Utility of Magnetic Resonance Imaging-Based Finite Element Analysis for the Biomechanical Stress Analysis of Hemorrhagic and Non-Hemorrhagic Carotid Plaques

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Background: Biomechanical stress analysis has been used for plaque vulnerability assessment. The presence of plaque hemorrhage (PH) is a feature of plaque vulnerability and is associated with thromboembolic ischemic events. The purpose of the present study was to use finite element analysis (FEA) to compare the stress profiles of hemorrhagic and non-hemorrhagic profiles.

Methods and Results: Forty-five consecutive patients who had suffered a cerebrovascular ischemic event with an underlying carotid artery disease underwent high-resolution magnetic resonance imaging (MRI) of their symptomatic carotid artery in a 1.5-T MRI system. Axial images were manually segmented for various plaque components and used for FEA. Maximum critical stress (M-Cstress_{SL}) for each slice was determined. Within a plaque, the maximum M-Cstress_{SL} for each slice of a plaque was selected to represent the maximum critical stress of that plaque (M-Cstress_{PL}) and used to compare hemorrhagic and non-hemorrhagic plaques. A total of 62% of plaques had hemorrhage. It was observed that plaques with hemorrhage had significantly higher stress (M-Cstress_{PL}) than plaques without PH (median [interquartile range]: 315 kPa [247–434] vs. 200 kPa [171–282], $P=0.003$).

Conclusions: Hemorrhagic plaques have higher biomechanical stresses than non-hemorrhagic plaques. MRI-based FEA seems to have the potential to assess plaque vulnerability. (*Circ J* 2011; **75**: 884–889)

Key Words: Atherosclerosis; Biomechanical stresses; Finite element analysis; Magnetic resonance imaging; Stroke

Plaque hemorrhage (PH) is a common feature of complex atheromatous plaques. It is associated with thromboembolic (ischemic) events in coronary¹ and carotid arteries.^{2–4} The importance of PH was suggested by Imparato et al, who reported, in 1979, that PH was responsible for 73% of focal neurological symptoms in patients with symptomatic carotid artery disease and that it played a significant role in plaque progression.⁵ Similar results have been reported by Takaya et al in a longitudinal magnetic resonance imaging (MRI) study.⁶ A recent systematic review (of 31 observational studies) also suggested a plausible contribution of PH to focal neurological symptom production.⁷ Because the location of carotid plaque is in a dynamic environment at the carotid bifurcation, the relationship between plaque morphology and biomechanical stresses cannot be overlooked. It was Lusby et al in the 1980s who suggested that mechanical stresses played a role in carotid plaque progression and in the development of symptoms of cerebral ischemia.^{8,9} The stress profiles of hemorrhagic and non-hemorrhagic plaques,

however, remain unexplored.

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Finite element analysis (FEA) is used in the biomechanical stress analysis of plaques and has been used to show differences between stress profiles of symptomatic and asymptomatic plaques,¹⁰ and also in subgroups of symptomatic plaques.¹¹ Recently we demonstrated that high biomechanical structural stresses are associated with subsequent cerebrovascular events in patients with mild–moderate carotid stenosis.¹² We have also recently reported the effectiveness of biomechanical stress analysis for plaque burden-based stress analysis of acutely symptomatic and asymptomatic patients.¹³ Because biomechanical stress analysis of plaques incorporates information about plaque morphology, material properties of various plaque components and local hemodynamic factors, it has the potential to provide a comprehensive assessment of the vulnerability status of plaques for the identification of high-

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Figure 1. (A) T₁-, (B) proton density-, (C) T₂- and (D) short τ inversion recovery (STIR)-weighted magnetic resonance imaging showing fresh plaque hemorrhage (green star), which is hyperintense on T₁-weighted imaging and isointense on T₂- and STIR-weighted imaging (white arrow, rupture). (E) Contours as exported into the simulation software with green contour indicating the plaque hemorrhage. (F) Fine mesh generated by ADINA 8.6 used for simulation (measurement of element edge was at least <0.1 mm for the plaque components and <0.05 mm at the lumen boundary to avoid computational artifact). (G) Band plot showing critical stress concentration at the vulnerable site (plaque shoulder in this case).

risk patients. In the present study we performed biomechanical stress profiling of hemorrhagic and non-hemorrhagic plaques.

Methods

Forty-five consecutive patients who had suffered a cerebrovascular ischemic event underwent high-resolution MRI of their symptomatic carotid arteries within 72 h of the acute event. A retinal transient ischemic attack (TIA) was defined as a partial or complete visual field loss of ischemic origin in 1 eye lasting <24 h, and a hemispheric TIA was defined as a focal cerebral dysfunction of ischemic origin lasting <24 h.¹⁴ A minor stroke was defined as a neurological dysfunction of ischemic origin with deficits persisting >24 h but with a Rankin score ≤ 3 . The neurological assessment was done by an experienced stroke physician. The 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 (1) internal carotid artery stenosis of ≥ 30 –99% on duplex imaging during screening assessment; (2) sufficient MRI image quality to identify the lumen wall and outer boundary of the arterial wall (the image quality [IQ] was rated before review using a previously published 5-point scale,^{15,16} and images with IQ >3 were included for morphological analysis); and (3) normal heart rhythm, confirmed on 24-h Holter monitoring and normal transthoracic echocardiography in patients in whom a cause of stroke other than carotid artery disease was suspected.

Exclusion criteria included (1) previous carotid endarterectomy of the symptomatic carotid artery; (2) cardiac arrhythmias; (3) known coagulation/clotting disorder responsible

Figure 2. Lipid core (yellow star), which is hyperintense on (A) T₁-weighted imaging and hypointense on (B) T₂-weighted imaging. (C) Band plot showing critical stress concentration.

for the symptoms; (4) thrombolysis following the acute cerebrovascular event; and (5) clinical contraindications to MRI, for example inner ear implants, pacemaker, and so on.

High-Resolution Multi-Contrast MRI

High-resolution carotid MRI of the research subjects was performed using a 1.5-T MRI system (Signa HDx GE Healthcare, Waukesha, WI, USA) with a 4-channel phased-array neck coil (PACC, Machnet BV, Elde, The Netherlands). Movement artifact 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-D time-of-flight (TOF) MR angiography was performed to identify the location of the carotid bifurcation and the region of maximum stenosis on each side. Three-mm-thick axial images were acquired from the carotid bifurcation for 12 mm below the carotid bifurcation to a point 12 mm distal to it to ensure that the entire plaque was imaged.¹⁷

The following electrocardiograph-gated fast spin echo pulse sequences were used to delineate various plaque components such as fibrous cap (FC), lipid-rich necrotic core (LRNC) and PH (Figures 1, 2): T₁-weighted (repetition time/echo time: 1×RR/7.8 ms) with fat saturation; proton density (PD)-weighted (repetition time/echo time: 2×RR/7.8 ms) with fat saturation; T₂-weighted (repetition time/echo time: 2×RR/85 ms) with fat saturation; and short τ inversion recovery (STIR; repetition time/echo time/inversion time: 2×RR/42 ms/150 ms). The number of acquired slices for an individual plaque depended on the plaque length.

MRI Analysis

Plaque components (ie, LRNC, fibrous tissue and PH) were manually delineated by an experienced MRI reader (U.S.) using CMR Tools (London, UK) and confirmed by a consultant neuroradiologist (J.H.G.) using previously published criteria.^{18,19} Briefly, LRNC appears to be hyperintense on T₁- and PD-weighted images, and hypointense on STIR and T₂-weighted images. Fibrous tissue appears isointense–hypointense on T₁- and PD-weighted images, and hyperintense on STIR and T₂-weighted images.²⁰ Calcium appears hypointense on all MR weightings. PH (when fresh as was the case in the present patients, being imaged within 72 h of acute event) appears hyperintense on T₁- and PD-weighted images, and isointense–hypointense on STIR and T₂-weighted

images. Following the plaque segmentation, the segmented contours were used for mesh generation.

Biomechanical Stress Modeling

The investigators responsible for the entire computational analysis were not involved in the acquisition of MRI data or image segmentation.

Pre-Shrink Process for In Vivo Data

In vivo MRI was done in diastole using cardiac gating. Therefore, a pre-shrink process was necessary to obtain the zero-pressure geometry, which was used as the numerical starting geometry, and to recover the in vivo diastolic plaque geometry when pressure was imposed in the lumen.²¹ The average lumen circumference shrinkage was $9.75 \pm 1.86\%$ for the 45 patients.

Mesh Generation, Computational Models and Solution Methods

The computational mesh was made and the model was solved using ADINA8.6 (ADINA, MA, USA; Figures 1F, 2). All plaque components including fibrous tissue, hemorrhage, lipid core, calcification and healthy arterial wall were assumed to be non-linear, isotropic, incompressible and hyper-elastic.²² The modified Mooney-Rivlin strain energy density function was used. A pulsating pressure was imposed on the lumen, using the systolic/diastolic arm pressure data for each patient at the time of the MRI, to perform patient-specific simulations.²³ Material parameters were used from available data.²⁴ Pressure at the out-boundary of each vessel slice was set to zero. The reproducibility of the biomechanical stress simulations has been determined previously by our group.²⁵

Definition and Calculation of Critical Stress

In continuum mechanics, stress is a measure of the average force per unit area of a surface within a deformable body on which internal forces act. The maximum critical stress was defined as the maximum principal stress at vulnerable plaque sites, that is, plaque shoulder and minimum FC thickness.²⁶ The “maximum critical stress” of a slice is indicated as M-CStress_{SSL} throughout the text. To obtain the maximum critical stress of the entire plaque (M-CStress_{SPL}), the maximum M-CStress_{SSL} for each slice of a plaque was selected.

Statistical Analysis

The normality of the data was assessed on Shapiro–Wilk nor-

Table. Patient Demographics and Morphological Characteristics of Carotid Plaques

	Non-hemorrhagic patients (n=17)	Hemorrhagic patients (n=28)	P value
Age (years) (SD)	75 (9)	73 (13)	0.98
Hypertension	6 (35)	17 (60)	0.12
Diabetes	2 (12)	3 (11)	1.00
Peripheral vascular disease	1 (6)	5 (18)	0.38
Ischemic heart disease	7 (41)	11 (39)	1.00
Coronary artery bypass graft	1 (6)	4 (14)	0.63
Aspirin	10 (59)	14 (50)	0.75
Statins	12 (70)	20 (71)	1.00
Clopidogrel	0 (0)	2 (7)	0.51
ACEI	5 (29)	6 (21)	0.72
ECST % carotid stenosis (SD)	49 (14)	55 (14)	0.18
Systolic blood pressure (mmHg)	144±26	140±20	0.44
Diastolic blood pressure (mmHg)	84±10	80±14	0.30
FC ruptures	10 (22)	23 (51)	0.10
Large lipid core n (%)	4 (9)	10 (22)	0.51

Data given as mean ± SD or n (%).

ACEI, angiotensin-converting enzyme inhibitors; FC, fibrous cap.

malinity test. Categorical variables were assessed on Fisher's exact test while continuous variables were assessed on Mann–Whitney test for non-parametric data and unpaired Student's t-test for parametric data. The level of statistical significance was set at <0.05. All statistical analyses were performed in GraphPad Instat (Version: 3.06).

Results

The patient demographics and comorbidities are summarized in **Table**. There was no statistically significant difference between hemorrhagic and non-hemorrhagic plaques regarding prevalence of FC rupture and the presence of large lipid cores (lipid core occupying >25% of plaque volume²⁷). In total, 173 MRI slices were analyzed for 45 carotid plaques. All slices used for analysis had image quality >3. Sixty-two percent of plaques (n=28) had MRI evidence of PH compared to 38% (n=17) without hemorrhage. The hemorrhage within all plaques was identifiable as fresh PH on MRI (**Figure 1**). It was found that the M-CStress_{SPL} of hemorrhagic plaques was significantly higher than that of non-hemorrhagic plaques (**Figure 2**; median [interquartile range]: 315 kPa [247–434] vs. 200 kPa [171–282], P=0.003).

Discussion

To our knowledge this is the first study to provide a snapshot of the biomechanical stresses within vulnerable atheromatous plaques in the presence of PH compared to those without PH. We found that hemorrhagic plaques had significantly higher biomechanical stresses than non-hemorrhagic plaques. Although it remains unknown whether PH leads to high stresses or vice versa, in biomechanical terms, high intrinsic mechanical stresses would result because of the soft nature of PH and its ability to undergo massive deformation when loading force is applied to it. In the dynamic environment of the carotid artery bifurcation this leads to extensive plaque morphology disruption and reconfiguration, as suggested by Lusby et al.^{2,3} This accounts for enhanced plaque vulnerability and predisposes to recurrent focal neurological symptoms in patients with mild, moderate and severe carotid stenosis. From the

pathological viewpoint, the disruption of neovessels within advanced atheromatous plaques resulting from underlying high inflammatory activity, leads to the oozing of blood from the leaky vessels resulting in hemorrhagic transformation of the plaque. The present observation that both groups had comparable prevalence of FC rupture despite the predominant presence of PH in 1 group supports the fact that PH results from the oozy neovessels within the plaque rather than from FC rupture. The transition from an asymptomatic state to a symptomatic state is rapid and often unpredictable.²⁸ The sudden occurrence of hemorrhage within plaques most likely results in sudden changes in the biomechanical properties of the plaque, making it rupture prone. Hemoglobin released from the red blood cells at the site of the hemorrhage also plays a large part in destabilizing the plaque because of its potent pro-inflammatory nature, thereby promoting the formation of reactive oxygen species.²⁹ All these factors, in addition to turbulent flow, changes in vessel wall stiffness due to atheroma, segmental variations in vessel wall distensibility and wall compliance,³⁰ and alterations in segmental tangential tension due to the asymmetric deposition of plaque,⁹ generate a high-risk environment within hemorrhagic plaques, making them extremely dangerous.

Strong evidence of the association of PH with plaque instability comes from the Oxford Plaque Study, a recent large-scale study of 526 symptomatic carotid plaques. It was found that in 65% of patients whose carotid plaques were removed sooner than 60–90 days after the most recent ischemic event or symptom onset, histological features of PH were present.³¹ The prevalence of PH in the present patients was 62%, which is in accordance with the aforementioned study and with our previous report.¹⁹

In the present study FEA was used for the biomechanical stress simulations. We have used this method extensively in the past to assess features of plaque vulnerability and compare different patient groups.^{10,11,32–38} The principle of FEA is that it breaks a very complex problem into many simpler problems that are much easier to solve. It does this by breaking down complex shapes and geometries into simple shapes called elements. In this way, complex systems such as atheroma can be modeled appropriately and structural stresses can

be quantified. Because FEA integrates information regarding plaque morphology, material properties of the plaque components and patient-specific blood pressure (used for loading) during the computational simulations, it provides a much more comprehensive assessment of plaque vulnerability compared to plaque morphology alone. The present study, however, has some limitations.

Relative material properties of various plaque components were used, which are probably only an approximate representation of the actual material properties but they are the best available choice for the biomechanical simulations. This limitation is difficult to overcome at present. Second, conventional black-blood imaging sequences were used to identify hemorrhage. Very recently Ota et al reported that the 3-D magnetization-prepared rapid-acquisition gradient-echo (RAGE) sequence demonstrates higher diagnostic capability for the detection and quantification of PH compared to 2-D fast spin-echo and 3-D TOF sequences.³⁹ Because fast spin echo sequences were used in the present study, it is possible that we could have underestimated the size of PH in the present study compared to what could have been achieved by using the RAGE sequence.³⁹ Perhaps for future studies this sequence may be used for better PH characterization. MRI comparison/co-registration was not done, because this has been validated by us previously.⁴⁰ Finally, transthoracic echocardiography was used to exclude cardiogenic source of thrombus. Ideally it is better to use trans-esophageal echocardiography and also perform strict exclusion of another thrombogenic source by performing imaging from aortic root to the aortic arch and proximal carotid arteries.

Conclusions

The present study suggests that MRI-based FEA of plaques has the ability to assess and differentiate the stress profiles of hemorrhagic and non-hemorrhagic plaques. Hemorrhagic plaques were observed to have high stresses. From previous studies, we know that hemorrhagic plaques are associated with thromboembolic events. This technique therefore appears to have the potential to identify high-risk plaques and may be useful in refining risk stratification criteria in future.

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