
U. Sadat a,b,*, Z. Teng a, V.E. Young a, M.J. Graves a, M.E. Gaunt b, J.H. Gillard a

a University Department of Radiology, University of Cambridge, Cambridge, UK
b Cambridge Vascular Unit, Addenbrooke’s Hospital, Cambridge, UK

Submitted 6 May 2010; accepted 6 September 2010
Available online 16 October 2010

KEYWORDS
Carotid plaque; Atherosclerosis; Magnetic resonance imaging; Biomechanical stresses; Stroke; Transient ischaemic attack

Abstract Background: Vulnerable carotid plaques are associated with cerebrovascular ischaemic events. High-resolution magnetic resonance (MR) imaging not only allows the morphological assessment of such plaques, but also provides geometrical data, which can be used for biomechanical stress analysis. We assess its utility to assess the plaque stress profiles of symptomatic (transient ischaemic attack (TIA) and non-disabling stroke) and asymptomatic patients.

Methods: A total of 70 consecutive patients with confirmed underlying carotid artery disease underwent carotid MR imaging of their carotid artery in a 1.5-T MR system using a standard carotid atheroma imaging protocol. MR images were manually segmented for different plaque components and used for biomechanical stress analysis. The maximum critical stress (M-CStress) for various clinical groups was determined and compared.

Results: M-CStress of symptomatic plaques (n = 45) was significantly higher than for asymptomatic plaques (n = 25) (median (interquartile range (IQR)): 275 kPa (190–390) vs. 165 kPa (120–200), p = 0.0001). Within the symptomatic group, no M-CStress differences were present between the TIA (n = 30) and stroke (n = 15) patients (260 kPa (190–370) vs. 295 kPa (200–510), p = 0.31). Within the TIA patient cohort, those who had presented with recurrent TIAs (n = 6) had significantly higher stresses than patients who had suffered a single episode (n = 24) (425 kPa (285–580) vs. 250 kPa (180–310), p = 0.001).

* Corresponding author. U. Sadat, Box 218, Level 5, University Department of Radiology, Addenbrooke’s Hospital, Hills Road, Cambridge CB2 0QQ, UK. Tel.: +44 01223 767834.
E-mail address: us229@cam.ac.uk (U. Sadat).

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Vulnerable carotid plaques are associated with ischaemic cerebrovascular events. The UK National Stroke Strategy recommends urgent management of patients who have suffered a cerebrovascular ischaemic event, suggesting high-resolution carotid artery magnetic resonance (MR) or computerised tomographic imaging within 48–72 h of the event and, preferably, carotid intervention as the risk of a recurrent event is high during this period. The Carotid Endarterectomy Trialists Collaboration (CETC) report favours carotid endarterectomy (CEA) within 2 weeks of the acute event, suggesting an annual risk reduction (ARR) of 23% for the severe stenosis (70–99%) group and a higher ARR of 14.8% for the moderate carotid stenosis (50–69%) group. The benefit would otherwise decline up to 12 weeks for the moderate stenosis group after which CEA confers no benefit. High-resolution carotid MR imaging can prove useful in identifying high-risk patients with vulnerable plaques, who could benefit maximally from urgent carotid intervention. This is because MR imaging is capable of reliably identifying features of plaque vulnerability. It is also capable of providing morphological information, which can be used for the biomechanical assessment of plaques. The biomechanical analysis of carotid plaques is important for their vulnerability assessment as these plaques are usually located in a dynamic environment of carotid bifurcation where biomechanical stresses have been observed to increase plaque vulnerability. The biomechanical assessment of plaques has shown differences between stress profiles of symptomatic and asymptomatic plaques and also in subgroups of symptomatic plaques. Recently, we have demonstrated that high biomechanical structural stresses are associated with subsequent cerebrovascular events in mild-to-moderate carotid stenosis patients. As biomechanical stress analysis of plaques incorporates information about plaque morphology, material properties of various plaque components and local haemodynamic factors, it has the potential of providing a comprehensive assessment of the vulnerability status of plaques for the identification of high-risk patients. In this study, we perform biomechanical stress profiling of plaques from patients who had suffered transient ischaemic attacks (TIAs) or minor strokes and compare it to that of asymptomatic plaques.

Methods

A total of 70 patients with underlying carotid artery disease were recruited for this study. Twenty-five consecutive patients were asymptomatic, that is, they either never had any symptoms (true asymptomatic) in the past or had been asymptomatic for more than 6 months. As many as 45 consecutive patients were symptomatic, that is, they had suffered focal neurological symptoms (TIA or minor non-disabling stroke) attributed to underlying extracranial carotid artery disease. The neurological assessment was done by experienced stroke physicians. A retinal TIA was defined as a partial or complete visual field loss in one eye of ischaemic origin lasting less than 24 h, with a hemispheric TIA being defined as a focal cerebral dysfunction of ischaemic origin lasting less than 24 h. A recurrent TIA was defined as a recurrence of retinal and/or hemispheric TIA symptoms. A minor stroke was defined as a neurological dysfunction of ischaemic origin with deficits persisting longer than 24 h but with a Rankin score ≤3. The study protocol was reviewed and approved by the regional research ethics committee and all patients gave written, informed consent.

The inclusion criteria for this study were:

- Internal carotid artery stenosis of ≥30–99% on duplex ultrasound imaging during screening assessment; and
- Sufficient MR image quality to identify the lumen wall and outer boundary of the arterial wall. (The image quality (IQ) was rated before review by using a previously published 5-point scale; images with IQ >3 were included for morphological analysis.)

Exclusion criteria included:

- previous CEA;
- cardiac arrhythmias;
- known coagulation/clotting disorder responsible for patient’s symptoms;
- patients undergoing thrombolysis following the acute cerebrovascular event; and
- clinical contraindications to MR imaging.

High-resolution multi-contrast MR imaging

High-resolution carotid MR imaging of the research subjects was performed in a 1.5-T MR imaging system (Signa HDx GE Healthcare, Waukesha, WI, USA) with a four-channel phased-array neck coil (PACC, Machnet BV, Elde, the Netherlands). For symptomatic patients, this was done within 72 h of the acute event to identify biomechanical features of plaques nearer to the time of symptom onset. Movement artefact was minimised using a dedicated vacuum-based head-restraint system (VAC-LOK Cushion, Oncology Systems Limited, UK) to fix the head and neck in a comfortable position and allow close apposition of the surface coils. After an initial coronal localiser sequence, axial two-dimensional (2D) time-of-flight (TOF) MR angiography was performed to identify the location of the carotid bifurcation and the stenosis on either side. Axial images (3 mm apart) were then acquired through the common

Conclusions: Symptomatic carotid plaques, particularly those associated with recurrent TIAs, have high biomechanical stresses. As there is pre-existing evidence to suggest that high biomechanical stresses are associated with plaque vulnerability, MR-imaging-based stress analysis has the potential to identify high-risk patients with vulnerable plaques.
carotid artery 12 mm (four slices) below the carotid bifurcation to a point 12 mm (four slices) distal to the extent of the stenosis identified on the TOF sequence. This method ensured that the entire carotid plaque was imaged.20

The following electrocardiography (ECG)-gated fast spin echo pulse sequences were used to delineate various plaque components such as fibrous cap (FC), lipid content and plaque haemorrhage (PH): T1 weighted (repetition time/echo time: $1 \times RR7.8 \text{ ms}^{-1}$) with fat saturation, proton density (PD) weighted (repetition time/echo time: $2 \times RR7.8 \text{ ms}^{-1}$) with fat saturation, T2 weighted (repetition time/echo time: $2 \times RR100 \text{ ms}^{-1}$) with fat saturation; and short tau inversion recovery (STIR) (repetition time/echo time/inversion time: $2 \times RR46 \text{ ms}^{-1} 150 \text{ ms}^{-1}$).21 The field of view was $10 \times 10 \text{ cm}$ and matrix size $256 \times 256$. The in-plane spatial resolution achieved was of the order of $0.39 \times 0.39 \text{ mm}$.21

Plaque components, that is, outer and inner arterial wall, lipid content, fibrous tissue, PH and calcification were manually delineated by an experienced MR reader (US) and confirmed by a consultant radiologist (JHG) using a specialised plaque segmentation software, CMR Tools (London, UK), using previously published criteria.6,22 Following plaque segmentation, the plaque contours were used for 2D mesh generation (Figs. 1 and 2). Cubic B spline technique was used for smoothing the plaque contours.

**Biomechanical stress modelling**

The investigator responsible for the entire computational analysis (ZT) were not involved in the acquisition of MR data and image segmentation and not aware of the patient groups.

**A pre-shrink process for in vivo data**

The in vivo MR images were obtained in diastole by cardiac gating. A pre-shrink process was used to obtain the zero-pressure geometry for each patient. It was used as the numerical starting geometry to recover the in vivo geometry when pressure was imposed in the lumen. The details of this method have been published earlier.2,23 The average inner circumference shrinkage was $9.70 \pm 1.80\%$ for the 70 patients.

**Mesh generation, computational models and solution methods**

The computational mesh was made and the model was solved using ADINA 8.6 (ADINA Inc., MA, USA). All plaque components including fibrous tissue, PH, lipid content, calcification and healthy arterial wall were assumed to be non-linear, isotropic, incompressible and hyperelastic. The modified Mooney–Rivlin strain energy density function was used to describe the material.24 Material parameters were used from experimental measurement data.25,26 A pulsating pressure was imposed in the lumen using the systolic/diastolic arm pressure data for each patient at the time of the MR imaging to perform patient-specific simulation. Pressure at the out-boundary of each vessel slice was set to zero.

**Definition and calculation of critical stress**

Stress is the force acting on a surface divided by the area of the surface. Stress can be 'tensile' or 'structural stress' when the force acts perpendicular to the surface, and referred to as 'biomechanical stress' and 'shear stress' when the force is acting parallel to the endothelium resulting from the viscous drag of the blood along the arterial wall. Biomechanical stresses play a greater role in plaque rupture compared with shear stress.27

![Figure 1](image.png)

**Figure 1** A, B and C showing symptomatic plaque of a transient ischaemic attack (TIA) patient at T1, proton density (PD) and STIR weightings. L indicates lumen; yellow star indicates lipid content, which is hyperintense on T1, PD weighted MR images and hypointense on STIR weighted images. D shows the contours as exported into ADINA 8.6 for biomechanical simulation. E shows the fine mesh generated for simulations measuring $<0.1 \text{ mm}$ for the plaque components (coloured) and at least $<0.05 \text{ mm}$ around the lumen boundary to avoid simulation artefacts. F shows the band plot showing the stress distribution in the plaque with M-CSstress (maximum critical stress) at the vulnerable site.
At every point in a stressed body, there are three planes with normal vectors called principal directions, where the corresponding stress vector is in the same direction as the normal vector and there are no shear components. The three stresses in the principle directions are called ‘principal stresses’. The maximum principal stress ($\text{Stress}_{P_1}$) would be the maximum of the principle stresses and is used to describe the stresses within the plaque. Critical stress (M-CStress) was defined as the maximum of the maximum principal stress ($\text{Stress}_{P_1}$) values over the vulnerable site, that is, minimum FC thickness or plaque shoulder. Healthy regions where no plaque components were present and rupture was unlikely were excluded from the analysis, even if a high stress concentration occurred there. For each slice within a plaque, $\text{Stress}_{P_1}$ distribution corresponding to peak-pressure condition was obtained from the 2D computational model. An automatic search was performed to find M-CStress for each patient.

Statistical analysis

The normality of the data was assessed by the Shapiro–Wilk normality test. Categorical variables were assessed by Fischer’s exact test while continuous variables were assessed using the Mann–Whitney test. The level of statistical significance was set to $<0.05$. All statistical analysis was performed in GraphPad Instat (Version: 3.06).

Results

The demographics and co-morbidities of the TIA, minor stroke and asymptomatic groups are tabulated (Table 1). Patients mostly had moderate luminal stenosis. M-CStress of symptomatic plaques ($n = 45$) was significantly higher than in asymptomatic plaques ($n = 25$) (median (interquartile range (IQR)): 275 kPa (190–390) vs. 165 kPa
(120–200), \( p = 0.0001 \)). Within the symptomatic group, no \( M\)-CStress differences were present between the TIA (\( n = 30 \)) and stroke (\( n = 15 \)) patients (260 kPa (190–370) vs. 295 kPa (200–510), \( p = 0.31 \)). Within the TIA patient cohort, those who had presented with recurrent TIAs (\( n = 6 \)) (Fig. 2, Panel 3) had significantly higher stresses than patients who had suffered a single episode (\( n = 24 \)) (425 kPa (285–580) vs. 250 kPa (180–310), \( p = 0.001 \)). The number of recurrent TIAs in these six patients ranged from two to six and had been ongoing for a variable duration (2 days–3 months). Although stresses in recurrent TIA patients were higher than those in stroke patients, they did not reach the level of statistical significance (\( p = 0.64 \)). Within the asymptomatic group (\( n = 25 \)), no \( M\)-CStress difference was observed between true asymptomatic (\( n = 13 \)) and previously symptomatic plaques (\( n = 12 \)) (165 kPa (150–190) vs. 155 kPa (115–205), \( p = 0.68 \)). Fig. 3 gives a graphical representation of these results.

**Discussion**

This study demonstrates the utility of MR-imaging-based biomechanical analysis to assess stress profiles of carotid plaques in different clinical groups of patients with carotid artery disease. We observed that symptomatic plaques had significantly higher critical stresses than asymptomatic plaques. It was also observed that plaques associated with recurrent TIAs had significantly higher stresses than those associated with a single episode of TIA. Previous studies suggest that the higher the biomechanical stresses, the greater the plaque vulnerability.\(^{16,29–32}\) Therefore, it can be deduced from our results that symptomatic plaques are more vulnerable than asymptomatic plaques. Furthermore, recurrent TIA plaques have a greater vulnerability index than those associated with single-episode TIA.

The pathomechanical explanation is that vulnerable plaques develop weakening of plaque structure such as thinning of FCs\(^{33}\) due to greater underlying inflammatory activity.\(^{34}\) Repetitive loading of the weak structure leads to higher mechanical stresses,\(^{35}\) increased material fatigue\(^{36}\) and, ultimately, fracture (commonly known as rupture in the medical field).\(^{13,37}\) The relationship between high atherosclerotic inflammatory activity and higher biomechanical stresses has already been demonstrated by our group.\(^{38}\) Our results are also in agreement with previously published imaging studies, which showed that symptomatic carotid plaques are more unstable than asymptomatic plaques,\(^{38}\) and so are the plaques associated with recurrent ischaemic attacks compared with those associated with a single event.\(^{39}\) Although TIA is globally considered a high-risk entity which warrants urgent management, and the difference

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**Table 1** Demographics and co-morbidities of various patients groups.

<table>
<thead>
<tr>
<th></th>
<th>TIA patients (1)</th>
<th>Stroke patients (2)</th>
<th>Asymptomatic patients (3)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 30 )</td>
<td>( n = 15 )</td>
<td>( n = 25 )</td>
<td></td>
</tr>
<tr>
<td>Age yrs median (IQR)</td>
<td>74 yrs (8)</td>
<td>76 yrs (68–81)</td>
<td>68 (56–76)</td>
<td>0.93</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>24 (53)</td>
<td>7 (16)</td>
<td>19 (76)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes n (%)</td>
<td>5 (11)</td>
<td>0 (0)</td>
<td>3 (12)</td>
<td>0.15</td>
</tr>
<tr>
<td>Peripheral vascular disease n (%)</td>
<td>4 (9)</td>
<td>2 (4)</td>
<td>5 (20)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ischaemic heart disease n (%)</td>
<td>13 (29)</td>
<td>5 (11)</td>
<td>10 (40)</td>
<td>0.74</td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>16 (36)</td>
<td>8 (18)</td>
<td>16 (64)</td>
<td>1.00</td>
</tr>
<tr>
<td>Statins n (%)</td>
<td>19 (42)</td>
<td>12 (27)</td>
<td>25 (100)</td>
<td>0.32</td>
</tr>
<tr>
<td>Clopidogrel n (%)</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>8 (32)</td>
<td>0.10</td>
</tr>
<tr>
<td>Warfarin n (%)</td>
<td>2 (4)</td>
<td>3 (7)</td>
<td>1 (4)</td>
<td>0.31</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors n (%)</td>
<td>7 (16)</td>
<td>4 (19)</td>
<td>13 (52)</td>
<td>1.00</td>
</tr>
<tr>
<td>ECST % carotid stenosis median (IQR)</td>
<td>54 (43–58)</td>
<td>52 (45–59)</td>
<td>52 (46–59)</td>
<td>0.85</td>
</tr>
<tr>
<td>Systolic blood pressure mmHg median (IQR)</td>
<td>138 (122–160)</td>
<td>140 (135–157)</td>
<td>133 (129–140)</td>
<td>0.58</td>
</tr>
<tr>
<td>Diastolic blood pressure mmHg median (IQR)</td>
<td>77 (70–85)</td>
<td>80 (74–90)</td>
<td>72 (68–80)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

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**Figure 3** M-CStress of different clinical groups kPa [Median (bar within the box) with interquartile ranges (upper and lower limits of the box) and range (whiskers)] with p-value; symptomatic (1) vs. asymptomatic patients (2), TIA (3) vs. stroke group (4), single episode TIA (5) vs. recurrent TIA group (6), true asymptomatic (7) vs. previously asymptomatic (8).
shown by this study between the single and recurrent TIA groups may not alter clinical management, this study shows the potential of biomechanical stress analysis in refining the associated risk-stratification criteria.

It may be useful for identifying high-risk patients with a lesser degree of carotid luminal stenosis, who may have a higher risk of subsequent ischaemic events, but would not be operated under present guidelines. This is because luminal stenosis continues to be a gold standard for clinical decision making for carotid interventions, although there is evidence to suggest that non-severe stenotic lesions can produce ischaemic syndromes41 and that plaque morphology can provide pivotal information about plaque vulnerability.42,43 Today, when there is a drive to offer urgent carotid intervention to patients, even with moderate stenosis,4 MR-imaging-based stress analysis may prove beneficial to identify high-risk patients. Moreover, this technique could help us adopt a different approach in managing patients with a >70% stenosis and a single TIA but a very low stress. These patients might, in the future, against current guidelines, no longer be treated by revascularisation but only by optimal medical treatment.

It can be observed from our results that there is an overlap of stress values for the different subgroups. This raises the question of whether biomechanical modelling can provide cut-off values to differentiate various clinical subgroups, which may be used for clinical decision making. There is still considerable work that needs to be done to achieve this goal. The reason is that the material properties used for computational simulations are only an approximated representation of the actual material properties, such as the assumption that the lipid core itself is a homogeneous region made up of lipid. In fact, this region contains both esterified and unesterified cholesterol as well as cellular debris in varying proportions among the population, thereby varying the material properties. Until direct material properties for this region can be obtained, such approximations will be used for simulations.44 Therefore, a large database containing information about material tests of various plaque constituents for various patient subgroups needs to be established first and then used for patient-specific simulations to enable a reliable cut-off value to be put forward.

It was observed that all asymptomatic patients were on a statin at the time of MR imaging, which they had been taking for more than 3 months; however, only 68% of symptomatic patients were taking a statin at the time of MR imaging (which they had been on for more than 3 months). Similarly, the use of anti-platelet medication and angiotensin-converting enzyme inhibitors was also higher in asymptomatic patients than those who had presented with TIA/stroke. This is something that could affect the results, as these medications have the ability to stabilise the plaques,45 potentially resulting in reduced stresses among asymptomatic patients. A dose–response study using various plaque-stabilising agents is warranted to assess their impact on structural stability and structural stresses. Other limitations of this study are: (1) Our sample size was small with only six patients suffering recurrent TIAS; nonetheless, important observations were made regarding the stress profiles of various clinical groups, which justify MR imaging studies with a larger sample size to confirm these findings. (2) High-resolution MR imaging has the inherent weakness of being less sensitive in identifying calcification within plaques; therefore, we may have underestimated the calcification and its biomechanical effect in our simulations. Most likely this will be insignificant, as demonstrated by Huang et al.46 During simulations, when calcification was eliminated and replaced with fibrous plaque, stress changed insignificantly; the median increase in stress was 0.1% (range, 0–8%; p = 0.85), indicating that calcification does not seem to decrease the mechanical stability. (3) MR image comparison/co-registration was not done, as we have validated this previously.47

Conclusions

MR-imaging-based biomechanical stress analysis can be used for atheromatous plaque stress profiling of different clinical groups of patients with carotid artery disease. It can be used potentially for identification of high-risk patients with vulnerable plaques, who may benefit from urgent surgical interventions, as suggested by the UK National Stroke Strategy. Whether the biomechanical stresses within plaques are a cause or effect of plaque vulnerability, and to what extent, remains to be answered; this finding may be used for the development of biomechanics-based risk-stratification criteria for vulnerable plaques in future.

Acknowledgements

Dr. Umar Sadat is supported by a Medical Research Council UK & Royal College of Surgeons of England Joint Clinical Research Training Fellowship. This research has also been supported by a Biomedical Research Centre National Institute of Health Research (BRC NIHR) grant.

Conflict of Interest

None.

References


