos P, et al. Uric acid levels and atrial fibrillation in hypertensive patients [J]. *Intern Med*, 2011, 50(8): 799-803.
- [22] Chuang SY, Wu CC, Hsu PF, et al. Hyperuricemia and incident atrial fibrillation in a normotensive elderly population in Taiwan [J]. *Nutr Metab Cardiovasc Dis*, 2014, 24(9): 1020-1026. DOI: 10.1016/j.numecd.2014.03.012.
- [23] Valbusa F, Bertolini L, Bonapace S, et al. Relation of elevated serum uric acid levels to incidence of atrial fibrillation in patients with type 2 diabetes mellitus [J]. *Am J Cardiol*, 2013, 112(4): 499-504. DOI: 10.1016/j.amjcard.2013.04.012.
- [24] Memetoglu ME, Kehlbar T, Yilmaz M, et al. Serum uric acid level predicts new-onset atrial fibrillation after coronary artery bypass graft operation [J]. *Eur Rev Med Pharmacol Sci*, 2015, 19(5): 784-789.
- [25] Tamariz L, Hernandez F, Bush A, et al. Association between serum uric acid and atrial fibrillation: a systematic review and meta-analysis [J]. *Heart Rhythm*, 2014, 11(7): 1102-1108. DOI: 10.1016/j.hrthm.2014.04.003.
- [26] Canpolat U, Aytemir K, Yorgun H, et al. Usefulness of serum uric acid level to predict atrial fibrillation recurrence after cryoballoon-based catheter ablation [J]. *Europace*, 2014, 16(12): 1731-1737. DOI: 10.1093/europace/euu198.
- [27] Zhao J, Liu T, Korantzopoulos P, et al. Association between serum uric acid and atrial fibrillation recurrence following catheter ablation: a meta-analysis [J]. *Int J Cardiol*, 2016, 204: 103-105. DOI: 10.1016/j.ijcard.2015.11.167.
- [28] Corry DB, Eslami P, Yamamoto K, et al. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system [J]. *J Hypertens*, 2008, 26(2): 269-275. DOI: 10.1097/HJH.0b013e3282f240bf.
- [29] Kang DH, Park SK, Lee IK, et al. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells [J]. *J Am Soc Nephrol*, 2005, 16(12): 3553-3562.
- [30] Perlstein TS, Gumieniak O, Hopkins PN, et al. Uric acid and the state of the intrarenal renin-angiotensin system in humans [J]. *Kidney Int*, 2004, 66(4): 1465-1470.

(收稿日期: 2016-05-20)