Relationship between brain large artery characteristics and their downstream arterioles

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Abstract

We aimed to test the hypothesis that brain large artery diameters relate to distal downstream arteriolar diameters. In a sample of 110 autopsied individuals (69% men, 76% HIV+, mean age 51), we used multilevel models to relate large artery lumen and lumen-to-wall ratio to left frontal lobe arteriolar lumen and lumen-to-wall ratio adjusting for demographics and vascular risk factors. Comparing the large artery characteristics of the whole brain did not disclose significant associations with frontal lobe arteriolar characteristics. However, restricting the comparison to large arteries upstream of the studied arterioles, demonstrated an independent association between left-sided frontal lobe arteriolar luminal diameter with large artery luminal diameters (B=1.82 ± 0.77, P=0.01) and with large artery lumen-to-wall ratio (B=0.58 ± 0.29, P=0.05). In stratified models, the point estimates in the HIV+ subsample were larger than in the HIV− subsample. These finding suggest coupling between higher proximal blood flow represented by large artery diameter and lower distal resistance represented by arteriolar dilatation. The relationship between arteriolar dilatation and brain parenchyma homeostasis should be further studied.

Keywords

dolichoectasia; hiv; arterial; cerebrovascular; cerebral hemodynamics; vascular pathology; remodeling

INTRODUCTION

Neurological manifestations of HIV infection have been a source of morbidity and mortality since the onset of the epidemic. (Morgello *et al*, 2002) Efficacious antiretroviral therapy has

decreased many of these complications, but the prevalence and incidence of stroke remains higher than in uninfected population. (Mateen *et al*, 2012; Weber *et al*, 2013) Stroke in individuals with HIV is often devastating and it may be caused by various etiologies. (Ortiz *et al*, 2007) Approximately one quarter of HIV patients with brain infarcts display a form of large intracranial artery disease characterized by dilatations and elongation. (Gutierrez *et al*, 2015b; Gutierrez and Ortiz, 2011) The mechanisms by which these dilated vessels contribute to stroke are unclear, but may include mechanical traction of penetrating arteries due to tortuosity,(Zhang *et al*, 2014) dampened blood flow due to severe dilatation which may then lead to artery-to-artery emboli or *in-situ* thrombosis,(Drake and Peerless, 1997; Kumral *et al*, 2005) arterial wall hemorrhage with potential occlusion of the penetrating branches,(Nakatomi *et al*, 2000) or increased risk for lacunar strokes. (Pico *et al*, 2003) Another possible mechanism by which large artery dilatation may increase the risk of stroke is the transmission of hemodynamic stress to distal arterioles, which are the sites of brain perfusion autoregulation. (Marmarou *et al*, 1980)

There are established relationships between large artery diameters in basal portions of the circle of Willis and arterioles. For example, the luminal diameter of a given artery in the circle of Willis is directly proportional to the density of the capillaries in the area of the brain corresponding to that artery. (van der Zwan *et al*, 1993; van Laar *et al*, 2006) Given that brain development is the pacemaker of embryogenesis of the circle of Willis, the association between large artery diameters and brain parenchyma vascularity is interpreted as evidence of coupling between supply and demand. (Padget, 1944) The brain can further regulate this demand by dilatation or constriction of the arterioles, thus preserving a steady brain blood flow within a wide range of systemic blood pressure variations. (Brown and Thore, 2011) Arterioles also remodel in various physiological and pathological conditions, which may lead to distal changes in resistance that may theoretically stimulate remodeling of the proximal large arteries. (Brown and Thore, 2011; Cipolla *et al*, 2011) In this scenario, arteriolar dilatation decreases resistance to flow more proximally, and with time, may lead to proximal outward remodeling of the large arteries. Thus, one could hypothesize that brain arteriolar outward remodeling would be associated with larger proximal brain arterial diameters.

Understanding the relationship between large arterial diameters observed among individuals with HIV and arteriolar remodeling may increase the understanding of stroke physiopathology in this population, as well as in the general population.

MATERIALS AND METHODS

We studied the relationship between brain large artery characteristics and their downstream arterioles in an autopsy sample from the Manhattan HIV Brain Bank (MHBB; U24MH100931); the cases were chosen for this study if they had been used in two prior and independent analyses of large artery characteristics (the Brain Arterial Remodeling Study) and a separate analysis of risks for cerebral small vessel disease. (Morgello *et al*, 2014) Individuals in the MHBB are followed prospectively and agree to donate their brain for research purposes upon death via a written anatomical gift consent approved by the Mount Sinai Institutional Review Board. Clinical information is obtained during ante-mortem visits;

where prospective assessment is not available, this information is obtained via post-mortem medical record review. Hypertension, diabetes, dyslipidemia, smoking, cocaine use, and Hepatitis C infection are defined by self-report and/or chart documentation, laboratory evidence supporting these diagnoses, or by self-reported or chart-extracted use of medications. Further details of the methods use in this study may be found elsewhere. (Morgello *et al*, 2002)

Brain large artery preparation

Brain large arteries forming the circle of Willis and the vertebrobasilar system were removed from the formalin-fixed brains or hemi-brains. Each artery was dissected individually and proximal and distal 5 mm segments were cut cross-sectionally to preserve the lumen, and embedded in paraffin. Embedded blocks were cut at 6 microns for staining with H&E and elastic Van Gieson (EVG). Each slice was digitalized using Olympus Soft Imaging Solutions software and a microscope with constant illumination, with a 10× objective lens and scale=0.643 μm/pixel in the Histology Shared Resource Facility of the Icahn School of Medicine at Mount Sinai. We used color-based thresholding with ImageJ software (WS Rasband, ImageJ, U.S. National Institutes of Health, Bethesda, Maryland, USA, imagej.nih.gov/ij/, 1997-2011) to quantify the areas of the lumen, intima, media and adventitia. From these areas, we derived the shrinkage-corrected luminal diameter and wall and layer thicknesses of each artery, as described previously. (Gutierrez *et al*, 2014b) We rated visually the presence of atherosclerosis (defined here categorically as the presence of an atheroma). The reliability of these measures has been reported as good to excellent. (Gutierrez *et al*, 2012)

Arteriolar preparation

Each formalin-fixed brain or hemi-brain was used to obtain sections from 57 pre-specified regions of interest, as previously described. (Morgello *et al*, 2001) For the purpose of this analysis, a section corresponding to the periventricular frontal area between the anterior and the middle cerebral artery territories (watershed area) was selected. All the observed arterioles in that section, which typically ranged from 15–20 per section, were measured. H&E sections were scanned at 200× with an Olympus VS110 virtual slide scanning system using VS-ASW software (Olympus America Inc, Center Valley, PA). Given obliquity of the arteriolar wall, we identified the longest axis first, and then in a perpendicular plane we measured the external and the internal diameters to derive the lumen, wall thickness and lumen-to-wall ratio in each arteriole (figure 1).

Statistical analysis—The arteriolar luminal diameters, wall thickness and lumen-to-wall ratio were the dependent variables, and variables listed in table 1 were independent variables. We used multilevel models clustering arteries by individuals to generate beta coefficients and their standard errors to account for the lack of independence between arteries from the same individual. (Bruin, 2006) Because the parenchymal area studied in each case may have varied in the number of arterioles present, we collected the number or arterioles per case and adjusted for it in all models. We first ran a statistical model relating the large artery characteristic in the whole brain with arteriolar characteristics in the anterior circulation. Then, we only used large artery characteristics supplying the parenchymal area

where the arterioles were measured (i.e. intracranial portion of the internal carotid artery, anterior cerebral artery and middle cerebral artery) to identify strengthening of the beta estimates that would support evidence of a direct mechanical relationship between large artery characteristics with their downstream arterioles. Lastly, we assessed whether the relationship between large artery characteristics with their downstream arterioles varied by HIV. A p value 0.05 was considered statistically. The statistical analysis was carried out with SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Population studied

We analyzed 110 autopsied individuals (68% men, 76% HIV+, 45% Non-Hispanic black) with a mean age of 51 ± 9 years (median 51, range 26–81). The characteristics of the sample by HIV status are described in Table 1.

On average, each case included 16 arterioles (median 15, range 5–23) and 6 large artery segments (median 6, range 2–9). The average arteriolar measures were as followed: luminal diameters 40 ± 15 microns; wall thickness 13 ± 4 and lumen-to-wall ratio 3.2 ± 1.4. The average large artery measures were: luminal diameters 2.4 ± 0.8 mm, wall thickness 0.4 ± 0.1 mm, lumen-to-wall ratio 7.0 ± 2.1. The prevalence of large artery atherosclerosis was 3.7%.

Relationship between large artery characteristics and their downstream arteriolar characteristics

Comparing the large artery characteristics of the whole brain did not disclose significant associations with frontal lobe arteriolar characteristics. However, restricting the comparison to large arteries upstream of the studied arterioles, demonstrated a positive association between large artery luminal diameters with arteriolar luminal diameter (B=1.82 ± 0.77, P=0.02, table 2). The same direction of the association was noted between large artery lumen-to-wall ratio and arteriolar luminal diameter (B=0.58 ± 0.29, P=0.05). A thicker large artery wall was also associated with larger arteriolar luminal diameters (B=8.06 ± 3.65, P=0.03) but not with arteriolar wall (-0.84 ± 0.77, P=0.27) or lumen-to-wall ratio (B=-0.56 ± 0.36, P=0.12).

Analysis by HIV status

The effects of large artery lumen diameter, wall thickness, and lumen-to-wall ratio on ipsilateral arteriolar luminal diameter and lumen-to-wall ratio varied by HIV status (table 3). In stratified models, the point estimates for the association between large artery characteristics with arteriolar luminal diameters were larger in the HIV+ subsample were larger than in the HIV− subsample. Among those with HIV only, and after adjusting for variables pertinent to HIV, there an even more significant association between ipsilateral large artery characteristics and the downstream arteriolar luminal diameter and lumen-to-wall ratio (table 2, model 2).

DISCUSSION

The arteries feeding the brain are intimately related to the integrity of the brain parenchyma, and are related to stroke mechanisms (Fisher, 1965; Sacco *et al*, 1995) as well as to less acute but equally important outcomes such as dementia. (Honig *et al*, 2005; Roher *et al*, 2004) Intracranial large and small artery disease are overrepresented as causes of stroke among HIV individuals compared with uninfected populations,(Gutierrez *et al*, 2014a; Vinikoor *et al*, 2013) which highlights the importance of brain arterial disease in this population. Arterioles control vital hemodynamic aspects of the brain circulation such as resistance to flow and autoregulation. (Faraci and Heistad, 1990; Haubrich *et al*, 2003) In our study, we found evidence that the histological characteristics of large brain arteries are related to the same histological characteristics of their downstream arterioles; a finding suggestive of a continuum that encompasses the most proximal branches of the circle of Willis down to the most distal arteriolar beds. The data presented here also suggest that emphasis on radiographically evident large artery disease underestimates the contribution of vascular disease to brain parenchymal integrity.

We confirmed the hypothesis that large artery luminal diameters relate to arteriolar luminal diameters. In principle this make physiological sense given than dilated arterioles would theoretically drop the resistance to flow, leading to greater proximal flow, and subsequent outward remodeling. (Faraci and Heistad, 1990; van der Zwan *et al*, 1993) However, due to the cross-sectional nature of our data, we cannot produce evidence of directionality and consequently we cannot rule out the possibility that outward remodeling occurs first in the large artery, with subsequent hemodynamic transmission to the arterioles. In the case of HIV, we have previously demonstrated that immunosuppression, defined by a lower nadir CD4 and lower CD4 counts prior to death, was associated with brain arterial dilatation in the form of dolichoectasia. (Gutierrez *et al*, 2015b) It is surprising that even after adjusting for HIV-related immune variables in this sample, the relationship between large artery diameters and arteriolar luminal diameter persisted, and in fact, became more significant (table 3, model 2). This suggests that chronic HIV-related immunosuppression might be associated with larger arteriolar lumen diameters via not only compromised arteriolar integrity, but also by increased proximal large artery dilation and its downstream mechanical effects of a proximally dilated artery. The association of chronic immunosuppression with apoptosis of the arterial wall economy that others and we have reported (Gibellini *et al*, 2012; Gutierrez *et al*, 2016b; Kim *et al*, 2003) would be a potential mechanism linking HIV infection to proximal and distal vessel dilation. By linking brain arterial disease to arteriolar remodeling, we aimed to construct a proposed pathophysiological model that explains the heightened risk of stroke and dementia among individuals with extreme arterial phenotypes such as atherosclerosis and dolichoectasia, particularly among those with HIV. (Gutierrez *et al*, 2016; Gutierrez *et al*, 2015a; Gutierrez *et al*, 2016a; Gutierrez *et al*, 2016b; Gutierrez *et al*, 2016c)

The strengths of this study include the systematic and reliable characterization of large arteries and arterioles in a relatively large sample size, considering the limited access to brain specimens in large populations. However, autopsied materials are inherently biased, and are less representative of the average general population, which is a limitation.

Furthermore, the low prevalence of atherosclerosis in this sample as well as the relatively small number of uninfected controls may have reduced our power to detect associations related to these characteristics. It is also uncertain if these findings would be relevant in other racial/ethnic populations or in predominantly non-Hispanic white samples.

In summary, we report evidence that large artery outward remodeling, as evidence by higher luminal diameters and higher lumen-to-wall ratio, is associated with arteriolar outward remodeling. This association is strongest among HIV individuals, and it may shed light on the relationship between large artery disease and parenchymal damage.

Acknowledgments

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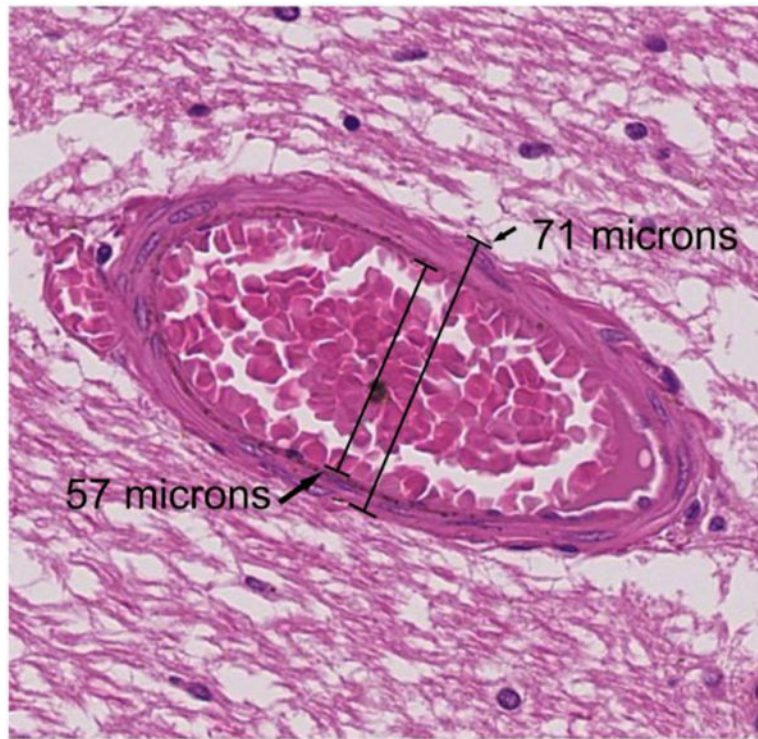
Figure 1.
Stain: H&E. Example of an arteriole, with measurements of the lumen and interadventitial diameters.
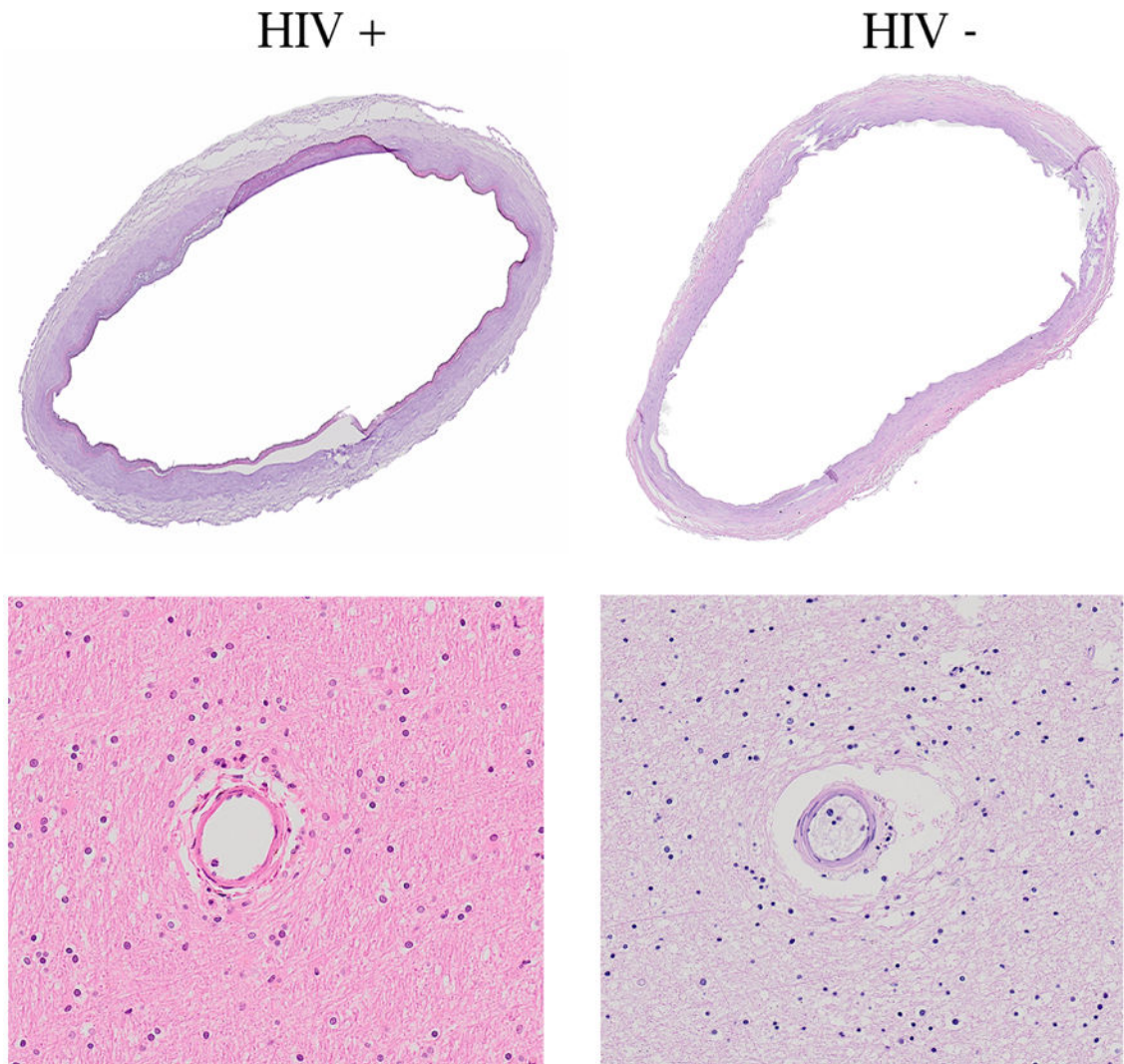
HIV +   HIV −

Figure 2.
Stain: H&E. Example of dilated middle cerebral arteries and their downstream arterioles, which appeared to have a thin wall relative to their lumen.

Table 1

Characteristics of the sample at death (N=110)

	HIV+ N=84	HIV− N=26
Mean age (in years, SD, median, interquartile range)	50 (8.4, 50, 44–58)	53 (11.8, 55, 55–81)
Male sex (%)	71	58
Ethnicity (%)		
Non-Hispanic white	20	39
Non-Hispanic black	50	27
Hispanic	30	34
Hypertension (%)	64	73
Diabetes (%)	19	46
Dyslipidemia (%)	23	19
Smoking (%)	60	35
Hepatitis C co-infection (%)	51	31
cART use at death (%)	69	Not applicable
Prior opportunistic infections (%)	80	Not applicable
Mean Nadir CD4 (per mm^3, SD, median, interquartile range)	114 (71, 142, 11–172)	Not applicable
Mean CD4 count at death (per mm^3, SD, median, interquartile range)	167 (82, 195, 15–268)	Not applicable
CD4 count < 200% at death (%)	67	Not applicable
Viral load at death > 50 copies/ml (%)	59	Not applicable
Brain large artery unadjusted characteristics		
Lumen diameter (in mm, mean ± SD)	2.4 ± 0.8	2.2 ± 0.6
Lumen to wall ratio	6.9 ± 2.08	7.1 ± 2.0
Wall thickness (in mm, mean ± SD)	0.36 ± 0.11	0.32 ± 0.08
Anterior frontal arteriolar unadjusted characteristics		
Lumen diameter (in microns, mean ± SD)	42.0 ± 0.33	31.5 ± 22.8
Lumen to wall ratio	3.36 ± 2.47	3.07 ± 2.13
Wall thickness (in microns, mean ± SD)	13.76 ± 8.59	11.00 ± 5.30

Abbreviations: N, number, SD, standard deviation; cART, combined antiretroviral therapy.

Table 2

Relationship between large artery characteristics and downstream arterioles

		Arteriolar characteristics		
		Lumen diameter (in microns) B estimate ± standard error	Wall thickness (in microns) B estimate ± standard error	Lumen-to-wall ratio B estimate ± standard error
Large artery characteristics				
Lumen-to-wall ratio	All large arteries	0.31 ± 0.40	−0.12 ± 0.10	0.04 ± 0.03
	Ipsilateral to the arterioles	0.58 ± 0.29 [†]	−0.02 ± 0.04	0.05 ± 0.03 [*]
Lumen diameter (in mm)	All large arteries	1.46 ± 3.88	−1.14 ± 1.16	0.33 ± 0.37
	Ipsilateral to the arterioles	1.82 ± 0.77 [†]	0.08 ± 0.11	0.14 ± 0.07 [†]
Wall thickness (in mm)	All large arteries	−2.92 ± 7.76	2.27 ± 2.31	−0.66 ± 0.74
	Ipsilateral to the arterioles	8.06 ± 3.65 [†]	−0.84 ± 0.77	−0.56 ± 0.36
Atherosclerosis (i.e. presence of atheroma)	All large arteries	0.31 ± 3.41	1.29 ± 1.09	−0.19 ± 0.29
	Ipsilateral to the arterioles	−0.09 ± 3.59	0.82 ± 1.12	−0.10 ± 0.33

[*] P value < 0.10–0.05

[†] P value <0.05

Analytic note: All models were adjusted for age, sex, race/ethnicity, hypertension, diabetes, dyslipidemia, smoking, hepatitis C, HIV, cocaine use, interadventitial size, large artery type and large artery proximal versus distal location.

Table 3

Models stratified by HIV status

	Arteriolar characteristics					
	Lumen diameter (in microns) B estimate ± standard error			Lumen-to-wall ratio B estimate ± standard error		
	Model 1		Model 2	Model 1		Model 2
Ipsilateral large artery characteristics	HIV −	HIV +	HIV +	HIV −	HIV +	HIV +
Lumen-to-wall ratio	0.05 ± 0.20	0.69 ± 0.35[†]	0.37 ± 0.18[†]	0.01 ± 0.02	0.06 ± 0.03[*]	0.04 ± 0.01[‡]
Lumen diameter (in mm)	0.39 ± 0.65	2.03 ± 0.89	1.56 ± 0.51[‡]	0.10 ± 0.07	0.14 ± 0.09	0.14 ± 0.04[‡]
Wall thickness (in mm)	3.63 ± 4.51	8.54 ± 4.17[†]	9.15 ± 3.52[†]	0.92 ± 0.49[*]	0.50 ± 0.40	0.75 ± 0.32[†]

[*]
P value < 0.10–0.05

[†]
P value <0.05

[‡]
P value < 0.01

Analytic note:

Model 1 adjusted for age, sex, race/ethnicity, hypertension, diabetes, dyslipidemia, smoking, hepatitis C, cocaine use, inter-adventitial size, large artery type and large artery proximal versus distal location. Model 2 includes model 1 plus prior opportunistic infections, use and class of antiretrovirals, nadir CD4 and CD4 counts prior to death, and viral loads > 50 copies per ml prior to death.