How Critical Is Fibrous Cap Thickness to Carotid Plaque Stability?
A Flow–Plaque Interaction Model

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Background and Purpose—Acute cerebral ischemic events are associated with rupture of vulnerable carotid atheroma and subsequent thrombosis. Factors such as luminal stenosis and fibrous cap thickness have been thought to be important risk factors for plaque rupture. We used a flow–structure interaction model to simulate the interaction between blood flow and atheromatous plaque to evaluate the effect of the degree of luminal stenosis and fibrous cap thickness on plaque vulnerability.

Methods—A coupled nonlinear time-dependent model with a flow–plaque interaction simulation was used to perform flow and stress/strain analysis in a stenotic carotid artery model. The stress distribution within the plaque and the flow conditions within the vessel were calculated for every case when varying the fibrous cap thickness from 0.1 to 2 mm and the degree of luminal stenosis from 10% to 95%. A rupture stress of 300 kPa was chosen to indicate a high risk of plaque rupture. A 1-sample t test was used to compare plaque stresses with the rupture stress.

Results—High stress concentrations were found in the plaques in arteries with >70% degree of stenosis. Plaque stresses in arteries with 30% to 70% stenosis increased exponentially as fibrous cap thickness decreased. A decrease of fibrous cap thickness from 0.4 to 0.2 mm resulted in an increase of plaque stress from 141 to 409 kPa in a 40% degree stenotic artery.

Conclusions—There is an increase in plaque stress in arteries with a thin fibrous cap. The presence of a moderate carotid stenosis (30% to 70%) with a thin fibrous cap indicates a high risk for plaque rupture. Patients in the future may be risk stratified by measuring both fibrous cap thickness and luminal stenosis. (Stroke. 2006;37:1195-1199.)

Key Words: atherosclerosis ■ carotid stenosis ■ rupture ■ stress ■ stroke

A cut cerebral ischemic events are associated with rupture of vulnerable carotid atheroma and subsequent thrombosis. Such strokes are potentially preventable by carotid intervention (eg, endarterectomy, angioplasty, or stenting). Luminal stenosis is commonly used in current clinical practice as an indicator for surgical intervention. Carotid endarterectomy has been shown to be beneficial in patients with high-grade (70% to 99%) stenosis, but conclusions cannot be drawn about possible benefits for patients with moderate stenosis (30% to 70%). The debate continues on whether we should be operating on asymptomatic patients with a moderate carotid stenosis despite the Asymptomatic Carotid Surgery Trial recent report. Previous studies have suggested that plaque fibrous cap thickness and biomechanical stress should also be considered major determinants for plaque vulnerability. Fibrous cap thickness could be an important factor for patient selection preintervention, especially for those with a moderate stenosis or in asymptomatic patient groups.

Advances in high-resolution MRI have enabled us to noninvasively determine plaque morphology. A vulnerable plaque can be described as a large, soft lipid pool covered by a thin fibrous cap. Plaque rupture occurs when the plaque structure cannot resist the hemodynamic blood pressure and shear stress. Hemodynamic blood flow acts as an extrinsic factor exerting pressure and shear stress on the plaque. The deformation of the plaque in turn will affect blood flow. It is therefore important to study the flow–plaque interaction when we investigate the mechanism of plaque rupture.

Computational simulations for blood flow and plaque rupture have been performed by many investigators on stenotic artery based on realistic plaque geometry. Hung et al used histology-based 2D solid models for arterial plaque and have found that plaques with thin fibrous caps and large lipid pools increases plaque stress. Cheng et al used a finite element model based on histology to analyze coronary lesions, and their data suggested that concentration of circumferential tensile stress in the lesion may play an important role in plaque rupture and myocardial infarction. Tang et al used an ex vivo, MRI-based, flow–structure interaction model to study the interaction between flow and plaque and suggested

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that large cyclic stress/strain variations in the plaque under pulsating pressure may lead to plaque fatigue and possible rupture. 

In this study, we simulated pulsatile flow through a stenotic artery and its interaction with an atheromatous plaque. We investigated the variation of stress on the plaque at different degrees of luminal stenosis and fibrous cap thickness to determine their effects on plaque vulnerability. This study is the first attempt to use a theoretical model to describe the plaque rupture mechanism and to show that luminal stenosis and fibrous cap thickness are critical to plaque rupture.

**Methods**

A coupled fluid–structure interaction model was used to demonstrate how blood flowed through a stenotic artery and deformed the plaque. The model scheme is shown in Figure 1. The shape of the plaque was governed by a sinusoidal function:

\[
y_1 = \frac{D - A}{2} (1 + \cos x)\]

and

\[
y_2 = \frac{D - A}{2} (1 + \cos x) - d,
\]

where \( D \) is the lumen diameter in the healthy part of the vessel (\( D = 10 \) mm was used), \( \phi = A/D \) indicates the degree of stenosis; \( L \) is the length of the diseased artery that was studied (\( L = 20 \) mm was chosen); and \( d \) represents the fibrous cap thickness.

The degree of stenosis was varied by changing the value of \( \phi \). The fibrous cap thickness was varied by changing the distance between the 2 curves, \( d \).

The flow was assumed to be laminar, Newtonian, viscous, and incompressible. The incompressible Navier–Stokes equations in Arbitrary Lagrangian-Eulerian formulation were used as the governing equations:

\[
\rho \frac{\partial \mathbf{u}}{\partial t} = \nabla \cdot ((-p) \mathbf{I} + \eta (\nabla \mathbf{u} + (\nabla \mathbf{u})^T)) + \rho (\mathbf{u} - \mathbf{\psi}) \cdot \nabla \mathbf{u} = \mathbf{F}
\]

and

\[
-\nabla \cdot \mathbf{u} = 0,
\]

where \( \rho \) indicates fluid density; \( \mathbf{u} \) is flow velocity field; \( p \) is fluid pressure; and \( \eta \) indicates fluid viscosity. The value of it was taken to be \( 3.4 \times 10^{-3} \text{Ns/m}^2 \) based on previously in vivo measurement. \( \mathbf{I} \) represents the unit diagonal matrix; \( \mathbf{F} \) is volume force affecting the fluid; and \( \mathbf{\psi} \) represents mesh velocity, which was introduced to the equation because of the movement of the coordinate system.

Inflow was assumed to have a fully developed laminar characteristic with a parabolic velocity profile on the left boundary, but the amplitude of the flow varied with time. The centerline velocity \( U_c \) with the steady-state amplitude \( U \) was given by the equation:

\[
U_{c0} = U \sqrt{(0.04 - r^2)^2 + (0.1 - r)^2},
\]

where \( U = 0.2 \text{ m/s} \) was used, and \( r \) was the time.

Outflow was the right boundary with a pressure \( p = 0 \) on all other boundaries. The fluid was not moving with respect to the boundaries, corresponding to the no-slip boundary condition.

Plaque components were assumed incompressible and nonlinear because ideally human tissue is hyperelastic. To model this hyperelastic effect, a 2-term Ogden strain energy formulation was chosen to simulate the nonlinear stress/strain relationship for the mechanical properties of plaque components. The parameters were chosen to be the same as our previous in vivo MRI study of plaque rupture.

The coupled fluid–structure interaction simulation was performed, and both fluid flow and plaque structure reached a balance at each time step. Fluid velocity, plaque deformation, and plaque internal principal stress were calculated at each time step. The simulation was performed using a finite element solver (FEMLAB 3.1; COMSOL Inc.).

Luminal stenosis (\( \phi \)) was varied from 10% to 95%, and the fibrous cap thickness (\( d \)) was varied from 0.1 to 2 mm. The flow field and stress/strain distribution within the plaque were calculated for every degree of luminal stenosis and fibrous cap thickness used. A previous in vitro study of human atherosclerotic material has shown that fibrous caps usually fracture when the static stress exceeds 300 kPa. Therefore, a rupture stress of \( \geq 300 \text{ kPa} \) was chosen to indicate a high risk of plaque rupture.

Three groups were divided according to different degree of luminal stenosis: 10% to 30%, 30% to 70%, and 70% to 95%. Thirty simulations were conducted for each group. A 1-sample test (based on a test value of 300 kPa) was used to compare the plaque stresses in each group (\( n = 30 \)) with the rupture stress to examine plaque vulnerability (SPSS v12.0).

**Results**

Flow velocity arrows and stress distribution in a vessel with a 70% degree of luminal stenosis are shown in Figure 2A. The fibrous cap thickness is 1.0 mm. The flow velocity arrows show the flow profile across the plaque. Reverse flow can be seen distal to the plaque. The principal stress contours are shown in the fibrous cap and the lipid pool, and high stress concentrations can be found within the fibrous cap. The stress concentrations are found at the shoulder regions of the plaque.

The streamlines of flow and flow velocities within the artery are demonstrated in Figure 2B (the luminal stenosis is 80%, and the fibrous cap thickness is 0.5 mm). The plaque can be seen to be deformed (maximum deformation is 2.44 mm) because of the large luminal stenosis (80%) and thin fibrous cap (0.5 mm). Severe stenosis and 100% eccentricity lead to high flow velocity, high pressure at the throat of the stenosis, and a large recirculation region distal to this.

Figure 3A shows an artery with a 40% stenosis (the blue curve) and the peak principal stress reached when varying the fibrous cap thickness from 0.1 to 2 mm. The plaque is stable when the fibrous cap is 0.7 to 2 mm thick. When the fibrous cap thickness is decreased to 0.2 mm, the stress within the plaque increases to \( \geq 300 \text{ kPa} \), indicating a high risk for plaque rupture. The red curve shows an artery with 50% stenosis and the variation of plaque stresses when changing the fibrous cap thickness.

The effect of fibrous cap thickness on plaque stress at different degrees of luminal stenosis is demonstrated in Figure 3B. A thinner fibrous cap and a higher degree of stenosis lead to a higher peak principal plaque stress. In cases...
in which the degree of arterial stenosis is >70% and the fibrous cap is varied from 0.1 to 2 mm, large stress concentrations can be found within the fibrous cap to suggest that there may be a high risk for plaque rupture. For moderate carotid stenosis (30% to 70%), a thinner fibrous cap thickness appears to confer instability to the plaque.

The peak principal stresses in arteries with 10% to 30% stenosis are significantly $<300$ kPa (156.08±116.33 kPa; $P<0.001$). The 95% CI of the difference is $-187.35$, $-100.47$ kPa. The peak principal stresses in arteries with 70% to 95% stenosis are significantly higher than 300 kPa (441.89±110.96 kPa; $P<0.001$). The 95% CI of the difference is 100.46, 183.32 kPa. The peak principal stresses in arteries with 30% to 70% stenosis are not significantly $<300$ kPa (271.78±97.63 kPa; $P=0.124$). The 95% CI of the difference is $-64.67$, 8.24 kPa. A box plot is shown in Figure 4 to illustrate the spread of the plaque stresses in the 3 groups.

**Discussion**

The degree of luminal stenosis has been a critical parameter in considering the risk/benefit ratio for carotid endarterectomy. Both the North America Symptomatic Carotid Endarterectomy Trial and European Carotid Surgery Trial have demonstrated an increasing benefit of intervention with an increasing degree of stenosis. It is current surgical practice to operate on symptomatic patients with ≥70% stenoses. The idealized geometry and computer simulation validate this point because there is a high risk for plaque rupture above this degree of stenosis (Figure 3B), whatever fibrous cap thickness is considered.

This model fits so well with the current literature that it would be reasonable to assume that the other findings also are of clinical relevance; plaque could still be vulnerable for a moderate luminal stenosis (30% to 70%). For example, in a 40% carotid stenosis and a thin fibrous cap (<0.4 mm), the model demonstrates a high risk for plaque rupture. The peak stress within a plaque at 40% stenosis with a fibrous cap thickness of 0.2 mm is similar to the stress within a plaque at 80% stenosis with a fibrous cap thickness of 0.5 mm. Both plaques are at high risk of rupture. When carotid stenosis is between 50% and 70%, there is a sharp increase in plaque stress when reducing fibrous cap thickness. This suggests that plaque with a thin fibrous cap is at high risk of rupture. The data are consistent with the facts that patients with symptomatic moderate or severe stenosis benefit by having a carotid endarterectomy. Therefore, for patients with a moderate carotid stenosis (30% to 70%), knowing the fibrous cap thickness in conjunction with the degree of luminal stenosis may be more important for risk stratification than thought previously.

Plaque on both sides was studied by modeling the concentric conditions with an artery of a 60% luminal stenosis and...
A mm fibrous cap thickness. Thirty percent on both sides (30–30), 20% on 1 side and 40% on the other side (20–40), and 10% on 1 side and 50% on the other side (10–50) were studied. The Table shows the simulation results of the plaque stress within the fibrous cap when plaque eccentricity is varied. When the plaque was changed from being concentric to eccentric, the maximal plaque stress was slightly increased. This is a smaller effect when compared with the effect of thinning the fibrous cap. This suggests that plaque eccentricity does not play a major role in plaque vulnerability.

The measure of luminal stenosis underestimates the degree of plaque burden attributable to vessel remodeling. Risk assessment of plaque vulnerability is thought to be a multifactorial process involving thinning of the fibrous cap by active macrophages and biomechanical stress applied on the plaque. Plaque morphology from in vivo high-resolution carotid MRI may be more helpful to determine risk of rupture. The amount of lipid core, although not assessed in this study, could also influence plaque stability and should be investigated.

This study is a theoretical investigation of the mechanism of blood flow and its interaction with atheromatous plaque. It

<table>
<thead>
<tr>
<th>Plaque Eccentricity</th>
<th>Peak Principal Stresses (kPa)</th>
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<tbody>
<tr>
<td>30–30</td>
<td>155.33</td>
</tr>
<tr>
<td>20–40</td>
<td>159.28</td>
</tr>
<tr>
<td>10–50</td>
<td>165.10</td>
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<tr>
<td>0–60</td>
<td>169.32</td>
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30–30 indicates 30% stenosis on both sides of the vessel; 20–40, 20% on 1 side and 40% on the other side; 10–50, 10% on 1 side and 50% on the other side; 0–60, 60% on 1 side of the lumen.
provides a better understanding of the mechanical parameters underlying plaque rupture. Human carotid atherosclerosis is a more complicated problem that involves not only a biomechanical but also a biochemical process. In this study, the flow was assumed to be well-developed laminar flow but not at the carotid bifurcation. The reason for that is, first, it is easier to quantify the flow effect. Using a bifurcation in this model will bring a lot other parameters that will make the model complicated. The purpose of this study is to investigate the effect of different fibrous cap thickness and luminal stenosis on plaque vulnerability. Second, plaque formation is recognized to be associated with a high shear stress gradient that can often be found at the carotid bulb. Plaque rupture is thought to be precipitated by a different mechanism. The impact of flow turbulence and shear stress was negligible compared with the effect of pressure or pressure drop on plaque stability. Finally, determining the exact stress value is not the purpose of this study. The main point is to determine the variation of plaque stresses when varying luminal stenosis and fibrous cap thickness. We acknowledge that plaque geometry is more complex than our model allows for. Although we briefly considered plaque concentricity, we did not feel it plays a major role in plaque rupture. Advances in high-resolution MRI have enabled us to noninvasively determine plaque morphology. In the future, to model atheromatous plaque in vivo, high-resolution MRI can be used to acquire the geometry and blood flow data of the artery. The data can then be used as the boundary conditions for the computer simulation.

The effect of blood pressure was tested in this model. By keeping the artery at 50% luminal stenosis and 0.5 mm fibrous cap thickness, the maximal stress within the fibrous cap increased from 209.12 to 361.23 kPa when the blood pressure was increased from 120 to 200 mm Hg. The plaque was at high risk of rupture at the higher pressure condition. This reduced the threshold when the plaque ruptured. This suggests that higher blood pressure could lead to plaque rupture even with a thicker fibrous cap.

The results show that when the fibrous cap thickness is <0.1 mm, even a small degree of luminal stenosis (10%) may induce a large plaque stress and could result in plaque rupture. This is consistent with the finding from histological data that when fibrous cap thickness is <0.1 mm, the plaque can be classified as vulnerable plaque.

In conclusion, this study has validated that plaques with thin fibrous caps and a severe luminal stenosis are at high risk of rupture. A plaque with a thin fibrous cap with a moderate carotid stenosis could also be vulnerable. Therefore, fibrous cap thickness could be considered a useful indicator for plaque vulnerability in addition to the traditional measure of luminal stenosis. Simulation of blood flow–plaque interaction based on in vivo MRI could prove to be a useful tool for risk stratification of patients with carotid atheroma in the future, particularly asymptomatic patients with a moderate carotid stenosis.

Acknowledgments
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