

# 瞬时弹性扫描仪在肝纤维化诊断中的应用价值

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## ■背景资料

肝脏活检目前仍然是诊断肝脏纤维化的金标准, 但是由于肝活检的有创性和抽样误差限制了其在临床的使用, Fibroscan是近年内研发的无创、简便的测定肝脏纤维化的仪器, 其诊断的价值对临床有指导作用。

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## Application value of Fibroscan in the diagnosis of hepatic fibrosis

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## Abstract

Fibroscan (FS) is a novel non-invasive method to assess hepatic fibrosis in patients with chronic liver disease by measuring liver stiffness. It is a rapid and user-friendly technique that can be easily performed with immediate results and good reproducibility. So far, FS has been used not only in patients with chronic hepatitis C but also in those with chronic liver diseases of other etiologies, such as chronic hepatitis B, alcoholic liver disease, and non-alcoholic liver disease. Moreover, FS appears to be an excellent tool for early detection of cirrhosis and complications of cirrhosis. As FS has excellent patient acceptance, it is useful for monitoring fibrosis progression and regression in the individual case. However,

some influencing factors and certain limitations exist in the clinical application of FS. The aim of this article is to review the application value of FS in the diagnosis of hepatic fibrosis.

**Key Words:** Fibroscan; Hepatic fibrosis; Application value

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## 摘要

瞬时弹性扫描仪(Fibroscan, FS)是一种新型的、无创性的通过测定肝脏硬度值来评估慢性肝脏疾病患者肝纤维化程度的仪器。它具有操作简单、快速、重复性好等优点。目前, FS不仅用于慢性丙型肝炎患者肝纤维化的测定, 也可用于其他原因引起的肝脏疾病的肝纤维化测定。FS对测定早期肝硬化及合并肝硬化并发症患者的肝脏硬度值有较大的价值。由于FS能被患者普遍接受及可以重复测定, 因此可用于监测肝脏纤维化的进展或逆转, 指导临床治疗。但FS在临床应用中也存在一些影响因素和一定局限性。本文就FS在肝纤维化诊断方面的应用价值作一综述。

**关键词:** 瞬时弹性扫描仪; 肝纤维化; 应用价值

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## 0 引言

肝脏纤维化是所有慢性肝脏疾病进展的结果<sup>[1]</sup>, 是肝硬化发展过程中的中间环节, 在代偿期肝硬化的患者中, 每年发展成失代偿期肝硬化, 肝癌的比例及死亡率分别为4%、3%、3%<sup>[2]</sup>。对肝纤维化的早期诊断有助于预测疾病的后果及早期制定合理治疗方案, 从而延缓肝纤维化发展成肝硬化甚至肝癌的进程。肝纤维化的诊断方法在最近几年进展很快, 研发无创性的、可靠的测定肝纤维化的方法一直是近年的研究热

## ■同行评议者

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点, 瞬时弹性扫描仪(fibroscan, FS)是2003年由Sandrin等研制的应用超声波技术测定肝组织弹性的方法, 他是一种新型、无创、快速、操作简单、可以重复及床旁测定肝脏纤维化的仪器。有许多研究证实, FS测定的肝纤维化值和肝脏组织纤维化程度的METAVIR分期相关<sup>[3-5]</sup>。但他对评价肝纤维化程度的准确性及各期的分界(Cutoff)值与肝组织纤维化METAVIR分期的对应性, 受一些因素的影响。

## 1 原理和结果解释

FS是以超声检查为基础, 通过测定肝脏硬度值判断肝纤维化和肝硬化分级<sup>[6]</sup>, FS由3个部位组成: 能产生超声波并作为超声波接收器的换能器, 位于换能器上能发出低频震动波的探头及记录数据的软件程序。超声换能器探头安装在振动器的轴上, 低振幅、低频率的振动通过换能器探头换能, 产生一种弹性剪切波在组织中传播, 脉冲-回波超声捕获装置跟踪剪切波并测定他的速度, 剪切波在肝脏组织中的传播速度直接反应肝组织弹性度, 组织越硬, 剪切波传播越快, 测定的值越高。测定时, 患者仰卧位, 右上肢上举放在头部, 换能器的探头放在患者右侧肝脏部位肋间隙的皮肤上, 垂直于皮肤, 测量位置定好后, 检查者按探头按钮开始采集图像, 软件会自动分析测定是否成功, 测定值的单位用千帕(kPa)表示, 成功测定10次后取中位数即是最后测定值, 测定的深度在距离皮肤25-65 cm, 测定的肝脏弹性度值的范围为2.5-75 kPa, 肝脏硬度测定结果的有效性取决于两个重要的参数, 四分位数间距: 反应了有效测定值的一致性, 不能超过中位数的20%-30%; 成功率: 是测定成功的次数除以总的采集次数, 至少60%以上。以测定的敏感度为纵坐标, 1-特异度为横坐标, 每个阈值的敏感度和相对应的特异度在坐标图上都成为一个点, 将这些点连成线, 即为接受者操作特性曲线(ROC曲线)。ROC曲线下面积(AUROC)反应测定组织硬度的准确性, 曲线下面积越接近于1, 准确性越高<sup>[7]</sup>。

## 2 FS在肝纤维化诊断中的应用价值

FS作为肝纤维化无创性诊断的检查方法之一, 评价其应用价值在于其诊断肝纤维化的准确性及其与金标准肝组织纤维化分期的相关性。肝活检仍然被看做是诊断肝脏纤维化的金标准, 但肝活检是有创性的检查, 可能给患者带来痛

苦及出现一些并发症甚至死亡(据报道死亡率为0.1%-0.01%)<sup>[8]</sup>。一部分患者不能接受, 而且肝活检难以重复进行、存在抽样误差, 不利于了解肝纤维化这个动态发展过程<sup>[9-11]</sup>。几种血清学的指标: 如透明质酸, 层粘蛋白, IV型胶原纤维及III型前胶原; 几种肝纤维化评分模型: 如APRI指数, AAR指数, Forns指数, FibroTest等, 均可以用于测定肝脏纤维化程度<sup>[12-15]</sup>, 但这些血清学指标易受肝外情况的影响<sup>[16,17]</sup>, 当这些评分模型单独用于研究时, 由于各实验室间的差异使他们的诊断性能降低<sup>[18-20]</sup>。多个研究证实: FS可以测定肝病患者的肝脏纤维化程度, 肝脏纤维化程度越重, FS测定值越高, 且FS测定值和肝脏纤维化METAVIR分期相关性高<sup>[6,21-23]</sup>。FS是无创性、简洁、快速的检查, 大多数患者都容易接受, 反复检测可以监测肝脏纤维化的进展或者逆转情况<sup>[24]</sup>。FS测定值是一个客观的物理学参数, 该参数与肝脏硬度直接相关, 不受肝外情况的影响, 理论上用于所有的慢性肝病患者<sup>[25,26]</sup>。因此FS的应用范围宽, 适用人群广, 可重复性好, 具有很大的应用价值。

## 3 FS在各种肝病所致肝纤维化中的应用价值

### 3.1 病毒性肝炎

3.1.1 FS在丙型肝炎后肝纤维化诊断中的应用价值: 丙型肝炎病毒所致的肝脏纤维化是丙型肝炎进展的结果, 其纤维化的程度作为疾病进展、是否需要抗病毒治疗及了解抗病毒治疗疗效的重要参考<sup>[27,28]</sup>。FS在诊断丙型肝炎后肝纤维化或者丙型肝炎病毒合并艾滋病毒感染致肝纤维化均有较大意义, 肝脏硬度测定(LSM)值与肝脏纤维化的METAVIR分期相关性较高, 尤其对于明显肝纤维化和肝硬化患者(表1),  $F \geq 3$ 的AUROC为0.85-0.91,  $F = 4$ 的AUROC为0.90-0.99。因此LSM值可以作为丙型肝炎治疗时机的选择和判定治疗效果的参考指标之一。Castéra指出, 在FS和FibroTest结果一致的情况下, 对 $F \geq 2$ ,  $F \geq 3$ ,  $F = 4$ 的患者分别有84%, 95%, 94%的患者肝活检可以证实, 联合以上二种检查方法能让大部分患者避免肝活检<sup>[29,30]</sup>。

3.1.2 FS在乙型肝炎后肝纤维化诊断中的应用价值: FS最先用于丙型肝炎后肝纤维化的诊断, 近年来对FS在乙型肝炎后肝纤维化的研究逐渐增多, 对乙型肝炎病毒致肝纤维化, 其肝脏硬度值与肝纤维化的分期的相关性也大, 特别是对于明显肝纤维化和肝硬化的患者(表2), 且与丙型肝炎病毒致肝纤维化具有相近的Cutoff值,  $F \geq$

### ■ 研发前沿

本文主要针对乙型肝炎病毒、丙型肝炎病毒、丙型肝炎病毒合并获得性免疫缺陷病毒感染、酒精性、非酒精性导致的肝脏纤维化各METAVIR分期与FS测定的Cutoff值的相关关系, 及FS值的影响因素。

## ■相关报道

FS测定的可重复性较好,对肝脏纤维化METAVIA分期 $F \geq 3$ 及 $F \geq 4$ 的患者,FS值和肝脏纤维化分期的相关性较好。

表 1 诊断慢性丙型肝炎纤维化分级的肝脏硬度阈值 (Cutoff)

作者	n	合并HIV	肝脏纤维化分级(Metavir)							
			F $\geq 1$		F $\geq 2$		F $\geq 3$		F = 4	
			Cutoff值(kPa)	AUROC	Cutoff值(kPa)	AUROC	Cutoff值(kPa)	AUROC	Cutoff值(kPa)	AUROC
Ziol等 <sup>[61]</sup>	327	否			8.7	0.79	9.6	0.91	14.5	0.97
Sandrin等 <sup>[48]</sup>	106	否	5.1	0.90	7.6	0.88		0.91		0.99
Castera等 <sup>[29]</sup>	183	否			7.1	0.83	9.5	0.90	12.5	0.95
Obara等 <sup>[4]</sup>	51	否	5.6	0.87	9.5	0.92	10.3	0.85	17.2	0.90
Ogawa等 <sup>[62]</sup>	161	否	6.7(中位数)		9.1(中位数)		13.7(中位数)		26.4(中位数)	
Ledinghen等 <sup>[63]</sup>	72	是				0.72		0.91	11.8–14.5	0.97
Vergara等 <sup>[64]</sup>	169	是			7.2	0.87			14.6–17.6	0.95

AUROC: ROC曲线下面积,反映试验的诊断价值, AUROC越接近1, 诊断的准确性越高. Cutoff值为各纤维化分期的肝硬度平均值。

表 2 诊断慢性乙型肝炎纤维化分级的肝脏硬度阈值 (Cutoff)

作者	n	肝脏纤维化分级(Metavir)							
		F $\geq 1$		F $\geq 2$		F $\geq 3$		F = 4	
		Cutoff值(kPa)	AUROC	Cutoff值(kPa)	AUROC	Cutoff值(kPa)	AUROC	Cutoff值(kPa)	AUROC
Marcellin等 <sup>[65]</sup>	202			7.2	0.81	8.1 <sup>m</sup> /10.5 <sup>n</sup>	0.93	11.0 <sup>m</sup> /18.2 <sup>n</sup>	0.93
Chan等 <sup>[5]</sup>	161	6.8/4.2	0.80			8.4	0.87	9.0 <sup>m</sup> /13.4 <sup>n</sup>	0.93
Ogawa等 <sup>[62]</sup>	68	6.4(中位数)		9.5(中位数)		11.4(中位数)		15.4(中位数)	

<sup>m</sup>灵敏度和特异度之和最大时; <sup>n</sup>诊断准确性最高时。

表 3 诊断肝硬化及其并发症的肝脏硬度阈值 (Cutoff)

作者	n	病因	Cutoff(kPa)	AUROC	预测并发症的肝脏硬度值(Cutoff(kPa))				
					食管静脉曲张 2级以上	肝硬化 ChildB/C级	腹水史	肝癌	食管出血
Ganne-Garrie等 <sup>[31]</sup>	1 257	各种 <sup>a</sup>	14.6	0.95					
Foucher等 <sup>[22]</sup>	711	各种 <sup>a</sup>	17.6	0.96	27.5	37.5	49.1	53.7	62.7
Kim等 <sup>[66]</sup>	194	各种 <sup>a</sup>	10.3	0.80					
Castera等 <sup>[33]</sup>	298	丙型肝炎病毒	12.5	0.96	21.5				

<sup>a</sup>包括丙型肝炎病毒、乙型肝炎病毒、丙型肝炎病毒和艾滋病毒合并感染、酒精性、非酒精性、自身免疫性等。

3的AUROC为0.87-0.93, F = 4的AUROC为0.93. 乙型肝炎与丙型肝炎后肝纤维化的F0-F4分期的Cutoff值是否一致, 需要积累更多的临床资料. 若有差异, 可根据病因来制定肝纤维化分期的Cutoff值。

3.2 肝硬化及合并并发症患者 FS对于诊断慢性肝病患者肝硬化的准确性高, 但报道的Cutoff值在10.3-17.6 kPa之间, 各报道存在差异(表3). 这和所选的研究人群和肝硬化的病因有关. Ganne-Carrie指出使用14.6 kPa作为肝硬化的分界, 排除肝硬化比预测肝硬化的意义更大, 假阴性率主要由于非活动性肝硬化或者大结节性肝硬化<sup>[31]</sup>.

因此在临床的应用中, 这个值可作为用来作为排除肝硬化的Cutoff值. Foucher还指出不同的Cutoff值不仅可以诊断肝硬化, 还可以区分肝硬化的并发症如食管静脉曲张, 腹水史, 肝癌和食管出血. 多个研究指出肝硬化的Cutoff值可区分有伴食管静脉曲张的肝硬化的患者, 报道的Cutoff值在21 kPa以上<sup>[23,32,33]</sup>, 肝脏硬度值的测定可以预示肝硬化的并发症, 肝脏硬度值越高, 越可能合并严重并发症, 通过肝脏硬度值测定, 临床医师可以评估患者发生并发症的风险及行食管内窥镜检查的风险, 积极预防并发症的出现<sup>[34,35]</sup>. 尽管Fibroscan测定值对预测严重肝纤维化和肝

硬化准确率更高,但可以较早发现早期肝纤维化的患者,从临床的意义来说,对预防其发展成肝硬化及出现并发症意义重大<sup>[4,36]</sup>。

**3.3 酒精性肝病及非酒精性脂肪性肝病** FS对酒精性及非酒精性肝病患者肝脏硬度测定的Cutoff值与其纤维化分期相关性好。NGUYEN-KHAC等指出酒精性肝病的患者,对METAVIR分期 $F \geq 2$ 的AUROC在0.90以上, METAVIR分期 $F \geq 1$ ,  $F \geq 2$ ,  $F \geq 3$ ,  $F \geq 4$ 的Cutoff值分别为5.9、7.8、11、19.5 kPa<sup>[37]</sup>。Yoneda等发现肝脏硬度值与非酒精性脂肪性肝病患者肝纤维化程度明显相关,且不受脂肪变性的影响,FS预测各期肝纤维化的ROC曲线下面积分别为 $F1: 0.93$ ,  $F2: 0.87$ ,  $F3: 0.90$ ,  $F4: 0.99$ , METAVIR分期 $F > 1$ ,  $F > 2$ ,  $F > 3$ ,  $F > 4$ 的Cutoff值分别为5.9、6.65、9.8、17.5 kPa<sup>[38,39]</sup>。对于明显肝纤维化和肝硬化的患者,其Cutoff值及AUROC与病毒性肝炎具有相近的值。

#### 4 FS测定值的影响因素

许多研究已经证实了FS的临床应用价值,他的测定值和肝脏组织的纤维化程度(F0-F4)均有高度的相关性<sup>[29,40-42]</sup>。但是,肝脏硬度值也受肝纤维化以外的其他因素的影响,几项研究显示了在转氨酶升高的慢性病毒性肝炎患者和急性肝脏损害的患者中肝脏硬度值可能受转氨酶影响,Coco对228例病毒性肝炎的患者研究后指出,在慢性肝炎患者中,除了肝脏本身纤维化,ALT是独立影响肝脏纤维化FS测定值的因素,对处于相同肝纤维化分期的患者,ALT正常者的肝脏硬度值较ALT升高者低,当ALT升高时,患者的肝硬度值升高1.3-3倍<sup>[43]</sup>。Sagir等报道20例各种原因引起的急性肝脏损害患者的肝硬度值,其中15个患者肝脏急性炎症期肝脏硬度值超过12.5 kPa,这些患者的超声检查没有提示肝硬化,11个患者肝活检也没提示肝硬化,6个患者在转氨酶恢复正常后肝脏硬度值都降到了12.5 kPa以下<sup>[44]</sup>。Arena等报道了18名急性病毒性肝炎的患者的肝硬度值和转氨酶水平的下降是平行的<sup>[45]</sup>。Chan等研究显示,转氨酶对肝脏硬度值有影响,特别是血清转氨酶的升高对无纤维化的患者的FS测定值影响大,而对桥接肝纤维化和肝硬化的影响较小<sup>[5]</sup>。因此对明显急性肝脏炎症的患者,临床医师对FS测定值的解释应多加注意,同时应动态观察,其值不一定反映肝脏硬度,肝脏硬度值除受肝纤维化程度影响外,还受肝细胞炎症、水肿、肝脏血管充血影响<sup>[44]</sup>。胆红素也是

影响FS测定肝纤维化的一个重要因素, Kim等测定急性肝炎患者炎症期和恢复后的肝脏硬度值,认为总胆红素的改变可能是影响肝脏硬度值改变的因素之一<sup>[46]</sup>。总胆红素的升高使肝脏硬度测定值升高, Millonig等测定肝外胆汁淤积的患者的肝脏硬度值提示,不管肝纤维化程度如何,肝外胆汁淤积使肝脏硬度值增加,15个胆汁淤积的患者有13个患者在胆汁淤积解除后FS测定值均下降。肝外胆汁淤积的患者解除梗阻后,FS评估肝脏硬度是有价值<sup>[47]</sup>。最近Lucidarme等提出IQR/M(四分位差/肝脏硬度平均值)影响FS测定值和肝活检不一致的影响因素,最适的值是0.21,而成功率不影响肝纤维化分级的准确性<sup>[3]</sup>。据报道:未发现肝脏脂肪变性对FS测定值有影响<sup>[43,48,49]</sup>,为提高FS诊断肝纤维化的准确性,减少这些因素的干扰,应该考虑在患者转氨酶水平或胆红素水平恢复正常后再行FS检查。

#### 5 FS的可重复性和局限性

FS对肝脏硬度值测量的可重复性是他能广泛用于临床的前提条件<sup>[50,51]</sup>。Sandrin等评估了106名丙型肝炎患者指出,FS检查的重复性好,操作者之内和操作者之间的变异系数小,分别为3.2%和3.3%<sup>[6,48,52]</sup>。Boursier对操作者之间的一致性进行了研究,对250例慢性肝脏疾病的患者,初学者和专家之间检查的肝脏硬度的一致性随着肝脏硬度的不同而有差异,对于FS测定值 $< 9$  kPa的患者,组间相关系数是0.49,对于FS测定值 $\geq 9$  kPa的患者,组间相关系数是0.87<sup>[49]</sup>。对肝脏硬度值更高的患者进行肝脏硬度的测定,初学者和专家测定的值的相关性更高。Quelli等对不同病因的慢性肝脏疾病的200例患者分别由2个操作者对每个患者测2次LSM,操作者之内和操作者之间的重复性极好,组内相关系数是0.98,对轻度的肝纤维化,操作者之间的一致性降低(F0-F1的组间相关系数是0.6,  $F \geq 2$ 的相关系数是0.99),对于肝脂肪变性细胞 $\geq 25\%$ 的相关系数是0.90,而肝脂肪变性细胞 $< 25\%$ 的相关系数是0.98,对于体质量指数 $\geq 25$  kg/m<sup>2</sup>相关系数是0.94,体质量指数 $< 25$  kg/m<sup>2</sup>相关系数是0.98<sup>[52]</sup>,体质量指数和肝脏脂肪变性对操作者的一致性无明显影响。有Meta分析表明:FS对肝硬化诊断价值大,但是对早期肝纤维化的诊断准确性有所降低<sup>[53]</sup>,FS对于测定明显肝纤维化或者肝硬化患者的LSM值重复性好。FS可以测定95%以上的慢性肝脏疾病患者的肝脏硬度值,在不同的研究中报道失

#### ■创新盘点

此文对Fibroscan在肝脏纤维化诊断中的临床应用及局限性进行了综述,有利于更好的指导临床应用。

## ■应用要点

Fibroscan对临床上无创性评估慢性肝病患者肝纤维化的程度具有一定的指导价值。

败率为2.4%-9.4%<sup>[29,48,52]</sup>。导致失败的因素主要是肥胖, Foucher测量2 114例慢性肝脏疾病患者的肝脏硬度指出, 通过多因素分析唯一影响成功率的因素是体质量指数 $>28^{[54]}$ , 肥胖或超重的患者由于使弹性波或者超声逐渐减弱, 导致肝脏硬度无法测定<sup>[54-56]</sup>。Kettaneh指出: 体质量指数和年龄影响成功率。肋间隙狭窄, 年龄偏大的患者<sup>[57]</sup>测定成功率降低, 但有报道称年龄不会影响肝脏硬度值<sup>[58]</sup>, 对于合并腹水的患者, 不能成功测定其LSM值<sup>[6,54]</sup>。有学者建议对提高Fibroscan检测的成功率, 可以通过改进超声的探头来实现。

## 6 结论

FS具有无创、无痛、快速、操作简单等优点, 对肝纤维化的诊断具有较高的准确性和较好的重复性, 尤其对于明显肝纤维化及肝硬化的患者, FS还可动态的随访肝病患者肝脏纤维化的变化。对各种原因引起的肝病所致的肝硬化的诊断及治疗后疗效判定等, 都有很大的应用价值。目前, 虽然FS还不能完全替代肝组织活检, 但他必将有很大的应用前景<sup>[59]</sup>。在我国一些医院已投入临床使用, 在不久的将来, FS将可能作为肝病患者一项常规的检查。FS对肥胖、肋间隙狭窄的患者成功率低, 有学者建议通过改进超声的探头来提高成功率。目前对肝组织METAVIA纤维化分期相对应的FS测定的界限值尚未固定, 因此需要积累更多的临床资料。有学者提出: 联合FS, 血清生化学指标及B超检查, 也许可以提高其诊断价值, 使一部分患者避免肝活检。但这些都需积累更多的资料进一步的研究证实<sup>[60]</sup>。相信随着临床应用的增多及经验的积累, FS将会在肝病的临床诊治中起到重要的作用。

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## 同行评价

本文提供的信息具有一定的新颖性, 对临床应用 Fibroscan 以评估慢性肝病患者肝纤维化的程度有一定的指导价值。

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