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Original Article
Imaging

Normalized Wall Index Specific and MRI-Based Stress Analysis of Atherosclerotic Carotid Plaques – A Study Comparing Acutely Symptomatic and Asymptomatic Patients –
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Background: Biomechanical stresses play an important role in determining plaque stability. Quantification of these simulated stresses can be potentially used to assess plaque vulnerability and differentiate different patient groups.

Methods and Results: 54 asymptomatic and 45 acutely symptomatic patients underwent in vivo multi-contrast magnetic resonance imaging (MRI) of the carotid arteries. Plaque geometry used for finite element analysis was derived from in vivo MRI at the sites of maximum and minimum plaque burden. In total, 198 slices were used for the computational simulations. A pre-shrink technique was used to refine the simulation. Maximum principle stress at the vulnerable plaque sites (i.e., critical stress) was extracted for the selected slices and a comparison was performed between the 2 groups. Critical stress in the slice with maximum plaque burden is significantly higher in acutely symptomatic patients as compared to asymptomatic patients (median, inter quartile range: 198.0 kPa (119.8–359.0 kPa) vs 138.4 kPa (83.8–242.6 kPa), P=0.04). No significant difference was found in the slice with minimum plaque burden between the 2 groups (196.7 kPa (133.3–282.7 kPa) vs 182.4 kPa (117.2–310.6 kPa), P=0.82).

Conclusions: Acutely symptomatic carotid plaques have significantly high biomechanical stresses than asymptomatic plaques. This might be potentially useful for establishing a biomechanical risk stratification criteria based on plaque burden in future studies. (Circ J 2010; 74: 2360–2364)

Key Words: Atherosclerosis; Biomechanical stresses; Cartoid; MRI; Plaque burden

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arotid artery disease is a predominant cause of cerebrovascular ischemic events.1 Traditionally, luminal stenosis has been used for the assessment of the severity of atherosclerotic disease.2,3 There is considerable evidence today which suggests that carotid plaque morphology is an important factor in determining the severity of the carotid disease.4 High resolution magnetic resonance imaging (MRI) is a non-invasive imaging technique, which has been successfully used for the morphological and functional assessment of plaques.5–7 It also offers a reliable platform for their biomechanical assessment.8–12 Biomechanical assessment is important because carotid plaques are located at the site of carotid artery bifurcation where there is significant interaction between atherosclerotic lesions and the local hemodynamic factors.13,14 It has been widely accepted that plaque rupture possibly occurs when the loading force exceeds the material strength of the fibrous cap (FC).8,15 Thus, an assessment of plaque morphology alone would be insufficient. Finite element analysis (FEA) is a basic technique in biomechanics, which has been used for the mechanical stresses analysis of atherosclerotic plaques.8,9 By extracting the plaque geometry from the corresponding magnetic resonance images and using it for biomechanical stress quantification, FEA provides an assessment of plaque morphology dependent-biomechanical stresses. In this study we investigate whether MRI-based stress analysis of carotid plaques can differentiate acutely symptomatic and asymptomatic patients.

Methods

Patients
In total, 99 patients with carotid artery disease were recruited...
Stress Analysis of Carotid Plaques

in this study, 54 patients were asymptomatic patients (i.e., either truly asymptomatic or had symptoms more than 6 months ago) and 45 acutely symptomatic patients (i.e., they had ischemic cerebrovascular symptoms within the last 72 h of undergoing MRI). The MRI study protocol was reviewed and approved by the regional research ethics committee and all patients gave written informed consent.

The criteria for inclusion in the study were:

- Sufficient MR image quality to identify the lumen wall and outer boundary of the arterial wall.
- Normal heart rhythm, confirmed by 24 h holter monitoring and normal transthoracic echocardiology in cases where a cause other than carotid artery disease was suspected.

Exclusion criteria included:

- Previous carotid endarterectomy of the symptomatic carotid artery.
- Cardiac arrhythmias.
- Known coagulation/clotting disorder responsible for patient’s symptoms.
- Patients undergoing thrombolysis following the acute cerebrovascular event.
- Clinical contraindications to MRI, e.g., inner ear implants, pacemaker, etc.

High Resolution Multi-Sequence MRI

The details of the MRI acquisition have already been published. Briefly speaking, patients underwent high resolution MRI of their carotid arteries in a 1.5 Tesla MRI system (Signa HDx GE Healthcare, Waukesha, WI, USA) with a 4-channel phased-array neck coil (PACC, Machnet BV, Elde, The Netherlands). Movement artefact was minimized 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 localizer sequence, axial 2-dimensional (2-D) time-of-flight (TOF) MR angiography was performed to identify the location of the carotid bifurcation and the region of maximum stenosis. Axial images were acquired through the common carotid artery 12 mm (4 slices) below the carotid bifurcation to a point 12 mm (4 slices) distal to the extent of the stenosis identified on the TOF sequence. This method ensured that the entire carotid plaque was imaged.

The following MRI parameters were used: T1-weighted (repetition time/echo time: 1×RR/7.8 ms) with fat saturation; T2-weighted (repetition time/echo time: 2×RR/100 ms) with fat saturation; proton density-weighted (repetition time/echo time: 2×RR/7.8 ms) with fat saturation and short tau inversion recovery (repetition time/echo time/inversion time: 2×RR/7.8 ms).
The field of view was 10×10 cm and matrix size 256×256. The in-plane spatial resolution achieved was of the order of 0.39×0.39 mm².

Manual segmentation of plaque components was performed by experienced MR readers (US, VY) using previously published criteria as shown in Figures 1A and B. The segmented contours were processed using B-Spline to avoid the imaging and segmentation distortion. The slices which did not contain atherosclerotic components were excluded. For each patient/plaque, the slice with the maximal and minimal normalized wall index (NWI) were picked (wall area is defined as the area between lumen and outer wall). NWI represents the wall area’s percentage in total vessel area, which provides information about the plaque burden of each slice. The degree of luminal stenosis was calculated using European Carotid Surgery Trial criteria.

Finite Element Simulation

A Pre-Shrink Method The in vivo MR images were obtained in diastole with electrocardiogram gating. A pre-shrink process was therefore necessary to obtain the zero-pressure shape. For each patient, the most circular slice which would recover its in vivo shape best when lumen pressure was imposed was picked to calculate the shrinkage rate. The shrinkage rates of lumen contour and outer wall were numerically determined following an iterative procedure so that: (1) the vessel cross-section area was conserved (conservation of mass); and (2) the pressurized morphology and the original in vivo morphology had the best match. The determined lumen shrinkage was applied to all the slices of this patient. The lumen shrinkage rate was 9.61±2.04% for the 99 patients in this study.

Material Property The plaque components were assumed to be hyper-elastic as described by modified Mooney–Rivlin strain energy density function,

\[ W = c_1(I_1 - 3) + D_1 \left( \exp(D_2(I_1 - 3)) - 1 \right), \]

where \( I_1 \) is the first strain invariant, \( c_1 \) and \( D_1 \) and \( D_2 \) are material parameters which are from earlier studies. The blood pressure for each patient, measured before MRI, was used as the loading condition to perform the patient-specific simulation. Maximum principle stress (Stress-P₁) was generated using finite element method and solved in ADINA8.6 (ADINA, Inc) (Figure 1C).

Definition and Calculation of Critical Stress Stress-P₁ of all integration nodes along the lumen contour was extracted. The healthy part where the rupture unlikely occurs was excluded from the analysis. The critical stress was defined as the maximum of Stress-P₁ over the vulnerable plaque sites (ie, minimum FC thickness and plaque shoulder).

<table>
<thead>
<tr>
<th>Table. Information of Patients in the Study</th>
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<tbody>
<tr>
<td><strong>Asymptomatic</strong></td>
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<tr>
<td>(n=54)</td>
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<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Peripheral vascular disease</td>
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<tr>
<td>Ischemic heart disease</td>
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<td>Stenosis</td>
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Figure 2. (A) Critical stress in the slice with maximum plaque burden is significantly higher in acutely symptomatic patients as compared to asymptomatic patients, P=0.04 (box indicates the interquartile range, line within the box indicates the median and whiskers show the range). (B) Critical stress in the slice with minimum plaque burden has no significant difference in acutely symptomatic patients as compared to asymptomatic patients, P=0.82.
Results

Patient demographics were comparable for both groups (Table) except for the age. There was no difference between the 2 groups regarding their percentage luminal stenosis (P=0.86). In total, 198 slices (2×99) were used for the computational study. Critical stress in the slice with maximum plaque burden was observed to be significantly higher in acutely symptomatic patients as compared to asymptomatic patients (median, inter quartile range: 198.0 kPa (119.8–359.0 kPa) vs 138.4 kPa (83.8–242.6 kPa), P=0.04). No significant difference was found in the slice with minimum plaque burden between the 2 groups (196.7 kPa (133.3–282.7 kPa) vs 182.4 kPa (117.2–310.6 kPa), P=0.82) (Figure 2).

Discussion

To our knowledge this is the largest study to date, in which 2-D FEA of atherosclerotic plaques has been used for their biomechanical stress assessment. By using this technique we report the quantified simulated stress differences between acutely symptomatic and asymptomatic plaques. Histologically it is well known that symptomatic plaques are unstable following an acute cerebrovascular ischemic event characterized by the presence of higher incidence of FC rupture and plaque hemorrhage. Biomechanically these plaques should have higher stresses because plaque rupture would occur when the loading force exceeds the material strength of FC. Sadat et al have reported the stress differences between acutely symptomatic and recently symptomatic plaques (ie, those who underwent MRI between 2 and 6 weeks after symptom onset), with acutely symptomatic plaques having significantly higher plaque stresses. In this study the critical stress difference between acutely symptomatic patients and asymptomatic patients is reported, with acutely symptomatic plaques observed to have significantly higher stresses than asymptomatic ones. In this study, as can be appreciated, that patients with moderate carotid stenosis were selected. This is because for this group of patients the benefit of surgery is considered borderline. Because conventional imaging techniques only provide information about arterial lumen but we know that plaques rupture even at mild to moderate stenosis, therefore using plaque imaging techniques and doing biomechanical stress analysis might help us identify those high-risk patients with moderate carotid stenosis, which would have otherwise been managed conservatively. This study demonstrates the potential of biomechanical stress analysis in determining the plaque vulnerability quantitatively. 2-D computational simulations have been widely used for stress analysis of vulnerable plaques. However, it is still not clear the critical stress on which plaque slices should be picked for stress assessment. Plaque burden has been reported to be a risk indicator of plaque vulnerability. Underhill et al found the high plaque burden was a strong predictor of new FC rupture and new intraplaque hemorrhage in the carotid artery. So in this study we decided to determine the stress differences between 2 plaque groups at 2 different locations of plaque burden, ie, maximum and minimum plaque burden calculated by maximum and minimum NWI. It was done to explore the best way by which we can distinguish different clinical groups. We find that the critical stress at the maximum plaque burden site was significantly different for the 2 groups with acutely symptomatic plaques having higher stresses than asymptomatic plaques. Previously it has been reported that NWI has no correlation with the plaque stresses. We found that by using maximum plaque burden site we can differentiate the 2 groups biomechanically. This, however, does not mean that stress is associated with NWI but our study shows that it can be as a landmark by using which symptomatic and asymptomatic plaques can be differentiated biomechanically. By picking the stress on the slices with maximal plaque burden we have refined the methodology of stress assessment. The pre-shrinkage technique was also employed in this study to improve the simulation accuracy since the loading free configuration was not measurable with the in vivo MRI. The stress will be over-estimated by approximately 20–30% if the simulation is directly based on the in vivo geometry.

Although an interesting conclusion has been drawn in this study, some limitations exist: (1) this is a 2-D structure-only model, so the blood flow and the pressure drop were not considered; (2) MRI is less sensitive in picking up calcium foci so we might have underestimated the effect of plaque calcification on biomechanical stresses; (3) the residual stress in the atherosclerotic vessels was not considered because present imaging techniques do not allow its quantification; (4) histology was not used for comparison with MR findings and therefore might be considered a limitation of this study but we have already shown a good correlation in plaque morphology between the 2 techniques. Although it is a relatively bigger scale study compared to the previous studies, it is clear that large scale longitudinal studies are necessary to determine the true diagnostic accuracy of these biomechanical characteristics for prediction of clinical risk of future cerebrovascular ischemic events.

Acknowledgement

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high resolution MRI. *J Biomech* 2006; **39**: 2611 – 2622.


