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在线全文

肥厚型心肌病心肌纤维化磁共振评价临床研究进展*

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【摘要】 肥厚型心肌病（hypertrophic cardiomyopathy, HCM）是导致青少年和运动员发生心源性猝死最常见的原发性心肌病。我国现有HCM患者超过100万，位居全球首位，且患病人数呈逐年上升趋势。心肌纤维化是HCM最重要的病理学改变，也是患者发生恶性室性心律失常、心室重构及心衰的首要原因。目前心脏MRI是无创检测心肌纤维化的“金标准”，包括钆对比剂延迟增强序列、T1 mapping序列等显示出良好的应用前景，不仅为阐释HCM组织学特征提供了切实可行的影像学手段，还有助于对患者远期预后进行评价。本文从钆对比剂延迟增强成像、T1 mapping组织特征成像、T1ρ mapping组织特征成像、基于MRI的影像组学与机器学习模型4个方面，就近年来HCM心肌纤维化MRI研究进展作一综述。

【关键词】 肥厚型心肌病 心肌纤维化 磁共振成像 综述

Clincial Research Progress in Using Magnetic Resonance Imaging to Assess Myocardial Fibrosis in Hypertrophic Cardiomyopathy

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【**Abstract**】 Hypertrophic cardiomyopathy (HCM) is the most common type of primary cardiomyopathy that causes sudden cardiac death in adolescents and athletes. With over 1 million HCM patients, China has the largest population of HCM patients in the world, and the total number of cases is increasing year on year. Myocardial fibrosis is the most important histopathological characterization in HCM and is regarded as the primary cause of malignant ventricular arrhythmia, cardiac remodeling, and heart failure. At present, cardiac magnetic resonance imaging (MRI) serves as the gold-standard imaging modality for noninvasive evaluation of myocardial fibrosis. Several techniques, such as late gadolinium enhancement and T1 mapping, are showing considerable promise for potential applications. These techniques have emerged as viable imaging approaches to the elucidation of HCM tissue characterization. They are also helpful in predicting the long-term prognosis of patients. Herein, we summarized recent advances in using cardiac MRI to assess myocardial fibrosis in HCM from four perspectives, including late gadolinium enhancement, T1 mapping, T1ρ mapping, and MRI-based radiomics and machine learning models.

【**Key words**】 Hypertrophic cardiomyopathy Myocardial fibrosis Magnetic resonance imaging Review

据《中国心血管健康与疾病报告2023概要》显示，我国心血管疾病患病率与死亡率仍处于上升阶段，目前心血管疾病已跃居成为我国城乡居民死亡的首要原因，其占比超过45%，在我国心血管病负担日益严重的背景下，心血管疾病防治已成为重大公共卫生问题[1]。肥厚型心肌病（hypertrophic cardiomyopathy, HCM）是最常见的具有遗传倾向的原发性心肌病，也是青少年和运动员发生心源性猝死（sudden cardiac death, SCD）最常见的原因。该病患者并发恶性室性心律失常、房颤以及缺血性脑卒中的风险显著高于普通人群，患者终末期心功能失代偿可导致心衰，严重影响患者的生存率与生活质量[2]。据不完全统计，我国HCM患病人数超过100万，位居全球首位，且近年来呈逐年上升趋势[1,3]。

HCM以左心室非对称性增厚为形态学特点，好发于室间隔，通常具有表型和遗传异质性[4]。组织病理学可见心肌排列紊乱、心肌纤维化伴小血管硬化，其中心肌纤维化是HCM最重要的组织病理学特点，可造成心脏电活动传导异常、心肌收缩功能障碍、顺应性降低，最终导致恶性心律失常、心室重构及心衰[5]。有证据表明HCM早期

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主要表现为可逆的弥漫性间质性纤维化,随病情进展,部分心肌细胞坏死或凋亡,进一步形成不可逆的替代性纤维化[6-7]。因此,HCM心肌纤维化的综合评价在检测心肌损伤、识别高危表型及构建风险预测模型方面有重要的临床价值。近年来,心脏MRI以其无创、无电离辐射、多参数序列成像的独特优势,在心血管病影像学检查中的应用日益广泛。心脏MRI可提供包括心脏结构、功能、组织学特征及血流动力学改变在内的多维度关键信息,为临床在体可视化研究各种心血管病的发生、发展及演变规律提供了可能,并进一步推动了心血管病早期诊断、危险分层及预后评估等方面的体系建立[8]。鉴于心脏MRI在无创评价HCM心肌纤维化中发挥的重要作用,本文就近年来HCM心肌纤维化MRI研究进展进行综述。

1 钆对比剂延迟增强(late gadolinium enhancement, LGE)成像

LGE成像是最经典的用于评价心肌纤维化的MRI序列,被视为判定心肌纤维化的"金标准"。替代性心肌纤维化是HCM-LGE成像主要的病理学基础,约50%~70%患者MRI增强扫描可检出LGE阳性[9]。既往大多数研究主要关注的是左心室有无LGE以及整体左心室LGE面积的临床价值,但就HCM-LGE的节段分布特点仍不清楚。LIU等[10]对798例HCM患者左心室16节段的MRI数据分析显示,HCM-LGE好发于左心室基底部及中间部的前壁及间隔壁,且室壁肥厚越严重出现LGE的可能性越大(r=0.35)。研究者进一步证实了节段左心室LGE比例预测患者发生不良心血管事件风险的效能与传统的整体左心室LGE比例相当。除此之外,该研究还发现,HCM-LGE节段好发部位较为恒定,与患者基因表型特点无显著关联。同时,尽管基因型阳性患者较阴性患者发生LGE的可能性更大,但该研究显示LGE范围与患者预后的关系并不受患者基因表型的影响。上述结果丰富完善了HCM-LGE节段分布的形态学特点,明确了LGE成像对HCM患者危险分层具有独立的预测效能,进一步凸显了LGE成像评价的重要临床价值。

HCM-LGE好发于肥厚心肌,表现形式多为心肌壁间点状或斑片状,其中尤以右心室插入点LGE最为常见,其可能的机制是该区域承受了较高的机械剪切力,导致心肌出现局灶性坏死与胶原纤维沉积[11]。传统观念认为左心室LGE面积是决定HCM患者预后的决定因素,与LGE的表现形式无关。近期,YANG等[12]创新性发现了左心室心内膜下LGE这一特殊的具有预后价值的LGE类型。该研究中患者左心室心内膜下LGE的发生率仅为18.3%,作为一种高危LGE表型,其存在可提示HCM患者远期预后较差。就此种类型LGE的成因,作者推测可能是由于HCM左心室心内膜下微血管管腔较小、扩张性较差,同时冠状动脉储备功能弱,在左心室流出道梗阻所致压力阶差升高以及左心室肥厚所致顺应性降低内外环境影响下,诱导左心室心内膜下微血管功能障碍,继之出现心肌缺血与心肌纤维化。左心室心内膜下LGE在终末期HCM患者中更为常见,往往伴有明显的心室肥厚、广泛的心肌纤维化与收缩功能降低,该LGE表型或可作为HCM左心室心肌缺血严重程度的评判依据,并用于早期预测患者远期发生心衰相关不良事件的风险[13-14]。因此,以上研究提示在定量评估HCM患者LGE面积同时,还应留意某些特殊的LGE表现形式,如左心室心内膜下LGE,将有助于筛选识别HCM不良预后高危人群。

SCD是HCM严重的并发症,成年患者5年内发生率约5%[15]。研究表明由心肌纤维化导致的心肌电生理活动异常在其中起到了决定性作用[16]。可植入式心脏除颤仪(implantable cardioverter defibrillator, ICD)作为HCM患者SCD的一级预防措施,可有效避免恶性心律失常,但实际情况下如何有效筛选此类潜在适宜人群仍具有挑战性[17]。LEVINE等[18]的研究观察到LGE百分比>10%的HCM患者发生阵发性室速的可能性显著升高。另有研究提示基于心脏MRI的LGE定量测定可有效提高现有临床SCD风险预测模型识别HCM高危人群的效能[19]。这表明完善LGE评价对预测HCM患者SCD以及评估ICD指征的必要性。因此,目前美国、欧洲两大心脏病学会均将左心室广泛LGE(>10%或15%)作为评估HCM患者SCD风险的重要依据之一[17,20]。近年来研究人员针对小范围LGE(5%~10%)是否与SCD发生有关也进行了系列探索。有关数据显示,左心室LGE范围>5%的患者发生SCD的风险是LGE阴性或LGE范围<5%患者的7倍,故研究人员认为当患者左心室LGE范围>5%就应充分评估其接受ICD的合理性,以5%为阈值的LGE定量评价有助于进一步优化现有的HCM-SCD风险预测模型[21-22]。

LGE的存在意味着替代性纤维化的发生,明确LGE的变化规律有助于了解HCM的自然病程。RAMAN等[23]通过对HCM患者中位时间超过5年的跟踪随访发现,26%的患者复查MRI时LGE范围增大(ΔLGE≥4.75 g),进一步分析显示这些患者更易出现左心室室壁变薄、心腔扩大与收缩功能降低。另有研究报道称HCM患者首次MRI检查评估若发现LGE范围>8%、标准化左心室质量>100 g/m^2、最大室壁厚度>20 mm、左心室射血分数≤60%以及心尖室壁瘤形成等,其日后左心室LGE进展的可能性更大,同

时远期植入ICD的可能性更大,因心衰住院的风险更高[24]。因此,LGE进展表明HCM不良左心室重构的发生,可为患者病情进展与否提供客观影像学证据。

LGE成像是无创评价心肌纤维化的重要工具,近年来研究人员利用该技术就HCM-LGE的节段分布特点、高危形态表现、优化SCD预测模型以及心肌纤维化自然病程演变等问题进行了相应探索,显示出LGE成像在评价HCM组织特征改变以及临床危险分层方面起到的关键性作用。但应指出,LGE成像适合评价替代性心肌纤维化,对于间质性心肌纤维化敏感性不足,此时需结合T1组织特征成像进一步完善评估。

2　T1 mapping组织特征成像

T1 mapping组织特征成像通过量化评估心肌组织T1弛豫时间获取定量反映心肌组织学特征的像素编码图像,利用对比剂增强前/后(native/post)T1 mapping序列以及红细胞比容可计算得到细胞外间质容积(extracellular volume, ECV)mapping。较经典的LGE成像,T1 mapping成像有两大技术优势:①可在不使用对比剂的情况下完成心肌组织特征评价,不仅缩短了检查时间,还提升了检查安全性,尤其适用于肾功能不全的患者。②不依赖参考心肌量化评价心肌组织T1弛豫时间。T1 mapping技术能够提供丰富的心肌组织学信息,为深入探索HCM病理改变提供了重要途径[25]。目前学界普遍认为HCM-LGE阴性患者属于SCD低风险人群,这部分人群左心室心肌组织病理学改变的认识较HCM-LGE阳性患者相对较少。XU等[26]筛选纳入了258例非梗阻性HCM-LGE阴性患者并比较了患者与健康对照者左心室整体native T1以及ECV的差异,研究发现即使前者没有明确LGE存在,其左心室整体native T1以及ECV均较后者升高,且心肌越肥厚测值升高越明显,提示HCM患者左心室心肌弥漫性胶原纤维沉积。CHUNG等[27]的研究同样也显示ECV识别LGE阴性心肌组织特征差异的能力,研究中肌小节基因突变患者相应节段ECV高于非突变患者。鉴于心肌活检的风险性,MRI-T1 mapping技术有望成为HCM组织学特征可替代的无创评价手段。

HCM形态学表现易与其他疾病造成的左心室肥厚相混淆,常规影像学检查鉴别存在一定困难,而T1 mapping技术在解决这一问题上展现了良好的应用价值,有助于探索左心室肥厚相关疾病的组织特征差异。HINOJAR等[28]的研究发现HCM患者native T1与ECV均高于高血压患者,表明HCM心肌胶原纤维沉积与细胞间隙扩大较高血压更为明显。另一方面,职业运动员由于长期高强度训练,其生理性心肌肥厚与HCM有着相似的影像表型。SWOBODA等[29]报道称与运动员相比,HCM患者左心室心肌native T1与ECV更高。而运动员与普通对照者相比,native T1差异无统计学意义,但前者左心室最厚处心肌ECV反而低于后者,表明前者心肌纤维更为粗大。更为重要的是,该研究发现运动员左心室ECV与最大室壁厚度(r= −0.40)和心肌质量(r= −0.37)均呈负相关,而HCM患者左心室ECV与最大室壁厚度呈正相关(r=0.43),据此作者推测生理情况下心肌质量增加主要是由心肌细胞肥大造成,而HCM心肌质量增加则是由胶原沉积造成。Anderson-Fabry病是一种罕见的X染色体连锁遗传溶酶体贮积症,以三己糖酰基鞘脂醇及其衍生物脱乙酰基为主的代谢产物贮积于组织器官,其心脏受累表现常被误诊为HCM[30]。KARUR等[31]利用T1 mapping发现Anderson-Fabry病室间隔native T1低于HCM,以1 220 msec作为阈值可区分二者不同的组织特征改变(敏感性97%,特异性93%)。

T1 mapping成像作为LGE成像的有力补充,让心脏MRI对HCM的组织特征改变评价趋于完善,同时有助于临床对左心室肥厚病因的鉴别诊断。然而在实际应用过程中需要注意,T1弛豫信号测定会受到磁共振机型、场强、成像序列及后处理软件等因素影响,故对于T1 mapping标准化成像方案以及正常参考范围的确立仍需进一步明确。

3　T1ρ mapping组织特征成像

与T1弛豫参数不同的是,T1ρ代表的是自旋锁定射频场中横向磁化矢量的衰减,T1ρ序列首先将纵向磁化矢量翻转至X-Y平面,然后沿磁化矢量翻转的轴线方向施加自旋锁定脉冲将磁化矢量锁定于该平面,此时磁化矢量只有幅度的变化而不会有相位衰减,自旋系统的能量传递在频率范围300 ~ 1 000 Hz内。因此,T1ρ弛豫参数提供的是组织的一种特殊的低频体系弛豫特性,对所测量组织中大分子成分如胶原蛋白较敏感[32-34]。近年来,研究人员就T1ρ mapping技术应用于HCM也进行了初步尝试,结果显示T1ρ评价HCM组织特征改变有着良好效果,其测值能够有效区分LGE阳性、LGE阴性与对照组心肌[35]。另有研究报道称HCM肥厚节段与非肥厚节段T1ρ测值具有显著差异,并与ECV呈正相关(r=0.88),显示出T1ρ mapping在不依赖对比剂的情况下可无创评价HCM心肌纤维化的技术优势[36]。“灰色组织”是指LGE信号强度介于远处心肌2 ~ 6倍标准差的区域,该区域心肌细胞与胶原纤维均占有一定比例,亦被认为与恶性室性心律失常存在关

联[37]。DONG等[38]的研究证实了T1ρ mapping可用于识别心肌“灰色组织”,而T1 mapping无法区分心肌“灰色组织”与正常心肌。最新的证据表明,T1ρ mapping在不依赖对比剂的情况下识别急慢性心肌损伤有着良好的效果,且可重复性高[39]。因此,与T1 mapping相比T1ρ mapping识别纤维化心肌的敏感性更高,扫描更加简便,且无需对比剂生成ECV图像,为评价心肌组织特征异质性提供了新途径。但由于目前其图像采集尚处于初步探索阶段,还存在诸多技术问题有待今后解决。

4 基于MRI的影像组学与机器学习模型

近年来以MRI原始图像为载体的影像组学与人工智能研究已成为医学领域极具潜力的研究和发展方向。影像组学通过分析图像像素灰度中的形态、纹理分布特征,进而提取、筛选人类视觉不可见的图像信息,用以反映疾病状态下的组织学改变,极大丰富了医学影像图像的信息内涵[40]。就HCM心肌纤维化相关评价,影像组学近年来取得了长足进展。NEISIUS等[41]基于native T1图像提取的特征可用于鉴别HCM与高血压心肌肥厚,其诊断准确性可达80%。该研究中如局部二值模式特征、游程矩阵特征的差异表明影像组学可对HCM与高血压心肌空间分布特征进行定量描述并加以鉴别,从而为临床鉴别左心室肥厚相关疾病提供了新途径。鉴于T1 mapping信号测定受扫描机型、场强及序列等影响,纤维化心肌与正常心肌差异较小时可造成假阴性结果,NEISIUS等[42]采用影像组学方法构建的native T1图像特征模型可显著提高对LGE阴性患者预测的敏感性,是对常规T1 mapping图像分析的有力补充。国内PU等[43]分别对未增强心脏电影序列左心室最大室壁厚度层面及整体左心室进行特征提取并构建预测模型,同时以LGE为参考标准,结果显示基于影像组学的心脏电影图像同样可对患者LGE状态作出准确判断。前述两项研究发现提示基于未增强MRI序列的影像组学途径有望减少不必要的对比剂使用,进而提升心脏MRI检查的有效性与安全性。值得注意的是,影像组学相关HCM预后评价也显示出良好的应用前景。CHENG等[44]认为即使LGE面积相当的HCM患者其远期预后也不尽相同,在该研究中LGE图像纹理越不均匀(能量/偏度)的患者远期预后更差,因此影像组学可进一步获取LGE图像中与预后相关的生物学信息。目前已有研究团队成功利用LGE图像构建了影像组学模型用于预测HCM患者SCD风险,其预测效能优于现有临床常规风险模型并有助于优化后者的完整性[45]。此外,熵值代表的是图像纹理的复杂性与随机性,熵值增高被证实与HCM左室肥厚、心肌纤维化及收缩功能受损有关[46]。国内不同研究团队尝试从LGE和native T1图像中提取相应熵值,发现熵值可用于预测HCM患者不良事件发生,预后较差的患者熵值较高[47-48]。

人工智能隶属于计算机科学范畴,其中机器学习,尤其是深度学习在医学影像学领域的应用尤为广泛。它通过人工神经网络处理大量原始图像,从中学习、训练并提取、组合特征形成高阶映射层,最终形成分类依据模拟人类思维过程对输入的图像信息作出反应和判断,达到辅助临床医生解决诸如疾病分型、疗效预测及预后评价等目的[49]。ZHANG等[50]将HCM患者增强前心脏电影及T1 mapping图像置于卷积神经网络深度学习模型用于生成一种虚拟原生增强图像,其显示心肌纤维化的效果可媲美增强后LGE图像,更为重要的是,获取该图像整个过程耗时不足1 s,同时患者无需接受增强MRI扫描,在缩短检查时间的情况下避免了对比剂使用的潜在不利影响。近年来也有机器学习算法与影像组学特征或临床特征联合构建模型用于预测HCM心肌纤维化及预后的报道,为HCM心肌纤维化的智能化诊断及预测提供了越来越多的证据[51-54]。尽管目前的研究展现出影像组学与人工智能模型良好的应用潜力,但任何稳健的诊断预测模型确立必然依赖庞大且优质的影像数据作为保障,在实施过程中如何形成有效的数据源难度较大;另外不同区域与种族间尚缺少充分的外部验证,故某种特定模型如何具备普适性仍需要继续探索[55]。

综上所述,心肌纤维化作为HCM关键的病理学改变,具有重要的临床研究价值。心脏MRI以其无电离辐射、无创及多序列成像等优势,在评价HCM心肌纤维化中发挥了决定性作用。心脏MRI的应用使得学界对HCM心肌纤维化与该病发生发展、临床分型以及预后的相互关联有了更深刻的认识,同时丰富并提升了现有HCM临床诊疗指南的内涵与完整性。随着心脏MRI技术的持续进步,相信今后会有更多手段用于精准、敏感检测HCM心肌纤维化,推动HCM临床诊断、危险分层乃至治疗效果评价不断完善,进而使更多患者获益。

* * *

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