·综述·

软骨定量 MRI 新技术的研究进展

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【摘要】 **目的** 探讨软骨定量 MRI 新技术在骨关节炎诊断和治疗中的研究进展和应用前景。**方法** 在 Medline 和 CNKI 数据库,分别以"Cartilage injury/damage, osteoarthritis, $T_1\rho$mapping, Sodium MRI, magnetization transfer MRI, Chemical exchange saturation transfer, Ultrashort echo time MRI, DWI, DTI, Pharmacokinetic MRI"和"软骨损伤,骨关节炎,T1ρ 值,钠磁共振成像,磁化传递磁共振成像,化学交换依赖性饱和传递技术,扩散加权成像,扩散张量成像,药物代谢动力学磁共振成像"为关键词,限定语言种类为 English 和中文,检索 2001 年 1 月—2014 年 7 月间发表的有关软骨损伤和软骨定量 MRI 研究的文章。就检索到的 200 余篇文献进行筛选,选择以软骨损伤和骨关节炎 MRI 的实验研究和临床研究为主要内容的文献 86 篇;其中研究相似的,以近 5 年且发表在较权威期刊者优先纳入分析。**结果** 软骨的 MRI 和定量分析一直是学界研究热点之一,近年来随着 MRI 硬件和软件的提升,各种 MRI 新技术被应用于软骨 MRI 的定量分析,这些新技术在检测早期软骨损伤及软骨生化成分和血管成分的量化分析方面展示了良好的应用和研究前景,但是仍存在一些固有的缺陷。**结论** 随着 MR 硬件和软件的升级、新序列的开发与运用及理论研究的不断深入,这些新技术或可成为骨关节炎诊断和治疗的 MRI 生物标志物。

【关键词】 软骨; 骨关节炎; 磁共振成像; 参量值

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【**Abstract**】 **Objective** To explore research progress and application prospects of new MRI technologies in diagnosis and treatment of osteoarthritis. **Methods** A computer-based online search of Medline database was undertaken to identify the articles about cartilage injury/damage and cartilage quantitative MRI published in English from January 2004 to July 2014, with the key words of "Cartilage injury/damage, osteoarthritis, $T_1\rho$mapping, Sodium MRI, magnetization transfer MRI, Chemical exchange saturation transfer, Ultrashort echo time MRI, DWI, DTI, Pharmacokinetic MRI". And the computer-based online search of CNKI database was also undertaken to identify relevant articles published in Chinese from January 2004 to July 2014 with the key words of "软骨损伤,骨关节炎,T1ρ 值,钠磁共振成像,磁化传递磁共振成像,化学交换依赖性饱和传递技术,扩散加权成像,扩散张量成像,药物代谢动力学磁共振成像". The first trial involved in 200 articles, and 86 articles of them referred to the experimental and clinical study of cartilage injury/damage and osteoarthritis. In which those had similar content and published on authority magazines in recent 5 years were preferred. **Results** Cartilage MRI and quantitative analysis have been one of the hot-point academic researchs. In recent years, with the enhancement of MRI hardware and software, the new technology has been applied to cartilage quantitative MRI analysis. In terms of early detection of cartilage damage and cartilage biochemical composition and vascular components, quantitative analysis of these new MRI technologies showed good application and research prospects, but there were still some inherent flaws. **Conclusions** With MR hardware and software upgrades, the development and application of new MRI sequences and deepening of theoretical studies using these new technologies, parameter values derived these new quantitative MRI analysis techniques may become MRI biomarkers in diagnosis and treatment of osteoarthritis in the future.

【**Key words**】 Cartilage; Osteoarthritis; Magnetic resonance imaging; Parameter value

骨关节炎(osteoarthritis, OA)是老年人最常见的关节病,起病隐匿,影响关节功能,我国发病率约 4%,每年治疗 OA 的费用超过 1 500 亿元[1]。随着人口老龄化和肥胖者增加,OA 患病率不断增长,早期发现软骨损伤并积极干预、防止进入不可逆改变是治疗 OA 的关键[2],临床评分及传统影像仅能评估 OA 后期严重程度和软骨形态学退化[3],对早期生化改变不敏感。近年,新的软骨定量 MRI 技术为评价软骨生化信息提供了更多可能性,为早期发现和无创监测 OA 发

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展及疗效带来新曙光。

1　软骨生化成分和生理机能

关节软骨用于减少摩擦力、均衡负荷及减震,其主要生化成分是由水(65% ~85%)、Ⅱ型胶原(15% ~20%)和蛋白多糖(proteoglycans, PGs)(3% ~10%)构成的细胞外基质。PGs 因富含羧基团和硫基团而带负电荷,使软骨具有恒定负电荷密度(fixed charge density, FCD),该特性决定了 PGs 能吸引某些阳离子(主要是 Na^+),产生渗透压,维持水含量,保护软骨弹性[4]。软骨胶原纤维网可限制其横向扩展,承载拉力和剪切力。软骨分为钙化层、辐射层、过渡层、切线层,不同软骨层可对抗不同压力,其生理特性随特定区域负载而变化,例如承重区辐射层厚且胶原方向更具一致性,边缘区的过渡层胶原排列与最强剪切力方向一致[5]。

OA 初期,软骨胶原基质降解,PGs 丢失及水份增加,这些改变降低软骨抗负载能力,引起胶原基质张力增加,软骨生化成分随之进一步破坏,生理机能进一步下降,使其趋向更严重的形态学退化,最终影响关节功能[6,7]。因此如何检测 OA 早期生化改变非常重要。

2　软骨定量 MRI 新技术

2.1　$T_1\rho$mapping

$T_1\rho$mapping($T_1\rho$)技术是在静磁场 B0 中的质子施加一射频旋转磁场 B1,所产生的磁矩绕着静磁场 B0 和旋转磁场 B1 运动,旋转磁场的 Z 轴磁矩相对静止,在相位 Y 轴 90°时,沿 Y 轴平面施加自选锁定脉冲将其自旋锁定,在相位为 X 轴 180°时施加第 2 个 90°反相脉冲,将自旋锁定的磁化矢量保存在 Z 轴,最后采用梯度回波或自旋回波序列实现自旋锁定 $T_1\rho$ 加权成像[8]。软骨内附着于 PGs 水分子的弛豫由于受到自旋锁定脉冲影响,比自由水的能量耗散得快,根据该特性,$T_1\rho$ 值与蛋白多糖/葡萄糖胺聚糖(Proteoglycan/Glycosaminoglycan, PG/GAG)含量相关。

体外和间接体内实验证实 $T_1\rho$ 值和 PG/GAG 量之间存在良好的负相关[9-11],但最新的体内研究表明两者之间相关性较弱[12-13]。尽管如此,$T_1\rho$ 已被尝试用于追踪软骨改变的临床研究,例如有利于前交叉韧带重建[14]和软骨修复术后的软骨退变和修复评价[14-15]。研究还发现,软骨 $T_1\rho$ 值随年龄增长而增加[16],软骨和半月板 $T_1\rho$ 在跑跳运动后降低[17-19]。

总之,$T_1\rho$mapping 是分子水平上检测软骨代谢和生化信息的 MR 新技术之一,无需注射造影剂,无需关节活动和长时间等待,能反映软骨蛋白聚糖含量,有望取代软骨延迟增强磁共振成像(delayed Godolinium - Enhanced MR Imaging of Cartilage, dGEMRIC)。但缺点是较高的特定吸收率和自旋锁脉冲的射频能量所致组织热量增加的风险[20]。

2.2　钠 MRI

钠离子被吸附在带负荷的葡萄糖胺聚糖体(glycosaminoglycans, GAGs)上,其分布状态与葡萄糖胺聚糖(glycosaminoglycan, GAG)一致。钠离子可产生 MR 信号,研究表明其可准确测量软骨内 FCD 并间接评估 GAG 分布与含量,并且有良好的再现性、重复性和敏感性[21-23]。然而,因为体内钠离子浓度很低,所以产生 MR 信号相当困难,只有在更高场强下及使用专用的传输和接收线圈并需要长的成像时间才能得到足够的信噪比[24]。

2.3　磁化传递 MRI 与化学交换依赖性饱和传递技术

MT-MRI 首先预饱和结合水,结合水能量因其与自由水质子的化学交换而传递给后者,成像脉冲施加时,被饱和自由水不产生信号,导致组织信号衰减。此技术可定量反映大分子蛋白含量,其指标是磁化传递率(magnetization transfer ratio, MTR)。软骨内束缚水分子的主要成分是胶原,因此可评估其含量变化[25]。但也有学者认为胶原 3D 结构、结合水含量、PGs 等均可影响 MTR,这些因素导致 MTR 的稳定性和重复性差,对早期软骨退化不敏感[26-27]。

磁化传递 MRI(magnetization transfer MRI, MT-MRI)与化学交换依赖性饱和传递技术(chemical exchange saturation transfer, CEST)是最近基于 MT 产生的新技术,它选择性激发饱和溶质中可从大分子蛋白移至自由水进行化学交换的质子,在关节软骨内选择的是 GAGs 残余羟基,可提供软骨 GAGs 含量高低区域间的信号对比,该方法称为 gagCEST,其定量值为磁化传递偏位值(magnetization transfer asymmetry value, MTRasym),$MTRasym(\delta) = S(-\delta) - S(+\delta)/S0$,$S(-\delta)$及 $S(+\delta)$分别代表高低偏中心共振频率的信号强度,S0 代表未施加偏中心共振频率的信号强度,MTRasym 值与 GAG 含量呈正相关性[28]。Schmitt 等[29]利用 7T MR 研究发现,gagCEST 与钠 MRI 一样,对 GAG 含量检测敏感性很高。最新的临床研究表明,可利用 gagCEST 跟踪自体骨软骨移植术后软骨修复,其与软骨修复 MRI 评分(magnetic resonance observation of cartilage repair tissue score, MOCART)间有良好相关性[30]。

尽管 gagCEST 是一个精确检测 GAG 含量的方法,但 3T MR 机上仍难以提供足够信噪比和更均匀的静磁场,因此,多用于超高场强 MR 的应用研究;另外,它必需一套复杂精细的后处理工具,这些都限制了它的临床实践[31]。

2.4　超短波回波时间 MRI

常规 T_2mapping 对固有弛豫时间短的组织评估能力不充分,因为这些组织在 T_2WI 不能产生足够的信号,如骨皮质、半月板、肌腱/韧带及其附着区、软骨钙化层等,它们的 T_2 值低于 5 ms,在常规序列上不产生或仅有少量信号,但这些组织的改变在 OA 病理生理机制中具有关键作用[32]。超短波回波时间(ultrashort echo time, UTE) MRI 是基于 UTE 脉冲序列使用一个极短的回波时间采集信号(可短达 50 μs),使这些组织能进行 T_2*加权成像,这种方法能够显示在常规序列上难以检测的组织层次[33]。Bae 等[34]利用 UTE MRI 成功显示了软骨辐射层、钙化层及软骨下骨板。尽管这种新技术面临诸多挑战,例如层面选择失真、K 空间充填误差、共振频率偏移等,但基于 UTE 技术的 T_2*mapping 为骨软骨区的 MRI 量化研究提供了可能性[35]。最近 Williams 等[36]基于 UTE 的 T_2*mapping 进行健康志愿者的软骨实验表明其定量分析有良好的重复性。

2.5　DWI 和扩散张量成像

DWI 可反映细胞外水分子的布朗氏运动状态,其参量值

为 ADC 值。软骨内水分子的运动由胶原纤维的质量和方向决定,ADC 升高被认为是胶原基质退化所致[37]。最近,Apprich 等[38]认为 DWI 可评估不同疗法的软骨修复品质。Friendrich 等[39]发现 DWI 能反映软骨修复和成熟状态。然而,学者们也强调了由于磁敏感伪影、空降分辨率和信噪比较低等原因导致精确测定 ADC 值困难。另外,DWI 与软骨生化成分之间相关性尚未得到充分证实。因此,DWI 用于人体软骨成像仍具有挑战性。

扩散张量成像(diffusion tensor imaging, DTI)能获得水分子扩散运动的方向性,Deng 等[40]的实验表明,PG 丢失的软骨内水分子扩散各向异性无明显变化,认为胶原纤维是影响软骨 DTI 主要因素。de Visser 等[41]用 7T MRI 发现 DTI 能检测软骨压缩后的结构改变。近年用超高场强(17.6T)DTI 实现软骨压缩 20% 的有限元分析[42],最近又实现超高场强 DTI 的软骨内流体压力有限元分析[43]。目前,由于软骨 DTI 扫描时间冗长、数据分析巨大,其临床实践仍很困难。

2.6 软骨药物代谢动力学 MRI

药物代谢动力学 MRI 的原理是病变区微血管通透性增加,对比剂分子从血管内渗漏到血管外细胞外间隙,血管内外对比剂分布发生改变,这种变化根据双室药物动力学模型理论运算即可获得相关参数值,包括 Ktrans 值、Kep 值、Ve 值等,这些值能反映血管通透性、药物在血浆与组织间交换率、血管外细胞外容积等[44]。OA 的血管发生和炎症反应、软骨细胞功能调节、软骨下骨髓异常灌注等相关,参与 OA 的发病和疼痛机制[45]。近年已有学者将这一新技术应用于 OA 临床研究,Sanz 等[46]发现与健康髌软骨相比,其退变时 Ktrans 和 Ve 增加。Martí-Bonmatí 等[47]对比髌骨软骨软化症安慰剂治疗组和硫酸氨基葡萄糖治疗组后发现,软骨 Ktrans 值有差异。药物代谢动力学 MRI 的软骨研究较少,但它可能在评估和探究 OA 血管化机制方面具有潜力[48]。

3 展望

尽管面临诸多挑战和需要超高场强的支持,但基于这些新技术的 OA 诊断及发病机制的 MRI 研究火热。展望未来,这些无创 MRI 定量检测方法必将在分子水平对预防 OA 进展的干预措施评估及对 OA 发展的动态跟踪发挥积极作用,随着 MR 硬件和软件的升级、新序列的开发与运用及理论研究的不断深入,这些新技术或可成为 OA 诊断和治疗的 MRI 生物标志物。

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