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## High Resolution MRI: An Emerging Tool for Evaluating Intracranial Arterial Disease

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### Keywords

intracranial stenosis; magnetic resonance imaging; cerebrovascular disease; plaque composition

### Introduction

Atherosclerosis occurs in diverse vascular beds and may result in tissue ischemia. Current understanding of atherosclerotic disease has been advanced by imaging techniques such as high-resolution magnetic resonance imaging (HRMRI) studies of the coronary and carotid arteries. In these vessels, atherosclerotic plaque components can be visualized to risk-stratify patients, select treatments and advance our understanding of atherosclerosis pathophysiology in vivo. These imaging techniques are now being applied to evaluate intracranial arterial disease, both atherosclerotic and non-atherosclerotic. This review highlights the mechanisms by which intracranial atherosclerotic disease (ICAD) causes ischemia, the potential of HRMRI for identifying intracranial arterial pathology, the limitations of HRMRI in the intracranial circulation, and future applications of HRMRI for ICAD.

### High Resolution MRI of ICAD

Image quality in MRI depends on several factors (e.g. slice thickness, field-of-view, signal-to-noise ratio, matrix size, magnetic field strength, etc.), but the term ‘high-resolution MRI’ is not well defined. In this review, the operational definition of HRMRI is limited to MR acquisitions using clinically available 1.5 – 3.0 Tesla magnetic field strengths targeted to intracranial arterial pathology that are of sufficient quality to visualize the arterial wall, separate from the lumen, of the proximal circle of Willis vessels. HRMRI can be accomplished at 1.5T by limiting the field of view to focus on a single vessel or point of interest, but higher field strength at 3T has many advantages over conventional (1.5T) MRI. Image acquisition is faster<sup>1</sup>, there is increased signal-to-noise<sup>2</sup> and contrast-to-noise ratios, with better image quality<sup>3</sup> for black-blood imaging. The increased signal and contrast that

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3T provides improves the detection of complex atherosclerotic plaque<sup>4</sup> and can identify plaque components in larger arteries<sup>5</sup>. Two dimensionally acquired HRMRI is time-consuming and must be monitored by a Neuroradiologist to ensure adequate sampling of the lesions of interest. HRMRI using three dimensional (isotropic) acquisitions permits imaging of ICAD with shorter scan times and generates better quality images.

## Mechanisms of Stroke in ICAD

The primary mechanisms by which ICAD results in ischemic stroke are: plaque rupture, occlusion of small penetrating arteries, and hypoperfusion. Plaque rupture exposes the thrombogenic core to clotting factors and the resulting thrombus either occludes the artery locally or embolizes distally. ‘Vulnerable plaques’ (those with a large lipid core, intraplaque hemorrhage, or a thin or ruptured fibrous cap) are prone to rupture and cause myocardial infarction due to coronary artery atherosclerosis<sup>6, 7</sup>. The second mechanism, unique to ICAD, is growth of plaque over the ostia of penetrating arteries resulting in occlusion, described by Caplan as ‘branch atheromatous disease’<sup>8</sup>. Lastly, high-grade narrowing or occlusion of the lumen may lead to hypoperfusion of the distal brain territory, particularly in patients with inadequate collateral flow<sup>9</sup>.

Typically, the mechanism of stroke is inferred from the clinical presentation and the pattern and size of infarction. But without detailed knowledge of plaque location, severity and morphology, determination of stroke mechanism cannot be directly determined. HRMRI may provide this information and thereby clarify the mechanism of stroke (Table 1). For example, an intracranial plaque with HRMRI features of intraplaque hemorrhage and a ruptured fibrous cap in a patient with downstream ischemia is likely associated with artery-to-artery embolism, whereas a stable plaque with a large amount of fibrous tissue and small lipid core resulting in high-grade stenosis may cause hypoperfusion. Thus, HRMRI may directly determine stroke mechanism and play a role in selecting secondary prevention therapies (e.g. patients with hypoperfusion may benefit from intracranial revascularization procedures that may not benefit patients with artery-to-artery embolism). Future studies of stroke prevention may be enhanced by patient selection based on mechanism using HRMRI.

## Conventional ICAD Imaging Compared to HRMRI

### Degree of Stenosis

Conventional imaging of ICAD focuses on the vessel lumen. Digital subtraction angiography (DSA), computerized axial tomography angiography (CTA), and magnetic resonance angiography (MRA) identify luminal patency and stenosis<sup>10</sup> while TCD indirectly estimates luminal stenosis by measuring blood flow velocity<sup>11</sup>. In contrast to these methods, HRMRI allows direct visualization of the vessel wall, permitting assessment of both luminal stenosis and features of vessel wall pathology<sup>12, 13</sup>, which can aid diagnostic specificity and sensitivity.

### Determining Etiology of Stenosis

Intracranial stenosis can be caused by diverse pathologies (e.g. atherosclerosis, inflammation, vasospasm), with diverse treatment implications. While conventional imaging detects luminal narrowing, different pathologies can result in similar patterns of stenosis. Currently, differentiating causes of intracranial stenosis require invasive testing such as a spinal tap or brain biopsy. However, HRMRI may non-invasively differentiate between etiologies of intracranial stenosis by identifying plaque components or unique enhancement patterns. Swartz et al. studied post-contrast HRMRI images in 37 patients with intracranial stenosis and found that symptomatic atherosclerotic vasculopathies (ICAD) had eccentric wall thickening and enhancement, but inflammatory vasculopathies had concentric

thickening and enhancement patterns<sup>14</sup>. Along those lines, idiopathic Moya-moya disease was associated with luminal narrowing with neither wall thickening nor enhancement<sup>14</sup> and vasospasm due to non-inflammatory processes (Reversible cerebral vasoconstriction syndrome) was associated with concentric wall thickening without enhancement<sup>15</sup>. HRMRI has identified a Moya-moya phenomenon due to atherosclerosis<sup>16</sup> and distinguished between atherosclerosis and basilar artery hypoplasia<sup>17</sup> by identifying plaque components.

### Detection of Non-stenotic Plaques

While conventional imaging can detect luminal narrowing, lumen diameter may be maintained in atherosclerotic arteries through compensatory vascular remodeling that results in minimal stenosis detectable by conventional imaging<sup>18</sup>. This process of 'positive' or 'outward' remodeling (Figure 1) results in plaque rupture in acute coronary syndromes<sup>19</sup> and has been reported in ICAD<sup>20-23</sup>. HRMRI can identify remodeling without stenosis that may be clinically important, but missed by conventional imaging. For example, HRMRI showed plaque in MCA and basilar arteries that appeared normal on MRA, but resulted in stroke due to occlusion of penetrating arteries<sup>24-26</sup>. In some cases, ICAD was identified in the setting of small lacunar strokes that would previously have been attributed to lipohyalinosis of the penetrating arteries<sup>26-28</sup>.

### Identification of Plaque Components

HRMRI can reliably identify plaque features in other vascular territories and shows promise for use in ICAD (Table 2). In other vascular beds, identification of atherosclerotic plaque components has helped risk-stratify patients and select treatments. Using imaging, clinical, and pathological correlations, studies of coronary and carotid artery disease have identified features that indicate plaque vulnerability: intraplaque hemorrhage, lipid core size, and fibrous cap thickness. These vulnerable plaque characteristics are also present in ICAD<sup>32</sup>, but are less well studied.

### Intraplaque Hemorrhage

Intraplaque hemorrhage (IPH) from rupture of plaque microvessels causing accumulation of erythrocyte membranes, deposition of cholesterol, macrophage infiltration and enlargement of the necrotic core results in atheroma growth and plaque destabilization<sup>7</sup>. In patients with extracranial carotid stenosis, HRMRI-defined IPH correlates well with pathological specimens<sup>33, 34</sup> and IPH is associated with stroke symptoms in both cross-sectional<sup>35</sup> and prospective observational studies<sup>36-38</sup>.

While HRMRI-defined IPH is a well-described predictor of ischemic events due to carotid stenosis, it is an emerging area of research in ICAD. One case report showed HRMRI-defined IPH in a patient with symptomatic ICAD<sup>29</sup>. Another case series using HRMRI identified intracranial IPH in 2 of 13 patients with ischemic stroke<sup>22</sup>. In the first systematic attempt to associate IPH with recent symptoms in ICAD in 107 patients with HRMRI of MCA stenoses, the prevalence of IPH in symptomatic patients (19.6%) was higher than in asymptomatic patients (3.2%)<sup>30</sup>. The prevalence of IPH in other (basilar, ICA, vertebral) intracranial arteries has not been systematically studied. The timing, initial appearance, and duration that IPH is detectable on HRMRI may be critical factors that require additional study. While these data suggest an association between IPH and recent symptoms, only prospective follow-up will determine if IPH predicts high risk.

### Lipid Core

A large amount of lipid within the necrotic core of a plaque is another sign of plaque vulnerability<sup>6, 35</sup>. HRMRI measurement of lipid-necrotic core area in carotid plaques

correlates well with pathology<sup>39</sup>. A large lipid core area relative to the plaque area on HRMRI has also been associated with stroke symptoms in cross-sectional<sup>35</sup> and prospective studies<sup>38</sup> of patients with carotid stenosis.

In patients with ICAD, the presence and amount of lipid core within plaque is not well reported. Turan et al. presented a case series of 8 intracranial plaques (MCA and basilar) evaluated using HRMRI, wherein the presence of lipid core was visualized in 75%<sup>40</sup>. However, the relationship between the presence or amount of lipid within the plaque and prognosis requires study.

### Fibrous Cap

The fibrous cap is a layer of connective tissue covering the lipid-necrotic core<sup>41</sup>. In patients with carotid stenosis, pathology specimens show that a thin fibrous cap overlying a lipid core is a feature of plaque vulnerability and that subsequent rupture of the fibrous cap exposes the thrombogenic lipid core to circulating blood, resulting in thromboembolism<sup>42</sup>. Thick fibrous caps are less prone to rupture<sup>6</sup>. HRMRI can identify fibrous cap characteristics (thin, thick, or ruptured) in carotid arteries<sup>43-45</sup>. HRMRI of carotid plaques showed patients with recent stroke symptoms had significantly more ruptured caps (70%) and thin caps (50%) than thick caps (9%), suggesting fibrous cap status may also be a predictor of stroke risk<sup>46</sup>.

While more difficult to visualize, fibrous caps have also been identified in patients with ICAD<sup>31, 40</sup>, but there has been no systematic study of the relationship between fibrous cap status and recent stroke symptoms.

### Limitations of HRMRI

Despite the advantages of HRMRI ICAD imaging, this technique currently has limitations. Imaging characteristics in ICAD have not yet been correlated with pathological specimens because, while HRMRI of the carotids can be correlated with endarterectomy specimens, intracranial vessels are not accessible to pathology sampling in live patients. Therefore, the signal characteristics of intracranial plaque components can only be extrapolated from carotid HRMRI studies at present. Pathological correlation with HRMRI signal characteristics will be a key step in validating this technique in ICAD.

Additional challenges in HRMRI ICAD imaging are due to the tortuosity and variable course of the intracranial arteries. 3D image acquisition and the ability to reconstruct images in multiple planes may be used to 'straighten' tortuous or angled arteries to provide a more accurate representation of the lesion. Another challenge is the small size (2.0-5.0 mm) and depth of the intracranial vessels, which require relatively long acquisition times, making HRMRI imaging difficult due to patient motion artifact and limitations in resolution. In the future, motion-correction algorithms may be used to evaluate challenging patients.

HRMRI is limited by its cost and availability. The average Medicare reimbursement for a brain MRI is \$533<sup>47</sup>, but as ICAD imaging is not standard of care there is currently no reimbursement for the extra scan time. A recent survey reported that MRI was available at 66% of hospitals, with small and rural hospitals having less access<sup>48</sup>. On the other hand, 3T MRI is available at most large academic centers and is the fastest growing MR market segment<sup>49</sup>.

Finally, a disadvantage of higher field strength is the increased specific absorption rate, which results in the potential for more tissue heating, raising safety concerns. While not as much of a concern with 3T, clinical imaging at 7T is performed in a few centers and its use

is strictly limited to patients without any possibility of metal implants, such as cardiac stents or metal clips, to prevent tissue injury<sup>50</sup>.

## Future Directions of Research

The use of HRMRI to characterize ICAD is an emerging field and has built upon cardiac and carotid studies. IPH, fibrous cap status, and large lipid core area are plaque components that can be detected in ICAD and have been associated with stroke in extracranial carotid plaques. Rigorous study of the prognostic value of HRMRI in ICAD will need to establish the reliability of HRMRI for detection of plaque features, the prevalence of plaque features, and describe the temporal relationship between the appearance and/or resolution of imaging abnormalities and ischemic symptoms.

Demonstrating that HRMRI ICAD plaque features are predictors of stroke could lead to changes in clinical management. Currently, conventional angiographic imaging is used to identify ICAD patients at highest risk of recurrent stroke, such as those with severe (70-99%) stenosis<sup>51</sup> and poor collateral flow<sup>9</sup>. However, HRMRI may non-invasively identify other predictors of recurrent symptoms. For example, a patient with 60% stenosis and thin fibrous cap may be at higher risk of recurrent stroke than a patient with 80% stenosis and an intact thick fibrous cap. While the association between stroke risk and HRMRI plaque features is not yet proven, the ability to identify plaque characteristics may enhance future risk stratification and individualization of treatment. Jiang et al. have already described cases of ICAD patients in which HRMRI plaque imaging helped guide the endovascular treatment<sup>52</sup>. In addition, the HRMRI identification of plaque components in arteries appearing normal using conventional imaging techniques may reclassify patients previously thought to have cryptogenic or lacunar stroke and thereby change their management.

Demonstrating that HRMRI ICAD plaque features are predictors of stroke could lead to changes in patient selection for future clinical trials that evaluate new prevention treatments, such as using IPH as an entry criterion rather than severe stenosis. Establishing that ICAD plaque features are predictors of atherosclerotic progression could also lead to the use of plaque features as surrogate markers to evaluate therapies targeted at preventing progression of atherosclerosis, such as statins, as has been done with carotid plaque features<sup>53</sup>.

In the future, HRMRI in ICAD may also lead to new understanding of the mechanisms of atherosclerotic pathology. The use of novel, targeted MRI contrast agents may allow visualization of biological processes such as angiogenesis or inflammation within the plaque wall to identify 'vulnerable' plaques using HRMRI. For example, Gadolinium-loaded paramagnetic nanoparticles<sup>54</sup> have been used to identify neovascularization in animal models. As these novel technologies continue to be developed and studied in other vascular territories, their application in ICAD will also warrant study.

## Conclusion

HRMRI of intracranial arteries is an emerging tool that can help identify stroke mechanisms, determine the degree and etiology of stenoses, identify non-stenotic plaques, and identify potentially high-risk plaque components. These plaque characteristics are not visualized with conventional luminal imaging and may be important predictors of stroke. Additional research is needed to establish the reliability of HRMRI for detection of high-risk plaque features in ICAD, which may set the stage for prospective studies to determine the predictive power of HRMRI in ICAD and for future therapeutic trials to investigate new treatments for this high-risk disease.

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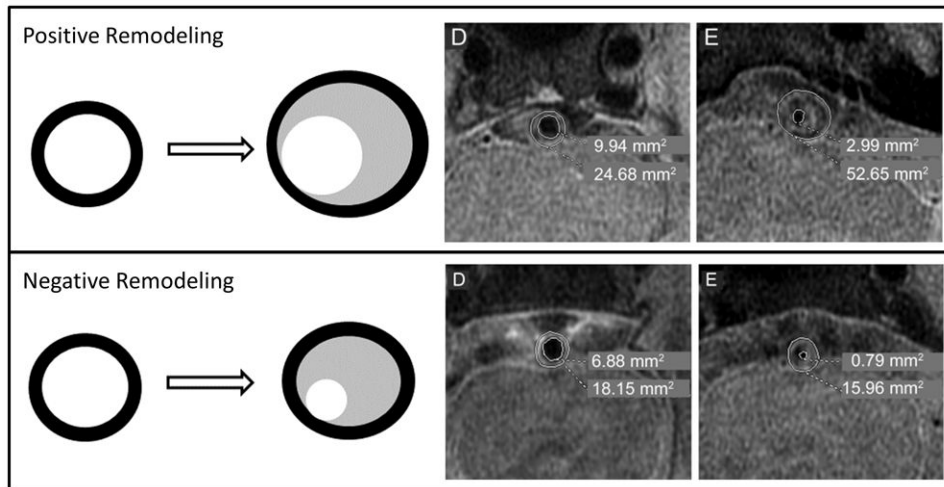


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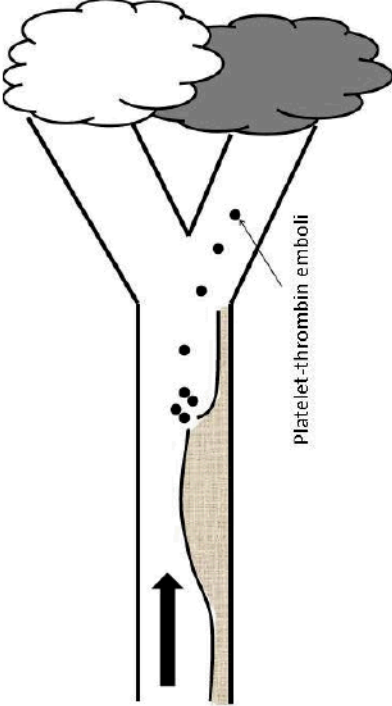
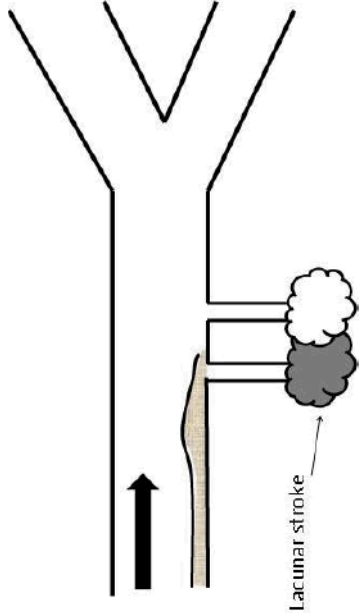
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**Figure 1. Illustration of positive (outward) and negative (inward) remodeling in ICAD**  
**Positive Remodeling:** Top panel (left) shows diagram of positive remodeling: the vessel wall (black) expands outward with accumulation of lipid (gray) and may or may not decrease the lumen (white). Top panel (right) shows an example of positive remodeling in a case of severe basilar stenosis (reproduced from Ma et al. Neurology, 2010<sup>20</sup>). At the level of maximal stenosis (E), the wall area is increased and the lumen area is decreased relative to a distal basilar segment (D). **Negative remodeling:** Bottom panel (left) shows diagram of negative remodeling: the vessel wall (black) does not expand outward with accumulation of lipid (gray) and results in decrease in the lumen (white). Bottom right panel shows an example of negative remodeling in a case of severe basilar stenosis (reproduced from Ma et al. Neurology, 2010<sup>20</sup>). At the level of maximal stenosis (E), the wall area is slightly decreased and the lumen is decreased relative to a distal basilar segment (D).

Table 1

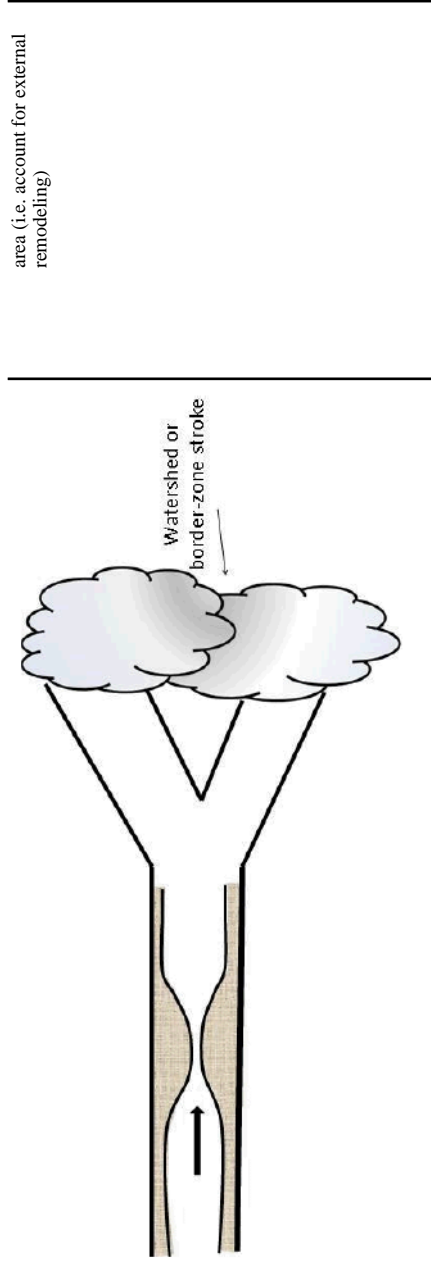
Use of HR MRI to determine mechanism of ischemia in ICAD

Mechanism of ischemia	HR MRI identification of mechanism	Impact on stroke care
<p>Plaque rupture with local occlusion or artery-to-artery embolization</p> 	<ul style="list-style-type: none"> <li>• Identification of characteristics consistent with plaque rupture (e.g. contrast enhancement of plaque or intraplaque hemorrhage)</li> </ul>	<ul style="list-style-type: none"> <li>• Consider more aggressive antiplatelet use to prevent clot propagation and statins to stabilize plaque</li> </ul>
<p>Plaque overgrowth of perforator artery ostia</p> 	<ul style="list-style-type: none"> <li>• Identification of plaque location within arteries, whether or not conventional imaging identifies stenosis</li> </ul>	<ul style="list-style-type: none"> <li>• Determine that a 'lacunar' stroke is due to ICAD</li> <li>• Determine that a cryptogenic stroke is due to ICAD</li> </ul>
<p>Hypoperfusion through stenotic artery</p>	<ul style="list-style-type: none"> <li>• Identification of relative lumen size by direct measurement of vessel area compared to lumen</li> </ul>	<ul style="list-style-type: none"> <li>• More accurately determine severity of stenosis and components of plaque, which may result in selection of</li> </ul>

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Mechanism of ischemia	HR MRI identification of mechanism	Impact on stroke care
 <p>The diagram illustrates the mechanism of ischemia. It shows a cross-section of a blood vessel with a significant stenosis (narrowing) in the center. An upward-pointing arrow indicates the direction of blood flow from the stenosis. Above the vessel, two shaded, cloud-like regions represent watershed or border-zone strokes, which occur in the areas between major arterial territories. A label 'Watershed or border-zone stroke' with an arrow points to these regions.</p>	area (i.e. account for external remodeling)	alternative treatments (e.g. angioplasty)

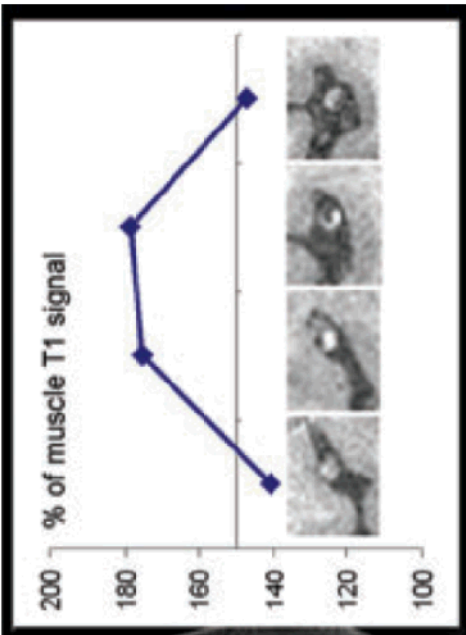
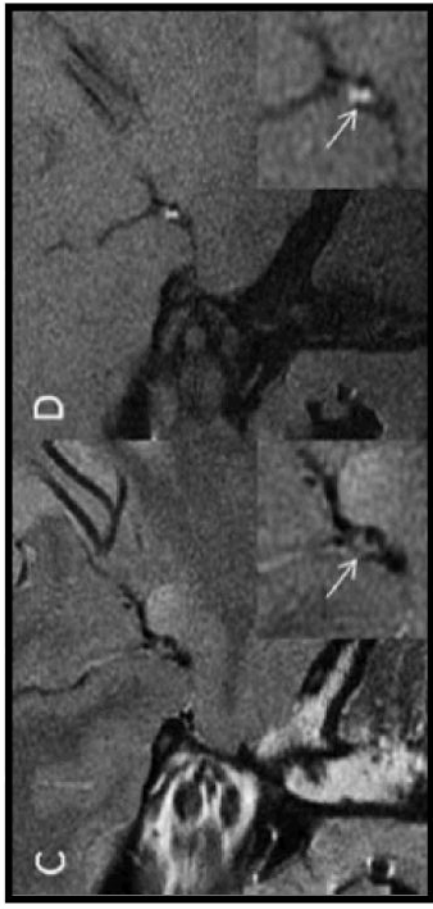
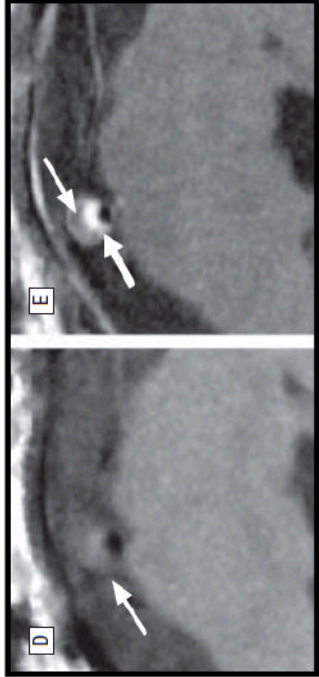
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Table 2

Examples of suspected plaque components identified by HR MRI in ICAD

<p>Intraplaque Hemorrhage</p>	<p>Sequential T1 sagittal images of the MCA showing intraplaque hemorrhage defined as &gt;150% of medial pterygoid muscle signal (2<sup>nd</sup> and 3<sup>rd</sup> images). (Turan et al., J Neuroimag, 2009<sup>25</sup>)</p>  <table border="1" data-bbox="349 1165 812 1795"> <caption>% of muscle T1 signal</caption> <thead> <tr> <th>Image</th> <th>% of muscle T1 signal</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>~140</td> </tr> <tr> <td>2</td> <td>~175</td> </tr> <tr> <td>3</td> <td>~180</td> </tr> <tr> <td>4</td> <td>~145</td> </tr> </tbody> </table>	Image	% of muscle T1 signal	1	~140	2	~175	3	~180	4	~145	<p>Sagittal T2 (panel C) and T1-weighted fat-suppressed (panel D) imaging of symptomatic MCA. Lower right corner shows central region magnified. IPH is defined as bright signal on T1 fat-suppressed images (arrow in panel D). (Xu et al, Annals Neuro 2012<sup>30</sup>)</p> 
Image	% of muscle T1 signal											
1	~140											
2	~175											
3	~180											
4	~145											
<p>Fibrous cap rupture and lipid core</p>	<p>T1 weighted axial images of basilar artery showing ruptured fibrous cap. Panel D is without contrast showing plaque (arrow). Panel E is post-contrast showing isointense lipid core (thin arrow) and plaque enhancement (arrow). (Vergouwen et al. Arch Neuro 2011<sup>31</sup>)</p> 	<p>Axial images of basilar artery stenosis (T1-weighted pre- and post-contrast, T2-weighted, and FLAIR) and normal volunteer FLAIR. Row A is unmarked and row B shows plaque features marked. Lipid is isodense on T1 and hypodense on T2 (white +). Ruptured fibrous cap is indicated by enhancement (black *). Artery wall to CSF boundary (white dash line) is not visualized in normal artery on FLAIR. (Turan, 2012 submitted)</p> 