

合并常见疾病对经导管主动脉瓣置换术患者预后的影响

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【摘要】近年来, 不适用外科手术的高风险主动脉瓣狭窄患者可应用经导管主动脉瓣置换术进行治疗, 其有效性和安全性已经得到证实。但是, 主动脉瓣狭窄患者往往合并多种慢性疾病, 这些合并疾病对主动脉瓣置换术患者预后的影响引起越来越广泛的关注。因此, 现分别就冠心病、外周动脉疾病、糖尿病、慢性阻塞性肺病、慢性肾脏病及贫血对主动脉瓣狭窄患者术后预后的影响做一综述。

【关键词】主动脉瓣狭窄; 经导管主动脉瓣置换术; 预后; 合并疾病

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Influence of Common Accompanied Diseases on Prognosis of Patients after Transcatheter Aortic Valve Replacement

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【Abstract】 In recent years, transcatheter aortic valve replacement has been a treatment for patients with high-risk aortic stenosis who is not suitable for surgery. Its effectiveness and security have been confirmed. However, patients with aortic stenosis often combined with a variety of chronic diseases. The impact of these accompanied diseases on the prognosis of patients undergoing aortic valve replacement has been attracted extensive attention. Therefore, this article reviews the effects of coronary heart disease, peripheral artery disease, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease and anemia on the prognosis of patients with aortic stenosis.

【Key words】Aortic stenosis; Transcatheter aortic valve replacement; Prognosis; Accompanied diseases

主动脉瓣狭窄(aortic stenosis, AS)在老年瓣膜性心脏病中较为常见^[1]。流行病学调查显示, 美国年龄在75岁以上老年人中瓣膜性心脏病的患病率达13.3%, 中度及重度AS的患病率达2.8%^[2]。尽管外科换瓣手术可以明确改善AS患者预后, 但是, 由于高龄、心功能不全以及合并疾病等导致33.3%的重度AS患者无法耐受外科手术治疗^[3]。2002年, 全球首例经导管主动脉瓣置换术(transcatheter aortic valve replacement, TAVR)成功应用于重度AS患者, 并且研究也证实了其疗效和安全性^[4]。目前, TAVR在全世界已累计30万例以上, 在国外某些中心早已成为常规治疗手段^[5]。ESC指南或ACC/AHA指南已将TAVR作为外科手术高风险患者选择的治疗方法^[6-7], 甚至

可用于中危患者。中国在2010年首次开展对重度AS患者实施TAVR治疗^[8]。随着TAVR的推广, 其预后成为关注的焦点, 而AS患者的年龄特点决定了其往往合并其他疾病, 因此本文将围绕常见合并疾病对TAVR预后的影响加以综述。

1 AS合并冠心病

冠心病(coronary artery disease, CAD)和老年退行性AS具有某些类似的病理生理基础及共同危险因素^[9], 因此AS患者中合并CAD的发生率为30%~50%, 并且随着年龄的增长而增加^[10-11]。纳入3195例TAVR患者的FRANCE-2注册研究显示有48%的患者合并CAD^[12]。U.K. TAVI研究^[13]显示, 纳入410例TAVR患者中, 既往行经皮冠脉介入术(percutaneous coronary

intervention, PCI) 的比率达到 14%。

一项纳入 201 例 TAVR 患者的回顾性研究显示, 合并 CAD 的患者术后 30 d 全因死亡率 (13.1% vs 1.2%, $P = 0.002$) 及 1 年全因死亡率 (35.7% vs 18.4%, $P = 0.01$) 均高于未合并 CAD 的患者, 而且, 合并 CAD 的 TAVR 患者 30 d 内死亡风险比未合并 CAD 的 TAVR 患者高 10 倍^[14]。一项荟萃分析结果显示, 合并 CAD 的 TAVR 患者 1 年全因死亡率高于未合并 CAD 的 TAVR 患者, 但是合并 CAD 并未对 TAVR 患者 30 d 全因死亡率造成影响^[15]。一项纳入 91 例 TAVI 患者的单中心注册研究^[16]结果显示, 合并 CAD 患者 2 年全因死亡率 (50% vs 24%, $P = 0.04$) 高于未合并 CAD 的患者, 研究所纳入的 CAD 患者包括既往行 PCI、冠状动脉旁路移植术、新发 CAD 以及 TAVR 同期行 PCI 的人群, 但关于 CAD 病变程度的缺失导致结果存在一定局限性。纳入 34 个中心 4 201 例 TAVR 患者的 FRANCE-2 研究, 排除既往行冠状动脉旁路移植术, 仅纳入冠状动脉狭窄 >50% 的 CAD 患者 (TAVR 术前是否行血运重建由心脏科治疗团队决定), 结果显示, 合并 CAD 患者 30 d 和 3 年的全因死亡率与未合并 CAD 患者并不存在差异^[17]。上述研究结果的差异导致判断 CAD 是否影响 TAVR 患者预后带来挑战。Goel 等^[18]认为, 在研究设计上对 CAD 的纳入标准不尽相同, CAD 病变程度的缺失和治疗与否均对研究结果造成直接影响。

Bern TAVR 注册研究纳入 256 例 TAVR 患者, 合并 CAD 的 167 例患者中有 59 例 TAVR 患者同期行 PCI, 结果显示, TAVR 同期行 PCI 的患者 30 d 死亡率 (5.6% vs 10.2%, $P = 0.24$) 及卒中发生率 (4.1% vs 3.4%, $P = 1.00$) 与未行 PCI 的患者不存在统计学差异^[19]。指南也推荐重度 AS 合并 CAD 拟行 TAVR 的患者可以对重要病变血管进行血运重建^[6-7]。目前多数学者认为, 对 AS 合并 CAD 拟行 TAVR 的患者而言, 当获益大于风险, 在术前或术中接受血运重建是安全的^[20]。但是, 关于血运重建的时机及安全性仍然有待于大规模的临床试验进行验证。

2 AS 合并外周动脉疾病

据报道全球约有 2 亿人罹患外周动脉疾病 (peripheral artery disease, PAD)^[21]。吸烟、高脂血症、糖尿病 (diabetes mellitus, DM) 以及慢性肾功能损伤这些危险因素不仅可引起 PAD, 也参与 AS 的发生发展, 所以 AS 也多合并有 PAD^[22]。现有关于 TAVR 的大规模临床试验, 诸如 PARTNER B 以及 Core Valve US 试验报道, 拟行 TAVR 的患者中 AS 合并 PAD 的比

例为 27.8% ~ 41.3%^[23-24]。PAD 作为 AS 患者常合并的一种血管疾病, 降低外科换瓣术后患者的生存率^[25]。作为侵入性治疗手段的一种, TAVR 会对患者血管阻力、顺应性以及弹性的改变产生不良影响^[26]。

一项纳入 27 440 例患者的观察性研究, 根据是否经股动脉路径行 TAVR 分成两组, 其中股动脉路径组和非股动脉路径组中合并 PAD 的比例分别为 24.5% 和 47.9%, 1 年的随访结果显示两组合并 PAD 的人群均易患冠状动脉及颈动脉疾病, 两组比较没有差异。经股动脉路径组合并 PAD 的患者 1 年后的全因死亡率、再入院情况及出血风险均高于不合并 PAD 的患者, 但是非股动脉路径组合并 PAD 与不合并 PAD 的患者在结果上并未表现出差异^[27]。

因此, 在未来 TAVR 术后的临床干预中, 应重视合并 PAD 尤其是经股动脉路径进行手术的患者, 减少该类患者不良事件的发生。

3 AS 合并慢性阻塞性肺病

慢性阻塞性肺病 (chronic obstructive pulmonary disease, COPD) 是导致 AS 患者不宜接受外科换瓣术的主要合并疾病之一。研究显示, 拟行 TAVR 的患者中 AS 合并 COPD 的比例为 28% ~ 55%^[23-24]。与外科换瓣术相比, 合并 COPD 的患者 TAVR 术后呼吸系统相关的并发症发生率明显减少^[28]。但是相关研究表明, COPD 是 TAVR 术后患者死亡率的独立影响因素。一项纳入 319 例 TAVR 患者的临床研究显示, 与未合并 COPD 的患者相比, 合并 COPD 的患者 TAVR 术后 1 年存活率降低 (70.6% vs 84.5%, $P = 0.008$), 而且心功能改善不明显 ($P = 0.036$), 同时, 研究发现合并 COPD 并且术前 6 分钟步行试验距离 < 170 m 的患者 TAVR 术后获益减少 ($P = 0.002$)^[29]。Core Valve US Pivotal Trial 纳入的 1 030 例 TAVR 患者中合并慢性肺部疾病的比率为 55% (轻度 20%、中度 13%、重度 22%), 研究显示, 合并中重度的慢性肺部疾病 1 年全因死亡率 (中度 28.1%、重度 26.9% vs 轻度 19.2%, $P = 0.030$) 及 3 年全因死亡率 (中度 53.0%、重度 51.9% vs 轻度 37.7%, $P < 0.001$) 均高于未合并慢性肺部疾病患者的变化^[30]。尽管 TAVR 可改善 AS 合并 COPD 患者的生活质量和心功能, 但上述研究结果揭示慢性肺部疾病依然影响 TAVR 患者的生存率, 导致部分合并 COPD 的患者 (重度 COPD 或术前 6 分钟步行试验距离 < 170 m) 获益减少。

4 AS 合并 DM

DM 被列入 Euro score II 和 Society of Thoracic Surgeons (STS) 评分中外科手术换瓣的重要危险因素

之一^[31]。研究显示,合并 DM 患者行 TAVR 治疗,其不良事件发生率明显低于外科手术治疗^[32]。

一项纳入 47 643 例 TAVR 患者的研究显示,17 849 例(37.5%)患者合并 DM,且其 1 年死亡率明显高于未合并 DM 的患者,对其是否使用胰岛素治疗进行亚组分析发现,胰岛素治疗组的死亡率高于非胰岛素治疗组^[33]。类似的研究显示,胰岛素依赖的 DM 患者在 TAVR 术后发生急性肾损伤的风险高于非胰岛素依赖以及未合并 DM 的患者^[34]。一项荟萃分析结果显示,合并 DM 与未合并 DM 的患者相比,合并 DM 的患者 1 年死亡率以及围手术期急性肾损伤的发生率明显高于未合并 DM 的患者^[35]。

上述研究结果显示,DM 影响 TAVR 患者预后。分析其原因,一方面 DM 患者术后容易出现高血糖状态,导致急性肾损伤的发生,进而影响患者预后;另一方面,TAVR 解决了瓣膜狭窄的问题,但 DM 可进展为 DM 肾病,影响患者的心功能进而影响患者的生存质量。因此,临床实践中应重视 AS 合并 DM 患者的血糖水平,预防围手术期急性肾损伤的发生,同时应强化术后血糖的管理,减少因 DM 进展对 TAVR 患者预后带来的不良影响。

5 AS 合并慢性肾脏病

慢性肾脏病(chronic kidney diseases, CKD)与 AS 的严重程度及发病率有一定相关性^[36],同时也影响高危 AS 患者 TAVR 术后的临床结局^[37]。

美国 NIS(National Inpatient Sample)数据库中 2012—2014 年期间共 41 025 例 TAVR 患者,对其进行研究分析,与不合并 CKD 的患者相比,合并 CKD(13 750 例,33.5%)或终末期肾病(1 690 例,4.1%)的患者住院死亡率显著增高(3.8% vs 4.5% vs 8.3%),合并 CKD 患者术后急性肾损伤发生率也显著增加(10.6% vs 34.1%, $P < 0.001$)^[38]。PARTNER 研究结果显示,与未合并 CKD 的患者相比,合并 CKD 且肾小球滤过率 $<30 \text{ mL}/(\text{min} \cdot 1.73 \text{ m}^2)$ 的高危 AS 患者术后 1 年的死亡率增加(34.4% vs 20.8%, $P < 0.001$)^[39]。但是,一项纳入 10 709 例患者的荟萃分析结果却显示,中低危 TAVR 患者的死亡率与 CKD 的进展无相关性^[40]。

6 AS 合并贫血

在 TAVR 人群的伴随疾病中,贫血也较为常见,其在重度 AS 患者中的患病率达 30%^[41]。OBSERVANT 研究结果显示,术前贫血(男性血红蛋白 $<130 \text{ g/L}$,女性血红蛋白 $<120 \text{ g/L}$)是 TAVR 患者术后 3 年死亡率的独立危险因素($HR 1.37$, 95% CI 1.12~1.68)^[42]。

一项最终纳入 6 项研究的荟萃分析得出类似的结论,即术前贫血可增加术后患者的长期死亡风险^[43]。另外一项纳入 438 例 TAVR 患者的研究中,术前有 282 例(64.4%)患者合并贫血,合并贫血的患者术前及术后随访时的 6 分钟步行试验距离均低于与未合并贫血的患者($P < 0.001$, $P = 0.023$),结果也显示贫血可影响 TAVR 患者的功能状态和生活质量^[44]。

7 总结与展望

目前,TAVR 作为 AS 患者的微创治疗,其应用已从高危和极高危患者发展至中、低危患者,具有创伤小、恢复快等优点。但合并疾病对临床决策及 TAVR 患者预后的影响已成为当下面临的主要问题之一。因此,在未来可开展大规模临床研究,评价影响 TAVR 患者临床结局因素的同时,应加强对 TAVR 患者合并疾病的干预,采用有效的中西医结合康复治疗手段,对患者进行综合健康管理,促进患者自身整体功能的恢复,提高生活质量,改善预后。

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