

导管消融术改善心房颤动患者肾功能受损的研究进展

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收稿日期: 2024年8月12日; 录用日期: 2024年9月5日; 发布日期: 2024年9月12日

摘要

心房颤动(Atrial fibrillation, AF)是最常见的持续性心律失常, 慢性房颤可通过各种机制引起肾功能损伤, 导致或加重慢性肾脏病(chronic kidney disease, CKD)。而CKD患者也常合并AF, 二者之间有着密切的相关性。目前导管消融术已成为AF的一线治疗, 在维持窦性心律、改善预后等方面较药物治疗更优。已有研究证实AF导管消融术后部分患者肾功能得到显著改善, 但其中具体的关系尚不明确。本文就AF与CKD之间复杂的病理生理学相关性及其AF导管消融延缓肾功能衰退的相关研究进行文献综述。

关键词

心房颤动, 导管消融术, 慢性肾脏病

Research Advances of Catheter Ablation Improving Renal Function Impairment in Patients with Atrial Fibrillation

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Received: Aug. 12th, 2024; accepted: Sep. 5th, 2024; published: Sep. 12th, 2024

Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. Chronic AF, through various pathophysiological mechanisms, can adversely affect renal function, leading to the initiation

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文章引用: 陈小玲, 李传伟. 导管消融术改善心房颤动患者肾功能受损的研究进展[J]. 临床医学进展, 2024, 14(9): 758-764. DOI: 10.12677/acm.2024.1492526

or exacerbation of chronic kidney disease (CKD). The bidirectional relationship between CKD and AF is well-documented, with both conditions frequently coexisting. Presently, catheter ablation (CA) is considered the first-line treatment for AF, demonstrating superiority over pharmacological therapy in maintaining sinus rhythm and improving prognosis. Numerous studies have indicated that CA can significantly enhance renal function, although the precise mechanisms underlying this improvement remain to be fully elucidated.

Keywords

Atrial Fibrillation, Catheter Ablation, Chronic Kidney Disease

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1. 引言

心房颤动(Atrial fibrillation, AF)是指规则有序的心房电活动丧失,代之以快速无序的颤动波,是常见且严重的心房电活动紊乱,易反复发作。慢性肾脏病(Chronic kidney disease, CKD)亦是老年人常见的慢性病之一,AF和CKD之间存在互相促进的关系,共同导致患者的不良预后[1]。导管消融(Catheter ablation, CA)现已成为药物难治症状性AF的主要治疗手段[2],CA不仅在维持患者窦性心律及改善房颤相关不良预后(生活质量、心力衰竭、痴呆、卒中)等方面效果显著[3]-[5],而且还可改善肾功能受损、延缓CKD进展。现就AF与CKD之间复杂的机制及AF导管消融改善肾功能及延缓CKD进展的相关研究做一文献综述。

2. CKD与AF的流行病学

AF与CKD之间密切相关,AF可促进CKD的进展过程,而CKD又可增加AF发作的风险。受到研究人群、年龄、性别和AF检测方法不同等诸多因素的影响,目前估计成人房颤患病率在2%至4%之间[6]。其中CRIC研究[7]及EGARDS研究[8]等国外的大型流行病学研究均证实CKD患者AF的发生风险明显高于非CKD患者,约为普通人群的2~3倍[1]。CRIC研究纳入3267例轻-中度肾功能不全的非透析患者,其中有18%的患者发作过AF,而在终末期肾病患者中预估AF的患病率可达13%~23%[7]。即使是在接受充分透析(每周3次)的CKD患者中,AF发病率也是高达15.4%[9]。ARIC研究对10,328例无AF病史的患者进行了长达10.1年随访,他们发现更低的估计肾小球滤过率(estimated glomerular filtration rate, eGFR)和(或)大量蛋白尿将显著增加AF的发生风险[10]。韩国一项对4,827,987例无AF病史的大型观察研究证实即使是轻度CKD也与AF发生率相关,且随着肾功能的下降房颤发作的风险逐步增加[11]。

虽然在一般人群中,肾功能将随着年龄增加而呈现生理性的逐年下降,但中度CKD患者AF发生比例明显高于轻度CKD及肾功能正常[12],国外关于CKD患者AF发病率的大型流行病学研究发现肾功能逐步恶化是AF发生发展独立于年龄、种族及性别之外的危险因素[7][8][10]。此外,AF患者也更容易出现肾功能损害,甚至可导致终末期肾病进展到肾脏替代治疗阶段[13][14]。国内一项纳入2298例既往无肾脏疾病的非瓣膜病AF研究中,有高达47.4%的患者在病程中出现了肾功能损害。而老年、非阵发性AF、使用血管紧张素转化酶抑制剂/血管紧张素受体拮抗剂、合并充血性心力衰竭、左室射血分数<50%、既往有短暂性脑缺血发作/卒中/血栓病史的AF患者更容易出现肾功能受损[15]。

CKD 患者 AF 的发病率较非 CKD 高, 且房颤发生率与 CKD 严重程度呈现正相关性[10]。故对 CKD 患者早期诊断及长期随访中行心电图评估, 及时发现 AF 并及早行 AF 节律控制将有助于改善 CKD 预后。

3. AF 与 CKD 之间的机制简述

AF 和 CKD 之间相互促进, 互为因果。首先 AF 与 CKD 具有多种共同的危险因素, 如高龄、高血压、糖尿病、动脉硬化等, 因此具有发病的“共同土壤”。此外还有多种病理生理学机制共同参与 AF 和 CKD 的发生发展。

1) **炎症反应:** 慢性炎症反应已被证实是 AF 和 CKD 发生发展的共同机制[16] [17]。

2) **神经内分泌激活:** 肾素 - 血管紧张素 - 醛固酮系统(Renin-angiotensin-aldosterone system, RAAS)的激活可以导致心房压力过载和心肌纤维化, 从而促进 AF 的发生[18]; 同时 RAAS 激活也是 CKD 发生发展的重要原因[19]。

3) **尿毒症毒素:** 尿毒症毒素硫酸吡啶酚可导致肺静脉钙泄漏[20], 而钙离子处理异常在房颤的发生及发展中起着核心作用[21]。尿毒症毒素不仅导致肾脏功能损害, 还与心血管纤维化、氧化应激、炎症和神经内分泌激活途径有关[22]。

4) **代谢异常:** CKD 患者的钙、磷等代谢异常导致心脏瓣膜钙化, 引起或加重瓣膜性心脏病[23], 这些结构变化可能通过压力过载进一步促进 AF 的发展。

5) **抗凝药的使用:** 抗凝药的使用可导致红细胞管型或血红蛋白尿引起肾小管堵塞, 以及红细胞破坏后铁离子对肾小管损伤可引起抗凝相关肾病(Anticoagulant-related nephropathy, ARN)。维生素 K 拮抗剂导致 ARN 的比例高达 37%, 而非维生素 K 依赖口服抗凝药约占 ARN 的 5%~14% [24]。

6) **血液动力学影响:** AF 导致房室不同步, 心房辅助功能丧失及心输出量减少致心肾综合征也能引起肾脏灌注减少。

7) **心房颤动引起的血栓:** AF 血栓脱落引起肾动脉栓塞或肾脏内微血栓形成, 均可引起肾缺血损伤。

4. CKD 与 AF 预后

CKD 的存在本身即可导致患者的远期预后不良, 而合并房颤则显著增加不良事件风险。由于 AF 卒中风险 CHA2DS2-VASc 评分和出血风险 HAS-BLED 评分间接或直接受到肾功能的影响, 因此 CKD4-5 期患者的 CHA2DS2-VASc 评分及 HAS-BLED 评分明显高于 CKD 1~3 期, 这表明 CKD 的存在显著增加了 AF 患者卒中及出血风险[25]。同时非维生素 K 拮抗剂类口服抗凝药需部分通过肾脏代谢, 肾功能受损时需根据 eGFR 调整剂量, CKD4-5 期时则存在使用禁忌, 导致很多合并 CKD 的 AF 患者未得到充分的抗凝治疗, 从而增加系统性栓塞(缺血性卒中、外周动脉栓塞)的风险。此外 CKD 的存在也影响了 AF 导管消融术后的预后, 多项研究均证实 CKD 与消融后 AF 复发相关, 更低的 eGFR 是 AF 复发的独立预测因素之一[26]-[29]。

5. 导管消融术对肾功能的保护作用

CA 不仅在 AF 节律控制方面疗效显著, 可有效降低心力衰竭和死亡风险[30] [31], 还可改善肾功能受损、延缓肾功能恶化。且 CKD 并不会显著增加 CA 术中并发症、AF 再入院、电转复的风险[32]。CA 不仅能显著降低 AF 患者的脑钠肽、尿酸、硫酸吡啶酚、尿酸/肌酐比值等生物标志物[33] [34], 还可以显著改善 AF 患者肾功能。已有研究报道了 CA 术使晚期、轻 - 中度 CKD 患者的 eGFR 普遍改善[35] [36]。虽然 Navaravong L 等的研究中 $eGFR > 90 \text{ ml}^{-1} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^2$ 的患者肾功能甚至出现下降[35], 但这可能与该部分人群中女性及糖尿病患者更多以及平均年龄更大相关。而在轻度肾功能受损($eGFR$ 在 $60 \sim 90 \text{ ml}^{-1} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^2$)的 AF 患者中, 即使是术后 AF 复发, 患者肾功能也得到了显著改善[36] [37]。这与 CA

术后 AF 负荷明显降低, 甚至恢复窦性心律, 改善肾脏灌注, 极大程度上阻止并逆转了心肾综合征对肾功能的损害相关, 这一点在轻度肾功能损害的患者中尤为明显。同时, 肾脏灌注的改善将大大增加尿素物质排除, 进一步改善肾功能。此外, 窦性心律情况下, RAAS 系统激活下调, 可进一步减少了肾功能损伤因素。CA 术均需住院完成, 医生对患者糖尿病、高血压等合并存在的共同危险因素进行规范化的治疗及管理或许也是 CA 术后肾功能改善的原因之一。

虽然 Diaz C L 等发现各类型的 AF 在 CA 术后肾功能均有改善, 但改善程度与房颤的分型无关[36]。但也有研究报道了持续性 AF 在 CA 术后 6 月的 eGFR 升高明显, 而在阵发性 AF 中肾功能的改善无统计学意义[34]。这可能是由于后者的研究人群中阵发性 AF 患者肾功能受损程度平均处于轻 - 中度, 其肾功能明显优于持续性 AF, 而术前 $\text{eGFR} > 90 \text{ ml}^{-1} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^2$ 的 AF 患者术后肾功能无明显变化[36]。同时前者是将肾功能不全各阶段的患者分别进行了不同类型 AF 患者肾功能改善程度的比较, 其中存在的统计分析差异也可引起上述结果的差异。此外, CA 术在改善肾功能方面显著优于药物治疗。Mimuro R 等[38]以及 Park J W 等[39]分别通过倾向性匹配分析法对比了药物治疗及 CA 术对肾功能的保护作用, 接受 CA 术的患者倾向于获得更好的肾脏功能保护。肾功能改善在 CA 术后可维持窦性心律者和非糖尿病患者中更为明显, 即使是 AF 复发的患者 eGFR 也可维持稳定。但另有研究却发现 AF 晚期复发患者的 eGFR 明显下降[40]。

一项多中心、前瞻性研究发现, 中度 CKD ($\text{eGFR} 30 \sim 59 \text{ ml/min/1.73 m}^2$) 患者的 AF 复发率明显高于轻度 CKD 或肾功能正常者[12]。同样地, 国内一项纳入 1407 例非瓣膜病 AF 的研究也发现随着肾功能逐渐恶化, AF 复发率逐渐增加[26]。一项荟萃分析表明合并 CKD 的 AF 患者消融后复发率高于非 CKD 患者[28]。而女性、末次消融后 AF 晚期复发、术后使用维生素 K 拮抗剂和醛固酮受体拮抗剂是术后 CKD 快速进展的可能危险因素[40]。术前 CHA₂DS₂-VASc 评分 < 2 , 左房内径 $< 45 \text{ mm}$, 或左室射血分数 $\geq 50\%$, 且无高血压、糖尿病、血管疾病等合并症, 非晚期 CKD ($\text{eGFR} > 60 \text{ ml}^{-1} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^2$) 的患者在消融术后更容易维持窦性心律及获得显著肾功能改善。但合并糖尿病会削弱 CA 术对肾功能的改善作用[39]。另外, 左房纤维化、AF 类型[35]、左房大小[41]、年龄、充血性心衰、体重指数[26]等也与 CA 术后 AF 复发也有关, 这与严重的心功能衰竭、老龄、非阵发性 AF 患者的肾功能更差是相一致的。目前的研究未能证实 CKD 与 AF 复发之间有明确的因果关系, 或是 CKD 仅仅反应了 AF 患者更差的心房基质及一般情况。但基于上述对 CA 术后 AF 复发的危险因素研究, CA 术后采取严格的 AF 上游治疗及肾功能保护措施, 如控制血糖、高血压、心力衰竭、慎用损伤肾功能药物等措施, 将有助于 AF 患者获得更好的 CA 术效果。

综上, 国内外研究结论表明 CA 可显著改善 AF 患者受损的肾功能, 尤其是术后维持窦性心律者。虽然目前也有研究表明术前 $\text{eGFR} > 90 \text{ ml}^{-1} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^2$ 的 AF 患者术后肾功能无明显变化, 但这或许证实了 CA 术对本身肾功能正常者影响甚微。由于掺杂了糖尿病、高血压等合并症, 性别、心脏大小等因素的影响, 目前 CA 术是否对术后 AF 复发者的肾功能也有明显保护作用仍有争议, 但可以肯定的是 CA 减轻了 AF 负荷, 亦能减少 AF 的亚临床器官损害, 可推迟 CKD 分期恶化的时间。虽然 CA 术对阵发性 AF 肾功能的保护作用是否优于持续性 AF 仍有待证实, 但是仅从阵发性 AF 的肾功能明显优于持续性 AF, 而 AF 的存在可进一步加重 CKD 这一方面来说, CA 术应尽早实施为宜。总体而言, 上述研究结论对临床工作中 AF 节律控制方案的选择提供了更多证据支持, 同时对于临床工作者术前判断手术成功率及推荐患者行 CA 术时机也提供了参考经验, 至少对存在相关复发高危因素的患者, 应该及早评估 CA 术。未来需更多的大型研究针对上述问题做出进一步探讨。

6. 总结

AF 可通过各种机制导致 CKD 的发生发展, 而 CKD 也易合并心房颤动。二者不仅共有多种危险因

素,同时潜在的多种机制,如炎症、RAAS系统激活、尿毒素物质体内蓄积等也参与了AF和CKD的发病。CA术在控制AF节律方面显著优于药物治疗,并可显著改善AF受损的肾功能及延缓CKD进展,尤其是术后窦性心律维持者获益更加显著。更低的eGFR是消融术AF复发独立预测因素之一,在AF患者CKD发生之前或早期行CA术,或许可降低AF的复发率。未来需要更多的研究来探索AF消融术对CKD患者肾功能影响。

基金项目

重庆市自然科学基金(CSTB2023NSCQMSX034),重庆市教育委员会科学技术研究计划项目(KJQN202300114)。

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