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Determinants of cerebrovascular remodeling: Do large brain arteries accommodate stenosis?

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ABSTRACT

Objective: It is hypothesized that outward remodeling in systemic arteries is a compensatory mechanism for lumen area preservation in the face of increasing arterial stenosis. Large brain arteries have also been studied, but it remains unproven if all assumptions about arterial remodeling can be replicated in the cerebral circulation.
Methods: The sample included 196 autopsied subjects with a mean age of 55 years; 63 % were men, and 74 % non-Hispanic whites. From each of 1396 dissected cadaveric large arteries of the circle of Willis, the areas of the lumen, intima, media, and adventitia were measured. Internal elastic lamina (IEL) area was defined as the area encircled by this layer. Stenosis was calculated by dividing the plaque area by the IEL area and multiplying by 100.
Results: Plotting stenosis against lumen area or stratified by arterial size showed no preservation of the lumen in the setting of growing stenosis. We could not find an association between greater IEL proportion and stenosis ($B = 0.44$, $P = 0.86$). Stratifying arteries by their size, we found that smaller arteries have greater lumen reduction at any degree of stenosis ($B = -23.65$, $P \leq 0.0001$), and although larger arteries show a positive association between IEL proportion and stenosis, this was no longer significant after adjusting for covariates ($B = 6.0$, $P = 0.13$).
Conclusions: We cannot confirm the hypothesis that large brain arteries undergo outward remodeling as an adaptive response to increasing degrees of stenosis. We found that the lumen decreases proportionally to the degree of stenosis.

1. Introduction

Cardiac and cerebral vascular diseases are among the top four causes of mortality and morbidity in the United States and the world [1,2]. Although the mechanisms in cerebrovascular disease are more heterogeneous than in cardiac disease, atherosclerosis can cause both. Most of what we know about atherosclerosis comes from studies of the aorta, extracranial carotid and coronary arteries. Large brain arteries have also been studied, but it remains unproven if many of the assumptions about atherosclerosis and arterial remodeling in the systemic circulation can be applied to the cerebral circulation.

It is believed, for example, that progressive intimal thickening can be accommodated in coronary arteries by outward enlargement of the vessel as an adaptive response to preserve the luminal area, usually until the degree of stenosis reaches approximately 40% [3]. This reported outward remodeling does not appear confined to human coronaries as it has been documented also in primates and other animal models of atherosclerosis [4,5]. However, compensatory dilatation does not occur equally in other non-coronary arteries and to our knowledge, it has not yet been evaluated in brain arteries [6]. It is unknown whether concentric (or diffuse) vs. eccentric intima thickening induces the same remodeling pattern or if arteries proximal or distal to a bifurcation have a different response [7]. The need to test prevalent hypotheses about arterial remodeling in brain arteries is further underscored by

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methodological aspects not yet fully addressed. For example, the fact that larger arteries will have larger plaques by virtue of their size has not been systematically taken into account when plotting the relationships between plaque area and internal elastic lamina (IEL) areas, i.e. larger arteries have logically larger IEL areas and larger plaque areas given the same degree of stenosis [8]. Furthermore, comparing arteries obtained from different individuals, expected differences in arterial size among taller individuals and between women and men have not always been accounted for, which might lead to biased estimations in cerebral arteries [4,9,10].

In this study, we hypothesized that brain arteries are capable of accommodating stenosis by undergoing compensatory outward remodeling as occurs in the coronary system, and that this presumptive dilatatory response varies by arterial size, type, and location. Enhancing the current knowledge about brain arterial remodeling might lead to new views of the pathogenesis of cerebral atherosclerosis and other intracranial arteriopathies.

2. Materials and methods

Subjects for this study were drawn from the Brain Arterial Remodeling Study, a collection of large and penetrating intracranial arteries assembled with the overall goal of studying brain arterial remodeling, with particular emphasis on HIV and cerebrovascular disease. The sources of the autopsy cases in the Brain Arterial Remodeling Study are the Manhattan HIV Brain Bank located at the Icahn School of Medicine in New York City, the New York Brain Bank/Alzheimer's Disease Research Center at Columbia University, and the Macedonian/New York Psychiatric Institute Brain collection, which includes brains from Macedonia and New York. The methods used in this study, as well as the characteristics of each brain bank have been previously described [11]. For this analysis, we excluded individuals with HIV to facilitate comparisons with prior studies that did not include this specific clinical population. Demographic and clinical information including age, sex, race-ethnicity, hypertension (HTN), diabetes (DM), dyslipidemia (DYS), and smoking prior to death were obtained from medical charts, family and participant interviews, or autopsy reports. Due to various methods and goals of each brain bank, height, weight, heart weight and brain weight were variably obtained. The diagnosis of vascular disease was obtained in the majority of the cases either from medical records or pathological evidence of any of these diseases. Alzheimer dementia was diagnosed prior to death and confirmed pathologically as previously reported [12].

All arteries were extracted systematically by the lead investigator of the Brain Arterial Remodeling Study (JosG). The circle of Willis was identified either in the whole brain or in one half (on occasions, the other half had been frozen). Each of the large arteries of the circle of Willis was identified, and 5-mm cross-sectional segments were cut, fixed in 10% formaldehyde, and then embedded in paraffin for further sectioning. When possible, a proximal and a distal segment from the same artery were obtained with the goal of identifying segments in respect to their bifurcation or origin. Six micron thick sections were obtained from each embedded artery and stained with H&E and elastin van Gieson. Each slices was digitized by JosG in the Histology Shared Resource Facility of the Icahn School of Medicine at Mount Sinai using Olympus Soft Imaging Solutions software and microscope BX61VS with constant illumination, with 10× magnification and scale = 0.643 μm/pixel.

Using color segmentation thresholding, areas of the lumen, intima, media and adventitia were obtained. Correction for shrinkage was applied by multiplying each area by a factor of 1.25 and the perimeter by 1.12, as suggested in prior reports [3,13]. To correct for artery folding, we assumed that the outer perimeter of the adventitia was the least likely to be affected by folding and it would represent the actual perimeter of a fully distended artery (Fig. 1a, b). Although adventitia stripping during preparation was a concern; data suggest that this does not significantly change the cross-sectional area [14]. We calculated the total artery area from the measured outer adventitia perimeter, and then subtracted the wall area to obtain the folding-corrected lumen area (Fig. 1c), and then derived the interadventitial diameter through standard geometrical formulas, as reported before [11]. The IEL area was obtained by adding the intima area plus the derived lumen and the IEL proportion was obtained by dividing the IEL area by the total artery area (Fig. 1d, e). Percent stenosis was calculated by dividing the plaque area by the IEL area and multiplying by 100 (Fig. 1f). Of note, arterial stenosis calculated in pathology is not the same as the stenosis measurement obtained from lumen-only studies since the former uses plaque area instead of luminal decrements to quantify it. By visual assessment the extent of the intima surface that showed any type of thickening additional to the endothelium was semi-quantitated into five categories: 0 = none, 1 = 1–25%, 2 = 26–50%, 3 = 51–75% and >75% = 4. A note was made whether the intima thickening appeared diffuse vs. focal to determine if the thickening phenotype appeared concentric or eccentric. The degree of stenosis was not used in this categorization. Visual assessments for all arteries were made by JosG. To obtain reliability of the visual assessment, we obtained kappa values in a random sample of 125 large arteries; the second reader was JamG. The intra- and inter-reader reliability were both $\kappa = 0.80$ for intima hyperplasia. The intra-reader reliability for concentric vs. eccentric hyperplasia was $\kappa = 0.92$. The intra and inter-reader reliabilities of the color thresholding segmentations have been previously reported as excellent (ICC > 0.90) [15]. Although the AHA classification of atherosclerosis was used to rate each artery, we did not use this classification in this analysis to allow a fair comparison with the original report by Glagov et al., who did not use atherosclerosis phenotype other than stenosis percentage [3,7,16,17].

We plotted stenosis against IEL and lumen areas, and categorized stenosis into three groups to see if slopes would vary by degree of stenosis, as has been done in prior studies to demonstrate compensatory enlargement [3]. The results from these plots would disclose if lumen preservation occurs in the initial stages of stenosis as previously postulated. A second aspect of the remodeling is that as the lumen is preserved with growing stenosis, the artery undergoes compensatory outward remodeling, which would presumably occurs through enlargement the IEL, media and adventitia, which then can be represented by a larger IEL proportion. To test this hypothesis, we created multilevel mixed models using IEL proportion as dependent variable and stenosis as independent variable.

2.1. Statistical analysis

For the simple plots, we used percentage stenosis and interadventitial diameter expressed in millimeters (mm) without transformation. Because we used parametric tests to evaluate predictors IEL proportion, we verified the distribution normality with stem and leaf and Q.Q plots, skewness and kurtosis. We found that IEL proportion was not normally distributed mainly due to large kurtosis (>2). We used exponential transformation for IEL proportion resulting in normalization of the distributions as verified by the Kolmogorov test. Since vascular risk factors affect all arteries in one individual and they are not independent among themselves, we used univariate and multivariate multilevel mixed models to account for this. The only case where we used simple linear regression was to calculate the slope of scatter plots. Our