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In vivo assessment of rapid cerebrovascular morphological adaptation following acute blood flow increase

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Abstract

Object—Pathological extremes in cerebrovascular remodeling may contribute to basilar artery (BA) dolichoectasia and fusiform aneurysm development. Factors regulating cerebrovascular remodeling are poorly understood. To better understand hemodynamic influences on cerebrovascular remodeling, we examined BA remodeling following common carotid artery (CCA) ligation in an animal model.

Methods—Rabbits were subjected to sham surgery (3 animals), unilateral CCA ligation (3 animals), or bilateral CCA ligation (5 animals). Transcranial Doppler ultrasonography and rotational angiography were used to compute BA flow, diameter, wall shear stress (WSS), and a tortuosity index on Days 0, 1, 4, 7, 14, 28, 56, and 84. Basilar artery tissues were stained and analyzed at Day 84. Statistical analysis was performed using orthogonal contrast analysis, repeated measures analysis of variance, or mixed regression analysis of repeated measures. Statistical significance was defined as a probability value < 0.05.

Results—Basilar artery flow and diameter increased significantly after the procedure in both ligation groups, but only the bilateral CCA ligation group demonstrated significant differences between groups. Wall shear stress significantly increased only in animals in the bilateral CCA ligation group and returned to baseline by Day 28, with 52% of WSS correction occurring by Day 7. Only the bilateral CCA ligation group developed significant BA tortuosity, occurring within 7 days postligation. Unlike the animals in the sham and unilateral CCA ligation groups, the animals in the bilateral CCA ligation group had histological staining results showing a substantial internal elastic lamina fragmentation.

Conclusions—Increased BA flow results in adaptive BA remodeling until WSS returns to physiological baseline levels. Morphological changes occur rapidly following flow alteration and do not require chronic insult to affect substantial and significant structural transformation. Additionally, it appears that there exists a flow-increase threshold that, when surpassed, results in significant tortuosity.

Keywords

basilar artery; carotid artery occlusion; dolichoectasia; rabbit; tortuosity; wall shear stress

Pathological extremes in cerebrovascular remodeling may contribute to cerebrovascular ectasia and fusiform aneurysm development. Factors regulating normal adaptive as well as pathological remodeling remain unclear but may be related to atherosclerosis, connective tissue disorders, or hypertension (through altered hemodynamics).^{12,23} Cerebral artery dilation and elongation often involve the vertebral artery and/or BA and have been linked to a megadolichobasilar anomaly or dolichoectasia (dilatative arteriopathy).^{3,7} This condition is uncommon but may cause serious neurological symptoms, including ischemic attack, compression of the brainstem and cranial nerves, or subarachnoid hemorrhage.^{1,4,6,33} Cases of BA ectasia and carotid artery occlusion have been reported, but no clear correlation was made.^{13,32} In animals with carotid artery occlusion, the BA enlarges its luminal size to compensate for the increased flow.⁸

A common feature found in ectatic BAs are defects or gaps in the IEL similar to those found in arteries that experience increased flow.^{18,25} It is possible that BA ectasia is a flow-modulated event. Basilar artery remodeling to compensate for altered physiological conditions may lead to dolichoectasia and associated complications. The pathophysiological factors that regulate vessel geometry are not well understood. To better understand these phenomena, we examined BA geometry adaptation following CCA ligation using serial TCD ultrasonography imaging measurements and 3D rotational angiography.

Methods

Animal Care

Adult female New Zealand white rabbits (each weighing 3–4 kg) were selected to allow accurate BA imaging and easy access to TCD ultrasonography velocity measurement. The animals were sedated using ketamine and xylazine and then randomly subjected to sham surgery (in 3 animals), unilateral CCA ligation (in 3 animals), or bilateral CCA ligation (in 5 animals) via a midline cervical incision. All procedures were performed in accordance with institutional guidelines for animal experimentation and approved by the University at Buffalo Animal Care and Use Committee.

Imaging Procedures

Three-dimensional rotational angiography was performed on postprocedure Days 0, 4, 7, 14, 28, 56, and 84 in an Infinix Vx-i (Toshiba Medical Systems) angiography suite. Contrast material was injected via a 4 Fr sheath in the ligated carotid artery (postprocedure Days 0 and 1), femoral artery, or central ear artery (postprocedure Days 4, 7, 14, 28, 56, and 84). The BA diameter was measured over its entire length at 6 different locations with the aid of calibration beads placed on the rabbit's head during image acquisition.

Flow Analysis and Hemodynamic Parameters

Transcranial Doppler ultrasonography (Spencer Technology) velocity measurements at the BA were obtained before ligation and on postprocedure Days 1, 4, 7, 14, 28, 56, and 84. Using the measured velocity and mean BA diameter measured from angiography images, the BA flow (Q) and WSS were estimated as follow:

$$Q = V \times A,$$

where V is the velocity and A is the BA cross-sectional area.

$$WSS = 4Q\mu/(\pi \times r^3),$$

where μ is blood viscosity ($0.0035 \text{ N} \times \text{s/m}^2$) and r is BA radius.

Geometric Parameters

The 3D geometry from the vertebrobasilar junction to the basilar terminus was reconstructed and used to quantify the tortuosity index (TI), a previously described measure of tortuosity.²⁹ Briefly, the tortuosity index is defined as

$$TI = (BA \text{ length} - SD)/SD,$$

in which “BA length” is defined as the length of the BA centerline,² and “SD” is defined as the straight line distance connecting the vertebrobasilar junction and the BA terminus.

In addition, the percentage change of the BA diameter is also quantified and defined as

$$BA \text{ diameter change (\%)} = \frac{BA \text{ diameters at given day} - BA \text{ diameter preligation}}{BA \text{ diameter preligation}} \times 100$$

The percentage changes of flow rate and WSS are defined similarly.

Tissue Preparation

Immediately after the animals were killed (on Day 84) via the administration of a solution of pentobarbital, the arteries were perfused at 150 mm Hg for 20 minutes using 10% formalin. The brain was then carefully removed and fixed in 10% formalin for at least 24 hours. Finally, the tissues were sliced longitudinally (4-μm thickness) and stained with elastica van Gieson to show elastin.

Statistical Evaluation

Statistical analysis was performed using orthogonal contrast analysis to evaluate within-group changes over time as well as repeated measures ANOVA (flow, BA diameter, and WSS) or mixed regression analysis of repeated measures (tortuosity index) to evaluate between-group overall population data. Baseline levels were treated as a covariant within the models to account for baseline population disparities. Differences were determined to be significant when the probability value was < 0.05. All calculations were performed using SYSTAT (for orthogonal analysis and repeated measures ANOVA) and SAS (for mixed regression analysis of repeated measures).

Results

Flow Analysis and Hemodynamic Parameters

Basilar artery flow increased slowly after the procedure in the unilateral CCA ligation group, peaked at Day 7, and remained stable thereafter (Fig. 1; Table 1). In contrast, the BA flow in the bilateral CCA ligation group increased drastically immediately after surgery (190% increase from baseline flow rate), with continued elevations beyond Day 14. Orthogonal contrast analysis demonstrated significant BA flow elevations immediately after the procedure in both ligation groups, with ANOVA demonstrating a statistically significant difference between all groups ($F [14,35] = 2.10, p < 0.05$) and post hoc analysis showing statistical significance for the bilateral CCA ligation group compared with the sham or unilateral CCA ligation group but not for the unilateral CCA ligation compared with the sham group.

The BA diameter increased significantly in both ligation groups, with the greatest rate of change occurring within the 1st week following ligation (Fig. 2; Table 1). The BA diameters in the unilateral CCA ligation group plateaued after the 1st week, whereas BA diameters in the

bilateral CCA ligation group continued to gradually increase beyond Day 28. Once again, population differences existed after repeated measures ANOVA ($F [14,35] = 5.03, p < 0.001$), but post hoc testing demonstrated significance only for the bilateral CCA ligation group versus the sham or the unilateral CCA ligation groups.

The BA WSS increased in both ligation groups immediately after surgery, but only the bilateral CCA ligation group reached statistical significance after orthogonal contrast analysis (Fig. 3; Table 1). Likewise, ANOVA analysis demonstrated true between-group differences in WSS ($F [14,35] = 8.22, p < 0.001$), but only the bilateral CCA ligation group compared with the sham or unilateral CCA ligation groups reached post hoc statistical significance. With morphological alteration of the BA, the bilateral CCA ligation group animals reduced their WSS to nonsignificant baseline-equivalent levels by Day 28.

Geometric Parameters

Orthogonal contrast analysis demonstrated that bilateral CCA ligation group animals developed significant BA tortuosity within 1 week of ligation, whereas the sham and unilateral CCA ligation groups did not. Mixed regression analysis of repeated measures also revealed between-group differences for the bilateral CCA ligation group, compared with the unilateral CCA ligation and sham groups. This difference can be visually appreciated in the morphological changes exhibited in Fig. 4. Once morphological alterations occurred, they remained throughout the study period with no evidence of regression back to preprocedural geometries.

Histological Analysis

In both the sham and unilateral CCA ligation groups, histological staining indicated that the IEL was well preserved, remaining continuous and intact (Fig. 5A and B). However, the IEL was substantially disrupted in the bilateral CCA ligation group, intermittently disappearing or becoming thinned (Fig. 5C).

Discussion

Our data demonstrate that BA blood flow increased significantly greater in the bilateral CCA ligation group than in the unilateral CCA ligation group. This is likely secondary to the BA becoming the only cerebral blood flow conduit in the bilateral CCA ligation group animals, whereas the unilateral CCA ligation group maintained a patent carotid artery to provide compensatory cerebral blood flow. In either case, increased blood flow initiated BA remodeling, an active process that resulted in structural changes to compensate for altered hemodynamics.

Wall shear stress arising from friction of blood flow against the vascular wall is a strong determinant of arterial remodeling.¹⁶ Our data demonstrate that the elevated WSS was reduced to baseline levels following morphological adaptation. This finding is consistent with data showing that vessels remodel in response to long-term flow changes to maintain a constant baseline shear level.^{10,14,15} However, our results demonstrate that structural changes can occur acutely with drastic and rapid morphological change. Additionally, it has been postulated that the baseline shear level is 10–15 dyne/cm² in all arteries, regardless of the location in the arterial network or the size of the animal (with the exception of rodents, in which the values are closer to 30–35 dyne/cm²).¹⁶ We found instead that rabbit BAs are exposed to a baseline WSS of approximately 130–140 dyne/cm², which is much higher than previously believed. A single constant WSS value across different arterial sizes, locations, or species requires further investigation. In fact, an allometric scaling law relating WSS and body mass has been proposed to be able to scale WSS across species.¹¹

Acute or chronic changes in WSS are perceived through molecular sensors, such as integrins and/or mechanosensitive ion channels on endothelial cells, that produce signals for vascular adaptation.^{5,10,16} Under chronic high WSS, endothelial cells produce matrix metalloproteinases that cause mild extracellular matrix degradation in the vessel wall to allow luminal expansion.^{26,31} In addition, in response to high WSS, endothelial cells also produce several growth factors that stimulate cell proliferation.^{24,28} Internal elastic lamina degradation allows the proliferating cells to migrate into new enlarged areas and allows smooth muscle cells to reorientate in the media to adapt to arterial enlargement.²⁶ As the arterial diameter increases, the WSS reduces and the matrix degradation stimuli fade.

Interestingly, although it took the bilateral CCA ligation group's BAs between 14 and 28 days to return to nonsignificant WSS levels following the postprocedural 2.5-fold WSS increase, 52% of the correction occurred within the 1st week. Excessive WSS elevation appears to lead to severe matrix degradation and a more rapid rate of morphological change, possibly contributing to the development of tortuosity. Although not conclusive, the severely degraded IEL in the bilateral CCA ligation group lends confidence to this hypothesis. This is also supported by our observation of rapid vessel remodeling, rather than the more chronic rate of change normally assumed.^{10,14,15}

Internal elastic lamina gaps and fragmentation are hypothesized to be necessary in arterial enlargement, because elastin is one of the key constituents of vascular wall integrity.^{25,26} However, the elevated WSS in the unilateral CCA ligation group did not induce the massive IEL degradation found in the bilateral CCA ligation group. It is possible that massive IEL degradation is a flow-dependent event that requires certain WSS thresholds to trigger the degradation process. Our data suggested that the WSS increase threshold necessary to induce massive IEL degradation is somewhere between 25% (the unilateral CCA ligation group WSS increase) and 140% (the bilateral CCA ligation group WSS increase).

The massive IEL disruption noted in BAs subsequent to bilateral CCA ligation may be related to the development of tortuosity. The focally fragmented IEL along the BAs in the bilateral CCA ligation group suggests local vascular structure weakening. When subjected to luminal pressure, these weakened areas may produce asymmetric regions of increased dilation, thereby initiating BA tortuosity. Our data suggest that the development of BA tortuosity is abrupt, occurring within 1 week after ligation. This finding supports the contention that vessels can undergo an acute remodeling process. Further investigation is required to better define the role of IEL degradation in BA dilation and elongation.

The change in arterial geometry from a straight segment to a tortuous branch can lead to sluggish flow and predispose the artery to thrombus formation or lipid deposition, potentially inducing atherosclerotic changes.^{7,30} The onset of atherosclerotic changes in intracranial arteries could further agitate the arterial structures' dilation and tortuosity through inflammatory cell infiltration and continued wall structure degradation.^{27,30} Some authors argue that atherosclerosis is the reason for tortuosity and dilation of an intracranial artery, but the absence of atherosclerosis in highly tortuous and dilated BAs has been reported.^{20,21} In the current study, tortuosity and dilation of the BAs were not induced by atherosclerotic changes but rather through hemodynamic alterations. Atherosclerosis or aneurysms associated with tortuous and dilated BAs could be outcomes of arterial remodeling rather than inciting events.²⁹

In addition to BA enlargement and morphological adaptation, we also observed aneurysmal morphological changes at the basilar terminus. These findings are discussed in a separate paper.⁹ In that paper, an index characterizing early aneurysmal changes at the basilar terminus was found to be dose-dependent with the degree of BA flow increase. In a separate study, Meng et

al.¹⁹ spatially mapped the local hemodynamic environment with aneurysm-like destructive remodeling events near the apex of a surgically created bifurcation in canines; the aneurysm-like changes were attributed to de novo impinging hemodynamics characterized by a combination of both high WSS and high WSS gradients. Taken together, these data implicate hemodynamic changes as critical to both physiological, as well as pathological, vascular remodeling.

Our data support a major role for hemodynamics in the pathogenesis of BA enlargement. We recognize that BA enlargement is likely a multifactorial process and the contribution of arteriopathies, such as connective tissue disorders,^{17,22} or congenital anomalies or minor trauma, require further exploration.

Conclusions

Our data demonstrate that increased BA flow results in adaptive BA diameter increases until WSS returns to baseline levels. Morphological changes can occur rapidly following flow alteration and do not require chronic insult to effect substantial and significant structural transformation. It appears that there exists a flow-increase threshold (~ 25–140% increase in baseline WSS) that, when surpassed, results in the development of significant BA tortuosity. The nature of biological responses to mechanical flow changes is an important and developing field of cerebrovascular investigation. The data presented provide an improved understanding of pathological processes involved in BA adaptive remodeling.

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Abbreviations used in this paper

ANOVA	analysis of variance
BA	basilar artery
CCA	common carotid artery
IEL	internal elastic lamina
TCD	transcranial Doppler
WSS	wall shear stress

Fig. 1.
Line graph showing the postprocedural BA flow measurements among the 3 groups. BCCA-L = bilateral CCA ligation group; UCCA-L = unilateral CCA ligation group.

Fig. 2.
Line graph showing the postprocedural BA diameter measurements among the 3 groups.

Fig. 3.
Line graph showing the postprocedural BA WSS measurements among the 3 groups.

Fig. 4. Postprocedure BA rotational angiography images and their corresponding tortuosity index (TI) values at Days 0, 7, 14 and 84.

Fig. 5. Photomicrographs showing BA morphological changes at Day 84 in each of the 3 groups. Histological staining indicated that the IEL (*arrows*) was well preserved in the sham control (A) and UCCA-L groups (B) but was substantially disrupted in the BCCA-L group (C). Elastica van Gieson, original magnification $\times 400$.

TABLE 1
Summary of the BA postprocedural measurements in each of the 3 groups at 8 different time points *

Measurement	Group	Day 0	Day 1	Day 4	Day 7	Day 14	Day 28	Day 56	Day 84
BA flow (ml/min)	sham	14.69 ± 2.52	14.54 ± 4.67	17.28 ± 7.55	16.18 ± 4.77	14.43 ± 2.33	13.04 ± 2.57	13.83 ± 1.67	16.02 ± 4.64
	UCCA-L	10.86 ± 3.02	12.65 ± 4.02	22.89 ± 5.47	24.93 ± 7.07	20.96 ± 8.09	22.33 ± 7.94	21.80 ± 8.78	22.56 ± 10.02
BA diameter (mm)	BCCA-L	10.65 ± 2.83	31.43 ± 11.86	41.89 ± 13.72	45.21 ± 16.08	52.53 ± 16.71	54.98 ± 9.00	48.47 ± 12.70	45.75 ± 10.95
	sham	0.83 ± 0.06	0.84 ± 0.07	0.85 ± 0.7	0.86 ± 0.08	0.84 ± 0.07	0.81 ± 0.08	0.85 ± 0.07	0.89 ± 0.12
BAWSS (dyne/cm ²)	UCCA-L	0.78 ± 0.10	0.82 ± 0.11	0.95 ± 0.13	1.00 ± 0.13	0.99 ± 0.11	1.00 ± 0.10	1.01 ± 0.12	1.02 ± 0.12
	BCCA-L	0.78 ± 0.07	0.82 ± 0.08	0.95 ± 0.13	1.07 ± 0.20	1.18 ± 0.19	1.30 ± 0.22	1.32 ± 0.24	1.37 ± 0.27
	sham	151.38 ± 26.19	149.12 ± 49.35	165.86 ± 56.87	151.70 ± 27.34	147.44 ± 34.98	147.89 ± 15.62	136.69 ± 26.39	135.48 ± 26.84
	UCCA-L	135.43 ± 31.20	130.79 ± 18.76	158.27 ± 25.33	142.22 ± 12.10	122.83 ± 9.77	126.44 ± 19.95	119.810 ± 7.28	121.37 ± 11.04
	BCCA-L	131.50 ± 19.16	335.77 ± 102.45	288.15 ± 41.15	220.45 ± 53.35	190.11 ± 32.53	158.12 ± 46.83	128.86 ± 31.97	112.08 ± 32.73

* Numbers in columns represent means ± SDs.
Abbreviations: BCCA-L = bilateral CCA ligation; UCCA-L = unilateral CCA ligation.