

梗阻性肥厚型心肌病的介入和外科手术治疗及进展

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【摘要】 肥厚型心肌病是一种最为常见的心血管遗传性疾病,主要病因是编码肌小节蛋白或肌小节相关结构蛋白的基因变异,目前肥厚型心肌病已成为青少年猝死的头号病因,分为梗阻性肥厚型心肌病和非梗阻性肥厚型心肌病,梗阻性肥厚型心肌病相对非梗阻性肥厚型心肌病死亡率更高,诊治更加困难。现从梗阻性肥厚型心肌病的治疗角度出发,对以往及近期有关的治疗手段尤其是介入和手术治疗方面的进展做一综述。

【关键词】 梗阻性肥厚型心肌病;介入治疗;手术治疗

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New Perspectives on Interventional and Surgical Therapy for Obstructive Hypertrophic Cardiomyopathy

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【Abstract】 Hypertrophic cardiomyopathy is one of the most common cardiovascular genetic diseases which is mainly caused by the variants in the genes encoding sarcomere or sarcomere related structural protein. Now, hypertrophic cardiomyopathy has become the first cause of sudden death in adolescents. It is divided into obstructive hypertrophic cardiomyopathy and non-obstructive hypertrophic cardiomyopathy. Obstructive hypertrophic cardiomyopathy has a higher mortality than non-obstructive hypertrophic cardiomyopathy. This article reviews the past and recent advances in the treatment of obstructive hypertrophic cardiomyopathy, especially in interventional therapy and surgical therapy.

【Keywords】 Obstructive hypertrophic cardiomyopathy; Interventional therapy; Surgical therapy

肥厚型心肌病(hypertrophic cardiomyopathy, HCM)是一种常见的遗传性心血管疾病,其表型和遗传学多样而复杂,全球年发病率为1/500~1/200^[1]。根据最新《中国成人肥厚型心肌病诊断与治疗指南2023》^[2],HCM是由于编码肌小节相关基因变异导致的以心肌肥厚为主要特征的心肌病,常表现为左室心肌肥厚。从Teare最初的病理描述和20世纪60年代初Braunwald首次全面的临床描述至今已有60年历史^[3]。然而在今日,从儿童到老年人,HCM的发病率均明显增加,尤其是青少年,HCM已成为青少年猝死的第一大病因^[4-5]。

HCM是一种常见的单基因遗传性疾病,主要病因是编码肌小节蛋白或肌小节相关结构蛋白的基因变异,表现为常染色体显性遗传,约60%的HCM存在致

病性或可能致病性基因变异,仍有约40%的HCM未找到明确致病基因^[2,6]。根据其血流动力学指标左室流出道压力阶差(left ventricular outflow tract gradient, LVOTG),可分为梗阻性肥厚型心肌病(obstructive hypertrophic cardiomyopathy, OHCM)和非梗阻性HCM。其中OHCM生存率相比较非梗阻性HCM更低,需通过多种途径进行控制和治疗,包括药物治疗、介入治疗、外科手术等手段减轻症状和降低风险。虽然治疗手段繁多,但目前的治疗方法仍无法完全治愈HCM,主要的治疗目标仍停留在降低心血管事件风险、减轻症状和减少并发症上。现结合近期OHCM相关研究和进展,对OHCM相关的治疗手段尤其是介入治疗和外科手术等疗法做全方位的综述,以期对该疾病后续的治疗与研究提供一定的参考价值。

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1 OHCM 相关介入和外科手术治疗

1.1 介入治疗

临床上主要包括经皮腔内室间隔心肌消融(percutaneous transluminal septal myocardial ablation, PTSMA)、经皮心肌内室间隔射频消融(percutaneous intramyocardial septal radiofrequency ablation, PIMSRA)和利用 CARTOSound® 的室间隔射频消融技术。

1.1.1 PTSMA

PTSMA 是最经典的 OHCM 介入治疗方法,是指经导管将纯乙醇注入冠状动脉左前降支局部间隔支,局部消融增厚的心肌。在闭塞部位形成适当的室间隔坏死,减少局部肥厚和控制左心室的心输出量,以减少二尖瓣的收缩期前向运动。该介入方法最早由 Sigwart^[7] 于 1995 年在 *Lancet* 上报道。据欧洲多中心 PTSMA 研究^[8] 报道,在 1996—2015 年共纳入 1 275 例 PTSMA 患者,术后患者 LVOTG 降低 > 50%。表明该治疗方法能有效改善患者的血流动力学表现,同时在纽约心功能分级、峰值耗氧量和运动能力方面也有所改善。虽然该介入治疗表现出良好的疗效,但其急性并发症不容忽视。PTSMA 的急性并发症包括房室传导阻滞(atrioventricular block, AVB)、束支传导阻滞、远端心肌梗死、室性心律失常、冠状动脉夹层、心脏压塞和肺栓塞^[9-10]。其中最常见的是完全性 AVB。据报道,10%~15% 的 PTSMA 患者有完全性 AVB,是室间隔切除术后出现 AVB 患者的 2 倍多。同时,关于 PTSMA 的预后,该手术预后影响因素包括患者年龄、解剖特征(尤其是 LVOTG 的严重程度、左心室肥大程度和左心室直径大小)和医疗中心的病例数量等。而备受关注的性别却并不是预后的预测因子^[11]。近年来,PTSMA 术后的远期预后相对较好^[12-13]。一项研究^[14] 报道,全因死亡率和心源性猝死的发生率很低,95% 的患者改善到纽约心功能分级 I 级或 II 级,这与一般人群中年龄和性别的预期生存率相当(1 年、5 年和 10 年的全因死亡率分别为 97%、92% 和 82%)。目前,PTSMA 已成为一项治疗 HCM 的常规且成熟的介入治疗技术,在符合其适应证且无禁忌证的前提下,可由专业的介入医师进行治疗。

1.1.2 PIMSRA

PIMSRA 又被称为 Liwen 术式,由中国刘丽文医生提出并开发,并于 2023 年写入《中国成人肥厚型心肌病诊断与治疗指南 2023》^[2,15-16]。PIMSRA 是一种特殊的技术,它是将射频电极针插入肥大的室间隔心肌,经皮经心尖心肌内入路,实时成像指导。针尖被用来发射高频交流电激活心肌细胞中的离子,可产生热量并导致不可逆的凝血坏死。该术式已被证明可

有效改善 OHCM 患者症状,消融完成后即可显著降低 LVOTG 和室间隔厚度,术后 1 个月相关指标则会进一步降低,纽约心功能分级亦展示出有效改善^[17-18]。手术半年后,相关指标依然保持在较低水准,显著改善患者心脏形态学和血流动力学表现,显著提高患者生活质量^[16]。2020 年刘丽文团队^[19] 开展的一项随机对照试验发现,在药物难治性 OHCM 患者中使用 PIMSRA 治疗,可有效缓解左心室流出道梗阻和减少并发症的发生。相比传统的室间隔切除术和 PTSMA 来说,该介入技术所受创面更小,术后患者恢复更快,体现出其在 OHCM 治疗领域明显的优越性,有望在未来成为 HCM 治疗领域的可靠工具。

1.1.3 利用 CARTOSound® 的室间隔射频消融

2016 年 Cooper 等^[20] 首次报道, CARTOSound® 即三维心腔内超声技术,是在传统心内膜射频消融技术的基础上,运用 CARTOSound® 技术,将梗阻区和心脏关键传导束直接描绘到电生理三维标测图上,用于指导消融的精准能量传导,以最大程度减轻消融带来的损伤。该研究首次报道的 4 例接受该手术的患者在 6 个月随访时均表现出不同程度的症状与心功能改善。2021 年蒋周岑等^[21] 报道了 11 例接受此治疗的患者在手术半年后检查发现室间隔厚度并未出现明显变化,而其心功能从原先的纽约心功能分级 III 级或 IV 级改善为 I 级或 II 级。可见该介入治疗在减轻心肌厚度方面并不突出,其主要通过降低心肌顺应性来降低 LVOTG 的方式,减轻血流动力学症状,但同样可起到改善心功能的作用^[22]。风险主要体现在术后早期消融区域可能产生严重的难以消退的心肌水肿,从而诱发急性左心衰竭和肺水肿,甚至导致死亡^[23]。因此,准确全面地评估患者的整体情况并完善手术方式,进行长期全面的随访,才能不断提高手术的安全性,减少并发症的发生。

1.2 外科手术治疗

1.2.1 室间隔心肌切除术

Morrow 术式为经典的室间隔切除术式,由 Morrow 于 1975 年提出。其可直接有效地减轻心肌厚度,改善流出道梗阻状况,但缺点为主要切除侧边室间隔肌肉,而中部的室间隔无法完全切除从而导致流出道疏通不充分,仍存在部分梗阻。在此基础上, Messmer 等^[24] 于 1994 年提出改良扩大 Morrow 术式,即切除范围向心尖延伸并超越左心室流出道梗阻最严重的部位后达到二尖瓣乳头肌根部水平,以最大程度地减少流出道梗阻。Liebregts 等^[12] 的荟萃分析发现,相比于使用 PTSMA 介入治疗的患者来说,接受 Morrow 手术的患者表现出更显著的心肌肥厚减轻,

但同时存在更高的 AVB 风险,每年约 0.5% 的 Morrow 术后患者出现 AVB 并需安装永久心脏起搏器。该手术适应证主要为心肌严重肥厚(≥ 30 mm)、有明显的流出道梗阻患者及经药物和介入治疗后症状难以减轻的患者。Morrow 术式的优点在于最大程度地缓解 LVOTG 和改善临床症状,需重复手术的概率较低;如同时合并其他相关需手术干预的心脏疾病时可同期手术;术后发生起搏器依赖的风险相对较低。但由于其作为技术难度较大的外科手术且对患者创伤性大,术后恢复难度相对较高,术后出现并发症概率较高。

1.2.2 二尖瓣相关手术形式

在 OHCM 中常出现二尖瓣结构异常,此时二尖瓣的修复或置换会成为患者的首要手术选择,且可缓解患者左心室流出道梗阻^[25]。相比较二尖瓣置换术,二尖瓣修复术成为 HCM 合并二尖瓣病变患者的首选。2016 年 Hong 等^[26]发表的 11 年长期随访研究发现,相比较二尖瓣置换术,二尖瓣修复术可提高约 25% 的 10 年生存率。此外,经导管二尖瓣夹合术(MitraClip)于 1998 年由 Alfieri 提出,至今已成为一项低风险微创治疗二尖瓣相关问题的技术^[27]。Thomas 等^[28]和 Long 等^[29]分别于 2017 年和 2020 年提出使用 MitraClip 治疗 HCM 相关二尖瓣结构异常患者,并报道了患者术后从二尖瓣反流情况、LVOTG 和纽约心功能分级等方面均获得了不同程度的改善。除上述二尖瓣相关手术外,目前也存在经二尖瓣口进入左心室进行梗阻疏通的手术形式,加以胸腔镜或机器人辅助,从而更加微创、精确、快速^[30-31]。

1.2.3 经心尖不停跳室间隔心肌切除术

经心尖不停跳室间隔心肌切除术,是华中科技大学同济医学院附属同济医院心外科魏翔团队^[32]于 2023 年发表于 JACC 中的一种新型的在心脏不停跳的情况下,经心尖搏动处进行心脏室间隔切除的术式,可显著改善患者梗阻情况,降低 LVOTG。该研究共纳入 47 例年龄 12~77 岁的患者,并成功完成 46 例患者的 3 个月随访,其中 42 例手术成功。最大 LVOTG 从基线时的 86 mm Hg(1 mm Hg=0.133 3 kPa; IQR 67~114 mm Hg)下降到 3 个月时的 19 mm Hg(IQR 14~28 mm Hg)。其中 1 例患者在术后第 10 天因与器械无关的原因死亡。其他主要不良事件包括 1 例迟发性室间隔穿孔和 1 例术中左心室根尖撕裂。虽然该术式可以更加微创的形式帮助患者摆脱肥厚梗阻的困扰,但需进行更加全面长期的随访从而获得更加详实的数据来帮助不断改良术式,在提高手术成功率的同时降低手术并发症的发生率。

1.2.4 经右心室心肌切除术

经右心室心肌切除术主要适用于合并右心室心肌肥厚的患者,通过左心室肥大区对应的右心室圆锥部进入左心室肥大区。在右心室圆锥部做一个 21~27 mm 的纵向切口。将室间隔前部与右心室前壁之间存在的所有附着物和附加小梁分离后,将室间隔不对称肥厚区切除。同时,由于左右心室腔内存在压力差,左侧静脉不对称肥大缓解而右侧静脉因上述切除而变薄。最终可实现恢复左心室腔自然形态的目的^[33]。Borisov 等^[33]于 2018 年对此项新手术方法进行了首次报道,其中 11 例接受此手术的患者于术后 14 d 内呼吸困难等症状完全缓解,6 年随访结果显示该 11 例患者未出现症状反复以及任何如 AVB 之类的并发症。

1.2.5 双腔起搏器和植入型心律转复除颤器植入术

永久性双腔起搏很早就被建议作为一种辅助治疗,可减轻症状明显的 OHCM 患者的症状^[34]。其机制主要由两部分组成,一种为收缩机制,一种为舒张机制;收缩机制依赖于左心室去极化引起的矛盾的室间隔运动,这种运动延迟了基底室间隔的收缩,从而降低 LVOTG^[35];舒张机制则依赖于改善了的心房收缩以改善左心室充盈,从而减轻心肌肥厚的相关症状^[36]。据报道^[37],双腔起搏器植入的 HCM 患者表现出 LVOTG 显著降低、纽约心功能分级改善和二尖瓣反流减少。心源性猝死是 HCM 最为严重的并发症,一项重大的临床研究^[38]表明植入型心律转复除颤器的使用可有效减少 OHCM 患者心源性猝死的发生,且标志着器械治疗在 OHCM 患者中的可行性。不过植入型心律转复除颤器的使用需从年龄、原因不明的晕厥、心源性猝死家族史、非持续性室性心动过速、左心室直径、左心室壁厚度等各个方面进行严格的风险评估,以避免可能出现的植入性器械的并发症的发生^[39-40]。

2 总结与展望

HCM 从首次被人们所认识和定义,已过去了 60 多年。其中,OHCM 以其复杂的病情、困难的治疗和较高的死亡率,成为心血管疾病的一大难题。在这 60 年间,随着人们对 HCM 认识的不断提升以及先进的影像学技术的出现,在 HCM 发病率在全年龄段不断增高的同时,人们对 HCM 的诊断和治疗水平不断提高。20 世纪以来,随着人类基因组计划的完成,基因诊断技术不断成熟,且影像学技术不断发展,尤其是心脏磁共振等技术不断发展,对于 HCM 的诊断更加完善,能实现早发现、早治疗的目标。近年来,随着新型靶向药物玛伐凯泰的问世,新型的介入治疗方式以及新

的术式例如经心尖不停跳室间隔心肌切除术的发明, HCM 尤其是 OHCM 的传统药物治疗和手术治疗进入到了一个新的发展阶段。同时,随着全新的基因治疗理念的出现,该疾病有望从根源上实现治愈。这些新兴的治疗方法虽然仍处于起步阶段,其长期的预后疗效和安全性仍有待考究,但笔者有理由相信,在未来, HCM 有可能成为本世纪能看到全面解决方案的一种心血管疾病。

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