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Deviation from optimal vascular caliber control at middle cerebral artery bifurcations harboring aneurysms

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ABSTRACT

Cerebral aneurysms form preferentially at arterial bifurcations. The vascular optimality principle (VOP) decrees that minimal energy loss across bifurcations requires optimal caliber control between radii of parent (r_0) and daughter branches (r_1 and r_2): $r_0^n = r_1^n + r_2^n$, with n approximating three. VOP entails constant wall shear stress (WSS), an endothelial phenotype regulator. We sought to determine if caliber control is maintained in aneurysmal intracranial bifurcations. Three-dimensional rotational angiographic volumes of 159 middle cerebral artery (MCA) bifurcations (62 aneurysmal) were processed using 3D gradient edge-detection filtering, enabling threshold-insensitive radius measurement. Radius ratio (RR)$= r_0^3/(r_1^3 + r_2^3)$ and estimated junction exponent (n) were compared between aneurysmal and non-aneurysmal bifurcations using Student t-test and Wilcoxon rank-sum analysis. The results show that non-aneurysmal bifurcations display optimal caliber control with mean RR of 1.05 and median n of 2.84. In contrast, aneurysmal bifurcations had significantly lower RR (0.76, $p < .0001$) and higher n (4.28, $p < .0001$). Unexpectedly, 37% of aneurysmal bifurcations revealed a daughter branch larger than its parent vessel, an absolute violation of optimality, not witnessed in non-aneurysmal bifurcations. The aneurysms originated more often off the smaller daughter (52%) vs. larger daughter branch (16%). Aneurysm size was not statistically correlated to RR or n. Aneurysmal males showed higher deviation from VOP. Non-aneurysmal MCA bifurcations contralateral to aneurysmal ones showed optimal caliber control. Aneurysmal bifurcations, in contrast to non-aneurysmal counterparts, disobey the VOP and may exhibit dysregulation in WSS-mediated caliber control. The mechanism of this focal divergence from optimality may underlie aneurysm pathogenesis and requires further study.

1. Introduction

It has been suggested that the cerebral arterial network follows to some extent the optimal design of biological vascular structures (LaBarbera, 1990; Pries et al., 1995), which enforces a minimization of metabolic cost on the expenditure of energy a system requires to build and maintain its infrastructure while performing its physiological tasks (Murray, 1926; Rosen, 1967). In the case of vascular trees, the optimality principle dictates the design of the branching hierarchy needed to maintain continuity of flow while minimizing energy losses at bifurcations, which leads to constant wall shear stress (WSS) across arterial bifurcations. This vascular optimality principle (VOP) (Zamir, 1976) is a parametric optimization model expressed as a balanced relation between the sizes and the angles of parent and daughter vessels. This principle of optimal caliber control states that the radius of the parent vessel (r_0) dictates the radii of its daughter branches (r_1, r_2, ..., r_i) according to the formula $r_0^n = r_1^n + r_2^n + \ldots + r_i^n$, in which n is the junction exponent. According to Rosen (1967) and confirmed by Rossitti and Lofgren (1993) and Ingebrigtsen et al. (2004), in human cerebral arterial bifurcations the junction exponent n approximates the theoretical value of 3. Previous studies have shown that arterial bifurcations in animals and humans, including the cerebral arterial tree, follow this golden rule (Rossitti and Lofgren, 1993; Zamir et al., 1983), mediated by an underlying endothelial regulatory mechanotransduction aimed at maintaining WSS constant on the arterial side. This regulatory pathway is thought to be a locally controlled global feedback loop, in which WSS is sensed by endothelium and transduced by the latter to regulate its autocrine and paracrine growth factor tion (Malek et al., 1999). The latter then signals to the smooth muscle cells, fibroblasts, and the extracellular matrix to alter vessel wall structure in such a manner as to maintain a constant wall shear, which constitutes a minimum energy expenditure state described by Murray's Law (LaBarbera, 1990; Langille and O'Donnell, 1986;

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Murray, 1926). The primordial role of the endothelium in this feedback loop has been previously demonstrated by Langille and O'Donnell (1986).

Some concerns have been raised regarding the application of VOP to bifurcations within the circle of Willis (Ingebrigtsen et al., 2004), and indeed research indicates that the hemodynamics within the circle of Willis do not follow VOP, likely because of the confluence of flow from the anterior and posterior communicating arteries (Alnaes et al., 2007; Ingebrigtsen et al., 2004). However, bifurcations of cerebral arteries outside the circle of Willis, such as anterior cerebral artery branches, have been shown to follow VOP (Ingebrigtsen et al., 2004; Rossitti and Lofgren, 1993).

The middle cerebral artery (MCA) bifurcation is one of the most common sites for aneurysm development (Juvela et al., 2000). With the advent of improved noninvasive vascular imaging methods, MCA aneurysms are often discovered incidentally. The prevalence of MCA aneurysms and consequent angiographic availability, coupled with the relatively larger size of MCA parent and daughter vessels, makes MCA bifurcations excellent candidates for evaluating the relationship of bifurcation size ratios and aneurysmal involvement. While other studies have investigated the anatomical differences between control and aneurysmal MCA bifurcations (Sadatomo et al., 2013), in this study we evaluate MCA bifurcations in the context of optimal caliber control as stated by VOP. More specifically, the objective of this study was to (1) confirm whether non-aneurysmal MCA bifurcations follow the golden rule of VOP and (2) test the hypothesis that the radii of aneurysm-bearing MCA bifurcations deviate from optimality due to local abnormal flow-mediated vascular caliber control.

2. Methods

2.1. Patient selection

All patients treated for intracranial aneurysms over an eight-year period were eligible for inclusion if high-resolution 3D catheter-based angiographic datasets were available. All MCA bifurcations harboring aneurysms, excluding mycotic and fusiform aneurysms, were consecutively included. Additionally non-aneurysmal MCA bifurcations from patients with aneurysms at other locations, as well as control patients (patients without aneurysms who had undergone cerebral angiography for different indications, excluding patients with familial history of intracranial aneurysms) were also included (Fig. 1). All angiograms were performed on unruptured aneurysms or in the acute setting of rupture (within 24–36 hours), before the possibility of vasospasm onset. Data on patient age, gender, and aneurysm rupture status was collected from a prospectively maintained database. The study was approved by Tufts Health Sciences Campus Institutional Review Board.

2.2. Data acquisition

Three-dimensional cerebral angiograms were obtained from either Philips Integris (Bothell, WA) or Siemens Artis (Malvern, PA) biplane systems and reconstructed using their respective clinical software package, to yield a 3D volumetric dataset. The dataset was then imported into and processed in the Amira visualization software platform version 5.4 (FEI Visualization Sciences Group, Burlington, MA).

2.3. Morphological feature extraction

Similar to Bescos et al. (2005), 3D gradient edge-detection filtering was employed in order to avoid the operator bias involved in manual thresholding and level choice of the aneurysm surface, which often limits quantitation in 3D

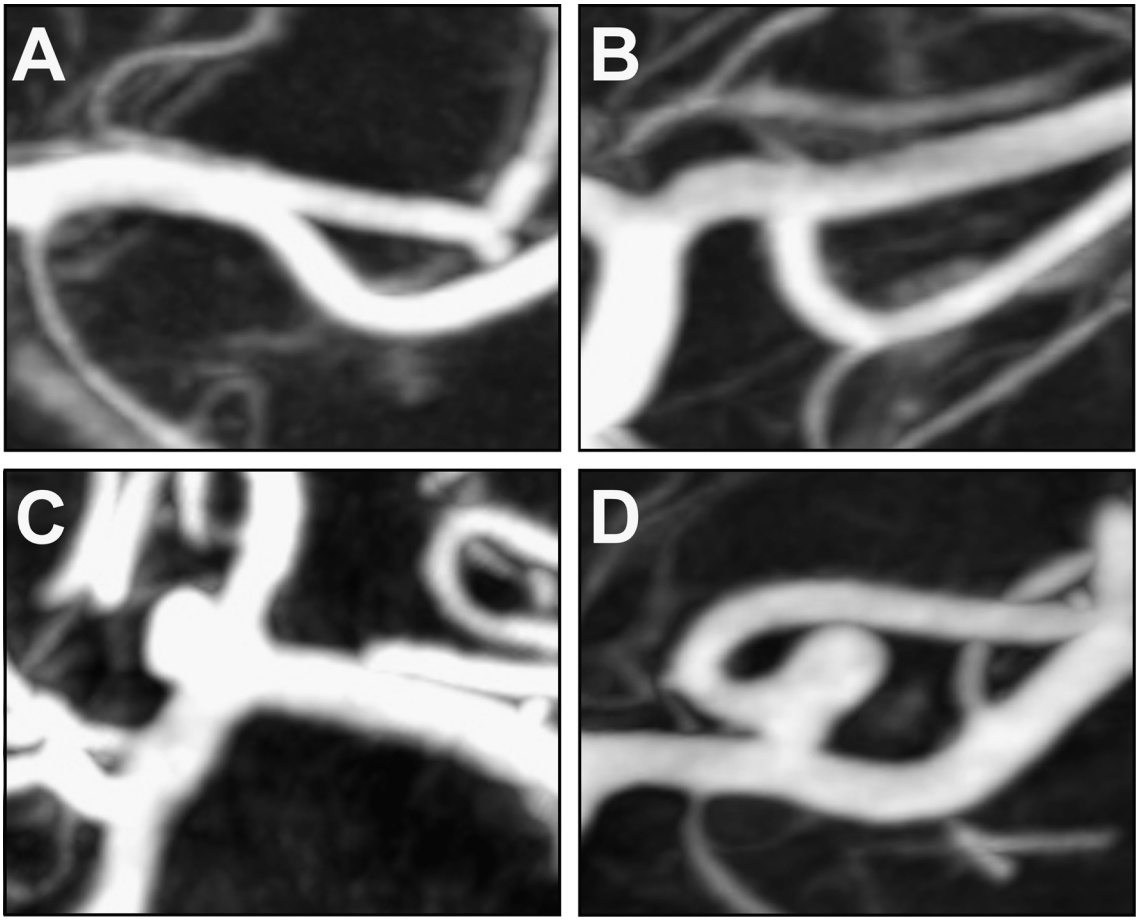

Fig. 1. Maximum intensity projection of 3D cerebral angiography showing (A) a control MCA bifurcation from a patient with no cerebral aneurysms, (B) a non-aneurysmal MCA bifurcation from a patient harboring an aneurysm on the internal carotid artery, and (C-D) aneurysmal MCA bifurcations.