

血清尿酸与心血管疾病的关系以及分子机制

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摘 要

尿酸是人类嘌呤代谢的最终产物, 体内尿酸水平异常升高, 可能导致痛风及关节炎。近年来高尿酸血症的患病率呈上升趋势, 流行病学研究表明, 尿酸水平与心血管疾病呈正相关, 包括冠状动脉疾病、心房颤动和心力衰竭等。多项临床和实验研究支持尿酸与传统危险因素一起作为预测疾病发展的独立危险因素。尽管进行了广泛的研究, 但潜在的分子机制仍不明确, 目前主要认为与炎症反应、氧化应激和内皮功能障碍等机制相关。本篇综述总结了国内外高尿酸血症与常见心血管疾病的关系及可能的相关机制, 为与尿酸相关性心血管疾病提供新的治疗靶点, 为基础研发提供思路 and 方向。

关键词

尿酸, 心血管疾病, 分子机制

The Relationship between Serum Uric Acid and Cardiovascular Disease and Its Underlying Molecular Mechanisms

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Abstract

Uric acid, the terminal metabolite of human purine metabolism, can lead to gout and arthritis when

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its concentration becomes abnormally elevated. The prevalence of hyperuricemia has been progressively increasing in recent years. Epidemiological studies have demonstrated a positive correlation between serum uric acid levels and various cardiovascular diseases, such as coronary artery disease, atrial fibrillation, and heart failure. Substantial clinical and experimental evidence supports that hyperuricemia serves as an independent risk factor, alongside conventional factors, for predicting disease progression. Although extensive research has been conducted, the precise molecular mechanisms remain incompletely elucidated; current hypotheses primarily involve inflammatory responses, oxidative stress, and endothelial dysfunction. This review comprehensively summarizes current knowledge regarding the association between hyperuricemia and common cardiovascular diseases, as well as the potential underlying mechanisms, with the aim of identifying novel therapeutic targets and providing insights for foundational research into uric acid-related cardiovascular disorders.

Keywords

Uric Acid, Cardiovascular Disease, Molecular Mechanism

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1. 引言

尿酸是人体嘌呤代谢的终产物，由黄嘌呤经黄嘌呤氧化酶经过几个步骤形成，由尿液排出体外。尿酸主要在肝脏、肠道和血管内皮中合成，作为外源性嘌呤库的最终产物，内源性来自受损、垂死和死亡的细胞，核酸、腺嘌呤和鸟嘌呤被降解为尿酸[1]。正常情况下大多数尿酸都是在尿酸酶的作用下将尿酸分解为 5-羟基异脲，进一步降解为尿囊酸和氨，经过肾脏排泄。在生理条件下，尿酸的生成和排泄呈动态平衡，一旦这种平衡被破坏，就会导致血尿酸水平异常。无论男性还是女性，非同日 2 次血尿酸水平超过 420 $\mu\text{mol/L}$ ，称之为高尿酸血症(Hyperuricemia)[2]。Borghi 等人对平均年龄 63.2 岁的 7531 名患者进行的 EURIKA 研究的亚组分析表明，SUA 水平升高与心血管疾病风险的发生率存在显著正相关[3]。

2. 尿酸与常见心血管疾病的关系

2.1. 冠状动脉疾病(Coronary Artery Disease, CAD)

近些年研究表明尿酸水平与 CAD 之间存在密切的关系，高尿酸血症是 CAD 的潜在致病因素。冠状动脉狭窄的程度决定了 CAD 的严重程度，这与高尿酸血症呈正相关[4]，冠状动脉狭窄由冠状动脉粥样硬化和冠状动脉斑块形成引起，与心负荷和缺血的严重程度呈正相关[5]。通过检测非钙化冠状动脉斑块的发生率来评估亚临床冠状动脉粥样硬化与高尿酸血症之间的关系，这证实了冠状动脉斑块的发生率随着尿酸浓度的增加而增加[6]。研究发现，通过光学相干断层扫描评估的冠状动脉斑块的严重程度与尿酸浓度相关，而尿酸浓度又与冠状动脉斑块的钙化长度、最大血脂弧和平均血脂弧呈正相关[7]，一项前瞻性研究表明，用于评估冠状动脉狭窄的 gensini 评分随着尿酸水平的增加而显著增加[4]，表明冠状动脉狭窄的严重程度与尿酸之间可能存在浓度依赖性关系。冠状动脉钙化作为动脉粥样硬化的标志之一，可预测心血管疾病的发生，荟萃分析显示，SUA 水平每增加 59.5 $\mu\text{mol/L}$ ，冠状动脉钙化进展的风险将增加 31% [8]。

许多研究表明，高尿酸血症与 CAD 患者发生不良心血管事件有关，Kim 等人研究高尿酸血症和冠心病的系统评价和荟萃分析结果显示血尿酸每增加 12 mg/dL ，CAD 导致的死亡风险就会增加 1% [9]，多项

研究表明高尿酸血症是冠心病的独立危险因素。意大利的一项大规模纵向研究纳入 22,714 人结果显示 SUA 水平与总死亡率(任何原因所致死亡率)和心血管死亡率独立相关,尿酸水平超过 333.1 $\mu\text{mol/L}$ 可作为预测心血管死亡率增加的阈值[10]。一项对没有心血管疾病的受试者进行的前瞻性队列研究发现,血清尿酸浓度 $> 7.0 \text{ mg/dL}$ 显著增加了普通人群(主要是成年女性)患 CAD 的风险[11]。sUA 每增加 1 mg/dL , 心血管死亡率和全因死亡率分别增加 12% 和 20% [12]。血尿酸水平升高已被证明是 PCI 后发生 MACE 事件的危险因素,最近的研究表明,与非高尿酸血症患者相比,接受 PCI 的慢性冠状动脉综合征(CCS)并发病的高尿酸血症个体的 MACE 发生率是非高尿酸血症患者的两倍,这突出了高尿酸血症是 PCI 后 MACE 的潜在预测因子[13] [14]。通过比较随访长达 6 年的患者的死亡率,发现高尿酸血症患者的百分比几乎是尿酸正常患者的两倍,从而得出高尿酸血症与 NSTEMI 长期死亡率相关的结论[15]。高尿酸血症和 CAD 之间的相关性因性别、种族和地域而异,这可能归因于不同的激素水平、生理组织、饮食习惯、环境和遗传学[16]。但新出现的证据表明,高尿酸血症是 CAD 死亡和并发症发生率的独立预测因子和独立危险因素。

高尿酸水平加剧氧化应激,过量 ROS 诱导的氧化应激是动脉粥样硬化的主要机制之一[17],在尿酸产生过程中,黄嘌呤氧化酶的活性增加,促使活性氧升高,ROS 升高可诱导小动脉平滑肌细胞的迁移和增殖以及单核细胞趋化蛋白-1 的产生,参与动脉粥样硬化的发展[18]。高浓度的尿酸参与烟酰胺腺嘌呤二核苷酸磷酸氧化酶的激活以及氧化应激,降低 NO 合酶活性,减少或消耗 NO 的产生,促进活性氧的产生,通过激活 ERK/AP1 信号通路刺激平滑肌细胞的增殖和内皮素-1 的表达,从而诱导血管收缩和成纤维细胞增殖,导致血管硬化和内皮功能受损[19]-[21]。动脉粥样硬化是一种炎症性疾病[22],尿酸本身和尿酸诱导的活性氧可以激活炎症小体和多个相关信号调节通路,导致炎症因子产生、血管平滑肌细胞增殖和迁移以及血管内皮功能障碍。例如,尿酸激活 EPK/p38 MAPK 级联反应、通过抑制 AKT 通路和引起胰岛素抵抗来参与动脉粥样硬化斑块形成[23] [24]。因此高尿酸血症是 CAD 的独立危险因素,可以通过以上作用机制来抑制高尿酸血症对 CAD 的损害来指导临床治疗。

2.2. 心力衰竭(Heart Failure, HF)

HF 作为一种全身性疾病, HF 代表血流动力学衰竭和多个其他器官和系统的神经内分泌激活,据报道,在发达国家, HF 是 65 岁以上患者非择期住院的主要原因[25]。高尿酸血症与 HF 之间的明确病理生理学联系尚未得到证实,但是高尿酸血症与许多已确定的 HF 危险因素有关,这意味着高尿酸血症可能在 HF 中起着至关重要的作用[26]。一项报告成年患者 HF 发病率和结局的系统评价和荟萃分析发现,高尿酸血症与 HF 发生风险增加相关,UA 每增加 1 mg/dL , HF 发展的几率增加 19% [27]。血清尿酸水平可以单独提供预后信息,也可以与其他心脏功能指标联合使用,包括左心室射血分数,有两种主要的 HF 表型,射血分数降低与保留的心力衰竭(HFrEF, HFpEF), Alberto 等人证明,在 HFrEF 和 HFpEF 患者中,高尿酸血症与原发住院或死亡有关,并且高尿酸血症的患病率及其与主要结局的关系强度在 HFpEF 患者中更大[26]。一项关于 NHANES 数据库的队列研究发现,在多变量二元 logistic 回归模型中,与没有高尿酸血症或痛风的患者相比,有高尿酸血症或痛风患者患 HF 的可能性分别高 2.46 倍和 2.35 倍;在多变量 Cox 比例风险模型和 Kaplan-Meier 生存曲线中,患有高尿酸血症或痛风的 HF 患者发生全因和心血管死亡的风险更高[28]。Deis 等人在他们的研究中发现,除了需要放置左心室辅助装置和心脏移植外,血清尿酸水平升高是全因死亡率的有力且独立的预测指标。血清尿酸水平每增加 15%,全因死亡风险增加 10%。这项研究还发现血清尿酸水平、左室充盈压和中枢血流动力学之间存在很强的相关性[29]。此外,作为一种降低尿酸的药物别嘌醇据报道,可以改善 HF 患者的预后,并且成为西雅图 HF 模型中生存率提高的标志物[26],尽管有力的证据证明高尿酸血症和 HF 之间存在因果关系,但大多数孟德尔随机化研究表明血清尿酸水平与 HF 无关[30]。血清尿酸是一种简单且廉价的实验室测量方法,具有广泛的临床应用价值,

因此高尿酸血症不仅可能是 HF 不良结局的危险因素,而且是 HF 不良结局的有力且独立的预测因子。

尽管高尿酸血症和 HF 之间的因果关系尚不清楚,但实验和临床研究表明,高尿酸血症可能是致病性的,并可能通过氧化应激、内皮功能障碍、血管炎症及左心室功能障碍等相关分子机制致病。上调的黄嘌呤氧化酶可通过衍生的尿酸和活性氧诱导的氧化应激促进 HF 的发病机制,活性氧和尿酸产生的增加会导致过度的氧化应激、蛋白质和脂质过氧化、DNA 损伤,并最终导致不可逆的心肌细胞损伤[26]。活性氧很容易与内皮衍生的 NO 相互作用产生 ONOO⁻,这会降低 NO 生物利用度[31],并开始对内皮细胞产生一连串有害的氧自由基效应,导致 HF 中的血管内皮功能障碍。此外,过度的心脏纤维化被认为是慢性心力衰竭(Chronic Heart Failure, CHF)的重要有害因素。活性氧通过诱导心脏成纤维细胞增殖和激活黄嘌呤氧化酶介导的基质金属蛋白酶在心脏纤维化中发挥作用,从而导致细胞外重塑[32]。James 等报道,活性氧抑制了肌浆网和肌浆网的 Ca²⁺ ATP 酶的 Ca²⁺积累,诱导心脏收缩力降低。别嘌呤醇降低了活性氧对肌丝 Ca²⁺敏感性,有助于改善左室收缩功能和效率[33]。Yue 发现了尿酸诱导的人内皮细胞衰老和死亡是通过氧化应激和肾素-血管紧张素系统的局部激活来治疗的,这为尿酸诱导的内皮功能障碍提供了一种新的机制[34]。积累的数据表明,这种氧化代谢受损是 HF 伴高尿酸血症的核心发病机制,它与内皮功能障碍、心肌纤维化、左心室重塑和收缩力障碍的发展有关,导致 HF 患者临床状况恶化。

高尿酸血症通过多种机制诱导血管炎症,包括氧化应激、血管平滑肌细胞增殖和内皮细胞损伤。一项研究结果表明,可溶性尿酸可以释放趋化因子和粘附分子[34],Hui 等揭示了尿酸通过 Nod 样受体蛋白 3(NLRP3)炎性小体介导的 VSMC 增殖诱导炎症[35]。AMP 活化蛋白激酶(AMPK)和核因子- κ B(NF- κ B)是介导炎症反应和参与尿酸诱导的炎症因子表达的主要通路[36][37]。因此,可溶性 UA 和 ROS 的炎症可能共同导致 HF 的进展。

2.3. 心房颤动(Atrial Fibrillation, AF)

高尿酸血症与 AF 之间的关联是众所周知的[38][39],高尿酸血症是导致心房损伤和 AF 的重要危险因素,临床证据表明,血清尿酸水平与未来 AF 患病率风险增加相关[40]。一项包含 31 项研究、共 504,958 名参与者的荟萃分析显示以及 8 项队列研究的结果表明,尿酸水平升高 AF 的发病风险显著相关,而 29 项研究的结果显示 AF 患者的尿酸水平会升高[41]。来自日本的一项针对 325,771 名接受常规体检者的横断面研究表明,在男性和女性中,尿酸水平均是独立于其他心血管危险因素的 AF 相关因素[42],事实上,迄今为止,性别对血清尿酸和 AF 之间关联的影响仍然存在争议。在一项纳入 7155 例患者的队列研究,以及一项纳入 970 例连续住院患者的病例对照研究结果显示,无论性别如何,SUA 水平均显著增加了 AF 的患病率,在调整了 AF 的多个相关因素后,血清尿酸对 AF 的影响仅在女性中是独立的[43][44]。但在一项涉及 11,956 名参与者的横断面研究中,血清尿酸与 AF 的患病率呈正相关,这种独立关联仅在男性中显著[45]。在一项纳入 15,382 名年龄在 45~64 岁之间的受试者的 ARIC 研究,结果表明 AF 的发生率与血清尿酸浓度的增加平行,血清尿酸每增加 1 个标准差 AF 风险增加 16%,主要在非裔美国人和女性中[46]。现有较少的研究报道血清尿酸水平与 AF 亚型之间的关系。一项早期研究纳入了 45 例阵发性 AF 患者、41 例永久性 AF 患者和 48 例对照组参与者,结果显示血清尿酸增加与永久性 AF 相关[40]。另一项荟萃分析表明,新发、阵发性和持续性 AF 参与者的 SUA 水平存在显著差异[47]。在一项纳入高尿酸血症组(n = 114)和对照组(n = 609),并在 AF 导管消融后随访中位数 24 个月,发现高尿酸血症患者在阵发性 AF 导管消融术后心律失常复发的风险可能很高。虽然饮酒可能导致尿酸水平升高,但高尿酸血症的存在可以独立预测 AF 复发[48]。此外,另一项横断面研究显示,即使没有任何合并症(高血压、糖尿病、血脂异常、慢性肾病以及高尿酸血症或痛风)的普通健康人群中,高尿酸血症也是心房颤动的一个独立竞争性危险因素[49]。高尿酸血症和 AF 的大规模队列研究表明,两者之间存在密切的联系,仍需进行

更大规模的临床试验进行验证。

高尿酸血症与 AF 相关的机制尚未完全明确,可能通过直接或间接机制促成 AF 的发生。高尿酸血症与高血压、糖尿病、代谢综合征及慢性肾病(CKD)相关,而这些疾病均被视为心房颤动的危险因素。高尿酸血症也可能通过其他危险因素间接诱发心房颤动。先前的研究表明,高尿酸血症通过多种机制(例如炎症,氧化应激,纤维化,凋亡,凋亡及其相关的免疫反应)与心脏电生理和结构重塑有关[36],可能通过炎症诱导效应和非炎症依赖效应直接影响心房颤动的发生。高水平的尿酸被认为是临床实践中的炎症因子[50],越来越多的证据表明炎症参与 AF 的发生和维持[51],尿酸盐结晶可通过激活巨噬细胞中含 NACHT、LRR 和 PYD 结构域的蛋白 3 (NLRP3)炎症小体引发炎症[52]。另外,可溶性尿酸可通过尿酸转运体进入细胞,通过尿酸转运体激活导致的细胞内尿酸积累, Maharani 等人发现尿酸导致 KV1.5 蛋白的表达增加,心房心肌细胞的电生理学中起着重要作用,通过调节动作势重极化并缩短动作电位持续时间,这有助于心房颤动折返环的形成[53] [54]。已有一些实验研究结果支持尿酸在心房颤动中发挥作用[52],但几乎没有临床证据表明降尿酸治疗可预防心房颤动的诱发。我们需要进一步开展大规模临床研究,以验证针对高尿酸血症或痛风患者的降尿酸治疗是否能预防新发心房颤动。

3. 降尿酸治疗与心血管结局: 从临床试验证据到实践指南

降尿酸治疗可分为两大类,使用 XO 抑制剂(例如别嘌醇、非布司他和托吡司他)减少尿酸的产生,以及使用尿酸排泄剂(例如丙磺舒、苯溴马隆和多替努拉)。别嘌醇是常规的降尿酸治疗方法,非布司他是一种最近得到充分研究的药物。在此背景下,CARES 研究对非布司他对心血管的安全性提出了质疑[55]。在这项双盲、非劣效性随机对照试验中,6190 名痛风患者被随机分配接受非布司他或安慰剂治疗,中位随访时间为 32 个月。非布司他组和别嘌醇组的主要终点分别为 10.8%和 10.4%,符合非布司他的非劣效性($p = 0.002$),但非布司他组的全因死亡率(7.8% vs. 6.4%, $p = 0.04$)和心血管死亡率(4.3% vs. 3.2%, $p = 0.03$)显著高于别嘌醇组[55]。根据结果,美国食品和药物管理局增加了一个黑框警告,警告非布司他会增加死亡风险。然而,在 CARES 研究中,大量患者停止了试验治疗,并未完成临床随访。最近发表的 FAST 研究($n = 6128$)是一项开放标签、盲法终点、非劣效性 RCT,在中位随访期 48 个月内,未发现非布司他组的死亡率高于别嘌醇组的信号[56]。非布司他符合非劣效性,非布司他组的全因死亡率甚至低于别嘌醇组(3.5% vs. 5.7%, HR 0.75, 95% CI 0.59~0.95)。此外, FREED 研究还提到了非布司他与别嘌醇相比可能获益[57]。在 35 个月的中位随访期内,非布司他组和非非布司他组的脑、心血管和肾脏事件以及所有死亡分别为 23.3%和 28.7% ($p = 0.02$),这主要是由蛋白尿恶化的差异驱动的。FEATHER、FREED 和 PRIZE 研究没有发现非布司他在日本患者中死亡率增加的迹象,以及 FAST 研究,这加强了该药物的安全性。除别嘌醇和非布司他外,抗高尿酸血症药物对临床结果的治疗影响大多未知。综上所述,尽管别嘌醇和非布司他抑制 XO 可能对特定人群的替代终点(如血压、内皮功能、蛋白尿和颈动脉内膜-中层厚度)有益,但降尿酸治疗对临床结局的疗效尚未确定[58]。

4. 讨论

高尿酸血症与高血压、高脂血症、糖尿病、代谢综合征和肾脏疾病相关,所有这些都可能导致冠心病和全因死亡率增加。在过去几十年中,相关研究提供了关于高尿酸血症与冠心病或全因死亡率之间关联的相互矛盾的证据;因此,高尿酸血症是否是冠心病死亡的独立风险和致病因素仍不清楚[58]。这种现象可能与入组人群的差异、高尿酸血症的定义、研究的结果、随访时间、样本量和统计调整有关。人们越来越关注降尿酸盐治疗是否能改善心血管结局。高血压患者经常出现高尿酸血症。与 SUA 水平正常的患者相比,高尿酸血症和高血压患者的冠心病增加 3~5 倍[59]。LIFE 是第一项证明降低 SUA 水平与高血

压患者心血管事件减少相关的研究[60]。别嘌醇是一种黄嘌呤抑制剂,常用于高尿酸血症患者以降低 SUA 水平。一项纳入 10 项研究的 meta 分析显示,别嘌醇可使血压微小但显著降低[61]。大剂量别嘌醇治疗可延长运动时胸痛的时间,并改善稳定型心绞痛患者的内皮功能障碍[62]。别嘌醇的这些作用可能有助于降低未来的心血管死亡率。令人鼓舞的是,一项前瞻性队列研究(n = 7135)表明,大剂量别嘌醇治疗可降低心血管事件和死亡风险[63]。尽管先前的研究尚未提供直接证据表明降尿酸盐治疗可降低高尿酸血症患者冠心病的死亡风险,但上述研究提供了一些积极的数据。因此,有必要进行进一步的研究。

高尿酸血症与心血管疾病的关系越来越清晰,这归因于高尿酸血症的研究进展。首先, Tomiyama 等人发现,高尿酸血症会增加动脉硬化程度和炎症的发生,这可能与高血压发生的风险有关[64]。其次, UA 通过 AMPK-mTOR-mROS 和 HIF-1 α 通路诱导 NLRP3 炎性小体依赖性炎症激活,相反, UA 水平的降低促进 AMPK 的激活,抑制动脉粥样硬化斑块的形成[35]。此外, UA 显著增强 Kv1.5 蛋白的表达,增强 Akt 和 HSF 磷酸化,导致 Hsp70 表达增加。这一结果表明,抑制 Akt-HSF1-Hsp70 通路可能是治疗高尿酸血症患者 AF 的一种新方法[65]。

SUA 水平升高与 CAD、心力衰竭、心房颤动等心血管疾病相关,且有助于风险分层。然而,关于高尿酸血症增加心血管风险的机制、降低尿酸水平对心血管疾病风险的益处以及高尿酸血症与冠心病等心血管疾病风险之间的关联等方面仍存在争议[66],降低尿酸治疗对心血管事件预后的有益影响虽然已经被提出,但其具体效力和临床收益仍不确定,未来对高尿酸血症与心血管事件风险的进一步研究是必要的。

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