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3.0T MRI 多回波 Dixon 技术对非酒精性脂肪性肝病患者肝脏脂肪的定量分析

李斯婕, 王 振, 陈录广, 傅彩霞, 陆建平*

第二军医大学长海医院影像医学科, 上海 200433

[摘要] **目的** 探讨 3.0T MRI 多回波(multi-echo, ME)Dixon 技术对非酒精性脂肪性肝病(NAFLD)患者的肝脏脂肪定量分析的可行性。**方法** 前瞻性纳入自愿加入本研究的志愿者 20 例,其中女性 NAFLD 患者 4 例,正常对照者 1 例;男性 NAFLD 患者 12 例,正常对照者 3 例。进行常规肝脏 MRI 平扫、ME 序列检查,之后再行单体素磁共振波谱分析(MRS)检查。检查结束后处理数据,记录 Screening Dixon 的脂肪分数(fat fraction,FF)值和 Histo 序列自动得出的单体素 MRS 的 FF 值,再手动在 ME Dixon 的 FF 图中测得 3 个感兴趣区(ROD)的 FF 值。最后分别对各 FF 值进行 Spearman 相关性分析。**结果** Screening Dixon 与 ME Dixon 的 3 个 ROI 区域测得的 FF 值呈高度正相关($r=0.842, 0.959, 0.945, P$ 值均 <0.001)。Screening Dixon 及 ME Dixon 的 3 个 ROI 区域测得的 FF 值与 Histo 得出的单体素 MRS 所测得的 FF 值呈高度正相关($r=0.971, 0.842, 0.959, 0.945, P$ 值均 <0.001)。**结论** 采用 3.0T MRI ME Dixon 成像技术对 NAFLD 患者进行肝脏脂肪含量的评估是可行的,并与单体素 MRS 所得结果呈高度正相关。其结果对于 NAFLD 患者的诊断、随访和干预监测均具有一定的临床价值。

[关键词] 非酒精性脂肪性肝病;磁共振成像;脂肪;定量分析

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3.0T MRI multi-echo Dixon technique in quantitative analysis of liver fat in patients with nonalcoholic fatty liver disease

LI Si-jie, WANG Zhen, CHEN Lu-guang, FU Cai-xia, LU Jian-ping*

Department of Medical Imaging, Changhai Hospital, Second Military Medical University, Shanghai 200433, China

[Abstract] **Objective** To investigate the feasibility of using 3.0T MRI multi-echo (ME) Dixon technique for liver fat quantification in patients with nonalcoholic fatty liver disease (NAFLD). **Methods** Twenty volunteers were enrolled in this prospective study, and they included 16 NAFLD patients (12 males and 4 females) and 4 healthy volunteers (3 males and one female). All volunteers were examined by routine liver MRI, ME Dixon technique and single-voxel MRS. After examination, the fat fraction (FF) value of Screening Dixon and the FF value of single-voxel MRS with Histo sequence were recorded, and the FF values of 3 regions of interest (ROIs) in the fat fraction map of ME Dixon were manually measured. Finally, the FF values were analyzed with Spearman correlation analysis. **Results** The Screening Dixon FF value was positively correlated with the FF values of three ROIs of ME Dixon ($r=0.842, 0.959, \text{ and } 0.945$ respectively, all $P<0.001$). Similarly, positive correlation was also found for the FF values of Screening Dixon and 3 ROIs of ME Dixon with the FF value of single-voxel MRS with Histo sequence ($r=0.971, 0.842, 0.959, \text{ and } 0.945$ respectively, all $P<0.001$). **Conclusion** It is feasible to use 3.0T MRI ME Dixon for evaluating liver fat content in patients with NAFLD, and its results are positively correlated with those of single-voxel MRS. It is valuable for the diagnosis, follow-up and intervention of NAFLD patients.

[Key words] nonalcoholic fatty liver disease; magnetic resonance imaging; fat; quantitative analysis

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非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)是一种与胰岛素抵抗(insulin

resistance, IR)和遗传易感密切相关的代谢应激性肝脏损伤,是指除外酒精和其他明确的损肝因素所

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[作者简介] 李斯婕,住院医师, E-mail: lisijeyichen@163.com

*通信作者(Corresponding author). Tel: 021-31152146, E-mail: cjr.lujianping@vip.163.com

致的,以弥漫性肝细胞大泡性脂肪变为主要特征临床病理综合征^[1-2]。2014年世界胃肠病学全球指南指出,非酒精性脂肪肝炎(nonalcoholic steatohepatitis, NASH)是NAFLD最严重的组织学表现,当NAFLD进展到NASH,可增高肝硬化、肝衰竭及肝细胞癌的风险^[3]。NAFLD与糖尿病及肥胖密切相关,世界范围发病率为25%~35%,亚洲范围发病率>10%^[4]。近年来随着我国人民生活水平的提高及生活方式的改变,NAFLD的发病率正逐年增加,并有年轻化的趋势。同时,NAFLD是可逆慢性疾病,然而当发展至肝硬化、肝衰竭等晚期阶段则不再可逆。因此,早期准确诊断、评估NAFLD患者的肝脏脂肪含量,对于患者的干预、治疗和随访等临床意义重大。在非创伤性影像学诊断中,磁共振(MR)特别是单体素磁共振波谱分析(MRS)是目前已被广泛认可的研究活体组织代谢、生化改变及化合物定量的方法,但仍然存在扫描时间长、患者配合要求高等限制因素。本研究以单体素MRS为对照,采用3.0T MRI多回波(multi-echo, ME)Dixon序列对肝脏脂肪含量进行定量测定,前瞻性研究其对于NAFLD患者肝脏脂肪含量定量检测的准确性和临床价值。

1 资料和方法

1.1 研究对象 前瞻性地纳入2015年7月1日至2015年12月30日期间自愿参加本研究的20例志愿者。其中女性5例中NAFLD患者4例,正常对照者1例;男性15例中NAFLD患者12例,正常对照者3例。年龄29~61岁,平均年龄(43.45±10.55)岁,中位年龄41岁。纳入标准:临床和超声检查确诊的NAFLD患者,以及此时间段内自愿加入本研究的正常人群。排除标准:MR禁忌证者;重度肝脏铁质沉积患者;肝脏肿瘤患者;脾脏切除术后患者;乙肝等肝炎病毒携带者及患者;血清学检查肝功能异常患者;酗酒史者(饮酒每个月>3次每次>5瓶啤酒,或女性>20 g/d、男性>30 g/d);近期3个月内有脂肪肝药物治疗史的患者;家族性遗传疾病者。

1.2 影像学检查方法 由同一名具有丰富MR操作经验的技师对所有受试者进行检查。扫描设备:西门子Skyra 3.0T MRI。扫描方法:首先屏气扫描

状位T₂加权像,并以此为定位像,依次扫描Screening Dixon、ME Dixon、横断位T₁加权及T₂加权像。定位标准:肝脏包括其中。自动生成Screening Dixon(初筛)报告和脂质含量伪彩图。SVS定位方法:在Screening Dixon图像出来后,在评估菜单下选择撤销二维失真矫正对水相图像进行处理;将处理出来的图像行3D重建冠状位和矢状位,然后将冠状位和矢状位拖进扫描界面,在肝脏最大面选取感兴趣区(ROI),尽量避开肝内汇管区。扫描Histo序列,得出波谱图及相应脂质含量报告。冠状T₂加权扫描参数:TR 1 000 ms,TE 99 ms,FOV 340 mm,层厚 7 mm,Averages 1,翻转角度160°;Screening Dixon扫描参数:TR 4.19 s,TE 1.23 ms,FOV 420 mm,层厚 4 mm,Averages 1,翻转角度7°;ME Dixon序列扫描参数:TR 9.15 ms,TE 1.05 ms,FOV 420 mm,层厚 3.5 mm,Averages 1,翻转角度4°;横断位T₂加权扫描参数:TR 1 200 ms,TE 95 ms,FOV 420 mm,层厚 7 mm,Averages 1,翻转角度160°;横断位T₁加权扫描参数:TR 3.97 ms,TE 1.23 ms,FOV 450 mm,层厚 4 mm,Averages 1,翻转角度9°;SVS-st-Histo扫描参数:TR 3 000 ms,TE 12 ms,Averages 1,翻转角度90°,volR>>L 30 mm, volA>>P 30 mm, volF>>H 30 mm。

1.3 影像学诊断及后处理数据 由同一名具有丰富肝脏疾病影像诊断经验的高年资影像专业住院医师观察图像,分析结果,并经过一名影像专业副主任医师复核。记录每例受试者Screening Dixon序列的肝脏总体脂肪分数(fat fraction, FF)值。在ME Dixon序列,每例受试者测量3个ROI区的FF值。选择区域:左肝1个、右肝2个。将右肝分为两部分:右前叶及右后叶,分别在两部分各选取一个ROI区域,其中一个是与Histo序列ROI区相对应的区域,记为ROI1。所有选择的ROI区域均尽量规避汇管区。观察Histo序列各受试者的单体素MRS的波谱图,记录脂质峰、水峰和FF值。

1.4 统计学处理 采用SPSS 20.0软件进行数据分析。分类资料采用百分比(%)表示。应用Spearman方法进行各类FF百分比的相关性分析。检验水准(α)为0.05。

2 结果

2.1 3.0T MRI ME Dixon 成像脂肪定量分析基本情况 通过初筛扫描(Screening Dixon),首先可以获得受试者全肝脂质含量、铁含量的初步定量,并自动给出受试者是否为 NAFLD 的初步诊断报告和脂质分布伪彩图(图 1、2)。然后通过一次采集,完成 ME 精确扫描(ME Dixon),回波数为 6(图 3、4)。Screening Dixon 及 ME Dixon 均可以得到同相位(in-phase, IP)、反相位(opp-phase, OP)、脂像、水像图。ME Dixon 还可得到 T_2^* 脂像、 T_2^* 水像、有效 T_2^* 图以及自动合成的脂肪分数图,并可在任意 ROI 测量肝脏 FF 值(图 5、6)。最后受试者可以通过 ME T_2 校正的单体素波谱技术(Histo),生成 MRS 波谱图,并自动生成所选 ROI 的脂肪定量报告(图 1、2)。本研究中,全部受试者均较好的配合完成检查。

2.2 NAFLD 患者肝脏脂肪的影像学表现 NAFLD受试者的肝脏 Screening Dixon 伪彩图中脂质(黄色)分布区域较正常受试者明显增大(图 2)。NAFLD 受试者 ME Dixon 同/反相位 T_1 WI(IP/OP) 序列表现为:OP 图像上肝脏的信号强度较 IP 图像信号降低;其脂像图像肝脏信号较正常受试者升高,而水像降低(图 6)。NAFLD 受试者的 Histo 单体素波谱中,得到左高右低的谱线,基线较平稳,左侧高耸的为水峰,右侧较低的为脂质峰(图 2D)。

2.3 3.0T MRI ME Dixon 成像与单体素 MRS 的相关性分析 通过比对每一位受试者在各序列测得的 FF 值,得出 Screening Dixon 与 ME Dixon 测得的 FF 值高度正相关($r=0.842, 0.959, 0.945, P<0.001$; 图 7);Screening Dixon 及 ME Dixon 与 Histo 测得的 FF 值高度正相关($r=0.971, 0.842, 0.959, 0.945, P<0.001$; 图 8)。

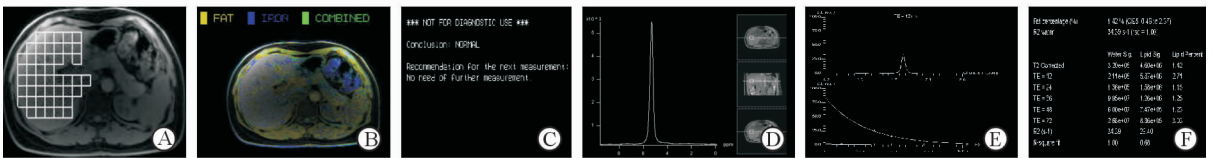


图 1 正常肝脏 Screening Dixon 扫描初筛结果和 Histo 波谱结果

Fig 1 Results of Screening Dixon and Histo spectra of normal liver

A: Computational region of the liver lipid content of the subjects of the Screening Dixon; B: Image of pseudo color of liver lipid content of Screening Dixon. There was no obvious area of yellow (lipid) in the liver; C: Preliminary screening report by Screening Dixon automatic generation, and the subjects were NORMAL; D, E: The single voxel spectra of the multi-echo T_2 correction was obtained by calculation of Histo technique. An obvious peak of water, but with almost no fat peaks; F: Spectral report generated by Histo technique, the liver lipid content of the subjects was 1.42% by automatic calculation

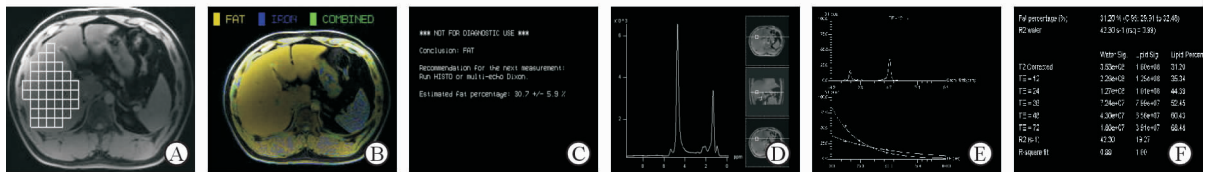


图 2 NAFLD 肝脏 Screening Dixon 扫描初筛结果和 Histo 波谱结果

Fig 2 Results of Screening Dixon and Histo spectra of NAFLD liver

A: Computational region of the liver lipid content of the subjects of the Screening Dixon; B: Image of pseudo color of liver lipid content of Screening Dixon. Liver parenchyma was almost filled with large patches of yellow color (lipid); C: Preliminary screening report by Screening Dixon automatic generation. The subjects were NAFLD patients, liver lipid content: $(30.7 \pm 5.9)\%$; D, E: The single voxel spectra of the multi-echo T_2 correction was obtained by calculation of Histo technique. The water peak was on the left of D, and the slightly lower peak on the right of D was lipid peak. In the upper part of E, the slightly lower peak of the left side was lipid peak. In the lower part of E, there was a low flat curve corresponding to the peak; F: Spectral report generated by Histo technique, the liver lipid content of the subjects was 31.20% by automatic calculation. NAFLD: Nonalcoholic fatty liver disease

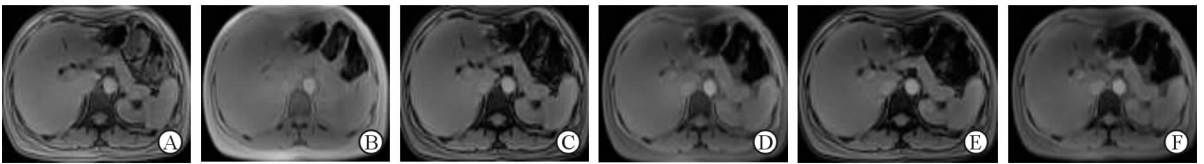


图 3 正常肝脏 ME Dixon 序列扫描所得 6 个(A~F)不同 TE 的回波图像

Fig 3 Multi-echo (ME) Dixon obtained 6 different TE echo images (A-F) of normal liver

One-time acquisiti. The liver signal of the normal subjects was uniform, and no region with reduced signal

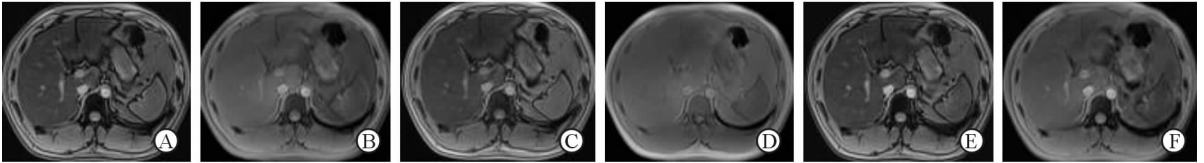


图 4 NAFLD 肝脏的 ME Dixon 序列扫描所得 6 个(A~F)不同 TE 的回波图像

Fig 4 Multi-echo (ME) Dixon obtained 6 different TE echo images (A-F) of NAFLD liver

One-time acquisiti. In Eco0, Eco2, Eco4 images, the NAFLD subjects had significantly reduced liver signal, and intra hepatic vascular had relatively high signal. NAFLD: Nonalcoholic fatty liver disease

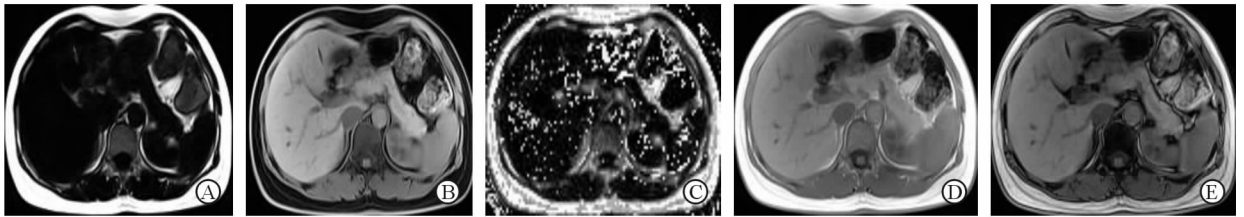


图 5 正常肝脏 ME Dixon 序列扫描所得四相位图和 FF 图

Fig 5 Four phase diagram and FF map of multi-echo (ME) Dixon of normal liver

A: Fat phase of ME Dixon, the liver of the normal subjects showed a uniform low signal, no abnormally high signal area; B: Water phase of ME Dixon, the liver of the normal subjects showed equal signal, no obvious abnormal low signal area; C: FF map of ME Dixon, the liver had no notably high signal area. In this figure allowed for free selection of ROI, the corresponding FF value can be directly measured; D, E: Image of in-phase and opp-phase of ME Dixon, the liver signal intensity of the normal subjects, opp-phase and in-phase images were similar, with no significant reduction. FF; Fat fraction; ROI; Region of interest

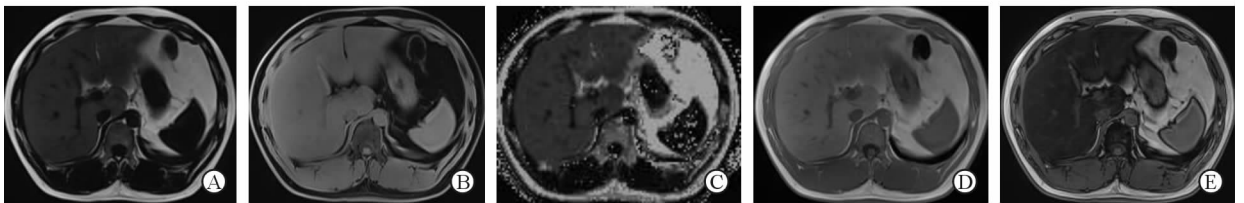


图 6 NAFLD 肝脏 ME Dixon 序列四相位图和 FF 图

Fig 6 Four phase diagram and FF map of multi-echo (ME) Dixon of NAFLD liver

A: Fat phase of ME Dixon, the NAFLD subjects had significantly increased liver signal, which was higher than the signal from the spleen at the same level; B: Water phase of ME Dixon, the liver signal of the NAFLD was decreased, being lower than that of the spleen at the same level; C: FF map of ME Dixon, liver signal was higher. In this figure FF values of arbitrarily selected ROI can be directly measured; D, E: Images of in-phase and opp-phase of ME Dixon, for the NAFLD subject, opp-phase images on the liver signal was significantly lower than that in-phase image, and intra hepatic vascular had relatively high signal. NAFLD: Nonalcoholic fatty liver disease; FF; Fat fraction; ROI; Region of interest

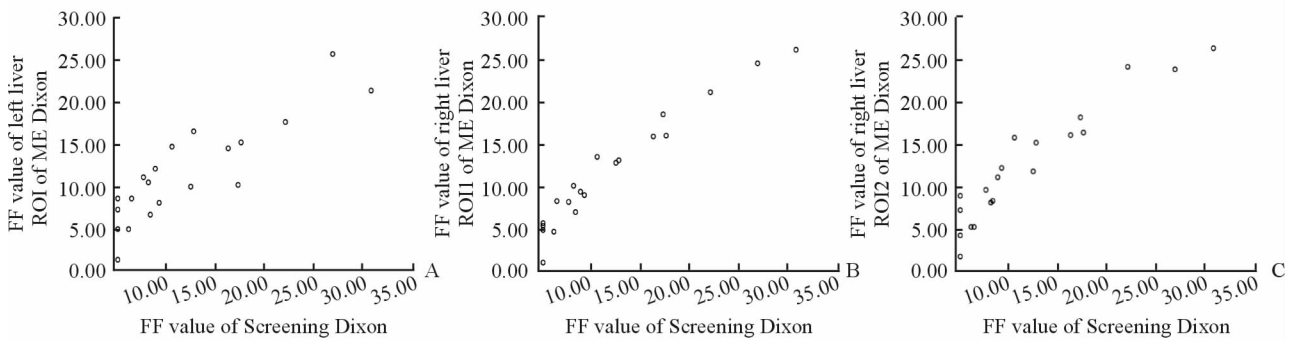


图7 Screening Dixon 与 ME Dixon 的 FF 值散点分布图

Fig 7 Scatter diagram of FF values of Screening Dixon group and multi-echo (ME) Dixon group

The FF values of the normal subjects was 5%. FF: Fat fraction; ROI: Region of interest

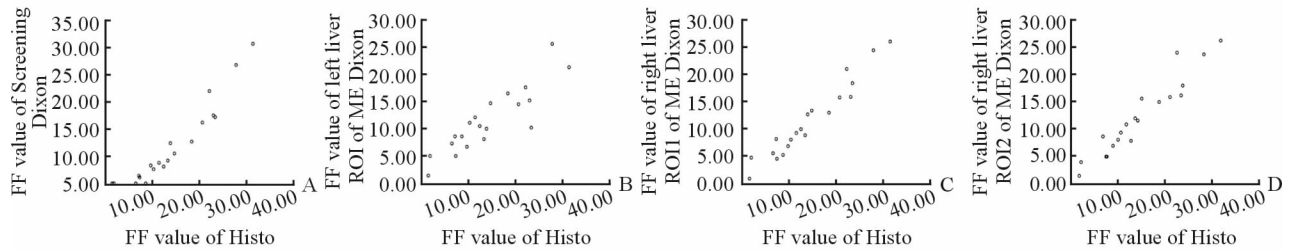


图8 Screening Dixon、ME Dixon 与 Histo 的 FF 值散点分布图

Fig 8 Scatter diagrams of FF values of Screening Dixon and multi-echo (ME) Dixon and Histo groups

The FF value of the normal subjects was 5%. FF: Fat fraction; ROI: Region of interest

3 讨论

NAFLD 不仅是西方国家最常见的慢性肝病,目前也已成为我国常见的慢性肝病之一,并有低龄化的趋势。Arulanandan 等^[5]指出,NAFLD 与心血管疾病风险有一定的关联。相当一部分代谢性或感染性疾病都以肝内脂肪的累积(即肝细胞脂肪变性)为前期信号。此外,肝脏脂肪变性的程度指导着活体肝移植术前评估(排除标准:脂肪变性>30%),亦提示肝脏手术患者的预后效果(肝脂肪变性将降低肝细胞功能储备,易导致术后肝衰竭^[6])。故而,定量分析肝脏脂肪含量对掌握 NAFLD 的早期诊断、动态监测、疗效评估及评价肝脏储备功能有重要价值。2015 年 2 月,日本胃肠病学会(JSGE)发布了《非酒精性脂肪性肝病/非酒精性脂肪性肝炎循证临床实践指南》,指出 NAFLD 的诊断是基于以下 3 个标准:(1)影像学或组织学检测出肝脏脂肪变性;(2)无饮酒史或饮酒量女性<20 g/d、男性<30 g/d;(3)排除如病毒性肝炎、自身免疫性肝脏疾病以及代谢性或遗传性肝病在内的其他可导致脂肪肝的慢性肝病。

虽然细针肝穿刺活检仍然是判断脂肪肝程度及定量分析的金标准,但是其作为创伤性检查,对于大部分 NAFLD 初期患者以及临床随访并不适用;同时由于穿刺活检的局限性,对于不均匀脂肪肝患者,其结果有一定的片面性。而影像学检查作为非创伤性检查,对 NAFLD 的脂肪定量分析的作用日趋显著。超声检查是一种行之有效和具有成本效益的脂肪肝的诊断成像技术,特别是用于筛查大量人口中的 NAFLD 患者。但是,过于依赖操作者^[7]、无法明确量化脂肪^[8]以及对于轻微 NAFLD 患者的低敏感性限制了其临床随访功能^[9]。CT 检查虽可通过绝对肝衰减(huliver)和脾脏衰减差值(ctl-s)的测量来测定肝脏脂肪含量,且其与病理程度有较强的相关性^[10],但仅对于中、重度 NAFLD 的准确性较高,而对于轻度 NAFLD 的测定是不准确的,而且结果取决于使用方法和受检群体的差异^[11]。到目前为止,双能量 CT 也尚未被证明在临床具有 NAFLD 脂肪定量的价值。某动物研究表明,双源、双能量 CT 相对于常规单能量 CT 并没有提高 NAFLD 患者脂肪含量评价的准确性^[12]。能谱 CT 可以通过物质分离技术及单能量成像来鉴别正常肝和轻度脂肪

肝并定量。但是,能谱 CT 配对的基物质并不是组织真实所含有的物质,且能谱 CT 尚未明确解决肝脏内铁质沉积因素造成的脂肪定量测量的误差。同时,虽然能谱 CT 称为低辐射的绿色 CT,但其仍旧存在射线辐射问题。

MR 检查已被认为是一种很敏感的 NAFLD 检测方法,特别是水脂分离技术和 MRS。MRS 和 MRI 均用来测量脂肪中相关细胞的质子数,彼此可直接比较。FF 值可以直接计算光谱,确定质子密度直接相关的分子三酰甘油含量,结果中可以明确剔除铁质沉积造成的影响。MRS 检查能利用磁共振现象和化学位移作用进行特定原子核及化合物定量分析,主要测定水峰、脂质峰及其峰下面积,是可无创研究活体组织代谢、生化改变及化合物定量的方法,具有空间定位准确、数据分析可靠、对呼吸运动不敏感、图像信噪比高等优点。有文献认为 MRS 检查可评价脂肪肝的严重程度,诊断效能要高于常规梯度回波化学位移 MRI,有望替代肝穿刺活检^[43]。常规水脂分离技术(双回波 Dixon 技术)是利用水和脂肪的共振频率的差异,借助向量运算,得出水、脂分量,实现水、脂分离。通过不同时间点水、脂之间产生的不同相位差,可以得到 IP 图像、OP 图像,还可以得到独立的脂肪信号图(脂像)和水信号图(水像),从而通过公式 $FF = (SIIP - SIOP) / (2 \times SIIP)$ 计算得出 FF 值(SIIP:同相位图信号值;SIOP:反相位图信号值)。普通的双回波因为磁场不均匀造成的 T_2^* 衰减效应、 T_1 偏移以及脂质谱的复杂性等因素的影响,其最终计算得出的 FF 值存在一定的偏移,并不能够确切反映出真实的肝脏脂肪含量^[44]。

本研究使用的改良后 ME Dixon 技术对磁场不均匀性不敏感,其回波时间可以灵活设定,并通过增加回波数减少 T_2^* 衰减导致的偏移;可以利用低翻转角度进行数据采集,使 T_1 偏移几乎可以忽略不计;亦可以通过定义扫描仪上的配置文件,对脂肪复杂的失相位因素进行灵活建模。这些优势使得 ME Dixon 技术的定量分析结果与 MRS 得到的分析结果具有高度的正相关性,表明运用该技术进行肝脏脂肪定量分析是可行的。同时,虽然 MRS 的结果能较为真实地反映 NAFLD 患者肝脏的脂质含量,但同时也暴露出明显的缺陷,MRS 单体素成像,其运用的 $ROI \leq 3 \text{ cm} \times 3 \text{ cm} \times 3 \text{ cm}$;虽然相对于活检穿

刺而言,其范围大得多,但所得到的结果仍旧具有局限性,并不能反映全肝的脂质含量。ME Dixon 技术可以在 FF 图像上自由选取 ROI,不限大小与位置,相较而言更具有临床价值。有学者运用与 ME Dixon 技术原理相仿的磁共振 IDEAL (Iterative Decomposition of water and fat with Echo Asymmetry and Least-squares estimation) 技术对 49 例供体肝脏进行了 MRI 检查评估及病理学的对照研究,结果显示 IDEAL 检测脂肪沉积的灵敏度为 100%,特异度为 91%^[15],从侧面证实了 ME Dixon 技术成像原理的可行性。且 ME Dixon 技术可以通过一次采集同时获得 6 回波数据,相较 IDEAL 技术的两次采集共获得 6 回波数据^[16],缩短了检查时间,减少了呼吸运动造成的误差,提高了该检查的可重复性。此外,本研究使用的 ME Dixon 技术在提供 ME Dixon 的精确脂质含量测定之前,还可以通过 Screening Dixon 扫描技术迅速进行初筛,初步判断受试者是否为 NAFLD 患者,并给出参考脂像含量报告和直观的伪彩脂质分布图。本研究显示,Screening Dixon 结果与波谱和 ME Dixon 也具有高度相关性,特别是脂质含量较高的 NAFLD 患者。其扫描简单,通过一次屏气,全肝扫描时间只需要约 13 s,使临床医师可以在得到精确的 FF 值之前,迅速对 NAFLD 患者的肝脏脂肪含量进行初步且较为准确的判断。

总之,运用经过改良的 ME Dixon 技术,可一次采集获得 ME 图像,并可在 FF 图中自由测得任何所需的 FF 值,对于肝脏脂肪含量的定量测定,特别是不均匀脂肪浸润的 NAFLD 患者的肝脏脂肪测定,其结果较为真实、可信。该检查快速、可靠、无创,对于 NAFLD 的诊断、随访和干预监测均具有一定的临床价值。

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