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文献综述 REVIEW

Fibroscan对肝纤维化诊断价值的研究进展

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Recent advances in the use of Fibroscan for diagnosis of liver fibrosis

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Abstract
In recent years, non-invasive methods for assessment of liver fibrosis have attracted worldwide attention. However, although many biochemical markers and imaging examinations have been used for evaluation of liver fibrosis, their sensitivity and specificity are low. Fibroscan (transient elastography) is a new non-invasive technology to assess the degree of liver fibrosis by measuring liver stiffness. Although Fibroscan has been extensively used to evaluate chronic hepatitis C and its complications in other countries, its use is uncommon in China. In this article, we will review its working principle, diagnostic value, and application status.

Key Words: Fibroscan; Liver fibrosis; Diagnostic value

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摘要
近年来, 国内外学者关注于肝纤维化的无创性诊断. 其中, 多种血清纤维化指标检验及影像学检查是目前临床较为常用的无创性评估肝纤维化的方法, 但敏感性和特异性不高. Fibroscan是一种对肝纤维化进行定量诊断的新技术, 以瞬时弹性成像为原理, 通过对肝脏硬度指标的测量进行肝纤维化程度评估. 本文就其工作原理、临界值确定、诊断价值及应用现状进行综述.

关键词: Fibroscan; 肝纤维化; 诊断价值

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0 引言
肝纤维化是各种慢性肝病损伤修复过程的共同结果, 也是各种慢性肝病向肝硬化发展的可逆中间环节. 肝纤维化甚至早期肝硬化得到及时治疗可发生逆转, 因此, 及时准确地判定肝纤维化的程度, 对慢性肝病的防治及其预后评价具有重要意义.

1 目前公认的诊断肝纤维化经典方法
1.1 病理组织学 目前诊断肝纤维化的最可靠指标是病理组织学检查, 但存在局限性[1-2]. 首先, 因其有创性而很难成为诊断肝纤维化的常规方法, 也不易反复取材来对肝纤维化动态观察. 其次, 肝穿取样组织只占整个肝脏的五万分之一, 加之纤维化分布不均匀, 导致肝穿刺活检存在取样误差(10%-45%), 影响准确性. 另外, 病理观察者自身以及观察者之间存在的差异, 也会对肝纤维化及其分级的评价产生影响.

1.2 血清生化学 血清纤维化指标是临床上最常用的无创诊断方法[3], 被应用较多的指标和模型包括:血清透明质酸、层粘连蛋白、Ⅲ型前胶原氨基端肽、Ⅳ胶原、基质金属蛋白酶, APRI(ALT/血小板指数), Fibrotest评分(包括α2-巨球蛋白、结合珠蛋白、载脂蛋白A1、γ-谷氨酰转肽酶和总胆红素五项指标), FIB-4评分[4-5](包

■背景资料
Fibroscan目前主要研究对象是丙型肝炎患者, 我国以乙型肝炎患者为主, 对此项技术的研究对其在我国的广泛应用有指导意义.

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■研发前沿
目前Fibroscan测量肝脏硬度值的分期临界值仍没有公认的确切数值, 其应用领域也是各学者研究的主要方向.

括年龄、血小板计数、ALT和AST 4项指标). 但通常认为血清学指标对肝纤维化的诊断特异性较低.

1.3 影像学 CT和普通超声等影像学检查, 可以通过观察肝脏大小、边缘、实质密度回声、血管走行及血流频谱, 为肝纤维化的诊断提供形态学参考, 但其诊断肝纤维化的敏感性并不高. 近年来, 许多学者对诊断肝纤维化的无创性方法进行研究. 2003年法国学者Sandrin *et al*[6]根据声波传导速率与组织硬度相关的原理, 用一种切变弹性探测仪, 测量106例慢性丙型肝炎患者的肝脏硬度, 结果测量值与肝纤维化分期有显著相关性. 这种仪器测量的可重复性好, 被认为是一种快速定量检测肝纤维化的方法, 因此众多学者对其深入研究, 对工作原理、应用价值以及影响因素有了更为准确的认识.

2 肝脏瞬时弹性探测仪–FibroScan

FibroScan是一种新型的肝纤维化检测仪器, 是一项建立在超声诊断基础上的快速便捷、非侵袭性新技术[7]. 通过测定肝脏瞬时弹性图谱来反映肝实质硬度, 当肝组织出现纤维化病理改变时, 可评估肝脏纤维化的程度并进行定量分级.

2.1 工作原理 超声换能器产生小振幅的低频振动, 在通过肝组织时引起弹性剪切波, 此波被一种脉冲回波超声捕获装置跟踪, 测得的波速与组织弹性直接相关, 组织硬度越高, 波速越快. 波速经运算转换为弹性值, 结果用千帕(kPa)表示. 被测处肝脏的厚度不少于6 cm, 且无大的血管结构. 探头下2.5-6.5 cm之间是实际被测部位. 每个被测者, 应成功捕获其10次回波, 取中位数代表肝脏的弹性值, 并要求四分位间距小于中位数的1/3. 成功率(成功捕获回波次数/总发射次数)≥60%, 才视其为可靠的肝脏硬度指标结果[8].

2.2 肝脏硬度指标临界值的确定及其诊断价值 目前, 越来越多的国内外学者致力于FibroScan的研究, 将其与肝穿刺活检进行对照, 得出各期纤维化肝脏硬度指标(LSM)的临界值. 现在普遍认为, LSM正常上限值为6.1 kPa, 而肝硬化患者的LSM值为12.5-75.5 kPa, 但如此界定的临床价值仍不确切[9-10].

Ziol *et al*[11]以327例丙型肝炎患者为研究对象, 采用Mmetavir评分系统对其肝纤维化分期, 并将F0和F1合并为无明显纤维化组, F2, F3, F4合并为有纤维化组. 发现以8.8 kPa为临界值诊断F≥2期, 敏感性为0.56, 特异性为0.91; 以9.6 kPa为临界值诊断F≥3期, 敏感性为0.86, 特异性为0.85; 以14.6 kPa为临界值诊断F4期, 敏感性为0.86, 特异性为0.96. 提示以9.6 kPa和14.6 kPa为分界值是诊断重度肝纤维化和肝硬化可靠的非创伤性指标.

Foucher *et al*[12]学者则选取各种病因的慢性肝病患者711例. 结果肝脏明显纤维化(F2)、严重纤维化(F3)以及肝硬化(F4)患者其ROC面积分别为0.80(95%CI: 0.75-0.84), 0.90(95%CI: 0.86-0.93)与0.96(95%CI: 0.94-0.98). 肝脏硬度临界值为17.6 kPa时, 诊断肝硬化的阳性预测值与阴性预测值均在90%以上.

另外, 法国学者Castera *et al*[13]测量了183例连续的慢性丙型肝炎患者的肝硬度值(2.3-75.4 kPa). 以7.1 kPa为临界值, 诊断F≥2期肝纤维化的敏感度为0.67, 特异性为0.89; 以9.5 kPa为临界值, 诊断F≥3期的敏感度为0.73, 特异性为0.91; 以12.5 kPa为临界值, 诊断F≥4期的敏感度为0.87, 特异性为0.91.

总之, Fibroscan对F3及F4期肝纤维化诊断临界值更为明确, 且诊断敏感性和特异性较F1和F2期更高[14]. Fibroscan诊断肝纤维化的硬度临界值范围分别为: F≥2期7.1-8.8 kPa, F≥3期9.5-9.6 kPa, F≥4期12.5-17.6 kPa时, 对肝纤维化各期别的划分更为确切.

2.3 Fibroscan评价肝组织硬度的应用 随着对Fibroscan认识的加深拓展, 专家学者对其在各种原因导致的病理性肝组织硬度评价的应用, 也有了更广泛的研究.

2.3.1 一般人群筛检: Roulot *et al*[15]在表现健康的一般人群中选取1358例为研究对象, 抽取45岁以上的1120例, 以14.6 kPa为临界值来诊断肝硬化, 特异性和阳性预测值为100%, 被筛选人群中有0.7%以上诊断为肝硬化. 在肝硬度测量值大于8 kPa者中, 有50%与非酒精性脂肪肝有关, 其肝硬度值可高度预测肝纤维化. 可见, Fibroscan可用于对一般人群肝纤维化存在状态进行筛选.

2.3.2 甲型病毒性肝炎: 韩国学者Seo *et al*[16]以31名急性甲型肝炎患者为对象, 研究其急性过程中肝脏硬度值的变化. 结果发现, 凝血化验指标INR(国际标准化比率)是肝脏硬度测量值LSM峰值的独立影响因素, 出现LSM峰值和INR峰值当日的胆红素水平是甲型肝炎急性期病程的影响因素. 可见, 急性甲型肝炎进程中肝硬度测量值是动态变化的, 变化形式可能与炎症程度

有关[17-18]. 另有研究表明, LSM值与转氨酶水平相关, 随着转氨酶的下降而明显下降[19], 因此有学者指出Fibroscan不适用于急性肝炎的检测[20].

2.3.3 乙型病毒性肝炎: Hilleret *et al*[21]对Fibroscan诊断乙型肝炎病毒携带者肝纤维化的价值进行研究, 发现在Fibrotest评分<0.21的携带者中, 有95.6%的肝硬度值<7 kPa, 可认为提示无明显纤维化. 在17个Fibrotest评分>0.21的携带者中, 有5人肝硬度值>7 kPa, Fibrotest评分范围为0.23-0.33, 肝硬度测量值范围为7.2-10.4 kPa, 可认为提示明显的肝纤维化. 携带者与e抗原阳性者比较, 前者肝硬度测量值(4.9 kPa)和Fibrotest评分(0.15)都分别明显低于后者(8.1 kPa, 0.28). Sporea *et al*[22]也通过以丙型肝炎患者做对比, 评价了乙型肝炎活动期患者和乙型肝炎病毒携带者肝脏的硬度. 结果表明, 同种程度的肝纤维化, 乙型肝炎患者和丙型肝炎患者的肝硬度测量值并无明显不同, 乙型肝炎病毒携带者的肝硬度测量值(2.7-20.1 kPa)比正常者高.

2.3.4 丙型病毒性肝炎: Cardoso *et al*[23]对136名丙型病毒性肝炎患者进行回顾性研究, 结果出现过腹水者测得的平均硬度值(37.6 kPa)高于未出现腹水者(12.1 kPa); 食管静脉曲张患者的硬度值(30.4 kPa)高于无食管静脉曲张者(11.8 kPa); 低于1.5×10^5/mm^{3}的血小板水平与高硬度测量值相关. 可见, 高硬度测量值与腹水史、低血小板计数及食管静脉曲张表现有关. 有研究发现, 合并HIV感染的丙型肝炎患者与单纯丙型肝炎患者的Fibroscan下表现并无差异[24-25]. 另有学者对肝移植后复发的丙型肝炎患者研究, 发现严重肝纤维化的LSM在6.9-8.5 kPa之间[26-27]. 上述皆可提示Fibroscan有助于对各种丙型肝炎患者进行随访病情监测[28-32].

2.3.5 酒精性肝病和非酒精性脂肪肝: 酒精性肝病者的肝脏呈现纤维化、脂肪变及胆汁淤积共存的状态, 而炎症和胆汁淤积都严重干扰肝脏硬度测量值[33-34]. Mueller *et al*[35]的研究发现, 当酒精性肝病患者AST水平低于100 U/mL且直接胆红素水平稳定时, 以14.7 kPa为诊断F4期的临界值, 肝硬度测量值的ROC面积为0.94. 另一项对非酒精性脂肪肝的研究结果显示了Fibroscan对F4期诊断的准确性达0.99[36].

2.3.6 药物性肝病: 长期应用氨甲蝶呤与肝纤维化的发生有相关性. 有学者对应用氨甲蝶呤的类风湿、炎性肠病、银屑病患者的肝硬度测量值做了研究[37-38]. Barbero-Villares *et al*[39]用Fibroscan分析了重度纤维化患者的进展与用药时间的相关性, 发现肝硬度值与氨甲蝶呤累积应用剂量无明显相关, 氨甲蝶呤的一般常用量不会导致严重肝纤维化的发生. 因此认为Fibroscan是一种无边缘效应的工具, 有助于对肝纤维化患者进行评价和随访.

2.3.7 肝移植适合者筛选: Vergniol *et al*[40]比较Fibroscan, Fibrotest, APRI, FIB-4, Child-Pugh评分等无创性诊断方法对慢性肝病肝硬化失代偿期者生存率的预测价值, 发现Fibroscan的测量结果>20 kPa, Fibrotest评分>0.74, APRI>2, FIB-4>3, Child-Pugh评分>6时, 生存率明显降低, 门脉高压、肝细胞癌的发生率也升高. 通过与Child-Pugh评分>6对比, 认为Fibroscan是唯一与生存率及门脉压力升高相关的预测方法, 因此提示, Fibroscan会对筛选进行肝移植的患者有应用意义.

2.3.8 食管静脉曲张: 有研究认为肝脏硬度指标可提示肝硬化患者是否患有重度食管静脉曲张[41], 有助于选择可进行内镜检查的患者. 当出现食管静脉曲张时, 反映肝脏硬度的ROC面积为0.84, 当静脉曲张程度≥Ⅱ度时, 该面积为0.83. 肝脏硬度测量值<19 kPa则明确提示不存在Ⅱ度及以上的食管静脉曲张[42].

2.3.9 门静脉高压: 有研究认为, Fibroscan诊断肝硬化门脉高压(门静脉压力>6 mmHg)的临界值为8 kPa时, 敏感性为90%, 特异性为81%. 诊断严重门脉高压(门静脉压力≥10 mmHg)临界值为11.7 kPa时, 敏感性为94%, 特异性为74%; 临界值为21 kPa时, 敏感性为90%, 特异性为93%. 由此, Fibroscan对门脉高压的诊断也有一定意义[43-44].

2.4 影响硬度测量值准确性的因素 在研究过程中, 学者们也发现了影响肝脏硬度指标准确性甚至导致失败值和不可靠值出现的诸多因素.

2.4.1 探头位置: Zelber-Sagi *et al*[45]以371名慢性肝病患者为研究对象, 取第7, 8肋间隙腋前线至腋中线右上腹的3处位置作为探头置放点, 测量肝脏硬度值. 结果有68.2%患者在3个位置处测量值相同, 另外31.8%存在不一致. Ingiliz *et al*[46]也发现以肝穿刺活检为标准, Fibroscan选取测量位置的不同会使LSM值出现差异.

2.4.2 食物摄入: Mederacke *et al*[47]选取56名慢性丙型肝炎病毒感染者为研究对象, 以其肝硬度值<6 kPa, 6-10 kPa和>10 kPa分为3组, 并且都进

■**创新盘点**
本文将目前国外Fibroscan的应用领域及肝纤维化分期较为公认的临界值范围加以总结, 对其在我国的应用具有指导作用.

■应用要点
Fibroscan能定量评价肝纤维化, 临床可联合血清生化学共同诊断, 并早期指导临床治疗.

行3种状态下的肝脏硬度测量: 空腹状态、摄取标准早餐后立即测量、早餐后1 h. 结果, 在摄入食物及其后1 h再次测得的硬度值, 较空腹时至少增加1 kPa, 3组增加的平均值分别为: 1.5、3.0和4.6 kPa.

2.4.3 valsalva动作: Millonig *et al*[48]评估了24例健康人在Valsalva动作前后的肝脏硬度值, 其平均值从4.4 kPa上升到6.6 kPa. 如以6.1 kPa为正常临界值, 则健康者的肝脏硬度值可因Valsalva动作从正常值上升至肝纤维化正常临界值以上.

2.4.4 受检者及操作者因素: 有研究发现, 糖尿病、肥胖者和肋间隙狭窄者的肝硬度值不易获得[49-51]. Castera *et al*[52]的研究检测中, 肝脏硬度值测量失败率为3.1%, 不可靠结果占15.8%. 与测量失败率独立相关的因素: BMI>30 kg/m^2、操作者经验500例、年龄>52岁以及糖尿病; 与不可靠测量值独立相关的因素: 操作者经验<500例、BMI>30 kg/m^2、年龄>52岁、糖尿病、高血压以及女性. 此外, 研究发现受检者血小板计数、总胆红素、白蛋白、碱性磷酸酶、AST及ALT水平的变化都可影响测量值[53-54].

因此, 应用Fibroscan得到的测量值一定要与临床、生物学及形态学相结合, 来综合评价各种原因导致的肝纤维化及其并发症[55-56].

3 结论

目前, Fibroscan在国外已有广泛研究, 最近又有关于联合血清生化学及放射学共同诊断肝纤维化的诸多报道[5,57-59]. 但研究对象仍主要集中在慢性丙型肝炎、酒精性肝病等疾病[60], 相对而言对于乙型肝炎病毒引起的纤维化或肝硬化的研究却较少[61]. 现在, 我国关于Fibroscan对乙型肝炎肝纤维化程度的诊断正在研究中. 相信在发现并总结可能影响肝硬度测量值的因素后, 有关乙型肝炎肝纤维化的大量更为准确的研究成果会为Fibroscan的应用提供良好的参考依据. 建立能监测纤维化发生发展的联合检查系统, 将有助于及时发现处于肝功能代偿状态但有进展性肝纤维化的患者, 减少慢性肝病患者肝活检的需要, 更对指导临床治疗有着极为重要的意义.

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■同行评价
本文对Fibroscan在我国的应用研究有一定的指导意义, 可读性较好.

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