Colocalization of thin-walled dome regions with low hemodynamic wall shear stress in unruptured cerebral aneurysms

Clinical article

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Object. Wall shear stress (WSS) plays a role in regulating endothelial function and has been suspected in cerebral aneurysm rupture. The aim of this study was to evaluate the spatial relationship between localized thinning of the aneurysm dome and estimated hemodynamic factors, hypothesizing that a low WSS would correlate with aneurysm wall degeneration.

Methods. Steady-state computational fluid dynamics analysis was performed on 16 aneurysms in 14 patients based on rotational angiographic volumes to derive maps of WSS, its spatial gradient (WSSG), and pressure. Local dome thickness was estimated categorically based on tissue translucency from high-resolution intraoperative microscopy findings. Each computational model was oriented to match the corresponding intraoperative view and numerically sampled in thin and normal adjacent dome regions, with controls at the neck and parent vessel. The pressure differential was computed as the difference between aneurysm dome points and the mean neck pressure. Pulsatile time-dependent confirmatory analysis was carried out in 7 patients.

Results. Matched-pair analysis revealed significantly lower levels of WSS (0.381 Pa vs 0.816 Pa; p < 0.0001) in thin-walled dome areas than in adjacent baseline thickness regions. Similarly, log WSSG and log WSS x WSSG were both lower in thin regions (both p < 0.0001); multivariate logistic regression analysis identified lower WSS and higher pressure differential as independent correlates of lower wall thickness with an area under the curve of 0.80. This relationship was observed in both steady-state and time-dependent pulsatile analyses.

Conclusions. Thin-walled regions of unruptured cerebral aneurysms colocalize with low WSS, suggesting a cellular mechanotransduction link between areas of flow stasis and aneurysm wall thinning. (http://thejns.org/doi/abs/10.3171/2013.2.JNS12968)

Key words • aneurysm • hemodynamics • shear stress • pressure • wall thickness • intraoperative microscopy • vascular disorders

Cerebral aneurysms represent a significant public health risk and constitute the underlying cause in 85% of SAH cases. Subarachnoid hemorrhage carries a high risk of morbidity and mortality, and preventative surgical and endovascular procedures are associated with nonnegligible age-dependent risks of complication. Understanding aneurysm pathogenesis and the patient-specific risk factors associated with rupture would, therefore, be useful in clinical decision making. Several approaches have been considered, including the identification of morphological, histological, and hemodynamic features associated with aneurysm growth and subsequent rupture, with an increasing trend toward the use of CFD in evaluating the role of hemodynamic shear forces on the arterial endothelium. These studies have yielded questions regarding the relative importance of regions with high or low flow, and the attendant WSS, in the events leading to aneurysm rupture. Wall shear stress, the frictional force exerted tangentially by the circulating blood on the vessel wall, is particularly important in endothelial gene expression regulation, cellular cytoskeleton organization, and the activation of ion channels.

Aneurysm wall thickness is not easily measurable from the image data currently used in many aneurysm visualization protocols, and recent studies on CFD applied patient-specific endoluminal geometries derived from multimodal angiographic images while assuming fixed wall thickness and constant material properties. However, as a cerebral aneurysm develops, destructive remodeling is thought to occur through spatial disorganization of the endothelium and thinning of the internal elastic lamina and tunica media, with accompanying inflammatory changes, T cell and macrophage infiltration, and the release of lytic enzymes. The net effect of this complex remodeling process is a modification in wall thickness that is readily visible during microsurgical dissection and observation, with thinning regions of the aneurysm dome identified during surgical observation and correlated with the site of rupture. These changes provide a rich source of readily quantifiable data that can be used to de-
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scribe systematic intraaneurysmal differences that vary in association with risk factors such as patient sex and aneurysm size. As of yet, there have been no data on the relationship between local hemodynamic variables within the aneurysm dome and direct in vivo observation of aneurysm wall properties in human studies.

The aim of this project is to elucidate the relationship between aneurysm wall thinning and the local prevailing hemodynamics. Specifically, we hypothesize that regions of intraoperatively observable thin translucent tissue co-localize with low WSS. To test this hypothesis, we analyzed visual intraoperative microscopy data corresponding to thin and normal adjacent tissue regions on the aneurysm dome obtained during microsurgical clipping procedures. These images were assessed and correlated with the matched comprehensive CFD analysis based on corresponding 3D high-resolution endoluminal vascular models derived from preoperative catheter-based rotational cerebral angiography.

Methods

Patient Selection

All image data were obtained in patients undergoing microsurgical aneurysm clipping at Tufts Medical Center between November 2006 and May 2011. Sixteen unruptured, saccular, cerebral aneurysms with regions of thin translucent tissue were selected based on simultaneous availability of high-quality intraoperative microscopy video and high-resolution 3D angiographic data of sufficient quality for accurate segmentation, reconstruction, and computational analysis. Thin regions were defined based on color intensity with respect to the parent vessel wall and adjacent thicker nontranslucent dome regions as previously described. Ruptured aneurysms were excluded from the current study because of potential obscuration of the aneurysm dome by subarachnoid blood. The study was performed under approval by the Tufts Institutional Review Board.

Intraoperative Video

All intraoperative images were captured using a Leica M525 OH4 surgical microscope video attachment with a Sony 3-chip CCD (charge-coupled device) color digital video camera at 640 × 480 resolution during aneurysm clipping procedures as recently described. Representative intraoperative photographs of the aneurysm dome were extracted from the video data, and regions of the dome were divided into thin- and thick-walled regions based on color and translucency of the aneurysm dome (Fig. 1). Special care was taken to ensure uniform tissue hydration during region selection. Cases involving light reflection off of the tissue sampled from the parent vessel wall, 20 circumferentially selected points corresponding to the aneurysm neck, 20 points corresponding to regions of thin, translucent tissue at the aneurysm dome as determined by user examination of the corresponding intraoperative video data, and 20 points corresponding to baseline thickness areas in the remaining aneurysm sac (Fig. 3A).

Postprocessing and Comparative Analysis

Postprocessing of the CFD data sets was performed using Ensight software (version 9). A total of 80 data points, each containing WSS, WSSG, and pressure values at a given vertex were sampled in a user-blind fashion from each 3D model by a user who was blinded to the CFD results. Each aneurysm contained 20 circumferentially selected points corresponding to baseline healthy tissue sampled from the parent vessel wall, 20 circumferentially selected points corresponding to the aneurysm neck, 20 points corresponding to regions of thin, translucent tissue at the aneurysm dome as determined by user examination of the corresponding intraoperative video data, and points corresponding to baseline thickness areas in the remaining aneurysm sac (Fig. 3A). From these data, derived values of normalized WSS (NormWSS), log WSSG PD, and log WSS × WSSG product were obtained. Normalized WSS (NormWSS) values at the aneurysm dome were calculated by dividing WSS by the mean parent vessel WSS for that aneurysm. The PD was defined as the difference between each pressure value sampled at a given aneurysm dome and the mean pressure at the aneurysm neck. All statistical analyses, including the matched-pair t-test and multivariate analysis, were performed using JMP (version 8.02, SAS Institute).

Briefly, a tetrahedral mesh was generated from the vascular shell model obtained by threshold segmentation at sufficient cell count to ensure mesh density independence. Fluent software (ANSYS, Inc.) was used to solve the Navier-Stokes equations, and Ensight software (CEI Software) was used for postprocessing and sampling. Steady-state analysis was performed under the assumption of a rigid wall with nonslip and nonpenetration in all models. To validate the steady-state results of the study, pulsatile time-dependent CFD analysis (which is computationally time intensive) was performed in a subset of 7 patients using a standardized carotid pulse wave as previously described. To ensure uniformity, the inflow velocity was set to achieve a mean WSS value of 1.5 Pa in the proximal parent vessel at the 5-diameter point distal to the inflow to account for the entrance effect. Computed 3D maps of constant color with underlying WSS, WSSG, and pressure coordinates were oriented to match the intraoperative images prior to comparative analysis (Fig. 3).

Patient-specific aneurysm surface models were constructed from each 3D rotational angiographic volumetric data set using previously developed methods (Fig. 2).
Evaluation of WSS Ability to Predict Thin-Walled Dome Regions

All 16 aneurysms underwent user-blinded analysis for an assessment of the predictive value of WSS in identifying focal weakness in the aneurysm wall. Using steady-state CFD models illustrating the distribution of WSS, 20 points were selected from regions of the lowest WSS and 20 points from regions of highest WSS. Each of these images was then mapped onto constant color shells illustrating the point location with respect to surrounding aneurysm and vessel geometry. A naive evaluator then reviewed microscopy recordings and labeled each set of constant color points painted above as corresponding to either thick or thin tissue by comparing unlabeled models with the intraoperative appearance of the aneurysm. This was used to obtain a measure of test sensitivity and specificity of WSS as a predictor of aneurysm wall thickness and to evaluate its utility for noninvasive WSS approximation in the assessment of aneurysm wall thickness.

Results

Mean values are presented as the mean ± SEM. Univariate and multivariate analyses of the 16 unruptured saccular aneurysms in 14 patients were carried out with
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respect to WSS, WSSG, PD, WSS × WSSG, log WSSG, and log WSS × WSSG. The study group consisted of 2 men and 12 women, with a mean age of 52.1 years (age range 28–69 years; Table 1). The aneurysms used in this study had a mean maximal dome dimension of 4.90 mm and a mean neck size of 3.16 mm. The mean parent vessel WSS across all patients observed via steady-state analysis was 1.52 ± 0.63 Pa.

Thin, Translucent Regions Are Characterized by Lower WSS

Matched-pair analysis was performed at each sampled dome vertex for WSS, PD, and WSSG and was compared between thin translucent and thicker baseline adjacent regions (Fig. 3). The mean WSS was 54% lower in regions of the aneurysm wall corresponding with thin-walled tissue (0.38 ± 0.029 Pa) than at the thicker sampled adjacent aneurysm dome regions (0.82 ± 0.029 Pa; p < 0.0001) (Fig. 4 upper). Conversely, the PD with respect to the aneurysm neck was found to be 47% higher at thin-walled regions than at the surrounding aneurysm wall (4.38 ± 0.24 Pa vs 2.98 ± 0.24 Pa; p < 0.0001) (Fig. 5 upper) The WSSG (p = 0.168) and WSS × WSSG (p = 0.052) alone were not statistically significant, potentially due to large magnitude intraaneurysmal differences between the 2 regions, but following logarithmic transformation, both log WSSG (p < 0.0001) and log WSS × WSSG (p < 0.0001) were found to be significantly lower in thin-walled regions, consistent with colocalization of the latter with regions of relative flow stagnation (Figs. 4 lower and 5 lower).

Logistic Regression Analysis of Thin Regions of the Aneurysm Wall

A stepwise multivariate logistic regression analysis with forward selection was performed on WSS, PD, log WSSG, and log WSS × WSSG with a probability to enter of 0.25 and a probability to leave of 0.1. The only significant independent variables were found to be WSS and PD: these were combined into a multivariate logistic regression model, yielding WSS (OR 1.24 [95% CI 1.17–1.31]; χ² = 110.3, p < 0.0001) and PD (OR 0.05 [95% CI 0.03–0.09]; χ² = 61.88, p < 0.0001), with a receiver operating characteristic having an area under the curve of 0.80 for detection of thin translucent tissue.

Time-Dependent Modeling

Confirmatory dynamic time-dependent CFD simulations were performed incorporating pulsatile flow in 7 patients; these stimulations revealed no fundamental difference in the flow pattern between static and dynamic results on the observed relationship between wall thickness and focal hemodynamics. A representative case is shown in Fig. 6 with WSS temporal profile for thin and adjacent normal-thickness dome regions of a distal MCA aneurysm. Time-averaged values of log WSS, log WSSG, and log WSS × WSSG over the entire cardiac cycle were each found to be significantly lower (p < 0.0001) in thin-walled regions, consistent with results of the steady-state flow modeling. When averaged over the cardiac cycle, the mean WSS was 69% lower at regions of the aneurysm wall corresponding to thin tissue (0.22 ± 0.03 Pa) than at the surrounding regions of a thicker adjacent aneurysm wall (0.72 ± 0.03 Pa). These differences in WSS between aneurysm dome tissue thickness were also confirmed at peak systolic (thin: 0.33 ± 0.19 Pa vs thick: 0.94 ± 0.19 Pa, p = 0.0192) and end diastolic (thin: 0.16 ± 0.09 Pa vs thick: 0.52 ± 0.09 Pa, p = 0.0079) time points via matched-pair analysis.

Assessment of Low WSS as a Predictor of Translucent Thin-Walled Regions by Blinded Analysis

To further evaluate the converse predictive utility of low WSS in correlating with thin-walled tissue, additional blinded analysis was performed on each of the 16 an-

<table>
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<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Aneurysm Location</th>
<th>Max Dome Size (mm)</th>
<th>Neck Diameter (mm)</th>
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TABLE 1: Patient demographics, aneurysm location, and size
eurysms included in this study. The assumption was made that low WSS would be associated with thin-walled tissue. A naive observer blinded to the CFD results and actual WSS maps was then provided with paired constant-color 3D models of the aneurysm geometry labeled only by points corresponding to high and low WSS regions (preselected based on the CFD results) along with the intraoperative microscopy images. When asked to assign the regions to low or high WSS based on the corresponding intraoperative tissue characteristics from images corresponding to the highlighted vertices on the constant-color 3D models, the observer correctly identified 13 of 16 patients with the corresponding CFD estimate of high versus low WSS. This corresponds to a test sensitivity of 81%, indicating a potential application of WSS maps based on 3D angiography models as a noninvasive predictor of underlying aneurysm dome wall tissue structure.

**Discussion**

A relationship appears to exist between aneurysm wall thickness and prevailing hemodynamic conditions, particularly WSS. Among the saccular aneurysms in this study, low WSS and high pressure were independently found to colocalize with thin, easily visualized translucent regions of the aneurysm sac. This finding is the first to demonstrate an association between the in vivo appearance of focal degenerative thinning and local mechanical forces in naturally occurring human unruptured cerebral aneurysms.

**High Versus Low WSS**

The local hemodynamic microenvironment and its influence on the pathophysiology of cerebral aneurysms has been examined at length and is being increasingly considered an important candidate feature in the prediction of aneurysm prognosis. Nonetheless, there remain conflicting data with respect to the relative importance of high versus low WSS in aneurysm rupture. Chronic high WSS has been shown to induce luminal expansion and adaptive arterial remodeling in rodent experiments. Other animal and in vitro studies, high local hemodynamic WSS and high positive WSSG with direct flow patterns have been associated with endothelial cell depletion, migration away from the high WSS area, and molecular changes in endothelial nitric oxide synthase expression, with prolonged high WSS potentially contributing to fragmentation of the ves-

![Graph comparing on a per-aneurysm basis the WSS in thin- and thick-walled regions of the aneurysm dome. Lower: Bar graph showing the mean WSS and mean WSS normalized with respect to the mean parent vessel WSS in all regions based on regional type. *p < 0.0001.](image1)

![Pressure differential with respect to neck (Pa).](image2)

![Logarithmic transformations of WSSG and WSS × WSSG product reveal lower values in thin-walled regions consistent with flow stasis. *p < 0.0001.](image3)
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The intraaneurysmal difference in pressure observed during steady-state modeling in this study between thin- and thick-walled regions of the aneurysm dome was relatively small at 1.4 Pa. However, the colocalization of this focal higher pressure with the translucent thinner regions of the aneurysm wall suggest potentially elevated wall tension, which is approximately inversely proportional to wall thickness and proportional to transmural pressure.

Pressure at Thin-Walled Regions

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Test Sensitivity

During primary user-blinded evaluations, the use of WSS as a pure predictor of the wall thickness status at a given locus was found to yield a sensitivity of 81%. Although this relationship was correctly identified in 13 of the 16 patients studied, divergence in the remaining cases may be explained primarily by errors in model orientation as well as the presence of diffuse foci of confounding calcification that may contribute to wall thickness by a secondary mechanism. Exploration of a calcification-specific model of aneurysm growth and degeneration may merit further study.

Measurement of Wall Thickness

Wall thickness is a metric that is frequently assessed in the study of vessel wall pathogenesis. Measurement of vessel wall thickness in cerebral aneurysms, however, provides a unique challenge that has been addressed through postexcisional measurement as well as in vivo intraoperative examination. Currently, there is no established noninvasive method of directly assessing intraparistoneal elastic lamina as a proposed mechanism of aneurysm initiation. Computational fluid dynamics studies of human vasculature have also supported a role for high WSS and elevated maximum WSS in the rupture of cerebral aneurysms. Increased hemodynamic forces due to smaller vessel diameter and increased flow velocity have also been associated with the higher incidence of SAH in females over males, which parallels statistically significant sex differences in intraoperatively observed wall thickness distributions at the aneurysm dome.

In contrast, low-flow environments and low focal WSS have been theorized to contribute to wall degradation through a static deleterious endothelial pheno-
cranial aneurysm wall thickness. Although intravascular ultrasonography may serve as a potential approach, there are not yet sufficient data to support the increased risk of intracranial navigation of a sampling microwire with its attendant risk of dissection, thromboembolism, or aneurysm rupture. Recent approaches to noninvasive measurement have included the use of electrocardiographically gated CT angiography to detect pulsation at the aneurysm wall as an approximation of the thinnest regions of the aneurysm dome. In the current study, albeit limited to unruptured aneurysms, high-magnification intraoperative examination failed to show any visible pulsation at thin regions of the aneurysm wall. The availability of a noninvasive methodology for accurate aneurysm wall thickness measurement would enable future studies on the clinical assessment of its link to aneurysm rupture risk.

Study Limitations

Only a small number of cases were examined, which were limited to unruptured aneurysms located at the MCA or ACoA in the anterior circulation. As a result, the observations described in this study may not apply to ruptured cerebral aneurysms or aneurysms found in the posterior circulation. As an inherent limitation of intracranial aneurysm surgery for clipping, intraoperative microscopy did not allow circumferential visualization of the entire aneurysm dome in all cases, although at least 180° visualization of the aneurysm dome was obtained for each patient in the study. Although it is implied that thin-walled regions of the aneurysm dome are more likely to be prone to rupture and SAH, it is possible that the latter occurs in an unrelated region. While extensive experience of surgical exploration of a ruptured aneurysm would suggest otherwise, an explicit link between the thinnest regions of the aneurysm wall and the actual ultimate focus of rupture cannot be inferred from the current study. In addition, as noted in Methods, the WSS distributions in this study were obtained via modeling under the assumption of a rigid vessel wall and population-based flow parameters and thus serve only as an approximation of the underlying hemodynamics.

The aneurysms used in this study had a mean maximal dome of 4.90 mm, which is considered small, especially in light of the low rate of only 0.7% per year rupture rate found in the International Study of Unruptured Intracranial Aneurysms (ISUIA) of asymptomatic unruptured lesions smaller than 7 mm. On the other hand, aneurysms smaller than 5 mm are often encountered in clinical practice and comprise greater than 50% of ruptured aneurysms enrolled in the International Subarachnoid Aneurysm Trial (ISAT). Although one can argue that this represents the effect of bias and that ruptured lesions may represent an inflammatory process that is distinct from the pathogenesis of asymptomatic lesions, the study of small aneurysms can potentially yield important data for the understanding of aneurysm development and pathophysiology.

Multiple Mechanisms

The study was limited to the most common classified subset of unruptured aneurysms, those containing regions of thin, translucent tissue, due to the ease with which differences in intraneurysmal wall thickness may be observed, as well as a suspected divergence in aneurysm pathogenesis from entirely thin-walled sacs as seen in blister aneurysms and aneurysms with thick-walled fibrotic lesions. Differences in the distribution of wall thickness and the presence of thick, calcified tissue at the aneurysm dome may consequently alter the relative importance of the underlying WSS and pressure, and act as a confounder in the use of hemodynamic measures as a determinant of rupture risk in CFD analyses for which wall thickness is not considered.

Conclusions

The results of the current study suggest a possible unifying mechanism for aneurysm progression to rupture, whereby low WSS is associated with thinning of the wall leading to a theoretical increased wall tension in these thin regions of the aneurysm wall. This is the first in vivo study in humans linking the local microhemodynamic environment of cerebral aneurysms estimated by CFD with local variations to aneurysm wall thickness. The uncovered strong relationship between WSS and changes in intracranial aneurysm wall thickness suggest a new avenue for future investigation.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Malek. Acquisition of data: Kadasi, Dent. Analysis and interpretation of data: Malek, Kadasi. Drafting the article: Malek, Kadasi. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Malek. Statistical analysis: Malek. Administrative/technical/material support: Dent. Study supervision: Malek.

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