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3D Critical Plaque Wall Stress Is a Better Predictor of Carotid Plaque Rupture Sites Than Flow Shear Stress: An In Vivo MRI-Based 3D FSI Study

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Abstract

Atherosclerotic plaque rupture leading to stroke is the major cause of long-term disability as well as the third most common cause of mortality. Image-based computational models have been introduced seeking critical mechanical indicators, which may be used for plaque vulnerability assessment. This study extends the previous 2D critical stress concept to 3D by using in vivo magnetic resonance image (MRI) data of human atherosclerotic carotid plaques and 3D fluid-structure interaction (FSI) models to: identify 3D critical plaque wall stress (CPWS) and critical flow shear stress (CFSS) and to investigate their associations with plaque rupture. In vivo MRI data of carotid plaques from 18 patients scheduled for endarterectomy were acquired using histologically validated multicontrast protocols. Of the 18 plaques, histology-confirmed that six had prior rupture (group 1) as evidenced by presence of ulceration. The remaining 12 plaques (group 2) contained no rupture. The 3D multicomponent FSI models were constructed for each

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plaque to obtain 3D plaque wall stress (PWS) and flow shear stress (FSS) distributions. Three-dimensional CPWS and CFSS, defined as maxima of PWS and FSS from all vulnerable sites, were determined for each plaque to investigate their association with plaque rupture. Slice-based critical PWS and FSS were also calculated for all slices for more detailed analysis and comparison. The mean 3D CPWS of group 1 was 263.44 kPa, which was 100% higher than that from group 2 (132.77, $p = 0.03984$). Five of the six ruptured plaques had 3D CPWS sites, matching the histology-confirmed rupture sites with an 83% agreement. Although the mean 3D CFSS (92.94 dyn/cm²) for group 1 was 76% higher than that for group 2 (52.70 dyn / cm²), slice-based CFSS showed no significant difference between the two groups. Only two of the six ruptured plaques had 3D CFSS sites matching the histology-confirmed rupture sites with a 33% agreement. CFSS had a good correlation with plaque stenosis severity ($R^2 = 0.40$ with an exponential function fitting 3D CFSS data). This in vivo MRI pilot study using plaques with and without rupture demonstrates that 3D critical plaque wall stress values are more closely associated with atherosclerotic plaque rupture than critical flow shear stresses. Critical wall stress values may become indicators of high risk sites of rupture. Future work with a larger population will establish a possible CPWS-based plaque vulnerability classification.

Keywords

carotid artery; atherosclerosis; vulnerable plaque; stroke; MRI; plaque rupture; fluid-structure interaction

1 Introduction

Cerebrovascular events, such as stroke, are closely associated with vulnerable carotid plaques [1]. In fact, more than 60% of all cerebral infarctions are caused by rupture of a vulnerable plaque [2]. These vulnerable plaques are characterized by complex composition such as large, soft lipid pools covered by a thin fibrous cap, intraplaque hemorrhage, and inflammation/erosion conditions such as infiltration of macrophages and a scarcity of smooth muscle cells [3–5]. Currently, interventional diagnosis is based on the degree of luminal stenosis/plaque severity as measured by angiography (X-ray, MRI, ultrasound, or computed tomography). However, there is growing evidence suggesting that plaque severity alone is insufficient for identifying the critical condition [6]. MRi techniques have been shown to be able to noninvasively characterize plaque morphology and composition, and in particular, to identify fibrous cap rupture [1,4,5,7–12]. Chu et al. [11] performed serial high-spatial-resolution, multicontrast MRi studies identifying fibrous cap rupture and a penetrating ulcer into carotid atherosclerotic plaque. Plaque morphological and composition information are being added to the patient screening process for better diagnosis and treatment decisions.

Image-based computational models have been introduced seeking critical mechanical indicators for use in atherosclerotic plaque vulnerability assessment and the prediction of potential plaque rupture risk [13–27]. 2D ex vivo and in vivo magnetic resonance image (MRI)-based models, have shown that 2D local critical stress values correlated better with plaque vulnerability, as identified by histopathologic and morphological analyses than global maximum stress values [28,29]. A recent study by Tang et al. [30], using in vivo MRI-based 3D fluid-structure interaction (FSI) models for ruptured human carotid plaques, reported that mean plaque wall stress (PWS) values from ulcer nodes were 86% higher than mean PWS values from all nonulcer nodes ($p < 0.0001$). Plaque wall stress at each node was defined as plaque maximum principal stress denoted by stress- P_1 . The study provided the initial in vivo evidence that plaque rupture may be linked to higher plaque wall stress [30]. However, the results about flow shear stress (FSS), when investigated at individual patient

level, were mixed. In this paper, the previous 2D critical stress study is extended by using 3D in vivo MRI data of human carotid plaques and FSI models to identify 3D critical plaque wall stress (CPWS) and critical flow shear stress (CFSS) and to investigate their associations with plaque rupture. In particular, by using plaque samples with ulcerations, we sought to determine whether CPWS and CFSS can be used to identify the site of rupture. The association between stenosis severity (by area) measured by normalized wall index (NWI) and plaque rupture was also investigated because stenosis severity is currently the indicator for diagnosis and surgical treatment decisions.

From a mechanical point of view, plaque rupture is likely to occur at sites where mechanical stresses exceed the ultimate strength of the material. The computational models combining mechanical factors and morphologic information have been introduced by several groups to perform plaque mechanical analysis and to identify additional critical mechanical indicators for a more accurate plaque vulnerability assessment [13–31]. Holzapfel et al. introduced multilayer anisotropic plaque models and showed that stress predictions from their models varied from single-layer isotropic models by 50–200% or more [13,14]. Li et al. [20] performed structural analysis based on in vivo MRI of carotid arteries and found that wall stress was higher in symptomatic patients than in asymptomatic patients. Loree et al. [24] studied effects of fibrous cap thickness and material properties on stress level and plaque rupture. Due to the importance of artery flow and structural stress geometrical parameters, Steinman and co-workers [16–18] investigated effects of plaque geometrical features on flow behaviors including disturbed flow using realistic plaque geometries. Correlations between indicators of disturbed flow at the normal carotid bifurcation were studied using 50 normal human carotid bifurcation samples [16]. Zhu et al. [19] categorized geometric features of human coronary arteries for predicting risk of coronary artery disease using 32 left anterior descending and 35 right coronary arteries acquired from 52 patients. The influence of curvature dynamics and cyclic bending on coronary plaque stress and flow behaviors was investigated by Prosi et al. [31] and Tang et al. [32]. Vengrenyuk et al. [25] demonstrated that fibrous caps with microcalcification inclusions are associated with elevated stress levels and may be related to plaque rupture. Suo et al. [21] studied blood flow patterns in the proximal human coronary arteries seeking relationships between spatial distributions of wall shear stress and reports of plaque occurrence in literature. Tang and co-workers [26–30, 33, and 34] used image-based FSI models to quantify critical mechanical conditions, which may be related to plaque rupture and progression. Recent reviews of image-based computational modeling effort can be found in Refs. [27,32,34].

In this study, in vivo MRI data collected from 18 patients due for carotid endarterectomy within two weeks of the scan were studied. Histological assessment of the 18 carotid endarterectomy specimens determined that six plaques contained ruptures (group 1, the rupture group). The other 12 plaques were not ruptured (group 2, the nonrupture group). The CPWS, CFSS, and stenosis severity measured by normalized wall index were calculated to investigate their association with plaque rupture. The predicted rupture sites by CPWS and CFSS were then compared with the actual ruptured sites. The novelty of this study is the use of 3D flow and structural modeling to identify critical PWS and FSS based on histology-validated in vivo MRI images of plaques with and without rupture to predict actual rupture sites.

2 Methods

2.1 MRI Data Acquisition

The 3D in vivo MR images of human atherosclerotic carotid plaques from 18 patients (age: 68.7 ± 8.2 , 17 male, one female) were acquired at the Vascular Imaging Laboratory (17 patients) at University of Washington (UW) and by Dr. Woodard and Dr. Zheng's group

(one patient) at Washington University (WU) using a protocol approved by their respective institutional review boards with informed consent obtained at both locations. The details of MRI sequences can be found in Ref. [18]. In brief, all images were obtained with the following parameters: 16 cm field-of-view; 256×256 matrix size; and 2 mm slice thickness. After interpolation, the in-plane resolution was $0.31 \times 0.31 \text{ mm}^2$. The MR images were segmented by self-developed software packages (CASCADE at UW [35] and APIA at WU) to identify lipid-rich necrotic core, loose matrix, calcification (Ca), thrombus, hemorrhage, and the presence or absence of an ulcerated surface as the indicator of fibrous cap rupture [4,5,8,9,11]. Disruption was confirmed by histology after matching the histology slices to the MR images [7]. The histology-validated MRI analysis of the status of the fibrous cap resulted in six arteries with ulcerated plaques. Figure 1 illustrates a human atherosclerotic carotid plaque sample with ulceration. Figure 2 shows ten MRI slices of the plaque (displayed sequentially from the common carotid (s1) to the bifurcated internal and external carotid arteries (s3–s10)), the segmented contour plots, a slice with time-of-flight (TOF) and proton density (PD) weighted MR, and the corresponding histology image showing an ulcerated surface.

2.2 The FSI Model

Blood flow was assumed to be laminar, Newtonian, viscous, and incompressible. A no-slip condition between fluid and the vessel wall was assumed. The incompressible Navier–Stokes equations with arbitrary Lagrangian–Eulerian formulation were used as the governing equations. The vessel wall and all plaque components were assumed to be hyperelastic, isotropic, incompressible, and homogeneous. A no-slip condition between all plaque components was assumed. The details of the complete fluid–structure interaction model can be found elsewhere [33,34]. The modified Mooney–Rivlin model was used to describe the material property of each component.

$$W = c_1(I_1 - 3) + D_1[\exp(D_2(I_1 - 3)) - 1] \quad (1)$$

where $I_1 = \Sigma C_{ii}$ is the first strain invariant, $\mathbf{C} = [C_{ij}] = \mathbf{X}^T \mathbf{X}$ is the right Cauchy–Green deformation tensor $\mathbf{X} = [X_{ij}] = [\partial x_i / \partial a_j]$, (x_i) is current position, (a_i) is original position, and c_1 , D_1 , and D_2 are material parameters chosen to match the experimental measurement [34]. In this paper, the following values were chosen: vessel material and fibrous cap, $c_1 = 36.8 \text{ kPa}$, $D_1 = 14.4 \text{ kPa}$, and $D_2 = 2$; lipid core/hemorrhage $c_1 = 2 \text{ kPa}$, $D_1 = 2 \text{ kPa}$, and $D_2 = 1.5$; loose matrix $c_1 = 18.4 \text{ kPa}$, $D_1 = 7.2 \text{ kPa}$, and $D_2 = 1.5$; and Ca, $c_1 = 368 \text{ kPa}$, $D_1 = 144 \text{ kPa}$, and $D_2 = 2$. Systolic and diastolic pressure conditions used in this simulation were from the last hospital admission of each patient.

2.3 3D Geometric Reconstruction and Mesh Generation

In vivo MRI data provides plaque morphology under in vivo pressure and stress conditions. A shrink–stretch process is needed [34] to: (a) shrink the in vivo geometry to obtain a starting no-load geometry and (b) apply pressure and axial stretch to 3+–recover original in vivo geometry with computed initial stress/strain and flow conditions. This process is necessary for computational FSI models based on in vivo plaque morphology data. The shrinking rate in the axial direction was 9% for all models in this study and the shrinkage rates of lumen and outer wall were determined so that: (1) the total volume remained constant and (2) the contour of the artery after pressurization and 10% axial stretch had the best match with the in vivo geometry from MRI.

Given that advanced plaques have complex irregular geometries with component inclusions, and that the FSI model involves large deformation and large strain, as all fluid and structural

domains deform under pulsating pressure over the cardiac cycle, the 3D FSI model would normally not converge if one uses the mesh automatically generated by ADINA, version 8.5 (ADINA R&D, Inc., Watertown, MA), a commercial finite element software used to solve this model or any other software available in the current market. We therefore developed a component-fitting mesh generation technique to generate mesh for these anisotropic FSI models [32]. Using this technique, the 3D plaque domain was divided into hundreds of small “volumes” to curve-fit the irregular plaque geometry with plaque component inclusions. Ulcers were replaced with lipid cores covered by a thin cap, which was done automatically by segmentation software for uniformity. This was our best approximation for the prerule geometry of these plaque samples. 3D surfaces, volumes and computational mesh were created within the ADINA computing environment. For each plaque, about 2000–4000 small volumes were created to fit the highly irregular structure, and about 500–1000 small volumes were created for the corresponding fluid domain. These small volumes were then meshed in ADINA environment. Normally, about 100,000 hexahedral elements would be generated for the solid part and fluid part, respectively, of each plaque.

The fully coupled FSI models were solved by ADINA. Mesh analysis was performed by decreasing mesh size by 10% (in each dimension) until solution differences were less than 2%. The mesh was then chosen for our simulation. The FSI simulation was performed for three cardiac cycles until solutions became periodic and the third period was used for analysis. Plaque wall stress (stress- P_1) and flow maximum shear stress at all lumen surface nodes corresponding to peak systole pressure were extracted for analysis and were referred to as PWS and FSS, respectively, as was previously published [28–30].

2.4 3D CPWS and CFSS

The 3D CPWS and the associated critical site were determined for each plaque following the previously published critical site selection method [28] with its natural 3D extension described as follows [28]: (a) for every slice of the plaque, select all vulnerable sites defined as sites on the lumen where the plaque is likely to rupture, which included sites with a thin cap covering a large lipid core, or a cap covering calcification or other plaque component but excluded healthy sites where rupture was not possible, even if extreme stress values were found there; (b) 3D CPWS was defined as the maximum of PWS values obtained from all vulnerable sites; (c) the site where 3D CPWS was found was called the PWS critical site for the plaque; (d) the maximum of FSS values from all vulnerable sites was defined as the CFSS value for that plaque; and (e) the site where 3D CFSS was found was called the FSS critical site for the plaque. It should be noted that CFSS and CPWS may be found at different sites. 3D CPWS and CFSS were obtained from the FSI solution from each plaque. Global maximum stress- P_1 value (i.e., maximum of stress- P_1 for the entire plaque domain) for each plaque was also recorded for comparison and correlation analyses. Figure 3 presents plots of PWS (stress- P_1) and FSS for the plaque sample in Fig. 1 showing that the critical site predicted by CPWS coincided with the site of rupture and that CFSS was not able to capture the actual rupture site. It also demonstrates that global maximum stress- P_1 may occur at a healthy site where rupture is not likely to occur. More details will be given in the Sec. 3.

2.5 Stenosis Severity and Normalized Wall Index

Using in vivo MRI data, stenosis severity (by area) was measured by the normalized wall index (NWI, also called plaque burden) defined as [36]

$$\text{Normalized wall index} = \text{vessel wall area} / \text{total vessel area (including lumen)} \quad (2)$$

As the term “stenosis severity” is more frequently used by researchers and physicians, it will be used interchangeably with NWI in this paper.

2.6 Statistical Analysis

A *t*-test was used for statistical analysis to compare CPWS and CFSS results from the rupture and nonrupture groups. Stenosis and global maximum stress- P_1 values from the two groups were also compared. The difference was considered significant if $p < 0.05$.

3 Results

3D CPWS and CFSS for each plaque (total 18 plaques: six with rupture and 12 without rupture) and slice-CPWS and slice-CFSS for each slice that contained plaque components and vulnerable sites were extracted from the 3D FSI simulation results. Forty-eight (48) slices in the rupture group (group 1) and 109 in the nonrupture group (group 2) were identified for a more detailed comparison analysis. Only slices containing plaque components were selected for this purpose. Units for CPWS and CFSS were in kilo-Pascal and dyn/cm², respectively, (1 kPa = 10⁴ dyn/cm²).

3.1 Linkage Between CPWS and Plaque Rupture

The following were observed.

- a. Group 1 had a higher mean 3D CPWS value than group 2. Table 1 lists 3D CPWS and CFSS values for all 18 plaque samples studied. CFSS results will be discussed in Sec. 3.2. The mean 3D CPWS of group 1 was 263.44 ± 116.72 kPa, 100% higher than that from group 2 (132.77 ± 42.67 kPa; $P = 0.03984$).
- b. Five of the six plaque samples in group 1 had 3D CPWS critical sites coinciding with sites of actual rupture. Figure 3 shows an example where the location of the critical site was also the site of rupture.
- c. The mean slice-CPWS value of group 1 ($n = 48$) was 110.20 ± 78.33 kPa, 32% higher than that from group 2 (83.40 ± 33.42 kPa; $P = 0.00152$). (Fig. 4). The slice-CPWS percentage difference was lower than the 3D difference because both groups contained slices of minimal disease, which averaged out the differences.
- d. For the 48 slices from group 1, the mean slice-CPWS value of ulcerated slices ($n = 11$) was 196.11 ± 114.25 kPa, which was 131% higher than the slice-CPWS value from slices without ulcerations (84.65 ± 38.19 kPa, $n = 37$, $P = 0.00001$).

3.2 CFSS and Plaque Rupture

Flow shear stress has been a focal point for plaque progression and rupture research. The results using data from 3D FSI models are as follows:

- a. Group 1 had a higher mean 3D CFSS than group 2. Table 1 shows that the mean 3D CFSS of the group 1 was 92.94 ± 28.77 dyn/cm², 76% higher than that of group 2 (52.70 ± 29.76 dyn/cm²; $P = 0.01922$). (b) Two of the six plaques with prior rupture had 3D CFSS occurring at the rupture sites. (c) Slice-CFSS values show that the mean slice-CFSS values of the group 1 ($n = 48$) and group 2 ($n = 109$) were 23.87 ± 32.40 dyn/cm² and 29.67 ± 30.62 dyn/cm², respectively, (see Fig. 5). The difference was not statistically significant ($P = 0.16017$). (d) The mean slice-CFSS values of the slices with ulceration ($n = 11$) and without ulceration ($n = 37$), from group 1, were 30.85 ± 25.31 dyn/cm² and 21.79 ± 34.25 dyn/cm², respectively. The difference was not statistically significant ($P = 0.26951$).

3.3 Global Maximum Stress- P_1 values for plaque rupture

The 3D global maximum stress- P_1 between group 1 ($n = 6$) and group 2 ($n = 12$) are listed in Table 2. Although the mean value from the group 1 (273.40 kPa) was 38% higher than that from the group 2, the difference was not statistically significant ($P = 0.14745$).

3.4 Association of NWI with CPWS, CFSS, and Plaque Rupture

Slice-CFSS was closely associated with NWI ($R^2=0.52$) while slice-CPWS showed almost no correlation with NWI having a Pearson correlation coefficient of $r = 0.0161$. Figure 6(a) shows that slice-CFSS increased exponentially as NWI approached 1.0.

An exponential function fitting the data is given by

$$\text{Slice-CFSS} = 0.01878 \exp(18.328 \text{ NWI}) + 117420 (\text{dyn/cm}^2), \quad R^2 = 0.52 \quad (3)$$

Plots for 3D CPWS and 3D CFSS versus NWI are presented in Fig. 7. The fitting function is

$$3\text{D-CFSS} = 2.938 \exp(12.834 \text{ NWI}) + 391152 (\text{dyn/cm}^2), \quad R^2 = 0.40 \quad (4)$$

and 3D CPWS had a weak positive correlation with NWI Fig. 7(b); $R^2 = 0.0094$).

3.5 3D CPWS Can Better Differentiate Ruptured Plaques From Nonruptured Advanced Plaques Than Stenosis Severity

Table 3 shows that the mean NWI from group 1 was 15% higher than that from group 2 and the difference is statistically significant ($p = 0.02132$). However, for plaques with $\text{NWI} > 0.8$, the mean NWI for the nonruptured plaques ($n = 7$) was 0.89 ± 0.049 , which was not significantly different from that of the rupture group ($p = 0.0886$). At the same time, mean 3D CPWS value for this seven nonruptured plaques ($\text{NWI} > 0.8$) was 125.32 ± 25.07 , which was statistically significantly different from that (263.44 ± 116.72 kPa) of group 1 ($p = 0.00532$).

4 Discussion

4.1 3D CPWS as an Indicator for Plaque Assessment

Extending our previous 2D effort, a method to identify localized 3D CPWS and its associated critical sites was introduced in this paper. Results from plaques based on in vivo MRI data with and without rupture supported the hypothesis that localized 3D CPWS may be a good indicator for plaque assessment in three ways. (a) The mean 3D CPWS of the rupture group 1 was about 100% higher than that from the nonrupture group 2 and (b) five out of six plaques in the Rupture group had 3D CPWS appearing at the rupture site, an 83% agreement rate. The only plaque for which 3D CPWS was not able to predict the actual rupture site did have high slice-CPWS at the rupture site. In this plaque a high 3D CPWS value was present at a location with a large curvature and high flow shear stress values. (c) For the six plaques with rupture, mean slice-CPWS values of the slices with ulceration ($n = 11$) was about 131% higher than that from the slices without ulceration ($P = 0.00001$). The mean 3D CPWS value for the rupture group 1 was 260 kPa, suggesting that plaques with 3D CPWS exceeding this threshold value could be considered high risk plaques. However, even with the strong indication that 3D CPWS is associated with plaque rupture, large-scale longitudinal patient studies are needed to establish that 3D CPWS values can be used as a quantitative indicator for plaque vulnerability. Furthermore, due to the multifactorial nature

of atherosclerosis, mechanical stress indicators need to be combined with other screening tools such as blood pressure and medications to get optimal assessment.

4.2 Association of Flow Shear Stress With Plaque Rupture

There has been great interest and a considerable effort spent to find the relationship between flow shear stress and atherosclerotic plaque progression and rupture [37–40]. Although intuitively we feel there must be a relationship and our results indicate that the mean 3D CFSS value of the rupture group was about 76% higher than that of nonrupture group ($P = 0.01922$), more careful examination of slice-CFSS slice by slice revealed that (a) there was no statistically significant differences between the mean values of slice-CFSS values of the rupture group 1 and the nonrupture group 2 and (b) there was also no statistically significant differences between the mean slice-CFSS values of the slices with ulceration and without ulceration for plaques with rupture (Sec. 3.2). Only two out of six plaques with prior rupture had 3D CFSS occurring at the rupture sites, a mere 33% agreement rate. These results suggested that flow shear stress may not be a good indicator for locating the rupture site. However, high flow shear stress on the lumen surface may have long-term effects leading to endothelial dysfunction, lumen surface weakening, and eventual rupture mechanisms governing those processes require further investigation.

4.3 Association of Stenosis Severity With Plaque Rupture, CPWS, and CFSS

Stenosis severity is the major indicator currently used by physicians in patient screening and treatment decisions. In this study a statistically significant difference for stenosis severity in the rupture and nonrupture groups is present. However, the main challenge remains for researchers and physicians to differentiate plaques, which are more likely to rupture from the ones that are stable among the advanced plaques with a stenosis severity (by diameter) $>70\%$ equivalent to $NWI > 0.91$. For the plaques included in this study with $NWI > 0.8$ ($n = 13$), our results indicated that there was no statistical difference between NWI (stenosis severity by area) for the nonruptured plaques ($n = 7$) and that of the rupture group ($p = 0.0886$). At the same time, mean 3D CPWS value from the ruptured group was 110% higher than that for nonrupture plaques with $NWI > 0.8$ ($p = 0.00532$). This is a strong indication that CPWS method may provide considerable improvement over stenosis severity-based plaque assessment methods.

4.4 Limitations

Atherosclerotic plaque progression and rupture are complex processes involving many factors that require investigation from multiple disciplines. We have moved from 2D modeling to 3D modeling by using in vivo MR data. However, this work, a computational mechanical study at the organ level based on in vivo MRI data, has the following limitations. (1) The resolution of in vivo MRI data was $0.31 \times 0.31 \times 3 \text{ mm}^3$, which is a considerable limitation in the accuracy of computational predictions derived from such data. (2) Patient-specific material and plaque properties were not available therefore assumptions about the those parameters were based on previous work and available literature. (3) Lumen erosion and surface weaknesses were not considered in this study. (4) Since 15 out of the 18 plaques had a stenosis severity (by diameter) $<75\%$, turbulent flow may exist in only a few of the plaque samples studied. Therefore, the laminar flow assumption is a proper approximation [41].

5 Conclusion

Previous work using 2D structure models demonstrated that critical plaque wall stress may be a better indicator for vulnerable plaque rupture than global maximum stress conditions (index). The 2D critical stress concept was extended to 3D by using in vivo MRI data of

human carotid plaques with and without rupture and 3D multicomponent FSI models to quantify 3D CPWS and critical flow shear stress and study their association with plaque rupture and their ability to predict actual sites of rupture. Five out of the six plaque samples in the rupture group had critical plaque wall stress sites coincided with sites of rupture while only two out of the six ruptured plaques had critical flow shear stress sites coincided with sites of rupture. The mean 3D CPWS of the rupture group was about 100% higher than that from the nonrupture group ($p = 0.03984$). A threshold CPWS value of 260 kPa was identified for high risk plaques, which is consistent with previously published results [42]. Critical flow shear stress was found to correlate closely with plaque stenosis severity.

3D critical plaque stresses introduced in this paper are more closely associated with plaque rupture and can better predict sites of plaque rupture, compared with critical flow shear stresses, plaque stenosis severity, and global maximum plaque wall stresses. Large scale studies are needed to further establish quantitative relationship between 3D CPWS and plaque vulnerability, which may provide valuable information for diagnosis and prognosis of the vulnerable atherosclerotic plaque.

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(a). 3D Rendered View

(b). 3D View with Transparent Lipid Core

Fig. 1.
A rendered 3D view of a human atherosclerotic carotid plaque with prior rupture verified by the presence of ulceration

(a) T1-weighted in vivo MR-images of a Human Carotid Plaque. **(b) Corresponding Segmented Contour Plots with Components.** **(c) Presence of ulceration validated by histology.**

Fig. 2.
Selected MRI slices, segmented contours, and histological data of the carotid plaque shown in Fig. 1. (a) T1-weighted in vivo MR images (red asterisks denote the lumen); (b) segmented contours showing lumen, outer wall, and atherosclerotic components; and (c) presence of a penetrating ulceration validated by histology (S6).

Fig. 3.

Band plots of plaque wall stress (stress- P_1) and FSS for the plaque sample given in Fig. 1 showing CPWS was able to predict the actual rupture site while CFSS failed to do so. (a) A stack view of PWS, (b) a stack view of FSS, and (c) PWS plot on a longitudinal cut showing the bifurcation.

(a) Mean Slice-CPWS from Group 1 and Group 2. (b) Mean Slice-CPWS from Slices with and without Rupture from the Rupture Group 1.

Fig. 4.

Comparison of mean slice-CPWS from groups 1 and 2 and from slices within group 1 showing that higher CPWS values may be linked to plaque rupture. (a) Comparison of mean slice-CPWS values between group 1 and group 2 (110.20 ± 78.33 kPa versus 83.40 ± 33.42 kPa; $P = 0.00152$) and (b) comparison of mean slice-CPWS values between the slices with ulceration ($n = 11$) and the slices without ulcerations ($n = 37$) in the rupture group (196.11 ± 114.25 kPa versus 84.65 ± 38.19 kPa, $P = 0.00001$).

Fig. 5.

No statistically significant differences were found from comparison of mean slice-CFSS from groups 1 and 2 and from slices within group 1 with and without ulceration. (a) Comparison of mean slice-CFSS values between the group 1 ($n = 48$) and group 2 ($n = 109$), $P = 0.16017$ and (b) comparison of mean slice-CFSS values between the slices with ulceration ($n = 11$) and the slices without ulcerations ($n = 37$), $P = 0.26951$.

Fig. 6. Correlation of slice-CFSS and slice-CPWS with NWI. (a) slice-CFSS increases exponentially as NWI increases ($R^2=0.52$) and (b) slice-CPWS shows a weak correlation with NWI ($r = 0.0161$).

Fig. 7.
Correlation of 3D CFSS and 3D CPWS with NWI

Table 1
Comparison of 3D CPWS and CFSS between group 1 and group 2 (1 kPa=10⁴ dyn/cm²)

3D CPWS (kPa)		3D CFSS (dyn/cm ²)	
Group 1		Group 2	
		Group 1	Group 2
P1	457.85	P7	P1
P2	241.90	P8	P2
P3	193.31	P9	P3
P4	160.23	P10	P4
P5	348.19	P11	P5
P6	179.14	P12	P6
		P13	P13
		P14	P14
		P15	P15
		P16	P16
		P17	P17
		P18	P18
Mean ± SD	263.44 ± 116.72	Mean ± SD	Mean ± SD
		132.77 ± 42.67	92.94 ± 28.77
			52.70 ± 29.76

Table 2Comparison of 3D global maximum stress- P_1 (maximum principal stress) between group 1 and group 2

3D Global maximum plaque stress			
Group 1		Group 2	
P1	468.29	P7	233.11
P2	241.90	P8	86.68
P3	195.79	P9	216.63
P4	206.35	P10	188.90
P5	179.86	P11	256.02
P6	348.19	P12	225.89
		P13	153.97
		P14	354.39
		P15	108.03
		P16	165.06
		P17	166.84
		P18	247.86
Mean $\pm$ SD	273.40 $\pm$ 112.99	Mean $\pm$ SD	197.92 $\pm$ 71.39

Table 3

Mean NWI for groups 1 and 2

Group 1				Group 2			
No.	NWI	CPWI		No.	NWI	CPWI	
P1	0.921	457.85		P7	0.888	127.59	
P2	0.941	241.90		P8	0.947	86.68	
P3	0.961	193.31		P9	0.888	129.31	
P4	0.954	160.23		P10	0.818	165.06	
P5	0.861	348.19		P11	0.782	103.68	
P6	0.901	179.14		P12	0.783	151.90	
				P13	0.829	143.70	
				P14	0.920	114.52	
				P15	0.925	110.38	
				P16	0.663	108.03	
				P17	0.652	104.57	
				P18	0.517	247.86	
Mean $\pm$ SD	0.923 $\pm$ 0.038	263.44 $\pm$ 116.72	Mean $\pm$ SD	0.844 $\pm$ 0.087		132.77 $\pm$ 42.67	
NWI > 0.8	0.923 $\pm$ 0.038	263.44 $\pm$ 116.72	NWI > 0.8	0.888 $\pm$ 0.049		125.32 $\pm$ 25.07	