MRI对易损斑块的临床研究进展

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［摘要］ 动脉粥样硬化斑块破裂和血栓形成是诱发心脑血管疾病的直接原因。及时识别斑块的易损性逐渐成为近年的研究热点。影像学技术能直观易损斑块相关特征，提供相应治疗策略 。核磁共振作为一项无创检查手段，可以对斑块的形态和功能进行综合评价。本文就核磁共振对颈动脉斑块的形态功能学检查做一简要综述。

［关键词］ 动脉粥样硬化；颈动脉；易损斑块；磁共振成像

Current status of MR imaging for vulnerable plaque in clinical application

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Abstract Atherosclerotic plaque rupture and thrombosis are considered to be induced cardiovascular event. Imaging plays an important role in the management of atherosclerosis, and cardiovascular magnetic resonance (CMR) of the carotid vessel wall is one promising modality in the evaluation of patients with carotid atherosclerotic disease. This review summarizes the current state of knowledge regarding carotid vessel wall CMR and its potential clinical application for management of carotid atherosclerotic disease.
Key words Atherosclerosis; Carotid arteries; Vulnerable plaque; Magnetic resonance imaging

心脑血管病是一种常见多发疾病，据世界卫生组织统计，该疾病已经逐渐成为威胁人类生命健康“头号杀手”。在心脑血管临床事件中，动脉粥样硬化斑块破裂和血栓形成是主要的发病机制，而斑块是否破裂取决于斑块的易损性。由于动脉粥样硬化斑块从稳定变为易损的过程涉及到炎症、免疫、代谢、凝血等多个环节，单纯显示动脉管腔或斑块形态的诊断技术已不能满足临床的需要。为了判断斑块的易损性，需要对斑块的形态和功能进行综合评价。因此，能够显示易损斑块形态和功能的成像技术如核磁共振（magnetic resonance imaging，MRI）已成为当前的研究热点。

MRI血管壁成像结合黑血及亮血技术，可以提供血管组织结构、管壁厚度、斑块成分等信息。这些信息对评价斑块的易损程度非常重要。MRI还可以对斑块的自然发展过程、治疗干预后疗效的评价进行无创的随访跟踪，以指导临床对动脉粥样硬化斑块的转归有更深层次的理解。

1　斑块定性、定量研究

动脉粥样硬化斑块形成的早期是由于血管内皮细胞功能受损，血中低密度脂蛋白颗粒进入血管壁，继而被巨噬细胞所吞噬形成脂质条纹(fatty streak)，血管壁反应性的增厚[1-3]。因此，早期的动脉硬化表现为血管壁增厚。研究证实MR不仅可以清楚地探测血管壁，准确测量血管壁的厚度[4]，而且不同的MR机型、不同扫描、不同阅片者之间都有很好的一致性(可重复性)[5-7]。另外，Underhill等发现MRI测量管壁与超声也有很好的一致性(r=0.93，P＜0.001)[8]。

随着病程的发展，脂纹表层沉积大量胶原纤维，平滑肌细胞(smooth muscle cell)增生并分泌大量细胞外间质(extracellular matrix)，构成薄厚不一的纤维帽(fibrous cap)。纤维帽下细胞外脂质、富含细胞内脂质的巨噬细胞和泡沫细胞以及脂纹则构成了脂核(lipid core)。脂核进一步发展可出现坏死

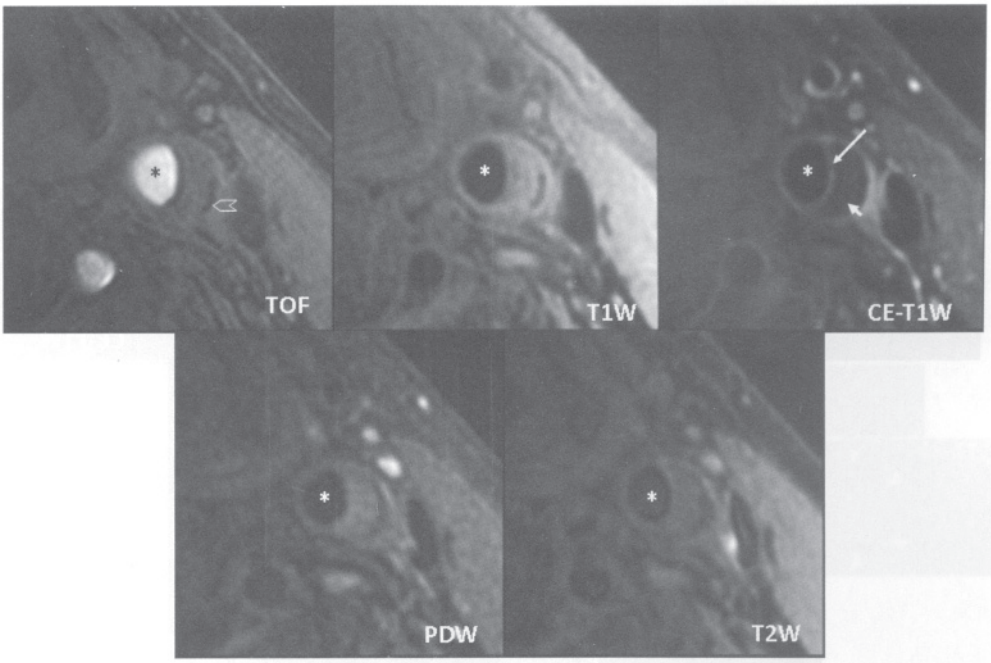

图1 颈动脉脂质斑块。多种MR加权图像示斑块内的脂质核在增强T1WI(CE-T1W)为低信号，而在其他加权像表现为等信号(短箭头)和完整的纤维帽(长箭头)。斑块的边缘还可见小钙化(空箭头)。*代表管腔

Fig 1 Atherosclerotic Carotid Artery Lipid-rich Necrotic Core. Multi contrast black and bright blood sequences show a large lipid-rich necrotic core (small arrow) with an intact thick fibrous cap best seen in the post contrast T1 weighted (CE T1W) image (long arrow). Calcification is also visible at the base of the plaque (chevron). Asterisks are placed on the lumen. Reprint from J Cardiovasc Magn Reson. 2009;11:53

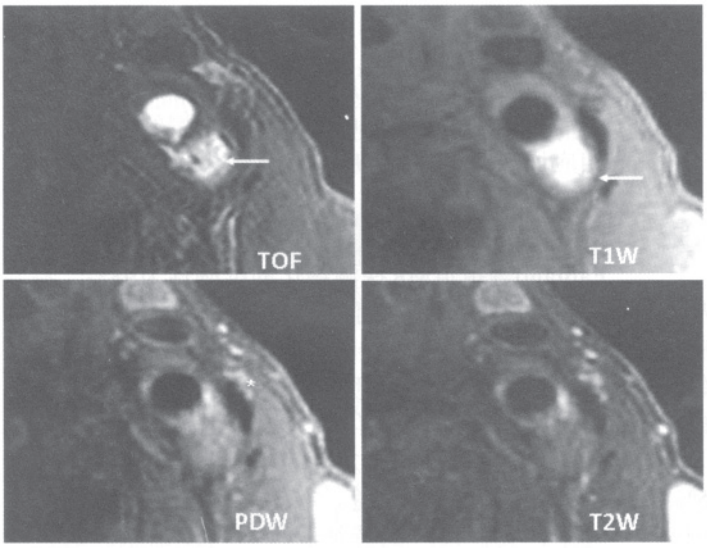

图2 颈动脉斑块内出血。多种MR加权图像示斑块内出血在TOF和T1WI为高信号，而在其他加权像表现为等或低信号(箭头)

Fig 2 MRI appearance of plaque hemorrhage in a patient who was scanned prior to carotid endarterectomy. The presence of hemorrhage is indicated by the hyperintense signal seen in the time-of-flight and T1-weighted images (arrows). Reprint from Circulation. 2002;106:1368

(lipid-rich necrotic core)、斑块内微血管出血(intraplaque hemorrhage)、钙化(calcification)和斑块内微血管化(mircovessels)。

1.1 脂核和纤维帽

病理学上将斑块分为稳定和不稳定斑块，其中不稳定斑块主要由脂质核心与纤维帽组成。有研究表明，当脂质成分超过斑块容积40%时，斑块易于破裂[9]。研究表明，多种MR加权成像(T1WI，T2WI/PDWI，TOF)可以显示脂核(图1)。与胸锁乳突肌信号相比，脂核在T1WI和TOF上为等信号，T2WI为低信号。Fabiano等用MR扫描离体斑块，发现其敏感性为92%，特异性为74%[10]。在活体，与病理相对照，MR敏感性为92%，特异性为65%[11]。如给予对比剂行增强扫描，可以显示脂核和纤维帽更多的信息[12-14]。对比剂可使纤维组织的信号提高79.5%，而脂核的信号下降28.6%[12]。强化的纤维帽和未强化的脂核形成了良好的对比，从而更容易勾勒出脂核的边界而得到准确的定量测量结果。Wasserman等还发现与T2WI相比，对比剂增强后T1WI可提升脂核与纤维帽间

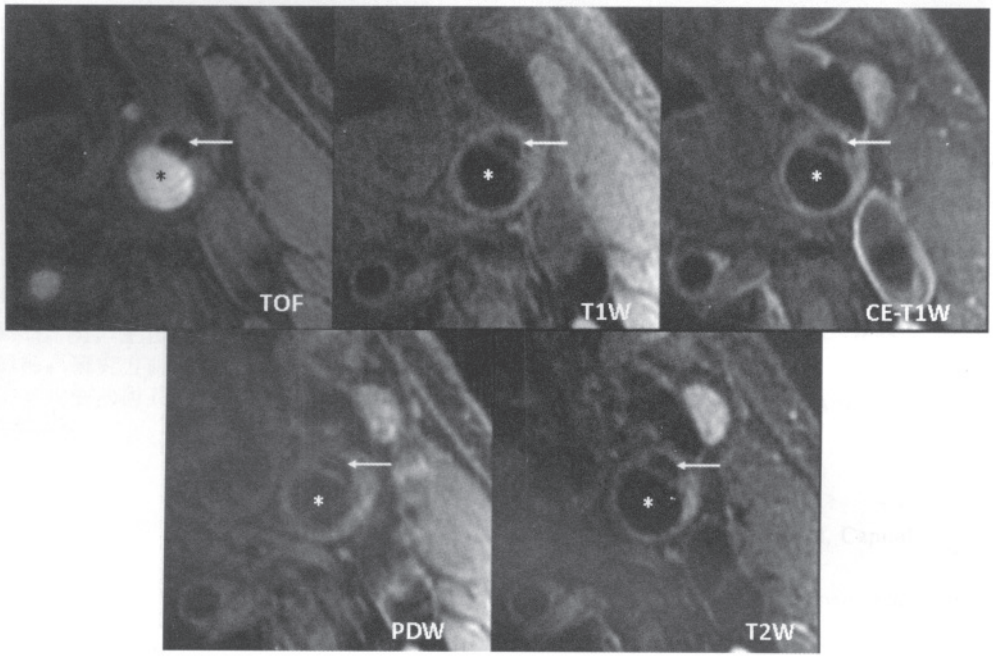

图3　颈动脉斑块内钙化。多种MR加权成像显示斑块内钙化在各个权重图像均表现为低信号(箭头)。*代表管腔

Fig 3 Calcification can be found in early atherosclerotic lesions. Black and bright blood multicontrast images show the presence of calcification in the wall of an early lesion of the left common carotid artery (arrow). Asterisks are placed on the lumen. Reprint from J Cardiovasc Magn Reson. 2009;11:53

的对比噪声比约2倍[13]。Cai等对纤维帽进行了定量分析，发现MRI与病理有很好的相关性(最大纤维帽厚度：r=0.78，P<0.001；长度：r=0.73，P<0.001；面积：r=0.73，P<0.001)[14]。

1.2 斑块内微血管出血

斑块内出血来自斑块内未成熟血管的红细胞渗漏[15]。尽管如何从斑块内出血发展成斑块破裂的机制还不十分清楚，但其可加速脂核的形成[16]。由于正铁血红蛋白可以不同程度地缩短T1弛豫时间从而在T1加权像上呈现高信号，因此斑块内出血在MR的信号特征主要取决于血肿内正铁血红蛋白的期龄。表现为在T1WI和TOF上为高信号，早期的正铁血红蛋白在T2WI为低信号，晚期的则为等或高信号(图2)。此信号特点与病理相对照，敏感性为85%～95%，特异性为70%～77%[17]。Moody等用三维重T1加权序列(magnetization-prepared rapid acquisition gradient-echo，MP-RAGE)观察出血，其敏感性为84%，特异性为84%[18]。

1.3 钙化

尽管钙化经常在斑块内出现，但其是否导致斑块的不稳定性尚无定论。一些研究表明出现大量钙化与增加斑块破裂的危险性呈正相关[19-23]，而另一些研究则提示钙化有助于斑块的稳定性[24-26]。最近，研究者开始提出钙化出现的位置有可能影响斑块的稳定性。Li等利用生物力学模型研究显示，如果钙化出现在薄纤维帽内，则纤维帽的最大剪切力相应增加47.5%。相反，如果钙化出现在脂核或远离纤维帽的位置，剪切力则没有增加[27,28]。钙化在MR的T1WI、T2WI、TOF均表现为低信号(图3)。Fabiano等报道MR探测钙化的准确性为98%，特异性为99%。Saam等用MR测量了钙化的大小，与病理有很好的一致性(r=0.74，P<0.001)[11]。

1.4 斑块内微血管化形成

细胞内微血管化的形成一方面是供给斑块营养的来源，另一方面也是传导、运输炎性细胞、炎性因子的渠道。在颈动脉粥样硬化进展过程中，炎性反应的特征表现为内皮细胞通透性增加、巨噬细胞浸润、血管壁缺氧和血管外膜层滋养血管增生。浸润的巨噬细胞吞噬脂质，发生凋亡，使粥样斑块中心坏死不断进展增大。 Moreno等发现微血管的数目不仅和炎性细胞的数量相关，也和斑块破裂有关[29]。Mofidi也发现微血管的数目和斑块内出血相关[30]。目前有两种MR技术探测斑块内微血管化。一种是利用动态增强(dynamic

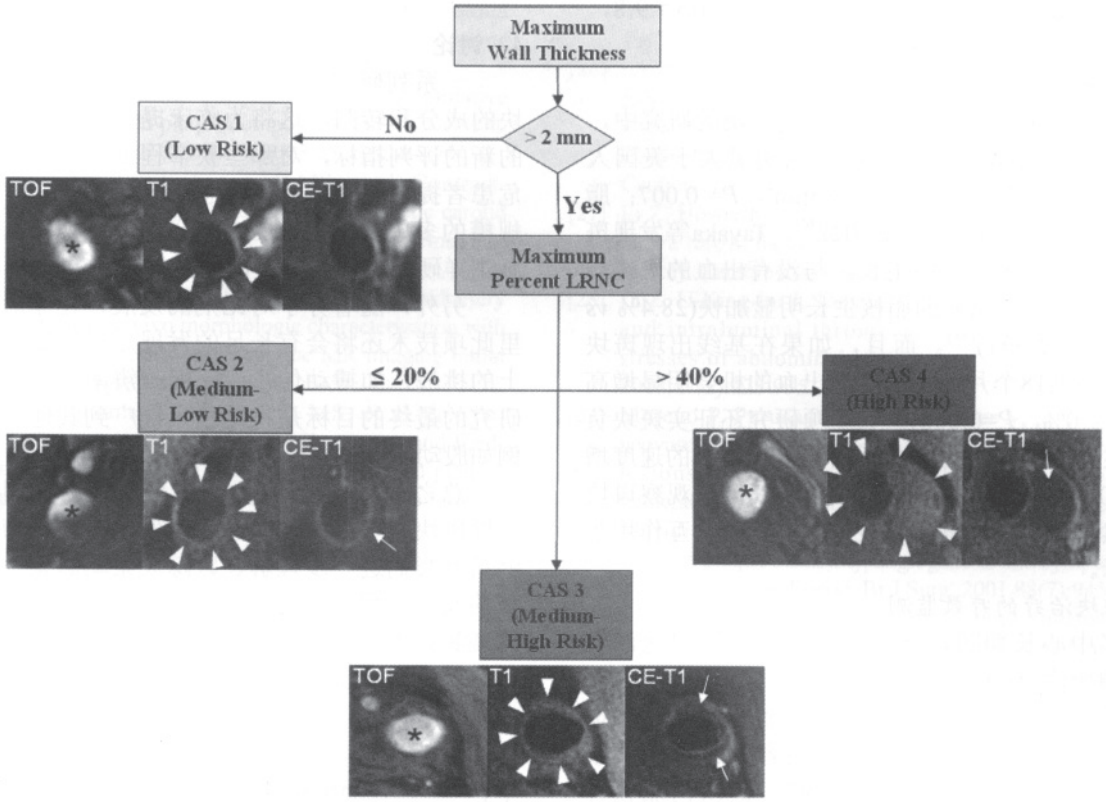

图4 颈动脉粥样硬化评分系统。对管壁小于2 mm的患者给予1分(低风险)，对管壁大于2 mm的患者进行进一步评估，已是否出现脂质核为界，无脂质核者给予1分，有脂质核者给予2分(中风险)或以上。根据脂质核的大小，将患者分为中风险(2分，脂质核≤20%)，中高风险(3分，脂质核＞20%但≤40%)，和高风险(4分，脂质核＞40%)。经作者同意摘自参考文献52(Am J Neuroradiol. 2010; 31(6): 1068-1075)

Fig 4 Flow diagram of CAS. Subjects with a maximum wall thickness >2 mm require additional evaluation. Further categorization of lesions can be determined by the size of the maximum percentage LRNC. CAS 1 is determined as maximum wall thickness <2 mm (low-risk). CAS 2 is determined as maximum percentage LRNC ≤20% (intermediate risk). CAS 3 is determined as maximum percentage LRNC >20% and ≤40% (intermediate-high risk). CAS 4 is determined as maximum percentage LRNC >40%(high risk). Reprint from Am J Neuroradiol. 2010;31:1068

contrast enhanced MRI，DCE-MRI)技术。这种技术最初被应用于肿瘤微血管化的研究。在斑块内部，利用这种技术同样可以观察微血管的数目和通透性[31,32]。有研究证实，分数血浆容量(fractional plasma volume，V_p)与微血管的面积相关[33]，而对比剂的转移常数(transfer constant，K^{trans})与微血管的通透性相关[31]。另一种MR技术是应用超顺磁性氧化铁颗粒(ultrasmall superparamagnetic iron oxide，USPIO)。USPIO颗粒可以通过受损的内皮细胞进入斑块内，并被巨噬细胞所吞噬，表现为信号缺失。Trivedi等发现这种局部信号的缺失出现在75%的易损斑块中，而只有7%在稳定斑块中[34]。

2 MR对斑块的进展与转归的随访

2.1 回顾性研究

一些回顾性研究探讨了脑卒中、短暂性脑缺血发作和斑块破裂的关系。Saam等报道患者的神经症状和斑块破裂具有相关性。在有症状组斑块破裂的发生率为78%，而在无症状组斑块破裂的发生率只有30%(P=0.007)[35]。Sadat等则发现斑块破裂出现在急性症状组约50%，35%在近期症状组，在无症状组没有发生斑块破裂[36]。另一些研究探讨了其他斑块特征和症状的关系。Murphy等发现斑块内出血与症状相关。Howarth等发现斑块内炎症与症状也相关，有症状的斑块内存在更多的炎症迹象[37]。

2.2 前瞻性研究

斑块内成分是否可以成为预测心脑血管事件的指标已逐渐成为研究的焦点。在一项154名患者随访38个月的研究中，Takaya等提示出现薄/破裂的纤维帽，斑块内出血，大的脂核可预示今后临床症状的出现[38]。同样，Altaf等也证实斑块内出血可以预

测两年内心脑血管事件的发生(hazard ratio＝9.8，*P*=0.03)[39]。

2.3 斑块自然进展

在一项对中国人斑块和美国人斑块的研究中，Saam等发现中国人颈总动脉脂核明显大于美国人的脂核(颈总动脉：52.5 *vs* 37.5 mm^2，*P*= 0.007；脂核：13.6 *vs* 7.8 mm^2，*P*=0.002)[40]。Tayaka等发现斑块内出血可加速脂核的生长。与没有出血的斑块相比，18个月内有出血的脂核生长明显加快(28.4% *vs* -5.2%，*P*=0.001)[38]。而且，如果在基线出现斑块内出血，则18个月内再次出现出血的机会明显增高(43% *vs* 0%，*P*=0.006)。另一项研究还证实斑块负荷也逐年增长。平均管壁面积每年以2.2%的速度增长(*P*=0.001)[41]。这些都证明MR不仅可以观察斑块的自然进展，还能够对斑块内成分间的相互作用予以揭示。

2.4 斑块治疗的疗效监测

多中心长期随访临床实验表明，使用他汀类药物调脂治疗(statin therapy)可以减少临床事件的发生[42-44]。一些MR研究证实调脂治疗可以减轻斑块的负荷[45,46]，还可以减小脂核容积。美国两项临床研究均发现，通过调脂治疗，斑块内脂核体积明显缩小[47,48]。值得一提的是，如果斑块内有出血，调脂治疗也许对脂核的改变没有帮助[49]。也有一些研究着重调查调脂治疗对炎性反应的干预。在一项美国临床研究中，经过一年的调脂治疗，DCE-MRI显示斑块内的炎症细胞明显下降(*P*＝0.02)[50]。在ATHEROMA研究中，USPIO显示的炎症也有明显的减低(6个星期：*P*＝0.003，12个星期：*P*＜0.0001)[51]。

3 MRI对危险分层标准制定的指导意义

对斑块危险进行评分，尤其是应用MRI这一理念可以对临床管理动脉粥样硬化的策略有所指导。Underhill等提出的CAS评分系统就是用MRI对易损斑块进行危险分层的很好的探索[52]。此研究为多中心、大规模临床研究，尽管是回顾性研究，仍然开启了评分系统的大门，为今后前瞻性研究奠定了基础。通过研究，他们发现如果斑块负荷小于2 mm，则认为是低风险斑块；超过2 mm，但脂核占斑块小于20%，也为低风险斑块；如斑块负荷超过2 mm，脂核占20%～40%，为中风险斑块，大于40%的情况下则为高危斑块(图4)。尽管此评分是提示斑块内出血和纤维帽的破裂，但由于这两种斑块的特征与心脑血管事件有着紧密的联系，所以此评分系统仍有一定的价值。如果今后的研究把对斑块评分与事件直接联系起来，将更有说服力。

4 讨论

一系列研究已表明血管壁MR成像可以观察斑块的成分和转归，这将为临床提供一种除狭窄之外的新的评判指标，对那些狭窄程度还不是很重的高危患者提供更多的诊断信息。今后，我们需要更大规模的多中心研究来证实血管壁MR成像在诊断动脉粥样硬化疾病的重要价值。

另外，随着分子对比剂的发展，在今后的十年里此项技术还将会有长足的发展。尽管还存在技术上的挑战，如搏动伪影、空间分辨率不足等问题，研究的最终的目标是将此技术推广到其他血管床，例如股动脉，甚至冠状动脉。

总之，血管壁MR成像在早期、中晚期动脉粥样性斑块病变中均能提供有价值的影像学信息，能够帮助我们进一步理解、跟踪观察动脉粥样硬化疾病的发展过程和药物治疗的疗效。相信随着研究的进展和技术的进步，这种无创手段最终将在临床拥有广泛的应用前景。

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