·综述·

射血分数保留的心力衰竭合并慢性肾功能不全的研究进展

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【摘 要】 射血分数保留的心力衰竭(HFpEF)是发病率及死亡率均较高的一种常见疾病,慢性肾功能不全(CKD)是HFpEF患者常见的伴随疾病。HFpEF合并CKD的发病机制尚未完全阐明,HFpEF与CKD常相互影响、交互促进疾病的进展。与单纯HFpEF患者相比,合并CKD的HFpEF患者通常预后较差,且随着肾损伤程度的加重,其死亡风险增加。治疗心力衰竭的基石类药物并不能使HFpEF患者明显获益,然而建议将沙库巴曲缬沙坦等新型抗心力衰竭药物应用于合并轻中度CKD的HFpEF患者。

【关键词】 射血分数保留的心力衰竭;慢性肾功能不全;肾功能恶化;预后;药物治疗

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Research progress in heart failure with preserved ejection fraction complicated with chronic kidney disease

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【**Abstract**】 Heart failure with preserved ejection fraction (HFpEF) is a common disease with high morbidity and mortality, and chronic kidney disease (CKD) is a common comorbidity in HFpEF patients. The pathogenesis of comorbidity of HFpEF and CKD has not been fully elucidated. The bidirectional interactions between HFpEF and CKD may promote their progression. HFpEF patients with comorbid CKD had a poorer prognosis than those with HFpEF alone, and the risk of death increased with the increasing severity of renal injury. HFpEF patients do not benefit significantly from the basic drugs used to treat heart failure. However, it is recommended that new anti-heart failure agents such as sacubitril/valsartan sodium tablets be used in these patients.

【**Key words**】 heart failure with preserved ejection fraction; chronic kidney disease; worsening renal function; prognosis; therapeutic strategy

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随着人口老龄化及高血压、糖尿病、心血管及肾脏疾病危险因素的增加,心力衰竭(heart failure, HF)及肾功能不全(chronic kidney disease, CKD)的患病率不断上升[1]。50%的HF患者合并有CKD,其中近1/3为中度或重度肾损伤[2]。与单一疾病相比,HF合并CKD患者的住院率、心血管病死亡率及全因死亡率均明显增加[3],将治疗心力衰竭的基石类药物用于HFpEF患者疗效欠佳,且药物毒性增加[4]。射血分数保留的心力衰竭(heart failure with preserved ejection fraction, HFpEF)约占HF患者的50%以上[5],其死亡率甚至高于射血分数降低的心力衰竭(heart failure with reduced ejection fraction, HFrEF)人群[6,7]。HFpEF患者常合并CKD[6,8,9],CKD在HFpEF患者中的发病率要高于HFrEF以及

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射血分数轻度降低的心力衰竭(heart failure with mid-range ejection fraction, HFmrEF)患者[10]。HFpEF 合并 CKD 患者预后较差[6,11],且随着肾损伤程度的加重患者死亡风险增加[12]。HFpEF 合并 CKD 的共病机制尚未完全阐明,且目前尚无公认有效的治疗策略。本文对 HFpEF 合并 CKD 的最新研究进展作以综述,以期为临床决策提供参考。

1 HFpEF 合并 CKD 的患病机制

HFpEF 临床常表现为由多种并发症和炎症介质引起的复杂综合征[13]。高血压是 HFpEF 的主要病因,其他危险因素包括糖尿病、高脂血症、心肌缺血及肥厚性心肌病等[14]。心脏舒张顺应性及舒张功能受损、亚临床性心脏收缩功能障碍、CKD 导致心内充盈压力升高、液体潴留和运动不耐受,以及伴随疾病导致的内皮炎症、氧化应激、微血管功能障碍、心肌肥厚及心肌纤维化等因素均可能与 HFpEF 发病相关[15,16]。HFpEF 合并 CKD 患者中,相关危险因素驱动肾功能障碍和心力衰竭并行发展、相互影响,交互促进合并症的进展[17]。

HFpEF 引起肾功能损伤的机制包括:(1)心脏舒张末期容积和压力升高,左心室舒张僵硬度增加,中心静脉压升高导致肾功能损害;(2)心脏舒张功能恶化和心脏机械功能异常,导致心排血量减少引起肾血流量减少,HF 又加重肾静脉充血,导致肾功能损害;(3)机体血流动力学的改变启动神经体液调节机制,增强机体炎症及氧化应激反应;(4)交感神经系统及肾素血管紧张醛固酮系统(renin angiotensin aldosterone system, RAAS)亢进;(5)有害的心肾交互作用也是 HFpEF 肾功能损害的可能机制[2,18]。

CKD 对 HFpEF 的影响机制包括:(1)HFpEF 合并 CKD 者常伴随贫血[6,19],贫血引起心肌缺氧,增加氧化应激反应,使交感神经兴奋,RAAS 活性增强,液体潴留增加,从而增加心脏前负荷;而贫血者血液携氧能力下降,机体通过代偿性增加心率导致心肌耗氧增加,能量代谢紊乱加重 HF。(2)蛋白尿、胱抑素 C 是新发 HFpEF 患者的强危险因素,蛋白尿以及肾小球滤过率(estimated glomerular filtration rate, eGFR)的降低皆与 HFpEF 患者心肌重塑相关[20]。(3)HFpEF 患者常见的心脏变时性功能不全与 CKD 导致的自主神经功能障碍有关[21]。(4)HFpEF 患者 CKD 与肺动脉压增高,左、右心室和心房应变力降低直接相关,CKD 与心功能恶化之间可能存在双向关联[11]。(5)CKD 导致内皮功能障碍,促进 HFpEF 病情进展。

2 CKD 在一定程度上影响 HFpEF 预后

CKD 对 HFpEF 患者预后的影响研究结论尚不一致。一项含 40 230 例 HF 患者的研究显示,HFpEF 患者 CKD 与死亡的关联性弱于 HFrEF 及 HFmrEF 患者[6]。另一项含 80 000 例 HF 患者的荟萃分析结果显示,CKD 对 HFpEF 患者的死亡风险预测价值较 HFrEF 患者更为明显[22]。总体而言,HFpEF 患者合并 CKD 后全因死亡、心血管疾病死亡风险及住院率增加[2,6,23]。

Rusinaru 等[23]一项含 358 例 HFpEF 患者的前瞻性研究显示,与估算的 eGFR≥60 ml/(min · 1.73m^2)的 HFpEF 患者相比,eGFR<60 ml/(min · 1.73m^2)HFpEF 患者 7 年总体死亡风险(*HR* = 1.43, 95% *CI* 1.10~1.86)及心血管病死亡风险(*HR* = 1.57, 95% *CI* 1.13~2.19)均增加。Chen 等[2]一项含 3 392 例 HFpEF 患者的分析显示,与 eGFR≥60 ml/(min · 1.73m^2)的 HFpEF 患者(2 080 例)相比,eGFR 30~59 ml/(min · 1.73m^2)的 HFpEF 患者(1 312 例)全因死亡风险显著增高(*HR* = 1.47, 95% *CI* 1.24~1.76),心血管病死亡风险增高(*HR* = 1.53, 95% *CI* 1.23~1.91),心力衰竭再住院率增高(*HR* = 1.21, 95% *CI* 1.00~1.47)。同样,Beldhuis 等[4]一项含 1 767 例 HFpEF 患者的研究显示,与 eGFR≥60 ml/(min · 1.73m^2)的 HFpEF 患者相比,eGFR<45 ml/(min · 1.73m^2)HFpEF 患者的心血管病死亡及住院风险显著增加(*HR* = 1.99, 95% *CI* 1.62~2.45)。但也有研究显示 CKD 与 HFpEF 患者预后无直接关联,Jin 等[19]一项含 1 604 例 HFpEF 患者的中国心力衰竭多中心登记研究数据显示,CKD 不是 HFpEF 患者全因死亡率及再住院率增加的独立危险因素(*HR* = 1.18, 95% *CI* 0.88~1.57; *HR* = 0.94, 95% *CI* 0.79~1.12)。

肾功能恶化(worsening renal function, WRF)对 HFpEF 患者预后的影响研究间也有争议。Löfman 等[24]研究显示,HFpEF 患者 WRF 发生率高于 HFrEF、HFmrEF 患者,HFpEF 患者 eGFR 下降 25%~49%、≥50% 均增加患者死亡率,≥50% 更为显著。Rusinaru 等[23]的研究也显示,针对 eGFR<60 ml/(min · 1.73m^2)HFpEF 患者,WRF 是患者 7 年总体死亡率及心血管病死亡率增加的独立

危险因素。而 Rusinaru 等[23]认为对于 eGFR ≥ 60 ml/(min·1.73m²)的 HFpEF 患者,其住院期间的 WRF 不增加患者7年总体死亡率及心血管病死亡风险。近期一项含10 902例 HFpEF 患者的研究也显示,尽管 HFpEF 患者 WRF 发生率比较高,WRF 未增加患者死亡及住院风险[25]。

3 HFpEF 合并 CKD 的药物治疗

3.1 HFpEF 合并 CKD 的药物治疗存在争议

目前,HFpEF 尚无公认的有效治疗方法[14],其治疗多基于临床经验,原则主要包括减轻症状、合并症的治疗以及加强疾病管理。血管紧张素转化酶抑制剂(angiotensin converting enzyme inhibitor,ACEI)、血管紧张素Ⅱ受体阻滞剂(angiotensin Ⅱ receptor blocker,ARB)、β受体阻滞剂等用于 HFrEF 患者的药物未能使 HFpEF 患者明显获益[26],因此对于 HFpEF 合并 CKD 人群的治疗更少有共识。比如 Fu 等[27]研究显示,β受体阻滞剂能够降低 HFrEF 合并进展期慢性肾病[eGFR<30 ml/(min·1.73m²)]患者死亡率(*HR*=0.85,95%*CI* 0.75~0.96),降低患者心血管病死亡及 HF 住院风险(*HR*=0.87,95%*CI* 0.77~0.98);但在 HFpEF 合并进展期慢性肾病患者中,β受体阻滞剂未能显著降低患者全因死亡(*HR*=0.88,95%*CI* 0.77~1.02)、心血管病死亡及 HF 住院风险(*HR*=1.05,95%*CI* 0.90~1.23)。

RAAS 系统在 HFpEF 发病机制中起重要作用,同时也是 CKD 的一线用药,而关于 RAAS 抑制剂能否使 HFpEF 合并 CKD 患者获益的研究结论并不一致。一项有关螺内酯在 HFpEF 合并 CKD 共病患者(n=1 767)中安全性及疗效的研究显示,应用螺内酯虽然使 HFpEF 患者发生高钾血症、肾功能恶化以及停药风险增大,但是螺内酯能够降低 HFpEF-CKD 患者心血管死亡风险及住院率[4]。Tsujimoto 等[28]一项纳入1 465例 HFpEF 患者的研究显示,单纯使用螺内酯未能显著降低患者主要结局事件风险(*HR*=0.97,95%*CI* 0.81~1.16),但 ACEI/ARB 类 RAAS 抑制剂显著改善 HFpEF 合并轻中度 CKD 患者的预后,使用 ACEI/ARB 的试验组患者发生主要结局事件、全因死亡、主要心血管事件和心力衰竭再住院风险皆明显低于对照组。需要注意的是,HFpEF 患者对心脏前负荷依赖性较强,而 RAAS 抑制剂能导致血压及心脏每搏输出量下降,引起肾脏血流量下降及肾功能损伤,甚至有研究显示 RAS 抑制剂增加 HFpEF 患者 WRF 及死亡风险[29,30],因此 HFpEF 合并 CKD 患者在使用相关药物时需监测肾脏功能指标。

3.2 建议血管紧张素受体脑啡肽酶抑制剂等药物用于轻中度 CKD 的 HFpEF 患者

以往绝大多数关于 HFpEF 的研究排除了重度 CKD 人群,因此可供参考的数据不多。尽管如此,一些新型药物如血管紧张素受体脑啡肽酶抑制剂为 HFpEF 合并 CKD 患者的治疗提供了思路,此类药物以沙库巴曲缬沙坦钠为代表。Mc Causland 等[31]在一项纳入4 796例患者的分析研究中显示,与缬沙坦相比,沙库巴曲缬沙坦钠片降低 HFpEF 患者肾脏综合结局事件(eGFR 下降≥50%、终末期肾病、肾脏原因死亡)发生率(1.4%和2.7%)。与此一致,使用沙库巴曲缬沙坦钠的 HFpEF 患者发生 WRF 风险低于使用缬沙坦的患者(*HR*=0.50,95%*CI* 0.33~0.77)[26]。Mc Causland 等[31]研究显示,eGFR<60 ml/(min·1.73 m²)与≥60 ml/(min·1.73m²)两类 HFpEF 人群皆可获益于沙库巴曲缬沙坦钠,但 eGFR<60 ml/(min·1.73m²)组患者因肾功能受损导致停药的概率增加。因此,HFpEF 合并 CKD 患者在使用药物过程中需权衡临床获益及药物相关毒性风险[29]。

钠-葡萄糖共转运蛋白2(sodium glucose cotransporter 2, SGLT-2)抑制剂也是新近几年流行起来的降糖药物,它不仅可以减缓糖尿病合并 CKD 患者的肾病进展,而且可以降低有或无心力衰竭病史的患者因心力衰竭住院的风险[32,33]。不断有临床研究证实,恩格列净、达格列净、卡格列净可显著降低2型糖尿病合并 CKD 患者的心力衰竭住院风险[34-36]。最新研究表明不论是否有糖尿病,恩格列净可降低 HFpEF 患者心血管死亡或心力衰竭住院的综合风险[37],SGLT-2 抑制剂成为了降糖药治疗心力衰竭的“跨界明星”,通过靶向心脏代谢异常,可以减轻 HFpEF 患者心肌损伤,改善患者心力衰竭症状和运动耐受情况[38],建议将此类药物用于 HFpEF 合并 CKD 患者。

4 总 结

CKD 是 HFpEF 患者常见的伴随疾病,两者相互影响,交互促进疾病的进展。HFpEF 合并 CKD 患者预后较差,其全因死亡、心血管病死亡及再入院风险均增加,且随着肾损伤程度的加重其各类事件

风险增加。针对 RAAS 的干预及对患者高血压、糖尿病等代谢性疾病的治疗能够一定程度上改善合并症患者的预后,由于不同研究之间结论的不一致性,相关药物的具体疗效及安全性仍有待于进一步大样本、高质量临床研究予以验证,并期望在动物模型中对其治疗机制进行深入研究。此外,严格控制血压、血糖、血脂等代谢危险因素是延缓合并症患者病情进展的可行之策。

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