Identifying vulnerable carotid plaques in vivo using high resolution magnetic resonance imaging–based finite element analysis


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Object. Individuals with carotid atherosclerosis develop symptoms following rupture of vulnerable plaques. Biomechanical stresses within this plaque may increase vulnerability to rupture. In this report the authors describe the use of in vivo carotid plaque imaging and computational mechanics to document the magnitude and distribution of intrinsic plaque stresses.

Methods. Ten (five symptomatic and five asymptomatic) individuals underwent plaque characterization magnetic resonance (MR) imaging. Plaque geometry and composition were determined by multisequence review. Intrinsic plaque stress profiles were generated from 3D meshes by using finite element computational analysis. Differences in principal (shear) stress between normal and diseased sections of the carotid artery and between symptomatic and asymptomatic plaques were noted.

Results. There was a significant difference in peak principal stress between diseased and nondiseased segments of the artery (mean difference 537.65 kPa, p < 0.05). Symptomatic plaques had higher mean stresses than asymptomatic plaques (627.6 kPa compared with 370.2 kPa, p = 0.05), which were independent of luminal stenosis and plaque composition.

Conclusions. Significant differences in plaque stress exist between plaques from symptomatic individuals and those from asymptomatic individuals. The MR imaging–based computational analysis may therefore be a useful aid to identification of vulnerable plaques in vivo. (DOI: 10.3171/JNS-07/09/0536)

KEY WORDS • carotid artery • finite element analysis • magnetic resonance imaging • vulnerable plaque

CAROTID endarterectomy is established as a definitive treatment option for individuals with severe carotid atherothrombosis.2,18 Currently, selection for surgery is based on stratification by degree of endoluminal stenosis, despite evidence that this does not reflect disease burden, composition, or activity,1,15,23,24 factors thought to be more accurate predictors of future ischemic events. Histological data suggest that plaques at high risk of rupture are characterized by large necrotic lipid cores with thin overlying fibrous caps, together with an abundance of inflammatory cells.22 Recent advances in ultrasonography and MR imaging have allowed these characteristics to be visualized in vivo.5,7,8,26 In particular, contrast-enhanced MR imaging appears useful for identifying plaque inflammation in vivo.12,30 Thromboembolism is a predictable consequence of plaque rupture, which itself represents structural failure of a component(s) of the diseased vessel. It is therefore possible that the biomechanical properties of atheromatous lesions may significantly influence the probability of rupture. Recognizing which features contribute to this increased vulnerability may improve risk stratification and allow aggressive interventions to be targeted to plaques at particularly high risk of rupture. Previously, such biomechanical profiling had relied on FEA of ex vivo histological or imaging data to generate 3D geometric vessel wall stress maps. The main disadvantage of using ex vivo–derived data relates to the geometric distortion of the plaque, as the luminal morphological and geometric relationships of the different plaque constituents will significantly influence the overall stress within the plaque. The advent of high-resolution imaging techniques such as intravascular ultrasonography and MR imaging has allowed detailed morphological and structural characterization of carotid plaques to be performed in vivo. The derivation of vessel geometries from in vivo images avoids structural alterations to the vessel wall and constituents from ex vivo processing, which can alter the fractional volume and morphological configuration as well as the material properties of the plaque components. This technique may provide a more accurate quantitative assessment of plaque stress.
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In this study we describe the role of in vivo MR imaging–derived plaque composition and geometry to determine mechanical stresses within carotid plaques using finite element analysis/modeling and evaluate whether symptomatic carotid plaques have higher internal stresses than asymptomatic plaques.

Clinical Material and Methods

Patient Population

In vivo multisquence MR imaging data were obtained in 10 nonconsecutive (five symptomatic and five asymptomatic) individuals recruited from a specialist neurovascular clinic after giving informed consent to participate. Eight of the individuals were men, and the median age was 73.5 years (range 55–79 years). The median time from onset of symptoms in the symptomatic cohort was 12 weeks (range 7–18 weeks), and all individuals had suffered either a retinal or cortical transient ischemic attack. Asymptomatic patients were recruited following referral for investigation of an incidentally discovered carotid bruit, or if they were known to have contralateral disease following previous surgery for symptomatic internal carotid artery stenosis. There was no significant difference in the ultrasonography-measured severity of stenosis between the symptomatic (median 72.5%) and asymptomatic (median 68.5%) groups (p = 0.34). At this point in the study, the images were made anonymous.

Multisquence MR Imaging

Imaging studies were performed using a 1.5-tesla whole-body system (CVi; GE Medical Systems) using a custom-designed four-channel phased array surface coil (Flick Engineering Solutions BV) that was wrapped around the neck and secured by a soft cervical collar. Additionally, the patient’s head was placed in a foam headrest to minimize motion artifact. After an initial coronal localizer scan, an axial 2D time of flight MR angiogram study was performed to identify the location of the carotid bifurcation and region of stenosis. Axial images were acquired through the common carotid artery, 6 mm (two slices) below the carotid bifurcation to a point 6 mm (two slices) distal to the extent of the stenosis identified on the time of flight sequence. This method ensured that the entire plaque was imaged and also facilitated image coregistration. The following 2D, electrocardiography-gated, blood-suppressed, fast spin echo pulse sequences were used: intermediate T2-weighted (TR 2*RR, TE 46 msc); with fat saturation, STIR (TR 2*RR, TE 46 msec, TI 150 msec), and T1-weighted (TR 1*RR, TE 7.8 msec) images. The pixel size was 0.39 × 0.39 × 3 mm in all cases. The field of view was 10 cm and the matrix size was 256 × 256. The MR imaging–based compositional analysis was performed using a previously published component classification algorithm based on multisquence MR imaging.21

Histological Analysis

Histological analysis was performed as previously outlined.21 The main purpose of the histological section was to confirm the constituent composition determined by multisquence MR imaging review.

Reconstruction of Vessel Geometry

For each image the vessel geometry was reconstructed from the in vivo MR imaging sequence images with the clearest vessel boundary demarcations; this was the STIR sequence image in seven cases and the intermediate T2-weighted sequence in the remaining cases. For one representative data set, all images were used to generate slice by slice vessel geometries which spanned the entire length of the vessel, including regions not obviously depicting plaques at either end of the vessel. This was done to determine the stress profile in relation to the degree of vessel stenosis along the length of the vessel (longitudinal profile) and refine MR imaging slice selection for FEA. Thereafter, only the three MR images from the center of the data set, depicting plaques, were used to generate geometries and meshes for FEA.

The following method was used: Images were viewed on the commercially available eFilm Workstation viewer (Di-com Solutions) and magnified 200%. Geometric contours of the vessel lumen and outer boundary were manually traced using a handheld digital tracing pen device (Wacom 3), which outlines a series of points along the boundary, which were then connected using the software program. On average for the outer vessel boundary, there were approximately 200 individual nodes. A similar method was used to trace out the perimeters of the internal regions within the vessel wall (lipid core, fibrous cap, and calcifications). This was performed when possible with the aid of the corresponding histological section.

Assignment of Material Properties

There have been very few studies in which authors have addressed the mechanical properties of the different materials that compose atheromatous plaque,19 and many types of material models have been proposed to describe the stress–strain behavior of the arterial wall. However, as only small to medium strains are observed (< 10%) in arterial walls in the physiological range, the linear component of experimental data was taken and the plaque components modeled as a Hooke linear elastic, isotropic, and incompressible (nearly) material, to simplify the model. This type of material is described by two physical constants: the Young modulus and the Poisson ratio. Based on the findings in a previous report,2 in the initial analysis stress models were generated to determine what impact varying the properties (Young modulus) of the various components would have on peak stress. The assigned Young (elasticity) modulus for the arterial wall, fibrous cap, and lipid core were varied experimentally for a finite element mesh generated from a representative vessel cross-section by using values adapted from ranges determined by ex vivo studies, so as to account for possible huge differences between “pure” ex vivo components and “true” in vivo biological components, which are more heterogeneous.7 A Poisson ratio of 0.3 was used for all materials (the value for lipid is unknown and the properties of the lipid core may be somewhere between compressible and incompressible). The internal luminal pressure was assigned at a level of 15 kPa (~115 mmHg) to reflect mean arterial pressure; the pressure on the external vessel boundary was assumed negligible and the plaque was considered stress-free at zero
pressure (no residual stress). In the subsequent interslice comparisons, a fixed set of material properties was used for inputting into the FEA.

**Finite Element Analysis**

The finite element solution was generated by defining the outer boundary as nonrigid. The mesh had approximately 5000 triangular elements with an average element dimension of 0.1 mm, with 10,000 nodes per analysis. Investigators responsible for the FEA were not involved in the acquisition of specimens or the reconstruction of the vessel geometries, and thus had no knowledge of the clinical status of any of the individuals.

**Statistical Analysis**

Nonparametric statistical tests were used to determine the significance of any differences in stress between different parts of the vessel and between plaques from symptomatic and asymptomatic individuals. Statistically significant differences were defined by a probability value of less than 0.05.

**Results**

**Plaque Characteristics**

Multisequence MR imaging studies were performed in all 10 individuals, and analysis revealed that all plaques had evidence of a lipid core and a fibrous cap; however, no foci of calcification were depicted. The relative amounts of fibrous tissue and lipid core were quantified as previously described; there were no statistically significant differences in the relative amount (percentage of total plaque area) of fibrous cap (48% compared with 42%, \( p = 0.29 \)) or lipid core (36% compared with 38%, \( p = 0.21 \)) between symptomatic and asymptomatic plaques, respectively.

**Longitudinal Vessel Profile**

In the initial longitudinal vessel analysis, a finite element solution was obtained for each slice using the following parameters: the Young modulus of arterial wall, fibrous cap, and lipid core of 16.8, 700, and 12.5 kPa, respectively. A varying profile of peak stress was observed along the length of the vessel; the highest peak principal stresses were observed in vessel sections with evidence of atheromatous plaque and the lowest in relatively disease-free vessel cross-sections (Fig. 1). In the three slices depicting large complex plaques on MR images the principal stresses were significantly greater than in disease-free vessel cross-sections at either end of the vessel (mean difference in peak principal stress 537.65 kPa, \( p < 0.05 \)). All three of these vessel sections had a similar geometry (eccentric plaque) that distinguished them from the other slices. The slice with the highest peak principal stress did not, however, have the greatest amount of luminal narrowing.

**The FEA Models**

The finite element mesh from a representative MR image depicting plaque was then used to generate finite element models of peak carotid plaque stress. This vessel section had an eccentric plaque with a relatively thick fibrous cap with a moderate-sized lipid pool. Strain maps generated for each simulation validated the assumption of 10% strain. Increasing the Young modulus of the arterial wall resulted in a decrease in the magnitude of the peak princi-

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**Fig. 1.** Variation in principal stresses along the length of a plaque-containing carotid vessel from a symptomatic individual. Peak stresses are observed in vessel segments containing thickened arterial walls although the vessel segment with the highest peak principal stress (Slice 5) is not the segment with the greatest luminal stenosis.
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Fig. 2. Finite element modeling demonstrating the impact on peak principal stress of varying the material properties of the arterial wall; the lower the Young modulus of lipid, the higher the overall peak principal stress (Young modulus of fibrous cap 700 kPa).

Fig. 3. Finite element modeling demonstrating the impact on peak principal stress of varying the material properties of the lipid pool; the lower the Young modulus of lipid, the higher the overall peak principal stress (Young modulus of arterial wall 16.8 kPa).

group this included two plaque sections with MR imaging evidence of fibrous cap rupture, whereas only one peak stress MR imaging slice in the asymptomatic group had evidence of fibrous cap rupture (distortion during processing prevents histological features from being shown, but this has been previously validated\(^1\)). Symptomatic plaques were found to have a statistically higher peak principal and von Mises stress (Fig. 4) compared with asymptomatic plaques (627.6 kPa compared with 370.2 kPa [p = 0.056] and 645.7 kPa compared with 352.5 kPa [p = 0.047]; Mann–Whitney U test) (Fig. 5). In seven of the vessel sections, there was a focus of high stress that in five vessels was located in the shoulder region of the plaque and in two in the center of the plaque (Fig. 6).

**Discussion**

Findings from this preliminary study suggest that by using in vivo MR imaging–derived templates, stress profiling can distinguish between clinical states. This may contribute to traditional risk assessment factors such as the degree of angiographic stenosis, which was not significantly different between the two groups in this study.

Although others have used vessel structure derived from ex vivo analyses are subject to environmental variables that can alter the geometric and other properties that underlie the interpretation of FEA.\(^16\) Unfortunately, there was an insufficient number of histological sections without significant distortion to permit a meaningful comparison between stress profiles generated by MR imaging– and histologically derived geometries.

There were significant differences observed between the symptomatic and asymptomatic groups, in keeping with the only other similar report in which the authors described a similar relationship in coronary plaque geometries derived from histological features, which suggests that MR imaging–derived stress maps are likely to mirror those derived from histological features.\(^3\)

**Comparative Analysis**

For each individual’s image set, FEA was performed on meshes generated from the geometries of three MR images (depicting large plaques) through the middle of the vessel. From these the slice with highest peak stress was selected from each set for comparative analysis; in the symptomatic group this included two plaque sections with MR imaging evidence of fibrous cap rupture, whereas only one peak stress MR imaging slice in the asymptomatic group had evidence of fibrous cap rupture (distortion during processing prevents histological features from being shown, but this has been previously validated\(^1\)). Symptomatic plaques were found to have a statistically higher peak principal and von Mises stress (Fig. 4) compared with asymptomatic plaques (627.6 kPa compared with 370.2 kPa [p = 0.056] and 645.7 kPa compared with 352.5 kPa [p = 0.047]; Mann–Whitney U test) (Fig. 5). In seven of the vessel sections, there was a focus of high stress that in five vessels was located in the shoulder region of the plaque and in two in the center of the plaque (Fig. 6).

**TABLE 1**

Summary of correlations between peak principal stress and change in the Young modulus of the fibrous cap and vessel wall components\(^*\)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Young Modulus of Lipid (kPa)</th>
<th>Pearson Rho</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>fibrous cap vs. peak stress</td>
<td>25</td>
<td>0.85</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0.93</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>0.96</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>0.45</td>
<td>0.37</td>
</tr>
<tr>
<td>arterial wall vs. peak stress</td>
<td>6.25</td>
<td>−0.99</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>−0.99</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>−0.99</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>−1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>−1</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\(^*\) There is a direct relationship between peak stress and fibrous cap Young modulus, but an inverse one with vessel wall Young modulus.

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The consistency in finding the peak stresses in the shoulder regions of the plaque seems to support the notion that plaque rupture may be associated with foci of high plaque stress. From a purely structural point of view, the appearance of these maximum stresses at these locations could be explained by the configuration of the various plaque components in relation to each other. For example, a thin fibrous cap in this region is likely to generate larger peak stresses than a thick fibrous cap, which would better “protect” a lipid core below it.

The modeling data described suggest that, in addition to the need for accurate geometrical reconstruction, it is important to have a better understanding of the physical properties of the constituents encountered in atheromatous plaques, as stresses within the plaque will differ considerably and, in the case of the fibrous cap, will vary in a nonlinear manner. Authors of previous reports have confirmed the observations described here, in that lipid pools with low Young moduli will result in higher peak stresses. However, much of the findings that belie such simulations make the assumption that the lipid core itself is a homogeneous region made up of lipid; the fact that this region contains both esterified and unesterified cholesterol as well as cellular debris limits any simulations to “model” lipids until direct material properties for this region can be obtained. This is a less significant problem for the collage- nous fibrous cap region, where Young modulus values of structures that have similar structural characteristics have been determined experimentally. Even here, however, there is heterogeneity in the composition of this region, as evidenced by varying intensity on MR images, which depends highly on proton quantity, physical compaction, and freedom of movement.

It is likely that other plaque components will alter the biomechanical stress distribution within carotid plaques; the plaques used in the aforementioned analyses lacked calcification and therefore it was not possible to determine the impact of this constituent on overall stress. Similarly, in this part of the study no attempt was made at characterizing plaque hemorrhage, as previous data (not shown) suggested that multisequence MR imaging is poor at doing so. Hemorrhage-containing regions are most likely to have been misclassified as lipid (in view of greater overlap with signal intensity than with fibrous tissue), and it is likely that this may not have affected too greatly the overall balance of peak stresses as we speculate that hemorrhage may have similar biomechanical properties to lipid.

It would appear that the relative amounts of lipid core and fibrous tissue may not be the only morphological determinants of plaque vulnerability, as no differences were observed between the asymptomatic and symptomatic groups.
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(although the sample size was small). It is therefore important to factor in the state and thickness of the fibrous cap, as studies of the coronary circulation have shown and engineering theory would suggest that a thinner cap will result in higher stresses.\(^3\) In this regard carotid plaques may be morphologically distinct, as thick capped fibroatheroma are frequently encountered in symptomatic individuals.\(^19\) The resolution of MR images is currently below that required for detection of critical fibrous cap thickness, so determination of the presence and/or intactness is subjective, with absence on MR images not necessarily implying rupture.

One could speculate that the differences observed in peak stresses between the two groups might be explained by differences in proximity, arrangement, and boundary conditions between components, particularly as there were no significant differences in fractional composition. This is born out from the modeling data, which suggest that the boundaries between vessel wall and fibrous tissue, where lipid is deficient, and between lipid and fibrous cap are likely to contribute significantly to overall plaque stress. An alternative explanation is that the two groups of plaques have a differential inflammatory load that might alter the structural integrity of both the periluminal cap region as well as the media, but the effects of which remain subcellular and not discernible by conventional MR imaging. Support for the latter explanation comes from data that suggest that asymptomatic and symptomatic plaques have differing amounts of inflammation.\(^4,6,9\)

An intraluminal pressure approximate to the mean arterial pressure in humans was used in our simulations, but as hypertension frequently accompanies atherosclerotic disease, it is possible that in the target group with carotid artery disease, the applied load may be higher despite concomitant antihypertensive medication. We have not investigated the contribution that plaque surface–turbulent flow interactions make to overall plaque stress, but this is also likely to be an important factor and is currently being investigated.

Finally, these data are based on 2D geometric structures, and although it is likely that more accurate information will be obtainable using 3D vessel configurations, we thought that 2D structures were more practical for this initial pilot work.

Conclusions

Magnetic resonance images obtained in vivo provide an opportunity to study plaque stress distribution and can demonstrate objective differences in plaque stress between symptomatic and asymptomatic patients. This might prove useful for long-term evaluation of natural history and/or the evaluation of novel interventions.

References


Fig. 6. Location of plaque stress in a symptomatic individual. The stress map (a) reveals peak principal stresses in the “shoulder” regions based on an FEA mesh derived from a STIR in vivo MR image (b) which depicts a fibroatheromatous plaque (c) as confirmed by the histological stain. Although no definite plaque can be seen, there are foci of high stress over the thinner regions of the fibrous cap. Red arrows indicate the fibrous cap; yellow arrows denote lipid. The asterisk represents the vessel lumen.


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