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扩张型心肌病治疗研究进展*

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摘要:扩张型心肌病是一种以单侧或双侧心腔扩大和收缩功能障碍等为特征,治疗困难、预后较差的临床常见疾病,致病因素及临床表现复杂多样,其治疗方法一直是医学研究的热点。扩张型心肌病的治疗手段涵盖常规药物治疗及非药物治疗,后者包括手术治疗及不断发展的免疫治疗、干细胞移植和基因治疗等,且每种治疗方法都有各自的优缺点,本文针对扩张型心肌病治疗方法的最新研究进展进行综述,以期临床治疗提供新的依据和方向,提高扩张型心肌病患者的生活质量和生存率。

关键词:扩张型心肌病;治疗;研究进展

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Progression in Treatment of Dilated Cardiomyopathy*

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ABSTRACT: Dilated cardiomyopathy, characterized by unilateral or bilateral chamber dilatation and contraction dysfunction, is a common disease with difficulty in treatment and poor prognosis. Both pathogenic factors and clinical symptoms are complicated and diverse. Thus, the treatment has been a hot point in the field of medical research. Dilated cardiomyopathy treatment covers routine drug and non-drug treatments including surgery and evolving immunotherapy, stem cell transplantation, gene therapy and so on. Each of them has its own advantages and disadvantages. This review summarizes the recent progresses in treatment of dilated cardiomyopathy, aiming to provide basis and direction to clinical treatment, as well as improve life quality and survival rate of patients.

Key words: Dilated cardiomyopathy; Therapy; Progress

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前言

扩张型心肌病(dilated cardiomyopathy, DCM)是最常见的一类心肌病,以单侧或双侧心腔扩大、心肌收缩功能障碍为主要特征,猝死风险高,属于难治性心血管疾病。其临床表现多为恶性心律失常、心肌肥厚、血管栓塞和胸痛等症状,其中大多数患者最终进展为心力衰竭。2013年,有学者评估原发性DCM的发病率已超过1/250,且具有逐年上升的趋势^[1]。DCM病因尚未明确,目前认为其发病机制可能与感染、自身免疫、遗传因素等有关,尚缺乏特异且有效的治疗手段。优化药物治疗是DCM的治疗基础,随着对介入技术、免疫疗法、干细胞移植和基因工程等研究的深入,DCM的治疗手段不断丰富,本文就DCM的主要治疗方法的研究进展作一综述。

1 DCM 的药物治疗

现阶段DCM的治疗基础依旧是药物治疗,心力衰竭是

DCM最突出的表现,但除常规的抗心力衰竭治疗外,对与心肌纤维化或心律失常合并症的防治也很重要。ACEI类药物自八十年代以来就已成为治疗DCM所致慢性心力衰竭(chronic heart failure, CHF)的主要药物。但长期使用ACEI所致的醛固酮逃逸现象可致药效降低,现临床上以ACEI联合醛固酮受体拮抗药以强化对肾素-血管紧张素系统的抑制。李戈雄等^[2]指出贝那普利和螺内酯合用可明显降低心胸比,延缓心室重构,对于慎用ACEI类药的患者可替换成ARB。张朝华等^[3]对90例小儿DCM患者治疗6个月后进行随访并发现,卡维地洛可改善心功能指标且明显优于倍他乐克。另外随机双盲对照研究表明在降低病死率方面,卡维地洛优于美托洛尔,但卡维地洛具备α与β受体双重阻滞作用,可能加重心衰症状,因此对于心功能IV级患者应慎用^[4]。当DCM患者出现肺淤血或外周水肿表现时应首选利尿剂,呋塞米是过去治疗CHF和心功能不全时较常用的袢利尿剂,而Watanabe等^[5]研究证实,托拉塞米可提高DCM大鼠心肌闰盘结构蛋白的表达从而防止心肌纤维

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化,且作用较呋塞米更明显、生物利用度更高。此外,磷酸二酯酶抑制剂、多巴酚丁胺和左西孟旦等正性肌力药可改善患者短期临床症状。近年来,一种新型心肌球蛋白激动剂 omecamtiv mecarbil 引起国内外学者的广泛关注,Bakkenhaug 等^[6]通过动物实验证实 omecamtiv mecarbil 可延长心脏射血时间,增加冠状动脉血流。2015 年美国心脏协会临床试验会议报告指出 omecamtiv mecarbil 可显著改善收缩期射血时间、搏出量以及 NT-proBNP 水平,不良反应发生率在组间具有可比性^[7]。近年利用中西医结合的方法治疗 DCM 伴心律失常引起广泛关注,研究显示,给予 43 例 DCM 心律失常患者以阿替洛尔联合稳心颗粒治疗后,ST 段明显下移,总有效率达 95.4%^[8]。

2 DCM 非药物治疗进展

2.1 心脏再同步化治疗

随着介入技术与植入性器械的不断发展,当药物治疗无法更有效地改善临床症状时,心脏再同步化治疗(cardiac resynchronization therapy, CRT)等人工心脏起搏技术为 DCM 治疗提供了新的途径。自九十年代初 Hochleitner 等首次提出将双心腔起搏器作为治疗心力衰竭的方法以来,CRT 的临床指征不断拓宽。目前认为,对 QRS 时限 ≥ 150 ms 及完全性左束支传导阻滞患者,CRT 治疗的获益最大,并已否定对窄 QRS 时限(< 120 ms)的疗效^[9]。晚期 DCM 患者易出现室内传导异常,导致心室收缩不同步及收缩前房室反流。陆娟等^[10]证实,CRT 治疗不仅改善 DCM 患者左室收缩功能和减少二尖瓣反流,且能明显改善左室舒张功能。对于心功能 II/III 级和左心室射血分数(Left Ventricular Ejection Fractions, LVEF) $\leq 35\%$ 的 DCM 患者,预防性植入埋藏式心脏转复除颤器(implantable cardioverter defibrillator, ICD)可显著改善其左心功能,降低猝死高危患者的死亡率,此外,CRT 联合 ICD 较单独应用 ICD 显著改善心衰患者 LVEF^[11]。再同步化并植入心脏复律除颤器(cardiac resynchronization and implantable cardioverter defibrillator, CRT-D)具有创伤小、迅速可靠的优点,研究发现 CRT-D 可显著提高 DCM 心力衰竭患者运动能力和生理活动方面的客观指标,且对女性改善较为显著^[12]。

2.2 左室减容术

终末期 DCM 常表现出心功能衰竭、心输出量下降及呼吸困难等临床症状。当常规药物治疗无法进一步改善 DCM 终末期患者的左心室功能时,临床上多考虑使用心脏移植等外科手术方法,但由于供体来源的缺乏,仍有 20%~30% 的病人死于等待供体期间^[13]。1996 年巴西 Batista 医生首创的左室减容术(partial left ventriculectomy, PLV)用于治疗终末期 DCM,为等待供体的病人赢得心脏移植的时间^[14]。DCM 是由先天性心脏病引起的儿科少见病,一名四岁女婴患先天性心脏病伴严重二尖瓣关闭不全,术前射血分数为 20%,经 PLV 术后第六年随访中发现,射血分数升至 65%,且无室性心律失常和心力衰竭症状,可维持窦性心律,进展良好^[15]。但对 DCM 患者的长期疗效仍不确定,有待临床试验进一步验证。目前 PLV、动态心肌成形术和左心室辅助治疗等外科手术均局限于终末期心力衰竭无法进行心脏移植的患者或心脏移植前的过渡阶段,心脏移植目前仍是治疗终末期 DCM 致心力衰竭患者的唯一方法。

2.3 免疫治疗

在特发性 DCM 中,约 35% 由病毒引起^[16]。传统药物治疗效果不佳,干扰素是临床上治疗病毒感染的主要药物,张凌等^[17]指出给予干扰素治疗可提高小儿病毒性心肌炎的疗效进而阻碍向 DCM 的进展。对于已患 DCM 的对象,将免疫制剂输注至其体内,或达到治疗目的。近些年开发了一种新型免疫抑制剂 FTY720,Boldizsar 等^[18]指出 FTY720 能轻微减缓转基因 Balb/c 小鼠的 DCM 病程进展,但只能延长短时间内的生存时间,且效果不明显。DCM 常伴多种自身抗体(autoantibodies, AABs)水平的增加,丙球蛋白的冲击治疗可中和 IgG 抗体,阻止 AABs 的产生。一项包括 42 名初发 DCM 患者的随机双盲实验证实,大剂量丙球蛋白可使心功能提高 I~II 级、LVEF 升高 5%、血 BNP 水平降低 50%,且对中青年初发 DCM 疗效好^[19]。除此之外,临床上还采用免疫吸附法在 DCM 患者体外进行血液净化,80% 的 DCM 患者血浆中可检测出 β_1 -AABs,且 β_1 -AABs 选择性免疫吸附可在短期内改善 DCM 患者的心功能及预后^[20]。DCM 血清中的许多 AABs 来自 IgG 亚类,其中 IgG3 属在介导免疫吸附治疗的功效中起关键作用,通过色氨酸柱免疫吸附法可特异性清除 IgG3 并改善 DCM 伴难治性心力衰竭的患者主观症状及运动耐量^[21]。

2.4 干细胞治疗

干细胞治疗通过重建功能正常的细胞和组织从而达到改善患者生活质量的目的,干细胞可来源于骨髓、心脏等^[22]。一项包含 1255 名患者的荟萃分析结果表明骨髓干细胞(mesenchymal stem cells, MSCs)治疗有效改善 LVEF^[23]。干细胞治疗手段多样,Alan 等^[24]证实经心内膜注射 MSCs 后可减少心肌梗死面积和左心室舒张末期容积。另有随机对照研究表明给予异源 MSC 治疗可改善非缺血性 DCM 患者的内皮功能等指标,且明显优于自体 MSC^[25]。CD34+ 被视为造血干细胞的标志物,其治疗非缺血性 DCM 时可明显改善 LVEF、六分钟步行距离等指标^[26]。Bojan 等^[27]证实经心内膜移植 CD34+ 可明显改善心肌保留率和左室功能且作用优于冠脉移植途径。冠脉内干细胞疗法也取得了很好的疗效,Roberto 等^[28]指出行冠脉内干细胞移植术可改善一年内患者的心室重构症状和运动耐量指标,降低一年病死率和进行心脏移植的例数,但对 DCM 患者生存率的长期影响仍需更大规模的研究来证实。

2.5 基因治疗

目前已证实超过 40 种基因与 DCM 有关,相关突变大多发生在肌节蛋白和细胞骨架蛋白的编码基因上^[29]。在编码肌节蛋白的基因中,MYH7 和肌联蛋白基因的突变最为常见^[30]。有研究显示,大约 8% 散发性和 25% 家族性 DCM 的发生与肌联蛋白编码基因的截断突变有关,反义寡核苷酸所介导肌联蛋白编码基因的移码突变是 DCM 重要的遗传形式^[31]。MicroRNA 可在心肌细胞中高度表达并对肌肉生长、再生及纤维化等过程有重要作用。有研究表明,miR-448-3p 的下调可引发 ROS 的产生并导致心肌肥大、房颤、心肌纤维化及炎症的发生进而引发 DCM、心率失常^[32]。Mattia 等^[33]证实腺相关病毒介导的 miR-NA-669a 的表达可显著改善短期内 Sgcb 基因敲除小鼠的心肌结构和心功能,并减少不良左心室重构,从而增加营养不良并

患严重心脏病小鼠的生存率。目前 DCM 的基因疗法大多处于动物实验阶段,有待大量研究进一步证实。

3 小结

DCM 病因复杂,可能与感染、自身免疫、遗传因素等因素有关,因此针对不同发病机制应采取不同的治疗。药物治疗的进步以及免疫、干细胞移植和基因治疗等技术的快速发展,为 DCM 患者带来福音,但大多数新型治疗仍停留在理论研究阶段,仍需进一步深入研究。

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