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终末期肾病患者难治性高血压致病机制及治疗研究进展

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摘　要

高血压是心脑血管疾病的主要危险因素之一，会增加心衰、脑卒中、冠心病等疾病的发生风险。难治性高血压是高血压的一种特殊类型，对于常规降压方案无效或不敏感。该类患者由于血压长期不达标，其心血管事件发生风险远高于一般高血压患者。在终末期肾病患者中由于液体潴留、动脉僵硬度增加、肾脏代谢异常等因素，难治性高血压发生率相对较高。然而目前关于该类患者高血压发生或进展的致病机制尚不明确且常规降压治疗效果欠佳。本文就终末期肾病患者难治性高血压致病机制及治疗策略作简要阐述。

关键词

终末期肾病，难治性高血压，致病机制，药物治疗，手术治疗

Research Progress on Pathogenesis and Treatment of Refractory Hypertension in Patients with End-Stage Renal Disease

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Abstract

Hypertension is one of the main risk factors of cardiovascular and cerebrovascular diseases, which will increase the risk of heart failure, stroke, coronary heart disease and other diseases. Treatment-resistant hypertension is a specific type of high blood pressure that is ineffective or insensitive to conventional blood pressure lowering regiments. Due to long-term substandard blood pressure, the risk of cardiovascular events in these patients is much higher than that in general hypertensive patients. The incidence of refractory hypertension is relatively high in patients with end-stage renal disease due to fluid retention, increased arterial stiffness and abnormal renal metabolism. However, the pathogenesis of hypertension in these patients is still unclear and the effect of conventional antihypertensive therapy is not good. In this paper, the pathogenesis and treatment strategies of refractory hypertension in patients with end-stage renal disease were briefly reviewed.

Keywords

End-Stage Renal Disease, Refractory Hypertension, Pathogenesis, Drug Therapy, Surgical Treatment

1. 引言

慢性肾脏病(CKD)已成为全球性公共卫生问题，是导致全球非传染性疾病死亡的主要原因之一。中国CKD 患病人数近 1 亿人，因终末期肾病(ESKD)接受透析患者的数量接近 110 万人，并呈现快速增长态势[1]。在我国 67.3%的非透析 CKD 患者合并有高血压，且高血压患病率随 CKD 分期进展而升高，ESKD 高达 91% [2]。高血压促进了肾功能的恶化，同时也可导致 CKD 患者心脏重构，增加心血管事件发生风险。临床上将应用了足量的 3 种降压药(包括一种噻嗪类利尿剂)血压仍不能控制在目标范围内或至少需要 4 种药物才能使血压达标的状态定义为难治性高血压[3]。随着肾功能恶化的进展，尤其发展成终末期肾病乃至透析时，因交感神经异常激活等因素，难治性高血压在 ESKD 患者中发生的比例很高[4]。这类患者即便服用多种降压药物，血压依旧难以达标，其心血管事件及死亡发生风险相较非难治性高血压患者明显增高，是目前临床亟待解决的难题。了解高血压进展的致病机制及治疗策略对于预防和管理终末期肾病患者的难治性高血压至关重要。

2. 终末期肾病患者难治性高血压的病理生理机制

2.1. 液体潴留

容量超负荷是导致 ESKD 患者血压升高的重要因素[5]。欧洲多中心数据显示，超过 60%的透析患者表现出不同程度的容量超负荷，其中容量超 2.5~5 L 的占到了 23%以上[6]。一项纳入 150 名高血压血液透析患者的随机临床研究发现透析达到干体重后患者 44 小时动态血压收缩压/舒张压平均降低 6.9/3.1 mmHg [7]。一方面肾小球滤过能力差导致尿量下降液体潴留。另一方面透析时为维持血流动力学稳定，通常透析液钠浓度较高，这可能会加重水钠潴留[8]。容量评估对于长期透析患者尤为重要，但也有人担心积极的容量管理可能会导致残余肾功能更快丧失。对于透析患者，观察性研究表明持续使用袢利尿剂

可减少透析中水肿事件和降低住院风险[9] [10]。然而使用袢利尿剂改善容量和血压控制能否保留残余肾功能的数据有限[11]。

2.2. 动脉僵硬度增加

动脉僵硬度增加是 ESKD 高血压，患者收缩期高血压的另一个重要原因[12]。在 179 例接受 ACEI 治疗的高血压透析患者中，主动脉脉搏波速度与 44 小时收缩压独立相关[13]。主动脉僵硬度增加通常见于合并糖尿病或终末期肾病的高血压患者，与心血管预后不良相关，并且独立于血压这一因素[14]。这类患者动脉硬化过程加速与血管钙化相关[15]。同样血压过高也会导致动脉僵硬度的增加，两者互为因果。2023 年欧洲高血压协会(ESH)高血压指南指出动脉僵硬程度评估是高血压介导的器官损害“基本检查”的一部分，若臂－踝脉搏波传导速度(baPWV) ≥ 18 m/s 或颈－股脉搏波传导速度(cfPWV) ≥ 10 m/s 认为动脉僵硬度异常。

2.3. 肾脏代谢异常

肾脏能量和底物代谢可能在调节血压和高血压的发展中起重要作用[16]。严重的代谢紊乱是终末期肾病的特征之一，如氧代谢、TCA 循环等[17]。

2.3.1. 氧代谢

肾脏氧代谢可能导致活性氧(ROS)产生的变化[18]。高血压动物模型的肾脏中存在过量的 ROS，特别是超氧化物和过氧化氢[18]。ROS 可以直接影响血压调控系统的细胞过程(如心血管、肾脏、免疫和中枢神经系统，或肾素－血管紧张素－醛固酮系统) [19]。在细胞水平上，ROS 是生理细胞信号传导中重要的第二信使，过量 ROS 促进异常氧化还原信号和细胞损伤，引起内皮功能障碍、血管损伤、心血管重塑等[20]。在离散的亚细胞微域中产生的 ROS 可以通过下游氧化还原敏感靶标的可逆氧化翻译后修饰(oxPTMs)改变蛋白质功能。高水平的 ROS 可导致 oxPTMs 的改变，包括蛋白质的不可逆氧化以及对 DNA 和脂质等大分子的损伤[21]。这些改变破坏了血压调控中氧化还原敏感的信号通路，导致细胞功能障碍，从而促进高血压的形成[20]。另外脂质过氧化也可导致异黑素(isoLG)修饰蛋白的形成，这些蛋白可以作为新抗原激活免疫系统，从而促进高血压的发展[22]。在许多实验性高血压模型中，抗氧化剂和活性氧清除剂治疗可持续降低血压[23]。但在临床试验中抗氧化剂的使用，如活性氧清除剂和抗氧化维生素补充剂，显示出了不同的结果[24]。这可能与非特异性抑制氧化应激反应有关。

2.3.2. TCA 循环

靶向代谢组学分析提示糖尿病肾病患者及糖尿病肾病小鼠模型均出现 TCA 循环紊乱[25]。一项纳入 1127 名老年人的横断面研究探索了 8 种 TCA 循环相关代谢物浓度与血压的关系，发现血浆中 2-酮戊二酸和苹果酸的浓度升高与高血压显著相关[26]。2-酮戊二酸，其在能量代谢中扮演重要角色，可能通过影响细胞代谢和血管功能参与高血压的发病机制[26]。苹果酸则已知能够影响一氧化氮的生成，进而调节血压[27]。此外在高血压大鼠模型中静脉注射 TCA 循环代谢产物琥珀酸可通过激活肾素－血管紧张素系统诱导高血压，而琥珀酸受体 GPR 91 缺陷大鼠的这种反应被消除[28]。其他与血压关联的 TCA 循环代谢产物仍在探索之中。

2.3.3. 其他

也有研究发现促红细胞生成素的使用与高血压的发生或进展相关[5] [29]。但这一现象个体差异较大，目前认为并不是导致终末期肾病患者血压进展的关键因素。其他参与终末期肾病患者高血压发病机制的因素还包括交感神经和肾素－血管紧张素－醛固酮系统的激活以及内皮功能障碍[30]，这些已被大量研

究所证实。

3. 治疗进展

3.1. 药物治疗

3.1.1. 传统药物

目前尚不清楚终末期肾病患者血压管理的最佳方案。终末期肾病患者的降压药物选择与指南推荐的一般高血压患者的药物选择有所不同[31]。临床上通常首选药物是β受体阻滞剂、螺内酯和长效二氢吡啶类钙通道阻滞剂，其次是肾素–血管紧张素系统(RAS)拮抗剂如血管紧张素转换酶抑制剂(ACEI)或血管紧张素II受体拮抗剂(ARB)。HDPAL研究是一项开放标签、随机、对照试验，纳入了200例高血压合并左室肥厚的透析患者，他们被1:1随机分到ACEI组和β受体阻滞剂组，结果显示ACEI组家庭血压始终高于β受体阻滞剂组，并且其心血管死亡、心肌梗死、卒中或因心力衰竭住院的复合终点发生率比后者高2.29倍[32]。指南也推荐盐皮质激素受体拮抗剂(MRA)螺内酯作为顽固性高血压的标准治疗[33]。但在透析患者中的降压效果并未有太多的数据证实。

3.1.2. 新型降压药物

多种新型降压药物正在探索用于治疗难治性高血压。最近的一项单中心研究显示针对ESKD合并难治性高血压患者，沙库巴曲缬沙坦治疗12周后，收缩压/舒张压分别下降20.7/8.3 mmHg，并且NT-proBNP浓度同样得到改善[34]。阿普昔腾坦(Aprocitentan)是一种内皮素双受体拮抗剂，可抑制内皮素-1与内皮素A (ETA)受体结合，同时可抑制内皮素-1与内皮素B (ETB)受体结合[35]。PRECISION研究[36]提示接受三联降压治疗(包括利尿剂)血压未控制的患者中，与安慰剂相比，12.5 mg和25 mg的阿普昔腾坦剂量在4周时均显著降低了诊室收缩压(分别为−3.7 mmHg和−3.8 mmHg)。传统的ACEI/ARB类药物可通过阻断RAS的不同阶段起降血压作用，但无法降低血管紧张素原(AGT)的水平。RNA干扰(RNAi)技术是前景良好的基因沉默技术，目前已在多种动物模型中证明靶向干扰肝源性AGT基因表达能够显著降低血压[37]。这种小干扰RNA有望成为新型RAS阻断剂，从而为难治性高血压治疗提供更多的药物选择。

3.2. 手术治疗

根据有限的证据，去肾神经可能是ESKD合并难治性高血压的有效干预措施。Hoye等人在9例ESKD患者(6例血液透析和3例腹膜透析)中发现去肾神经后，患者12个月后的动态血压结果显示降低收缩压平均下降24 mmHg (95% CI: 5~42 mmHg)；舒张压平均降低13 mmHg (95% CI: 4~22 mmHg) [38]。Scalise等人的研究中，将24例终末期肾病合并难治性高血压患者随机分为去肾神经组和仅药物治疗组，结果显示去肾神经后收缩压及舒张压均能够早期降低且持续维持[39]。5个病例研究提示尽管存在较小的肾动脉管腔直径和萎缩的肾脏，但去肾神经手术在ESRD中依然是可行和有效的[40]。

4. 展望

难治性高血压在终末期肾病患者中发生率相对较高，其中涉及容量超负荷、动脉僵硬度增加、代谢异常等多种致病机制。导致终末期肾病的病因复杂多样，未来需要结合具体病因探索终末期肾病高血压进展的关键机制。在治疗方面，针对这一特殊群体的研究进展较少。因肾功能不全或透析的影响，常规降压药物在终末期肾病患者中使用受限或效果不佳。目前一些针对血压上游调控机制的新型降压药物如内皮素拮抗剂、AGT阻断剂等为治疗RH提供了新的策略。但相关的研究证据仍不足，这类新型降压药的开发及应用需要充分考虑这类患者的临床特征，尤其是异常的代谢紊乱。肾动脉去神经有望成为终末期肾病患者降压的新选择，但目前证据不足，其有效性及安全性临床研究进一步证实。

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