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述评 EDITORIAL

莫迪司、普美显增强磁共振与肝纤维化分期的相关性研究

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Staging of liver fibrosis using Gd-EOB-DTPA and Gd-BOPTA enhanced magnetic resonance imaging

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Abstract

The severity of cirrhosis is closely related to its clinical treatment. Therefore, it is important to stage liver fibrosis accurately. Although liver biopsy can accurately stage the degree of cirrhosis, it has certain limitations in clinical application because of its invasive nature. Magnetic resonance imaging (MRI) has been used in the diagnosis of liver diseases. In recent years, two new contrast agents, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) and gadobenate dimeglumine (Gd-BOPTA), have been successfully used for noninvasive liver imaging. They can be used for liver fibrosis staging and assessment of liver function. Cirrhotic patients with different liver function levels have a statistical difference in the liver parenchyma enhancement after giving contrast agents. This article briefly summarizes the progress of Gd-EOB-DTPA and Gd-BOPTA enhanced MRI in staging liver fibrosis stage.

Key Words: Liver fibrosis; Magnetic resonance imaging; Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid; Gadobenate dimeglumine

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摘要

肝硬化的严重程度与临床治疗密切相关, 因此, 对肝纤维化进行准确分期尤为重要. 穿刺活检虽然能对肝硬化程度进行准确分期, 因其为有创检查, 在临床应用中有一定的限制. 临床磁共振(magnetic resonance image, MRI)检查已常规用于肝脏疾病的诊断. 近年来, 两种新型对比剂莫迪司和普美显已成功用于肝

脏成像, 可以无创地用于肝纤维化分期以及肝功能的评估, 肝功能不同程度的肝硬化患者的肝实质强化程度具有统计学差异. 本文将近十年来莫迪司、普美显增强MRI用于评估肝纤维化分期的研究现状与进展进行简要综述.

关键词: 肝纤维化; 磁共振; 莫迪司; 普美显

核心提要: 莫迪司、普美显增强磁共振根据肝实质的强化程度不同可以对肝纤维化程度进行分期, 为临床治疗提供参考依据.

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0 引言

肝硬化是临床上常见的一种慢性进行性肝病, 由一种或多种病因长期或反复作用而导致的弥漫性肝损害. 它的病因复杂, 在我国大多数由病毒性肝炎引起, 尤其是乙型或丙型肝炎[1], 少部分为酒精性肝硬化和血吸虫性肝硬化. 增强计算机断层扫描(computed tomography, CT)和磁共振(magnetic resonance image, MRI)扫描是临床上广泛应用的无创性检查技术, 增强扫描对比剂的应用可以反映肝脏的血供情况和内部结构, 为临床病变定性、定量诊断提供客观依据, 但临床中最适合进行肝硬化诊断的对比剂仍然存在争论. 临床及科研中的肝脏MRI对比剂大致可分为五类: 肝细胞特异性对比剂、非特异性细胞外间隙(extracellular fluid space, ECS)对比剂、血池对比剂、网状内皮系统摄取的对比剂以及其它对比剂等.

钆塞酸二钠(gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid, Gd-EOB-DTPA), 其商品名称为普美显, 是MRI的一种非特异性ECS对比剂, 它能够通过细胞膜上用于转运多肽的有机阴离子有选择性地转运至肝细胞[2]. 还有其特有的亲脂性EOB基团, 能够使得大约50%的Gd-EOB-DTPA被正常的肝细胞摄取[3], 在团注这种对比剂20 min后能够获得较为清晰的肝细胞特异性图像, 在国内外研究中成为热点. 可以合理推测, 在晚期肝硬化患者中, 功能性肝细胞的数目将减少. 正确评估肝脏储备功能可指导临床医师对肝脏疾病病人采取正确的治疗方案, 提高病人生存率及生活质量. 以往的研究表明硬变的肝脏内, 其血管的走行关系紊乱可用于提示肝硬化的诊断[4-6]. 然而, 对于GD-EOB-DTPA MRI增强扫描后, 肝功能与肝实质信号或者T1弛豫时间的相关性, 这一方面的临床研究报道较少[7-10].

钆贝葡胺(gadobenate dimeglumine, Gd-BOPTA), 商品名莫迪司(MultiHance, Bracco SpA, Milano), 是一种钆类MRI对比剂. 临床主要用于肝脏成像、中枢神经系统成像、血管成像以及心脏成像. Gd-BOPTA是用一个苯氧甲基基团替换了Gd-DTPA的一个乙酞基部分, 从而增加了Gd-BOPTA的亲脂性, 这使它能被肝细胞选择性的摄取并排入胆道. 所以, 通过Gd-BOPTA可以获得肝脏的延迟静态图像[11]. 对Gd-BOPTA进入肝细胞及胆道排泄的具体机制还有待进一步明确, 以期对病强化信号的正确分析提供更多的信息和依据.

本文结合国内外最新文献综述了莫迪司、Gd-EOB-DTPA对肝肝纤维化分期诊断价值的研究现状与进展, 旨在引领读者对该领域的研究兴趣.

1 Gd-EOB-DTPA和Gd-BOPTA概述

Gd-EOB-DTPA对比剂分子中存在一个亲脂的EOB基环, 这个亲脂的EOB基环使得它与血浆蛋白结合, 进而通过肝细胞膜上的阴离子转运系统转运多肽8(organic anion transporter, OATP8)被肝细胞选择性地吸收, 与常规的Gd-DTPA一样, 分子中顺磁性的Gd可以有缩短T1的作用, 也具有动态增强的作用, 注药后10-20 min, 有约50%的剂量与常规Gd-DTPA一样经肾脏排泄, 另外有大概50%的剂量可通过位于肝血窦的肝细胞膜表面的有机阴离子转运系统[organic anion transporter, OATP(OATP8)]被正常肝细胞吸收, 再通过位于胆道面的肝细胞膜上的多耐药蛋白载体[multi-drug resistance protein , MRP(MRP2)]排入胆道系统, 达肝脏强化的平台期[12]. 在动态增强过程中, 肝实质强化特点与Gd-DTPA动态增强扫描类似, 注射后20 min延迟期扫描时, 肝实质信号进一步增高, 为各期内最高, 较平扫信号强度增加了79.07%[13].

研究表示注射Gd-EOB-DTPA维持2 h, 在20 min时肝实质的强化效果最好, 此时具有最高的信号强化[14]. 在动态灌注和肝脏特异性肝胆磁共振图像上肝胆管均可强化. 有研究表明, Gd-EOB-DTPA与Gd-DTPA的动脉强化效果类似[15]. Gd-EOB-DTPA的标准注射剂量低于Gd-DTPA, 另外, 在正常肝脏, 50%的Gd-EOB-DTPA经胆道排泄, 对于轻度肾功能不全的患者, Gd-EOB-DTPA是一种很好的造影剂.

Gd-BOPTA是一种新型对比剂, 由顺磁性钆离子和螯合剂BOPTA结合形成, 不仅可以缩短人体组织氢原子的纵向弛豫时间(T1) , 还能轻微缩短横向弛豫时间(T2)[16,17]. 许多Ⅱ、Ⅲ期临床试验结果也已证实[18-20], 对

于临床最大剂量(0.3 mol/kg体重)以下的剂量给药, Gd-BOPTA是一种安全的对比剂, 患者耐受性良好, 其不良反应的发生率<10%.

2 Gd-EOB-DTPA和Gd-BOPTA对肝纤维化的分析

有大量文献报道了肝硬化与Gd-EOB-DTPA摄取的相关性, 肝硬化患者的肝细胞对Gd-EOB-DTPA的摄取延迟并减[21-40], 另有研究对患者行1.5T MRI Gd-EOB-DTPA增强扫描, 肝硬化患者肝功能的Child分级和正常肝实质强化的相关性进行了研究报道[8,41-49]. 肝硬化患者的肝细胞功能受损比非肝硬化患者严重. 因此, 在1.5T磁共振上, 与非肝硬化的肝实质相比, 硬化的肝实质肝细胞期期强化程度减低, 导致肝硬化患者的病变-肝脏强化对比度降低[9]. 随着场强强度的增加, 造影剂缩短T1时间的效应会增强. 肝功能A级的患者提示轻度肝硬化, 在注射Gd-EOB-DTPA 20 min后的肝胆期表现为肝实质显著强化, 随着时间的增加, 其相对信号强度(relative enhancement, RE)值显著增加[49]. RE的增加以及肝胆期肝脏的强化与非肝硬化患者表现类似. 然而, 肝功能A级的患者, 其RE的升高程度不及肝功能正常的患者. 部分严重肝脏疾病的患者, 比如肝功能B级或C级的患者, 门脉期平均RE并没有增高. 可能是由于晚期肝硬化患者的肝功能不全所致. 采用3.0 T MRI进行Gd-EOB-DTPA增强扫描, 对Child分期不同的肝硬化患者的强化效果进行比较分析, 这一方面的相关研究报道较少.

动物模型已经显示晚期肝脏疾病与肝细胞内转运多肽的有机阴离子的下调或低表达相关. 在肝脏的动脉期和门脉期, 肝硬化的影响因素仍存在争议. Annet等[50]报道在晚期肝硬化患者中, 整个肝脏灌注在动脉期增高. 患有严重肝脏疾病的患者在肝胆期的RE有降低, 可能是由于Gd-EOB-DTPA的摄取减低所致, 也就是由于患者的肝细胞功能低下或功能性的肝细胞数量减少, 导致患者肝脏聚集造影剂的量较正常减少所致. 此外, 晚期肝硬化的患者由于肝纤维化程度较重, 导致Gd-EOB-DTPA的摄取延迟. 所有这些因素都可能导致注射造影剂20 min之后肝胆期的强化程度降低.

Gd-EOB-DTPA对肝脏疾病的敏感性在晚期肝硬化患者中有所降低, 是由于这些患者肝脏实质的RE明显降低. RE的降低可能导致肝脏-病变的对比度降低. 尽管在肝细胞期, RE也会降低, 但仍可以用于肝硬化的分期, 反之亦然.

Gd-EOB-DTPA增强MRI在肝脏疾病的诊断方面较常规对比剂MRI增强具有明显的优势, 达到分子级别[51-53], 具有更高的敏感度和特异度, 极大提高了肝硬化分期诊断的准确率. 由于其高胆管排泄率, 能提供更多肝内外胆道系统的解剖结构与通畅情况的信息. 该技术在肝硬化分期评估应用中同样具有明显的优势, 可以为临床治疗提供重要参考依据[54], 未来有可能在临床上广泛推广, 为临床判断肝脏储备功能提供更多参考依据, 可成为肝脏的“一站式”检查. 限于Gd-EOB-DTPA投入的临床应用还不太久, 很多潜在的应用尚没有完全开发, 还需要进一步的深入研究, 去积累更多经验.

肝硬化患者肝实质Gd-BOPTA的动态强化百分比较正常肝实质的强化百分比明显降低, 而且呈不均匀结节样强化, 静态正常肝实质强化百分比为102%±30%, 肝硬化者, 61%±13%. Child A级和B级肝硬化患者增强后图像中肝实质的强化程度的差异有近似统计学显著性.

3 Gd-EOB-DTPA和Gd-BOPTA对肝功能的评价

Gd-EOB-DTPA是一种能够被功能正常肝细胞特异性摄取的MRI对比剂, 其摄取的多少取决于功能正常肝细胞的数目. 因此, 通过对比增强前、后肝实质的强化程度可以无创地评价患者肝功能, 对肝纤维化进行分期. 根据肝细胞摄取Gd-EOB-DTPA的机制, 对比剂的量与肝细胞摄取、肝脏功能相关联, 肝细胞特异对比剂由肝脏摄取, 再经胆道排泄. 经静脉注入对比剂后行动态MRI扫描, 除了平扫、动脉期、门脉期以及延迟期外, 还增加了肝细胞期 (肝脏实质显像期: 主要体现了肝细胞对对比剂的摄取能力), 可以无创地定量评估肝病患者的肝功能.

有研究通过进行Gd-EOB-DTPA特异性增强扫描前后得到的信号强度(signal intensity, SI)肝/脾值与Child分级、是否存在肝硬化以及临床指标的关系进行分析, 发现随着Child分级的增加肝实质的MRI强化信号程度逐渐减低, 肝硬化患者较未发生肝硬化患者的信号强化程度明显减低, 肝脏信号强度上升趋势平缓[22]. 正是由于随着受损肝细胞数目增加, 肝细胞膜上有机阴离子转运多肽表达减少, 影响对Gd-EOB-DTPA的摄取, 导致肝实质的MRI强化程度逐渐减低[4]. Gd-EOB-DTPA特异性增强扫描能够反映一般患者肝功能的变化, 为临床评估肝功能提供更多影像方面的信息, 研究表明注射对比剂20 min后SI肝/脾数值与肝功能密切相关, 可以为肝功能的判断提供直观无创的方法[5-7].

Nilsson等[31]研究者使用Gd-EOB-DTPA对原发性胆汁性肝硬化患者行动态肝细胞特异性对比增强磁共振成像(dynamic hepatic specific contrast enhancement, DHCE-MRI)检查, 通过图像后处理获得不同肝段的参数: 相对摄入血流量(relative blood flow, rBF)、平均通过时间(mean transit time, MTT)以及肝细胞排泄率(HEF),

得到全肝中位数(global liver median, GLM), 这些指标与正常对照组比较, 有显著的差异, 并与肝功能、终末期肝病模型(model for end-stage liver disease, MELD)评分有比较好的相关关系. 另有国外学者Yamada等[55]也使用Gd-EOB-DTPA对患者行增强的MRI检查, 获得肝脏体积、肝摄取率和吲哚氰绿(ICG)清除率有很好的相关性, 根据肝脏和脾脏的MRI图像上的体积和信号强度对肝功能定量分析, DHCE-MRI凭借图像的高分辨率和特异性造影剂可以准确评估区域肝功能水平. 国外学者Utsunomiya等[56]研究者采用Gd-EOB-DTPA评估50例肝移植患者的肝储备功能, 对肝肿瘤患者行Gd-EOB-DTPA磁共振成像, 得出结论, Gd-EOB-DTPA对肝储备功能的评估与吲哚氰绿15 min滞留(ICG-R15)、二烯三胺五醋酸半乳糖人血清白蛋白受体指数以及凝血酶原时间具有相关性, 可以作为一种区域肝储备功能的临床评价的方法.

有研究报道[8], Gd-EOB-DTPA磁共振增强扫描(肝脏或胆总管信号强度或信号强度比)可以定量体现肝功能水平, 与ICG-R15具有显著关联性. 采用Gd-EOB-DTPA动态增强的磁共振成像扫描得到主动脉和肝脏的时间-强度曲线, 再采用去卷积方法分析处理肝摄取分数, 可以用来评价肝脏功能, 并且发现肝脏摄取分数和ICG-R15具有显著相关性[57].

另外Yamada等[55]学者大量研究发现, ICG清除率能够通过磁共振成像的肝脏信号强度进行定量分析. 因此, ICG排泄试验和Gd-EOB-DTPA磁共振增强扫描与肝脏功能的定量评估相结合的可能性是值得进一步研究, 结合Gd-EOB-DTPA和ICG排泄试验以评估肝功能ICG也许会是未来的ICG排泄试验综合应用的新方向. 另一项研究表明GD-EOB-DTPA磁共振增强扫描中, 血浆凝血酶原时间以及血清白蛋白的与肝脏增强有显著的相关关系[58,59], 凝血酶原时间、血清白蛋白可预测肝胆期肝脏强化的情况. Gd-EOB-DTPA对比增强磁共振成像速率的示踪动力学分析的细胞有可能成为新评价肝脏功能的指标.

Gd-BOPTA的动态强化特点同Gd-DTPA, 延迟相肝实质呈高信号, 但肝实质强化的程度受肝功能影响. 患者的肝功能越差从正常至Child C级, 图像显示的对比噪声就越大[20,60-62].

4 结论

对于肝实质病变, Gd-EOB-DTPA和Gd-BOPTA基于分析动态灌注时期和肝细胞期的双相图像, 对临床诊断非常有用. 此外, Gd-EOB-DTPA和Gd-BOPTA MRI增强扫描通过评估他们的强化形式, 可以对肝纤维化分期提供有意义的临床价值.

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• 消息 •

《世界华人消化杂志》正文要求

本刊讯 本刊正文标题层次为 0引言; 1 材料和方法, 1.1 材料, 1.2 方法; 2 结果; 3 讨论; 4 参考文献. 序号一律左顶格写, 后空1格写标题; 2级标题后空1格接正文. 以下逐条陈述: (1)引言 应包括该研究的目的和该研究与其他相关研究的关系. (2)材料和方法 应尽量简短, 但应让其他有经验的研究者能够重复该实验. 对新的方法应该详细描述, 以前发表过的方法引用参考文献即可, 有关文献中或试剂手册中的方法的改进仅描述改进之处即可. (3)结果 实验结果应合理采用图表和文字表示, 在结果中应避免讨论. (4)讨论 要简明, 应集中对所得的结果做出解释而不是重复叙述, 也不应是大量文献的回顾. 图表的数量要精选. 表应有表序和表题, 并有足够具有自明性的信息, 使读者不查阅正文即可理解该表的内容. 表内每一栏均应有表头, 表内非公知通用缩写应在表注中说明, 表格一律使用三线表(不用竖线), 在正文中该出现的地方应注出. 图应有图序、图题和图注, 以使其容易被读者理解, 所有的图应在正文中该出现的地方注出. 同一个主题内容的彩色图、黑白图、线条图, 统一用一个注解分别叙述. 如: 图1 萎缩性胃炎治疗前后病理变化．A: …; B: …; C: …; D: …; E: …; F: …; G: …. 曲线图可按●、○、■、□、▲、△顺序使用标准的符号. 统计学显著性用: $^{a}P<0.05$, $^{b}P<0.01$($P>0.05$不注). 如同一表中另有一套P值, 则$^{c}P<0.05$, $^{d}P<0.01$; 第3套为$^{e}P<0.05$, $^{f}P<0.01$. P值后注明何种检验及其具体数字, 如$P<0.01$, $t = 4.56$ *vs* 对照组等, 注在表的左下方. 表内采用阿拉伯数字, 共同的计量单位符号应注在表的右上方, 表内个位数、小数点、±、-应上下对齐. “空白”表示无此项或未测, “-”代表阴性未发现, 不能用同左、同上等. 表图勿与正文内容重复. 表图的标目尽量用t/min, c/(mol/L), p/kPa, V/mL, t/℃表达. 黑白图请附黑白照片, 并拷入光盘内; 彩色图请提供冲洗的彩色照片, 请不要提供计算机打印的照片. 彩色图片大小7.5 cm ×4.5 cm, 必须使用双面胶条黏贴在正文内, 不能使用浆糊黏贴. (5)志谢 后加冒号, 排在讨论后及参考文献前, 左齐.

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