Characterization of Critical Hemodynamics Contributing to Aneurysmal Remodeling at the Basilar Terminus in a Rabbit Model

Eleni Metaxa, PhD; Markus Tremmel, PhD; Sabareesh K. Natarajan, MD, MS; Jianping Xiang, MS; Rocco A. Paluch, MS; Max Mandelbaum, ME; Adnan H. Siddiqui, MD, PhD; John Kolega, PhD; J Mocco, MD, MS; Hui Meng, PhD

**Background and Purpose**—Hemodynamic insult by bilateral common carotid artery ligation has been shown to induce aneurysmal remodeling at the basilar terminus in a rabbit model. To characterize critical hemodynamics that initiate this remodeling, we applied a novel hemodynamics–histology comapping technique.

**Methods**—Eight rabbits received bilateral common carotid artery ligation to increase basilar artery flow. Three underwent sham operations. Hemodynamic insult at the basilar terminus was assessed by computational fluid dynamics. Bifurcation tissue was harvested on day 5; histology was comapped with initial postligation hemodynamic fields of wall shear stress (WSS) and WSS gradient.

**Results**—All bifurcations showed internal elastic lamina loss in periapical regions exposed to accelerating flow with high WSS and positive WSS gradient. Internal elastic lamina damage happened 100% of the time at locations where WSS was >122 Pa and WSS gradient was >530 Pa/mm. The degree of destructive remodeling accounting for internal elastic lamina loss, medial thinning, and luminal bulging correlated with the magnitude of the hemodynamic insult.

**Conclusions**—Aneurysmal remodeling initiates when local hemodynamic forces exceed specific limits at the rabbit basilar terminus. A combination of high WSS and positive WSS gradient represents dangerous hemodynamics likely to induce aneurysmal remodeling.

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**Key Words:** destructive remodeling ■ regional blood flow ■ hemodynamics ■ imaging ■ mapping

Pathogenesis of intracranial aneurysms (IAs) is considered multifactorial. Locations of most IAs at proximal arterial bifurcations and along the outer curvatures of intracranial vessels implicate a preeminent role for hemodynamics.1–3 These locations represent a distinct hemodynamic microenvironment: blood flow impingement and directional changes at the wall cause an increase in the frictional force known as wall shear stress (WSS) as well as significant flow acceleration or deceleration along the wall, namely WSS gradients (WSSGs).4,5

In our previous studies of a canine carotid bifurcation model,4–6 the conversion of one common carotid artery (CCA) to a bifurcation that supplied both carotid territories led to increased flow in the feeding artery and complex patterns of increased WSS and WSSG at the periapical portions of the newly created bifurcation. Distinct types of remodeling were observed in different segments: intimal hyperplasia and matrix deposition at the apex (subjected to flow impingement), aneurysm-like morphological4,5 and molecular changes4 at the periaxial wall experiencing flow acceleration, and no changes in the distal segment of flow deceleration. Because we subjected a previously uniform carotid arterial wall to new bifurcation hemodynamics at a zero time point (on bifurcation creation), we were able to observe the development of vascular responses to specific hemodynamic microenvironments in various regions.

To further elucidate vascular responses to hemodynamic insults at existing intracranial bifurcations, we examined the hemodynamic environment and associated vascular responses at the rabbit basilar terminus in a carotid ligation model first reported by Hassler8 and re-established in our laboratory.7 We showed that increasing flow in the basilar artery, secondary to CCA ligation, resulted in nascent aneurysm development at the basilar terminus.7 In these flow-induced nascent aneurysms, outward bulging of the vessel wall is associated with destructive remodeling events: matrix degradation, loss of

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From the Toshiba Stroke Research Center (E.M., M.T., S.K.N., J.X., M.M., A.H.S., J.K., H.M.), University at Buffalo, State University of New York, Buffalo NY; Departments of Mechanical and Aerospace Engineering (E.M., M.T., J.X., M.M.), Pediatrics (R.A.P.), Neurosurgery (E.M., S.K.N., A.H.S., J.M., H.M.), Radiology (A.H.S.), and Pathology and Anatomical Sciences (J.K.), University at Buffalo, State University of New York, Buffalo, NY; and Department of Neurosurgery (J.M.), University of Florida, Gainesville, Fla.

E.M. and M.T. contributed equally to this work.

Correspondence to Hui Meng, PhD, Toshiba Stroke Research Center, University at Buffalo, State University of New York, 3435 Main St, Buffalo, NY 14214. E-mail huimeng@buffalo.edu

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were consistent with those reported by Hassler, we observed large, thin-walled aneurysms at the basilar terminus at the same location (Meng et al, unpublished data, 2010) 6 months after carotid ligation.

The precise nature of the inciting hemodynamic stress and how it relates to the initiation of the destructive remodeling at the basilar terminus has not been studied previously. To this end, we applied a hemodynamics–histology comapping technique to correlate early morphological responses (5 days after bilateral carotid ligation) at the basilar terminus with the initial, peak hemodynamic insult after ligation to gain insight into critical hemodynamics associated with the onset of the aneurysmal, destructive remodeling.

Methods

The experimental procedure is summarized in Figure 1. Detailed methods pertaining to imaging, computational fluid dynamics (CFD), and comapping were described previously.11

Animal Surgery

Eleven adult female New Zealand White rabbits (3 to 4 kg; Harlan Sprague Dawley; Indianapolis, Ind) were used in this study. A transdermal fentanyl patch (25 μg/h) was applied on the day before surgery and left on for 72 hours for analgesia. Anesthesia was induced with an intramuscular injection of a mixture of ketamine and xylazine (35 and 5 mg/kg body weight, respectively). After induction, animals were maintained on anesthesia using 2% isoflurane gas. Immediately after euthanization (IV administration of 100 mg/kg sodium pentobarbital), the posterior circulation was perfused with heparinized saline and pressure-fixed in situ at 150 mm Hg with 10% buffered neutral formalin for 30 minutes. After pressure fixation, a bifrontal craniotomy was performed, the dura was removed, and the brain, along with the brain stem and surrounding pia arachnoid coverings, was removed from the rabbit. The basilar bifurcations were then excised, along with the supporting tissue of the brain stem, embedded in paraffin, and sectioned longitudinally, 4 μm apart. Multiple consecutive sections from the median longitudinal segment of each bifurcation were stained with van Gieson and trichrome to identify the IEL and media, respectively.

Histology and Quantitation of Destructive Remodeling

Destructive remodeling was defined as presence of IEL damage, medial thinning, and outward bulging of the vessel lumen. All histological measurements were made using National Institutes of Health (NIH) ImageJ. IEL damage was defined a priori as a loss of IEL preserved, and smooth muscle and endothelial cells proliferated. In addition to these nascent aneurysms (which were consistent with those reported by Hassler), we observed large, thin-walled aneurysms at the basilar terminus at the same location (Meng et al, unpublished data, 2010) 6 months after carotid ligation.

Figure 1. Experimental procedure.

Imaging and Flow Measurement

Three-dimensional rotational digital subtraction angiography was performed immediately after ligation and before euthanization. Basilar artery flow velocity was measured using transcranial Doppler sonography (TCD; Spencer Technologies) in conscious rabbits before surgery (baseline, day 0) and on postoperative day 1, after recovery from anesthesia. The luminal geometry reconstructed from the 3D angiography gave geometric boundary conditions for CFD simulations, and TCD measurements provided inlet velocity boundary conditions.

Computational Fluid Dynamics

One of the ligated rabbits had poor angiographic image quality that did not permit image segmentation and CFD. For the remaining 7 experimental and 3 control animals, CFD was performed as de-
scribed. CFD simulates the flow motion by solving the equations governing fluid motions, giving the 3D space- and time-resolved velocity fields inside the lumen. To obtain baseline and postligation flow fields, preligation and postligation TCD velocity measurements, respectively, were used as the inlet conditions. Velocity fields, pressure fields, and WSS and WSSG distributions were calculated on the entire basilar bifurcation at baseline and day 1 after ligation, when flow velocity through the basilar artery was at its peak.

**Hemodynamics–Histology Mapping**

To register vascular damage at 5 days with the inciting peak hemodynamic insult, the histology of each rabbit was spatially mapped with its own initial postligation hemodynamic stress distribution as described. Briefly, we started with the histology section presenting the most significant IEL damage at day 5 and identified this plane in the 3D vessel geometry reconstructed from angiography at the time of euthanization (day 5). Then we located the corresponding plane in the vessel geometry at day 0. The postligation luminal WSS and WSSG (based on CFD using day-1 TCD velocity) were calculated in this plane. These hemodynamic distributions were morphed to conform to the end-point vessel geometry and overlaid onto the digitized histological image.

**Localized Comparison of IEL Damage, WSS, and WSSG**

WSS and WSSG along the luminal surface were plotted versus distance from the apex to both posterior cerebral arteries. A region of interest was defined as the region between the 2 ends of flow deceleration across the apex, thus encompassing both acceleration and deceleration zones (Figure 2). The region of interest was then divided into 100 uniform microsegments for examining the presence or absence of IEL damage. This approach was scaled for variations in bifurcation geometry and size. Further, it gave equal weight to each rabbit in the statistical analysis. The mean WSS and WSSG within each microsegment in the region of interest, as well as the presence or absence of IEL damage, were recorded for statistical analysis.

**Statistical Analysis**

To examine hemodynamic factors correlated with the IEL damage, stepwise forward logistic-regression models were constructed using SAS statistical software (SAS Institute). Mixed-regression models were used to account for repeated data in the same animal.

To identify critical WSS and WSSG values, thresholds (WSS<sub>T</sub> and WSSG<sub>T</sub>) were defined in 2 ways. Optimal threshold indicates the pair of WSS and WSSG values yielding maximum sensitivity and specificity in predicting IEL damage. These were found separately for WSS and WSSG from receiver operating characteristic analysis using Matlab software (The Mathworks, Inc.). The maximum distance of each curve from the null predictor gave the corresponding optimal threshold, whereas area under the curve indicated the discriminating ability of the threshold. Conservative threshold refers to WSS and WSSG providing maximum sensitivity given 100% specificity (i.e., the threshold above which all microsegments demonstrated injury). In receiver operating characteristic analysis, we first specified 100% specificity and then maximized sensitivity for IEL damage prediction.

**Hemodynamic Score**

To test whether the degree of initial hemodynamic insult correlated with the degree of destructive remodeling, a single hemodynamic score for each rabbit was calculated that accounts for the total vascular segment length exposed to higher-than-threshold hemodynamics (>WSS<sub>T</sub> and WSSG<sub>T</sub>) and the magnitudes of WSS and WSSG in these segments (referred to as insulted segments). Specifically, the following equation defines the hemodynamic score as total area under the WSS curve in insulted segments normalized by WSS<sub>T</sub>, plus total area under the WSSG curve in insulted segments normalized by WSSG<sub>T</sub>. The combined result is then normalized by the basilar artery diameter (D<sub>BA</sub>) to correct for variability in rabbit size:

\[
\text{Hemodynamic Score} = \frac{\sum_{x_i} (WSSdx) + \sum_{x_i} (WSSGdx)}{WSS_{T} + WSSG_{T}} \cdot \frac{1}{D_{BA}}
\]

where \(x_{i}\) and \(x_{j}\) mark the beginning and end of each insulted segment and \(\Sigma\) represents the sum of all such segments. By this definition, the larger the regions exposed to higher-than-threshold hemodynamics (>WSS<sub>T</sub> and WSSG<sub>T</sub>) and the higher the magnitude of WSS and WSSG in these regions, the stronger the hemodynamic insult. Two hemodynamic scores were calculated based on the optimal and conservative thresholds.

**Results**

**Hemodynamic Environment at the Basilar Terminus Before Surgery**

Three hemodynamic forces that act directly on the vessel wall were obtained from CFD simulations: pressure, WSS, and streamwise WSSG (spatial WSS derivative taken along streamlines). Figure 2A shows time-averaged distributions of these quantities from pulsatile CFD simulations at baseline for one basilar terminus. These quantities were distributed roughly symmetrically about the apex. Pressure (Figure 2A1) presented a local maximum at the apex corresponding to impingement, but the resulting local elevation (1 mm Hg) was rather insignificant compared with physiological blood pressures (mean blood pressure = 80 mm Hg). The WSS distribution (Figure 2A2) exhibits a local minimum at the apex, flanked by a pair of closely spaced maxima on either side. The minimum indicates flow impingement; it was nonzero because of 3D motion. Baseline WSS at the basilar terminus wall before surgery ranged from 6 (±3.5) Pa to 53 (±27.8) Pa in all animals. As flow accelerated and thus WSS increased along the streamlines away from the apex, the WSSG (Figure 2A3) was positive from the apex out to both WSS maxima before turning negative. Baseline WSSG at the basilar terminus ranged from −199 (±155) Pa/mm to 191 (±137) Pa/mm.

**Hemodynamic Insult Induced by CCA Ligation**

After bilateral CCA ligation, flow rate in the basilar artery increased 3-fold to 4-fold over baseline (average = 3.25; SD = 0.38), with concomitant changes in the basilar terminus hemodynamic environment. Pressure at the basilar terminus actually decreased after carotid ligation (by 13 mm Hg) because of higher frictional losses along the basilar artery at the increased flow rates. The magnitudes of WSS and WSSG across the basilar terminus increased whereas the WSS peak and valley locations remained the same as baseline (Figure 2B). The region of increasing WSS corresponds to positive WSSG and was termed the acceleration zone (solid shaded). Different from our previous canine bifurcation, the rabbit basilar terminus had no stagnation point; the entire region between the WSS...
Figure 2. Baseline and postligation hemodynamics at the basilar terminus. A, 3D surface distributions of baseline hemodynamics in one typical rabbit. A1, Pressure. A2, WSS. A3, Streamwise WSSG. B, Line plots of baseline (light colors) and postligation (darker colors) WSS (left) and WSSG (right) vs distance along a line shown in the 3D surface plots in A. C, Line plots of the fold increase of postligation WSS and WSSG from the baseline showing roughly 5-fold increase (ignoring discontinuity in WSSG fold increase caused by the zero denominator). D, Correlation between maximal WSS (left) or maximal WSSG (right) at the basilar terminus and the corresponding TCD-measured flow velocity at the basilar artery for individual rabbits.
maxima comprised the acceleration zone. Immediately downstream of the WSS maxima, WSSG was negative; these regions were termed deceleration zones (cross-hatched). Figure 2C plots the relative or fold increase of postligation WSS and WSSG compared with baseline, showing an ≈5-fold increase in both WSS and WSSG. The plots in Figure 2D include preligation and postligation (day 1) TCD measurements, and CFD-calculated maximal WSS and WSSG at the basilar terminus for all animals. The maximal WSS and the maximal WSSG at the basilar terminus were correlated with the corresponding TCD-measured flow velocity at the basilar artery.

Destructive Remodeling Characteristics
To assess how the vessel responded to hemodynamic insult, bifurcation tissue was examined on day 5. Day 5 was chosen because previous studies have indicated that flow-induced expansion of the basilar artery has begun by this time. The left and right columns of Figure 3 show histology of the basilar terminus (van Gieson staining). In all sham rabbits (n=3), the apex was V-shaped with a smooth wall, intact IEL, and uniform media thickness (Figure 3A). In contrast, all ligated rabbits (n=8; 7 are shown in Figure 3B–H) exhibited prominent IEL loss. The IEL-damaged regions flanked the apex (3B), extended continuously across the apex (3C), or...
concentrated on one side (3H). The IEL-damaged regions also presented medial thinning and a depression in or outward displacement of the vessel wall. In one case (Figure 3D), a deep groove was found near the apex within an IEL-damaged region. Multiple sections confirmed that this indentation was not a branch vessel.

Localization of IEL Damage in the Acceleration Region

Hemodynamics–histology comapping (Figure 3, left and center columns) reveals that IEL damage was primarily located in the acceleration zone associated with higher WSS and WSSG magnitudes compared with undamaged microsegments. The IEL-damaged and undamaged microsegments are represented on a map with their local WSS and WSSG values (Figure 4A). On the WSS–WSSG map, IEL-damaged microsegments (red circles) are concentrated on the top half (positive WSSG) and right side (high WSS values), whereas undamaged microsegments (black symbols) are distributed on the lower half and left side. The cluster on the far left near the horizontal axis was primarily from sham rabbits (triangles). This shows that the IEL-damaged segments had been exposed to high WSS and positive WSSG. To determine whether the actual WSS and WSSG values or their relative increases over baseline were the critical component for initiating aneurysmal remodeling, IEL-damaged and intact microsegments for the ligated rabbits were also plotted against the relative-fold increases of WSS and WSSG to which these microsegments were initially exposed (Figure 4B). No segregation between the damaged and undamaged groups was found, indicating that IEL damage was not a result of fold increase of hemodynamics but of the absolute levels.

Hemodynamic Thresholds for IEL Damage

The strong segregation of IEL-damaged and undamaged microsegments on the WSS–WSSG map (Figure 4A) suggests existence of a hemodynamic threshold above which IEL
loss is likely to ensue. Receiver operating characteristic analysis found that the optimal threshold was WSS = 90 Pa (sensitivity = 0.57; specificity = 0.95) and WSSG = 146 Pa/mm (sensitivity = 0.85; specificity = 0.72). Their area under the curve values were 0.80 and 0.81, respectively. A conservative threshold (specificity = 1; sensitivity = 0.4612) was obtained at WSS = 122 Pa and WSSG = 530 Pa/mm, meaning that above these values, IEL damage happened 100% of the time. These thresholds are indicated on the map in Figure 4C.

Logistic-Regression Analysis
Logistic regression showed that increased WSS and WSSG significantly increased the probability of IEL damage ($\beta = 0.0128, P < 0.0001$ for WSS; $\beta = 0.00241, P < 0.0001$ for WSSG). Inclusion of WSSG improved the predictive model; log likelihood improved from −456.22 to −228.12, and $\chi^2$ test showed this to be significant; $P < 0.0001$). The interaction term of WSS and WSSG did not have a significant effect when incorporated in the analysis. Logistic regression confirmed that the effect of relative-fold increase of WSS or WSSG on IEL damage was not significant ($P = \text{NS}$).

Extent of Destructive Remodeling Correlated With Degree of Initial Hemodynamic Insult
The destructive remodeling score at day 5 for each rabbit was plotted against the hemodynamic score calculated using the optimal (Figure 5A) and conservative (Figure 5B) thresholds.

The destructive remodeling score increased linearly with the hemodynamic score based on the conservative threshold ($R^2 = 0.90$). This means that with stronger WSS and WSSG at the basilar terminus and with larger vascular area subjected to hemodynamics above the conservative threshold, more destructive remodeling developed at day 5.

Discussion
Preferential location of aneurysms at bifurcation apices and outer curvatures of intracranial vessels has long encouraged speculation that hemodynamic forces contribute to aneurysm pathogenesis.\textsuperscript{1,2,4,12} It has been postulated that absence of a robust adventitial layer and presence of surrounding cerebrospinal fluid increase the impact of hemodynamics on intracranial vasculature compared with extracranial vessels. However, the complexity of intracranial hemodynamic...
were exposed to high WSS but not positive WSSG (ie, in the potential importance of positive WSSG. Regions that accompanied by positive WSSG, providing strong evidence of aneurysmal remodeling occurred where high WSS was ac-

ing at intracranial bifurcations. These findings are corroborated dangerous hemodynamics likely to trigger destructive remodel-

ment, suggests a threshold phenomenon: destructive remodel-

ing, but the probability increases when both are present. Further, WSS and WSSG not only predict the IEL damage, but when their effect is assessed by the hemodynamic score, they also predict the severity of overall destructive remodeling, including IEL loss, media thinning, and luminal bulging.

Sharp segregation of IEL-damaged from undamaged re-

gions, when mapped according to hemodynamic environ-

ment, suggests a threshold phenomenon: destructive remodel-

ing takes place when local hemodynamic forces exceed tolerable limits for homeostasis. We considered such limits in 2 ways, with a conservative threshold performing better at predicting destructive remodeling.

Although destructive remodeling was strongly associated with higher WSS and WSSG values (Figure 4A), it bore no correlation with the relative-fold increases in WSS and WSSG from baselines (Figure 4B). This suggests that the remodeling at the basilar terminus is a response to specific magnitudes of hemodynamic insult. In other words, the wall is not responding to a proportional change but to an absolute level of insult. We noticed that at day 5, areas flanking the apex displayed destructive damage (IEL loss and media thinning or bulging) more frequently than the apex itself, although the latter experienced higher relative-fold increases in WSS and WSSG (albeit lower absolute postligation insult).

Thus, we speculate that there exist certain WSS and WSSG (albeit lower absolute postligation insult). This finding is consistent with our previous results from a canine carotid bifurcation model, in which well-defined impinging flow produced aneurysm-like remodeling in high-WSS positive-WSSG regions.1–6 The relevance of this finding to human IAs requires additional study.

Scant knowledge exists about the effect of high WSSG and only in conjunction with low-WSS conditions14,15 with a propensity for atherogenesis.14 The role of WSSG in high-WSS conditions such as near a bifurcation apex is unknown. Research into how endothelial cells sense the spatial gradient (positive or negative) is substantially lacking. Preferential localization of destructive remodeling in the positive WSSG region, as found in this study, suggests that positive and negative WSSG forces act differently on the endothelium. For WSSG >0, the flow drag force (ie, WSS) on the endothelium increases along the flow direction, thus generating a net stretching force within the luminal surface of the endothelium, whereas for WSSG <0, decreasing drag force imposes a net compression on the luminal surface. If this imposes a sufficiently large pulling force on endothelial cell junctions, it could impair normal endothelial function and cause destructive remodeling. Because destructive remodeling is confined in the region with not only positive WSSG but also high WSS, the mechanisms initiated by such a hemodynamic environment still require additional exploration.

Certain limitations of this study should be noted. First, we only correlated the peak hemodynamic insult (a single time-point) with morphological changes at a later timepoint and did not perform a longitudinal study. Second, the dangerous hemodynamic conditions were identified in reference to the basilar bifurcation and not other locations. Third, well-known simplifications were used in CFD modeling. Finally, translation of these findings to human IAs requires additional investigation because other factors such as hypertension, smoking, female gender, and familial preponderance are also associated with aneurysm formation.16,17

Summary and Conclusion

Increased flow onto the basilar terminus exerts significant hemodynamic insults as elevated WSS and WSSG across and abutting the basilar apex. These hemodynamic stresses initiate morphological changes that localize in high-WSS, positive-WSSG regions and bear specific hallmarks also noted in human IAs. These destructive morphological changes were noted in our model despite the elimination of many confounding features relevant in human aneurysmal disease (eg, smoking and hypertension). Inclusion of such features would likely lower the hemodynamic threshold for aneurysmal initiation and potentially increase vascular wall vulnerability to WSS and WSSG abnormalities.

To our knowledge, this is the first time histological and CFD techniques have been combined to evaluate the interplay of hemodynamic factors with intracranial vascular remodeling. Future studies will investigate molecular mechanisms of vascular response to these hemodynamic insults. Clinical studies to determine human hemodynamic thresholds are needed to assess the relevance of these finding to human IAs.
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References
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The article entitled, “Characterization of Critical Hemodynamics Contributing to Aneurysmal Remodeling at the Basilar Terminus in a Rabbit Model,” by Metaxa et al, which published in the August 2010 issue of the journal (Stroke. 2010;41:1774–1782), the authors failed to credit the source of images that were adapted from a previously published article by Tremmel et al. “Mapping vascular response to in vivo hemodynamics: application to increased flow at the basilar terminus” Biomech Model Mechanobiol. 2010;9:421–434.

Specifically, insets in Figure 1 depicting a typical angiograph, histological section, and overlay of CFD calculations on histology were adapted from panels 1, 3, and 4, respectively, of Tremmel’s Figure 1. The representative images and graphs in Figure 3 were adapted from panels B–D of Tremmel’s Figure 8. The copyright of the adapted images belongs to Springer-Verlag, publishers of Biomechanics and Modeling in Mechanobiology.

The authors regret this error. These errors have been corrected in the online version of the article.