Characterization of Carotid Plaque Hemorrhage
A CT Angiography and MR Intraplaque Hemorrhage Study

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Background and Purpose—The main objective of this study was to evaluate CT angiographic (CTA) features that are able to predict the presence of intraplaque hemorrhage (IPH) as defined by MR-IPH.

Methods—One hundred sixty-seven consecutive patients (mean age 69 years, SD 12.8; 58 females) underwent both MR-IPH and CTA within 3 weeks. MR-IPH, the gold standard, was performed at 1.5 T using a neurovascular phased-array coil as a coronal T1-weighted 3-dimensional fat-suppressed acquisition. CTA was performed using a 4-slice or a 64-slice CT machine and evaluated, blinded to MR-IPH findings, for carotid stenosis, plaque density, and plaque ulceration. Plaque density was defined as the mean attenuation of plaque at the site of maximum stenosis and 2 sections above and below. Plaque ulceration was defined as outpouching of contrast into the plaque at least 2 mm deep on any single plane.

Results—Prevalence of IPH increased at higher degrees of carotid stenosis. Mean CT plaque density was higher for plaques with MRI-defined IPH (47 Hounsfield units) compared with without IPH (43 Hounsfield units; \( P = 0.02 \)). However, significant overlap between distributions of plaque densities limited the value of mean plaque density for prediction of IPH. CTA plaque ulceration had high sensitivity (80.0% to 91.4%), specificity (93.0% to 92.3%), positive predictive value (72.0% to 71.8%), and negative predictive value (95.0% to 97.9%) for prediction of IPH. Interobserver agreement for presence/absence of CTA plaque ulceration was excellent (\( \kappa = 0.80 \)).

Conclusions—CTA plaque ulceration, but not mean CTA plaque density, was useful for prediction of IPH as defined by the MR-IPH technique. (Stroke. 2010;41:1623-1629.)

Key Words: carotid artery ■ carotid stenosis ■ CT ■ MRI

The benefits of surgery in recently symptomatic patients with severe carotid stenosis have been clearly demonstrated.1–3 In clinical practice, decision-making with regard to carotid revascularization still relies primarily on severity of luminal narrowing as determined by ultrasound and/or other angiographic modalities. There are, however, subgroups of patients such as asymptomatic patients or symptomatic patients with moderate stenosis in which the benefits of revascularization over medical therapy are less clearcut.1,4 In such patients, decision-making based on stenosis alone can be more difficult and there is a need for more advanced methods of risk stratification to guide optimal therapy.

Histopathologic studies have shown that certain morphological characteristics of the carotid atherosclerotic plaque such as intraplaque hemorrhage (IPH), ruptured or ulcerated fibrous cap, or large necrotic lipid core are associated with increased risk of stroke, findings independent of the severity of luminal stenosis.5,6 From a histopathologic point of view, neoangiogenesis is closely associated with plaque progres-

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1623
with MRI, there has, however, been relatively less work focusing on CT identification of the vulnerable plaque. This is not surprising due to the inherent superior soft tissue contrast of MRI, but several recent studies suggest that CTA may provide some information on carotid plaque morphology.20–23

The main objective of this imaging study was, therefore, to identify CTA features that may predict presence of carotid IPH as defined by the MR-IPH technique, which was used as the gold standard method.

Materials and Methods

This study had approval from the local ethics committee (Study No. 411-2004); requirement for written informed consent was waived for this retrospective study.

At our institution, MR-IPH is routinely performed as an additional sequence as part of our clinical MRI protocol for evaluation of stroke/transient ischemic attack. This protocol also includes routine brain imaging (diffusion-weighted, fluid-attenuation inversion recovery, and T1-weighted sequences) as well as contrast-enhanced MR angiography from the aortic arch to the circle of Willis. From a prospectively collected database, we identified all patients who underwent both MR-IPH and CTA, within a 3-week interval, for evaluation of carotid stenosis, during a period ranging from December 2003 to December 2008. Patient referral for the clinical stroke MRI stroke protocol (which included contrast MR angiography) and/or CTA was at the discretion of the referring physicians but at our institution, decision for revascularization is often based on both MR angiography and CTA, because the combination of noninvasive tests has been shown to be more accurate locally.

MR-Intraplaque Hemorrhage

MR-IPH was performed on a 1.5-T GE Twin Speed MR machine (GE Medical Systems, Milwaukee, Wis) using an 8-channel neurovascular phased-array coil (USA Instruments) as a free-breathing coronal T1-weighted magnetization-prepared 3-dimensional gradient-echo acquisition (TR 6.7 ms, TE 1.7 ms, TI 20 ms, flip angle 15° with 2-mm thickness, field of view 350×300 mm, effective pixel size 0.94×0.94×1 mm [interpolated], number of excitations=3). The sequence included a selective water-excitation radiofrequency pulse (Spectral Inversion at Lipids, SPECIAL; GE Healthcare) to suppress fat and the effective inversion time (TI 20 ms) was chosen to null the blood signal. The resulting acquisition time was 3.5 minutes.

Assessment of the MR-IPH was performed using both carotid source data together with standard multilayer reformats in the axial and sagittal plane on commercial Picture Archiving Communications System (PACS) workstations (AGFA Impax Version 4.5). MR-IPH was reviewed by 4 neuroradiologists as to presence or absence of IPH blinded to CTA findings. A positive scan was diagnosed if high signal material (at least twice the signal intensity of the adjacent atherosclerotic plaque, causing only a 50% stenosis but with a small ulcer (black arrow) within the plaque.

In parallel with these new developments in MRI of carotid plaque, there is little doubt that, with multislice technology, CT angiography (CTA) has fast emerged as 1 of the noninvasive modalities of choice for carotid stenosis due to its high spatial resolution, speed, and ready availability.19

Figure 1. A, MR-IPH showing IPH (white arrow) as high signal within the wall of the left carotid bulb of a recently symptomatic patient. Sagittal (B), axial source image (C), and coronal CTA reformats of the left carotid artery in same patient shows a large atherosclerotic plaque, causing only a 50% stenosis with a small ulcer (black arrow) within the plaque.
paque 320; GE Healthcare) was injected at a rate of 4.0 to 5.0 mL/s with a 17-second delay or the use of SmartPrep software (GE Healthcare) at the pulmonary artery.

Postprocessing multplanar reformats were created at the CT operator’s console. Coronal and sagittal multplanar reformat images were created 7.0 mm thick spaced by 3 mm. All images were viewed on Impax 4.5 (AGFA Healthcare, Mortsel, Belgium) PACS workstations. Images were initially reviewed on CTA settings (window 96, level 150 Hounsfield units [HU]), which were then modified as required on an individual basis to better depict the residual stenotic internal carotid artery lumen, the vessel wall, and plaque and also to decrease beam-hardening artifact from dense calcifications. CTA was evaluated, blinded to MR-IPH findings, for (1) severity of stenosis; (2) plaque density; and (3) presence or absence of plaque ulceration. Both carotid vessels were evaluated for each patient.

Stenosis was measured using the axial source data and multplanar reformats according to standard North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.2,24 Plaque density was measured by placing a circular region of interest in noncalcified portions of the plaque and recording the average HU (Figure 2). The mean plaque density for the plaque was defined as the average of the HU of the plaque at the site of maximum stenosis and at 2 CT sections above and below, that is, a total of 5 HU measurements for each lesion. Plaque ulceration was defined as contrast outpouching into the plaque at least 2 mm deep on any single plane (Figure 1). Presence or absence of plaque ulceration was recorded after review of CTA axial source images with sagittal and coronal multplanar reformats by 2 independent neuroradiologists; for the purposes of this study, surface irregularity without definite ulceration was recorded as absence of ulceration because the evidence regarding their clinical significance is unclear.

Statistical Methods
All data were analyzed by using the statistical software package SPSS for Windows (Version 12.0.0; SPSS, Chicago, Ill). Comparison between means was performed using the Mann-Whitney U test for nonparametric data. A P value of <0.05 was defined as statistically significant.

Figure 2. CTA (left) showing a moderate carotid stenosis. Corresponding axial images (right) at the site of maximal stenosis and 2 sections above and below. Mean plaque attenuation was derived from a circular region of interest placed in noncalcified sections of the plaque (example shown in midfigure; white circle) and averaged for all 5 sections.

Receiver operating characteristic curve analysis was used to determine the most appropriate plaque density cutoff value to classify presence or absence of plaque hemorrhage as defined by MR-IPH. Plaques were classified as low density (0 to 50 HU) and mixed density (51 to 120 HU) based on their mean CT attenuation values.23,25

Sensitivity, specificity, positive predictive values, and negative predictive values, with 95% CIs, were calculated for the presence of CT plaque ulceration to predict the presence or absence of IPH as defined by MRI based on standard 2×2 contingency tables. Interobserver agreement was calculated using Cohen κ statistics with 0 to 0.40, 0.40 to 0.60, 0.60 to 0.80, and 0.80 to 1 defined as poor, moderate, good, and excellent agreement, respectively.

Results
Patients
One hundred sixty-seven consecutive patients (mean age 69 years, SD 12.8; 58 females) underwent both MR-IPH and CTA during the time period of the study. One hundred fifty-three patients were symptomatic with suspected strokes or transient ischemic attacks and the remainder was asymptomatic. Of a total of 334 arteries analyzed, 15 arteries were excluded due to occlusions (n=13) or previous carotid endarterectomy (n=2), yielding 319 arteries for analysis. MR-IPH showed 56 cases of carotid IPH.

Stenosis Severity and IPH
Distribution of carotid stenosis was as follows: mild stenosis: n=193 (60.5%), moderate stenosis: n=60 (18.8%), and severe stenosis: n=66 (20.7%). Mean stenosis severity for the group with positive MR-IPH studies was 58% (SD 25) compared with 20% (SD 26) for the group with negative MR-IPH studies (P=0.001, Mann-Whitney U test). Figure 3 shows the distribution of cases of hemorrhagic plaques (ie, positive MR-IPH studies) per category of stenosis severity. This confirms that plaque hemorrhage was more frequent at higher degrees of stenosis severity, although there was a nonnegligible number of cases of IPH seen at mild and moderate degrees of stenosis.
Mean CT Plaque Density and IPH

Mean CT plaque density was higher for plaques with MRI-defined IPH (47 HU, SD 15) compared with without IPH (43 HU, SD 14; \(P<0.02\), Mann-Whitney \(U\) test). However, significant overlap between distributions of plaque densities suggests that mean plaque density is of limited value in distinguishing between the 2 groups. This is confirmed by the poor receiver operating characteristics of CT mean plaque density for classification of IPH as shown in Figure 4.

Two hundred twenty-three plaques (69.9%) were of low density on CT (mean 50 HU) compared with 96 plaques (30.1%) of mixed density (51 to 120 HU). Thirty-six (64.3%) of the cases of plaque hemorrhage were seen in plaques of low CT density compared with 20 cases (35.7%) of plaque hemorrhage in plaques with mixed CT density. The presence of low density on CTA would have sensitivity of 64.3% (95% CI 51 to 76), specificity of 28.9% (95% CI 24 to 35), positive predictive value of 16% (95% CI 12 to 22), and negative predictive value of 79% (95% CI 70 to 86).

CT Plaque Ulceration and IPH

CT plaque ulceration had excellent diagnostic accuracy for presence or absence of MRI-defined IPH. The 2×2 contingency tables for presence/absence of CTA plaque ulceration and presence/absence of IPH on MRI for the 2 CTA readers is shown in the Table.

Diagnostic performance for Reader 1 was as follows: sensitivity of 80% (95% CI 68 to 88), specificity of 93% (95% CI 89 to 96), positive predictive value of 72% (95% CI 59 to 81), and negative predictive value of 95% (95% CI 92 to 98).

Diagnostic performance for Reader 2 was as follows: sensitivity of 91.4% (95% CI 81 to 96), specificity of 92.3% (95% CI 89 to 95), positive predictive value of 71.8% (95% CI 60 to 81), and negative predictive value of 97.9% (95% CI 95 to 99).

Interobserver agreement between 2 readers was excellent (\(\kappa=0.80\)).

Discussion

Our imaging study is the first to show a strong in vivo association between CTA plaque ulceration and IPH as defined by MR-IPH. Given the increasing use of CTA to quantify stenosis, these results emphasize the importance of diagnosing plaque ulceration on CTA and recognizing their importance as a significant marker of stroke risk.

Plaque ulceration has long been recognized as a risk factor for neurological complications independent of stenosis. A histopathologic study comparing microscopic plaque morphology from patients with and without stroke symptoms involving patients from the Asymptomatic Carotid Atherosclerosis Study (ACAS) and NASCET studies showed that plaque ulceration was significantly more common in plaques taken from symptomatic patients than those without symptoms (36% versus 14%; \(P<0.001\)). Moreover, in patients with high-grade stenosis in the NASCET study, the presence of ulceration on conventional digital subtraction angiography increased the relative risks of stroke from 1.24 to 3.43. Furthermore, a large study comparing surface morphology with detailed histology showed that ulceration on digital subtraction angiography was strongly associated with both plaque rupture and IPH. Complementing these findings, our results confirm that CTA plaque ulceration can be used a surrogate marker for IPH and therefore as a surrogate risk factor for stroke.

Although the sensitivity of single-slice CTA for detection of plaque ulceration has previously been questioned, it is likely that with the advent of multislice technology and the improved higher spatial resolution, CTA will now show much better diagnostic performance. For instance, recent studies have shown high sensitivity and specificity of multidetector row CTA (up to 93.75% and 98.59%, respectively) for detection of plaque ulceration with respect to histology. Both Wintermark et al and de Weert et al showed that in vivo multidetector row...
fibrous tissue, hemorrhage, lipid core, and calcification on histological carotid endarterectomy specimens, and by directly matching CT images with the histological sections in an unblinded manner, calculated the range of HU for each component. The mean in vivo CT HU was 97.5 (95% CI 53.5 to 141.6), 46.4 (95% CI 6.6 to 86.2), 32.6 (95% CI −7.4 to 72.5), and 256.7 (95% CI 216.3 to 297.1) for hemorrhage, fibrous tissue, lipid core, and calcification, respectively. They also found significant overlap between the HU of different plaque components. In the second part of the study, they used the derived fibrous values to calibrate an automatic classifier to predict plaque components on CT images based on HU. Not unsurprisingly, CTA did not perform well in classifying plaque hemorrhage or lipids because of the overlap with fibrous tissue; the performance of CTA, however, improved slightly for detection of large plaque hemorrhage.

Similarly, de Weert et al characterized plaque components on histology and calculated HU of plaque components by matching corresponding CT and histological sections. The measured HU were 88 (SD 18), 25 (SD 19), and 657 (SD 16) for fibrous tissue, lipid core, and calcification, respectively. They calculated cutoff values of 60 HU for differentiation of lipid core and fibrous tissue and 130 HU for differentiation of fibrous tissue and calcification based on receiver operating characteristic analysis. They, however, found that calcification was a significant confounding factor because of beam-hardening artifacts and that quantification of the lipid core was only accurate in mildly calcified plaques. However, de Weert et al also found that hemorrhage and thrombus could not readily be identified from fibrous tissue and lipid core due to the overlap in plaque densities of these components; these data corroborate our findings.

Walker et al, using similar methodology to our study, compared plaque density on single-slice CTA to histology of excised carotid endarterectomy specimens. They found similar limitations regarding the use of CTA for plaque components. They found that the poor reliability of HU measurements for the prediction of the amount of lipid, fibrous tissue, or hemorrhagic components within an individual plaque may be explained, at least partly, by the great heterogeneity observed on histological examination of individual plaques. Walker et al argue that the main reason behind the poor performance of CTA was that the relatively homogeneous appearance of plaque on CT imaging did not adequately represent the plaque heterogeneity that was evident on microscopic analysis. We agree with Walker et al and accept this factor as 1 of the limitations of our study. Our approach to calculate mean density of the plaque on CTA images does not take into account the heterogeneity of the plaque and its different constituents and the mean HU values calculated is the overall mean HU value of the plaque. Because plaques have a homogeneous appearance on CTA, it is not possible to target a specific component such as hemorrhage with the naked eye and specifically place a region of interest over a particular component. More complex approaches such as the automatic classifier developed by Wintemark et al will be therefore necessary if CTA is to become useful for plaque characterization. However, these approaches are still very preliminary and not robust enough...
for clinical practice currently. It was the objective of our current study to test a simple, rapid, and practical method, easily performed within minutes, on commercially used workstations for plaque density measurements rather than the more complex approaches as used by Wintermark et al.

Finally, it is interesting that few studies have shown that plaques with low density on CTA were often found to have hemorrhagic components on histology.\(^{23,35}\) However, the low density seen on CTA is clearly not directly measuring the CT attenuation of hemorrhage but reflecting the presence of large necrotic lipid cores within the plaque. Although lipid cores and hemorrhage can be associated in vulnerable plaques, 1 feature is often seen without the other and it is possible that this association was found to be significant in these studies mainly because of the small sample size of the population studied. In our study, 36 of the cases of plaque hemorrhage were seen in plaques with low CT density (≤50 HU) compared with 20 cases of plaque hemorrhage in plaques with mixed density (50 to 120 HU). Despite moderate sensitivity and negative predictive value, the presence of low density on CTA had very poor specificity and negative predictive value for presence or absence of IPH.

One of the limitations of our study is that we used MR-IPH as the gold standard technique for detection of IPH. Histology of excised carotid specimens remains the gold standard, but this was not available in this study. However, histology is an ex vivo standard with its own limitations such as plaque damage during surgical excision. However, MRI is currently, in our opinion, the best in vivo modality for IPH and the technique used in this study has previously been validated in comparison with histology.\(^{11}\) High signal on T1 within the plaque has good sensitivity and specificity for IPH; previous studies and our own observations during this study have shown that high signal is not related to the presence of plaque calcium, a recognized but very unusual cause of high T1 signal on MRI.\(^{18}\) We did not perform additional high-resolution MRI to fully characterize plaque morphology in this study and limited ourselves to the identification of IPH. This would have required additional MRI sequences with additional weightings, requiring significantly more imaging time (≥30 minutes). These additional sequences would not have been possible currently at our institution in a busy clinical setting and in such a large number of patients. This puts into context the practicality and robustness of our technique with an acquisition time of 3 minutes only and which can easily be added to any clinical MRI stroke imaging protocol.

Finally, it was outside of the scope of this imaging-based study to correlate the imaging findings with clinical events. There are, however, multiple studies from several groups correlating positive MR-IPH studies with increased risk of stroke.\(^{14,17,24}\) More recently, Singh et al showed that the presence of MR-defined IPH predicted the risks of subsequent neurological complications in a cohort of asymptomatic men.\(^{35}\)

**Conclusions**

In our study, presence of CT plaque ulceration, but not mean CT plaque density, was useful for prediction of IPH as defined by our gold standard technique, MR-IPH. Recent studies suggest that CTA may have high accuracy in detection of plaque ulceration and we found high interobserver agreement for CT plaque ulceration.\(^{30}\) Given the increasing use of CTA to quantify carotid stenosis, this study emphasizes the importance of diagnosing plaque ulceration on CTA and recognizing their importance as a marker for plaque hemorrhage and thus as a potential surrogate marker for stroke risk.

**Disclosures**

None.

**References**

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颈动脉斑块出血的特征：
CT 血管造影和磁共振观察斑块内出血的研究
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背景和目的：本研究旨在评价 CT 血管造影 (CTA) 对磁共振明确的斑块内出血 (MR-IPH) 是否具有预测价值及其相关特点。

方法：三周内 167 例连续患者（平均年龄 69 岁，标准差 12.8；女性 58 例）进行 MR-IPH 和 CTA 检查。MR-IPH 作为检测斑块内出血的金标准，采用 1.5 T 神经血管相位序列成像序列，冠状位 T1 加权三维脂肪抑制成像。CTA 采用 4 层或 64 层 CT 机，在颈动脉狭窄、斑块密度及斑块溃疡方面与 MR-IPH 的检测结果进行盲法对比评估。斑块密度定义为颈动脉最大狭窄处及其上下两个平面的斑块平均衰减值。斑块溃疡定义为任何一个平面上斑块内至少 2 mm 深的龛影。

结果：颈动脉狭窄的程度越高，IPH 的发生率也相应提高。MRI-IPH 者，其 CT 平均斑块密度 (47 HU) 较没有斑块内出血 (43 HU) 者高 (P=0.02)。然而，斑块密度分布的明显重叠性限制了 CT 平均斑块密度值对于 IPH 的预测。CTA 显示的斑块溃疡对于预测 IPH 具有高敏感性 (80.8%-91.4%)、高特异性 (93%-92.3%)、高阳性预测值 (72%-71.8%) 和高阴性预测值 (95%-97.9%)。不同观察者对于 CTA 斑块溃疡的识别一致性较好 (κ=0.80)。

结论：对于 MR-IPH，CTA 显示的斑块溃疡，而非 CTA 平均斑块密度值，有助于预测 IPH。

关键词：颈动脉；颈动脉狭窄；计算机断层扫描；磁共振成像

手术治疗对症状性严重颈动脉狭窄病人的获益已得到明确证实 [1-3]。临床实践中，颈动脉血管再通的决定主要取决于超声和 / 或其它血管造影检查明确血管腔狭窄的程度。然而，对于无症状或症状性颈动脉中度狭窄的病人，血管再通较药物治疗的获益情况尚不明确 [1,4]。在这些病人中，仅根据狭窄程度决定是否行血管再通有时会很困难，因此需要更先进的方法进行风险分层，以选择最佳的治疗。

组织病理学研究显示：颈动脉粥样硬化斑块的某些形态学特征，如斑块内出血 (IPH)，破裂或溃疡性的纤维帽以及大的坏死性脂核等，与卒中风险的增加相关，而与血管腔的狭窄程度无关 [5,6]。从组织病理学角度看，新生血管的再生与斑块的进展密切相关，而且有可能是微血管机能不全部位 IPH 的主要来源。血管生成因子促进滋养血管的增生，导致成熟血管的形成和功能性毛细血管周围基底膜的缺失。上述过程可进一步导致红细胞从血管腔内漏出进入斑块内，从而引发炎症反应以及新一轮血管再生，循环往复，最终增加斑块破裂及溃疡形成的危险 [7]。

因此，当前研究者们对能更好在体识别易损斑块特征的影像学模式的发展饶有兴趣，以完善血管狭窄的评估。与离体颈动脉样本组织学作为金标准相比，许多研究小组已经证实 MRI 在识别颈动脉斑块形态质和量方面的可靠性 [8-13]。此外，根据美国心脏病学会的组织病理学分类标准，MRI 可以对颈动脉斑块进行分类。更重要的是，研究证实 MRI 可以对颈动脉斑块进行分类。更重要的是，研究证实 MRI 可以对颈动脉斑块进行分类。更重要的是，研究证实 MRI 可以对颈动脉斑块进行分类。
成的重脂肪抑制 MRI 技术对识别颈动脉斑块内的出血性产物极其敏感 [11,16,17]。这是一项成熟稳健的技术，很容易在市售 MR 机上进行操作。颈动脉IPH在抑制性背景上为高信号（图 1）。前期研究结果表明 MRI-IPH 对于颈动脉IPH的检测准确性极高，以组织学为金标准时，其敏感度达84%-100%。特异度为80%-88%[11,18]。这项技术的可重复性，包括不同观察者和同一观察者不同时间所得结论的变异性尺度亦相当好 [11]。在伴有相应症状的病人中，病灶同侧血管中出现 MR-IPH 识别的IPH阳性率明显高于对侧无症状侧血管的IPH阳性率（60% vs. 36%，χ² P < 0.001），这在血管中有中度狭窄时尤为明显 [19]。研究表明，在症状性和无症状性颈动脉轻中度狭窄的病人中，MRI 上IPH的存在与后续的神经性事件发生的风险增高相关 [17]。

MRI 在颈动脉斑块诊断方面已取得诸多进展，同样，多层 CT 血管造影技术 (CTA) 的发展也不容小觑。CTA 因其空间分辨率高、快速高效及普及性强，迅速成为一种检测颈动脉狭窄的非侵入性方法 [19]。然而，较 MRI 而言，应用 CT 识别易损斑块的研究仍相对较少。这并不令人觉得奇怪，因为 MRI 对软组织的识别具有固有的优势。不过，近年来一些研究发现 CTA 也许能提供关于颈动脉斑块形态学方面的一些信息 [20-23]。因此，本影像学研究的主要目的在于确定 CTA 是否也能像金标准 MRI-IPH 技术一样预测颈动脉IPH。

### 材料与方法

本项研究得到当地伦理委员会的批准 (研究号 411-2004)；此项回顾性研究免除了书面知情同意书的要求。

在我们的研究所，MR-IPH 常规作为临床评估卒中 / 短暂性脑缺血发作 MRI 扫描的附加序列，还包括常规头颅影像 (弥散 - 加权，水抑制反转恢复序列，T1 加权序列)，以及从主动脉弓到 Willis 环区域的对比增强 MR 血管成像。从前瞻性采集的数据库中，我们选取了 2003 年 12 月至 2008 年 12 月期间，所有在三周内接受 MR-IPH 和 CTA 检查的病人体影像学结果以评估颈动脉狭窄程度。接受临床评估中 MRI 扫描常规（包括增强 MR 血管造影）和/或 CTA 检查的病人由临床医生慎重选择，而在我们研究所，是否进行血管再通经常是结合 MR 血管影和 CTA 结果而决定，因为不同的非侵入性检查相结合可以将局部病变看得更清楚。

#### MR斑块内出血

**MR-IPH**在 1.5-T GE 双梯度 MR 机器上执行 (GE 医疗系统, Milwaukee, Wis)，使用 8 通道神经血管相位序列 (USA Instruments)，自由呼吸下冠状位 T1 加权磁化的三维梯度回波序列 ((TR 6.7 ms, TE 1.7 ms, TI 20 ms, 角度翻转 15°, 2 mm 层厚，视野 350×300 mm, 有效体素0.94×0.94×1 mm[ 插值 ]，信号激发次数=3)。该序列包括选择性的水激发射频脉冲的脂肪抑制序列 (Spectral Inversion at Lipids, SPECIAL; GE Healthcare)，选择有效翻转时间 (20ms) 使其血流信号为零。扫描时间是 3.5 分钟。

**MR-IPH**研究的评估涉及到在市售的图片存档交流系统 (PACS) 工作站 (AGFA Impax 4.5 版) 上读取冠状位原始数据及标准多层面轴位及矢状位图像重建。在不知道 CTA 结果的情况下，四位神经放射学家中的一位评阅 MR-IPH 是否发现IPH。在颈动脉狭窄处的血管壁内见高信号（至少较邻近胸锁乳突肌的信号强度高 2 倍）时，可诊断为IPH 阳性。记录每个病人颈动脉分叉处是否存在高信号，本项研究中，MR-IPH 作为诊断的金标准。
CT血管造影

自 2003 年 12 月至 2005 年 9 月，所有的 CT 检查均通过 LightSpeed Plus 4 层 CT 扫描机（GE Healthcare）进行。使用 7.5 mm/转及 1.25×1.25 mm 准直器（120 kVp，350 mA）的高速螺旋模式自 C6 至头顶扫描。自 2005 年 10 月至 2008 年 12 月，所有后续的检查都是使用 LightSpeed VCT 64 层 CT 扫描机（GE Healthcare）完成。64 层 CT 机上的影像采集范围是从主动脉弓至头顶部，0.625 mm 层厚（120 kVp，auto-ma）。静脉通路是通过肘前静脉置入 18 或 20 号血管导管。共 100-120 mL 碘海醇（欧乃派克 300; GE Healthcare）或碘克沙醇（威视派克 320; GE Healthcare）以 4-5 mL/s 的速度，延迟 17 s 或在肺动脉处使用 SmartPrep 软件 (GE Healthcare) 注入。

多层面图像后处理在 CT 工作站完成。冠状位和矢状位多平面图像重建层厚 7 mm，层间距 3 mm。所有的图像可在 Impax 4.5(Agfa Healthcare, Mortsel, Belgium)PACS 工作站上看到。图像最初是在 CTA 设置（窗宽 96, 150 HU）上评估，其后根据个体需求修改设置，以更好显示颈动脉管腔、血管壁及斑块，并减少致密钙化导致的硬化伪影。在不知道 MR-IPH 的情况下，CTA 盲法评估（1）狭窄的严重程度；（2）斑块密度；（3）斑块溃疡存在与否；并评价每个病人的双侧颈动脉。

根据北美症状性颈动脉内膜切除术试验（NA-SCET）的标准，我们使用轴位原始数据及图像多平面重建来分析血管狭窄程度 [2,24]。斑块密度的测量，采用在斑块非钙化区选取的一环形感兴趣区域 ( 图中白色画圈处) 及上述选取的 5 个层面的平均值。

统计学方法
所有的数据采用 Windows 系统的统计软件包 SPSS(12.0 版; SPSS, Chicago, IL) 进行分析。对于非参数型数据，使用 Mann-Whitney U 检验比较均数。P<0.05 认为有统计学意义。受试者操作特性曲线分析用于明确最佳斑块密度临界值，以区分有无 MR-IPH 定义的斑块内出血。根据斑块的平均 CT 衰减值，分为低密度 (0-50 HU) 和混合密度 (51-120 HU) 斑块 [23,25]。基于标准的 2×2 列联表，分别计算 CT 斑块溃疡预测 MRI 定义的 IPH 存在与否的敏感性、特异性、阳性预测值及阴性预测值，以及 95% 可信区间（CI）。Cohen κ 统计中 0-0.4，0.4-0.6，0.6-0.8，及 0.8-1 依次定义为差、适中、良好、优秀的一致率，被用来
评估不同阅片者之间结论的一致性。

结果

患者

167例连续病人(平均年龄69岁，标准差12.8；58名女性)在研究期间均经过MR-IPH及CTA检查。153例症状性病人有可疑卒中或短暂性脑缺血发作史，其余病人无临床症状。共检查分析了334条动脉。其中15条被排除(13条阻塞，2条既往有颈动脉内膜切除术史)，最终纳入研究的有319条动脉。MR-IPH显示出56例颈动脉IPH。

狭窄程度和IPH

颈动脉狭窄程度的分布如下：轻度狭窄193例(60.5%)，中度狭窄60例(18.8%)，重度狭窄66例(20.7%)。MR-IPH阳性组平均狭窄程度58%(标准差25)，MR-IPH阴性组平均狭窄程度20%(标准差26)(P=0.001，Mann-Whitney U检验)。图3显示了各种狭窄程度下出血性斑块病例的分布(如阳性MR-IPH组内)。这表明血管狭窄程度越大，斑块出血越常见，尽管也有不少的轻中度狭窄的血管也可见IPH发生。

CT平均斑块密度和IPH

MRI证实IPH存在者(47HU，标准差15)较IPH不存在者(43HU，标准差14)，CT平均斑块密度较高(P=0.02，Mann-Whitney U检验)。然而，斑块密度分布的明显重叠性提示平均斑块密度在区分有无IPH方面的重要意义有限。这一点也得到CT平均斑块密度区分IPH的受试者操作特性曲线(图4)所证实。

CT斑块溃疡和IPH

CT斑块溃疡对于MRI识别的IPH的诊断准确性极高。以上2×2列联表(表1)显示了两名CTA阅片者对于CTA上斑块溃疡的存在与否和MRI上IPH的存在与否的各自判断结果。

1号阅片者的诊断表现如下：敏感度80%(95% CI: 68-88)，特异性93%(95% CI: 89-96)，阳性预测值72%(95% CI: 59-81)，阴性预测值95%(95% CI: 92-98)。

2号阅片者的诊断表现如下：敏感度91.4%(95% CI: 81-96)，特异性92.3%(95% CI: 89-95)，阳性预测值71.8%(95% CI: 60-81)，阴性预测值97.9%(95% CI: 95-99)。

两名阅片者诊断结果的一致性良好(κ=0.8)。

讨论

本影像学研究表明CTA斑块溃疡和MR-IPH密切关联的在体研究。鉴于CTA在量化血管狭窄方面的广泛应用，此项研究结果强调了CTA在诊

![ROC曲线](image)

图4受试者操作特性曲线(ROC)分析用于明确最佳斑块密度临界值，以区分有无MR-IPH定义的斑块内出血。
断斑块溃疡方面的重要性和其在卒中风险评估方面的重要意义。

长期以来，斑块溃疡一直被认为是独立于血管狭窄外的导致神经系统疾病并发症的危险因素。一项比较症状性和无症状性病人的显微镜下斑块形态的组织病理学研究显示，在症状性病人中，斑块溃疡更常见（36%比14%，P<0.001），该研究的病人来自于无症状颈动脉粥样硬化研究（ACAS）和NA-SCET[26]。此外，NASCET研究中严重血管狭窄的病人，常规数字减影血管造影（DSA）发现存在溃疡后可将卒中的相对风险自1.24提高至3.43[27]。

更有一项比较斑块表面形态和详细的组织学研究显示，DSA上发现的斑块溃疡与斑块破裂和IPH的发生密切相关[28]。在此，我们的研究结果证实，CTA对于斑块溃疡的识别可以被用作提示IPH的替代指标，继而成为一项卒中风险的评估指标。

尽管CTA对于斑块溃疡的识别率遭到质疑[29]，但是随着多层技术的兴起，以及更高空间分辨率的进一步发展，如今CTA也能表现出更好的诊断价值[30]。例如，近来研究显示，多排CTA对于斑块溃疡的识别较之组织学诊断表现出更高的敏感度及特异度（分别为93.75%和98.59%）[30]。Wintermark等和de Weert等研究均显示，多排CTA对于斑块溃疡的识别性良好[28,31]，他们的研究结果与我们的相似。我们认为，与传统的数字减影血管造影（DSA）比较，CTA的明显优势在于不损失任何空间分辨率的情况下，能在任意一个垂直平面上进行图像重建。我们发现轴位的原始图像对于斑块溃疡的识别度较高，尤其当冠状位或矢状位上斑块钙化遮掩了斑块成像时（图5）。这一经验也在其它研究中有所报道；例如，Saba等研究显示轴位原始图像对于斑块溃疡的识别度高达90.9%，特异度达87.9%[32]。

本研究中，我们没有发现斑块平均密度是预测IPH（经MRI证实的）的有用因素。出血性和非出血性斑块的平均密度存在明显的重叠，且受试者操作特性曲线也没有显示合适的临界值，以用于在可接受的敏感度及特异度范围内预测IPH。这和之前的几项体内、体外研究的结果相一致。Wintermark等在组织学颈动脉内膜切除术的标本上比较了经鉴定的不同斑块成分，比如纤维组织、出血、脂质核心和钙化，然后在非盲法的情况下，将这些组织切片与CT图像进行匹配，得出各种斑块成分的HU值范围。出血、纤维组织、脂质核心和钙化成分的平均体内HU值依次为：97.5(95% CI: 53.5-141.6)，46.4(95% CI: 6.6-86.2)，32.6(95% CI: 7.4-72.5)和256.7(95% CI: 216.3-297.1)。他们也发现不同斑块成分的HU值存在明显重叠。在该研究的第二部分，他们使用衍生的纤维值校正自动分类器，以根据HU值预测CT图像上的斑块成分。让人意外的是，CTA不能很好地区分斑块出血和脂质成分，因为两者有重叠。然而，对于大的斑块出血，CTA的识别率还是略有改善。

类似的是，de Weert等也在组织学上区分斑块成分，并将组织学切片与相应的CT图像匹配，然后得出斑块成分的HU值。纤维组织、脂质核心和钙化成分的HU值依次为88(标准差18)，25(标准差19)，657(标准差16)。根据受试者操作特性曲线分析，他们计算出60 HU为区分脂质核心和纤维组织的临界值，130 HU为区分纤维组织和钙化的临界值。但是，他们也发现了由于存在硬化伪影，钙化是一个重要的混杂因素，只有在轻微钙化斑块中，脂
质核心的量化才是准确的。此外，de Weert 等还发现，出血和血栓不能很好地与纤维组织和脂质核心区分开来，因为这些成分的斑块密度均有重叠。以上研究数据也证实了我们的研究结果。

Walker 等使用了和我们类似的研究方法，比较了单层 CTA 的斑块密度和离体的颈动脉内膜切除术样本的组织学 [29]。他们也发现 CTA 对于斑块成分识别的类似局限性。他们发现，根据 HU 测量值预测单个斑块内脂质、纤维组织或出血成分的可靠性较低，这至少部分可以用组织学上个体斑块极大的异质性来解释。Walker 等还提出，CTA 对于斑块成分鉴别的有限性主要是因为 CTA 图像上斑块外观的相对均一性不足以反应显微镜分析下斑块的异质性 [29]。然而，这些尝试和检测手段也都是很初步的，其稳定性尚不能应用于临床实践。我们当前研究的目的是：使用一种简单、快速、实用的方法，在市售的工作站上测量斑块密度，而不是像 Wintermark 等所用的较复杂的检测方法。我们同意 Walker 等的观点，也认为这是本研究的局限性之一。我们在计算 CTA 图像上平均斑块密度时并没有将斑块的异质性及斑块的不同成分考虑在内，我们计算的斑块平均 HU 值为整个斑块全部的 HU 值的平均。因为 CTA 上斑块外观相对均一，我们不可能用肉眼区分某个特定的斑块成分，例如出血，也就不可能对某一个特别的成分设立感兴趣区域。如果 CTA 成为斑块识别的有用工具，那么许多更复杂的检测手段，例如 Wintermark 等发明的自动分类器，将成为必需 [29]。然而，这些尝试和检测手段也都是很初步的，其稳定性尚不能应用于临床实践。我们当前研究的目的是：使用一种简单、快速、实用的方法，在市售的工作站上测量斑块密度，而不是像 Wintermark 等所用的较复杂的检测方法。

最后，有趣的是，很少研究显示 CTA 上低密度的斑块常常被组织学证实其内含有出血成分 [23,33]。然而，CTA 上所见的低密度不能直接用来测量斑块出血成分的 CT 增益值，但是可以反映斑块内大的坏死性脂核的存在。尽管脂核和出血在易损斑块中相关联，但是两者并不一定是同时存在的，既往研究中发现两者紧密相关，这主要是因为研究样本量小。在我们的研究中，CT 显示低密度斑块（≤50 HU）中有 36 例斑块出血，而混合密度斑块（50-120 HU）中有 20 例斑块出血。CTA 上低密度对于IPH 识别的特异性和阴性预测值较差。

本研究的另一个局限性在于我们使用 MR-IPH 作为检测 IPH 的金标准。离体颈动脉样本组织学分析也是金标准，但此项研究中不适用。体外样本组织学检查也有其自身的限制，比如在手术切除过程中斑块受损。鉴于此，我们认为 MRI 目前是体内检测 IPH 的最佳手段，而且本研究中应用的技术也已在之前与组织学对比的研究中得到验证 [21]。T1 上斑块内高信号对于识别 IPH 有很好的敏感性和特异性；既往研究以及本研究中的观察显示，高信号与斑块钙化无关，斑块钙化是不常见的但可能导致 MRI T1 高信号的原因 [18]。我们没有继续采用高分辨率 MRT 来充分观察斑块形态，这也限制了对 IPH 的识别，因为这需要更多的 MRI 序列，更多权衡序列，以及更长扫描时间（≥30 分钟）。这些额外的序列不适用于当前我们这个为繁重临床工作而设计的研究所。我们的技术具有实用性和可靠性，仅需 3 分钟的扫描时间，可以很方便地应用于任何一项 MRI 检测中影像学检查流程中。

下一步，将影像学发现与临床事件相关联，已超出了本研究的范围。然而，其他研究小组的多项研究结果显示 MR-IPH 阳性结果与卒中风险的升高相关 [14,17,34]。近来，Singh 等对无症状性男性病人进行的研究结果显示，MR 明确的 IPH 可预测继发的神经系统并发症 [35]。

结论

本研究中，CT 上斑块溃疡的存在，而不是平均斑块密度，对于金标准 MR 明确的 IPH 有预测价值。近来研究提示 CTA 对于斑块溃疡的识别准确性高，并且我们发现不同的阅片者对于斑块溃疡识别的一致性良好 [30]。鉴于 CTA 在颈动脉狭窄量化方面的越来越广泛的应用，本项研究强调 CTA 诊断斑块溃疡的重要性，是斑块出血的重要标志物，因此也可作为卒中风险评估的潜在替代指标。

参考文献


