Compensatory intracranial arterial dilatation in extracranial carotid atherosclerosis: The Northern Manhattan Study

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Background **There is a scarcity of data supporting the association between atherosclerosis and dolichoectasia in unbiased samples.**

Aims **To test the hypothesis that the association between dolichoectasia and extracranial carotid atherosclerosis depends on the degree of collateral circulation.**

Methods **The Northern Manhattan Study magnetic resonance imaging substudy consists of 1290 participants who remained stroke-free at the time of magnetic resonance imaging. Arterial diameters were collected in all participants with available magnetic resonance angiography. Dolichoectasia was defined as a head-size adjusted diameter >2 standard deviation for each artery. Carotid Doppler was used to evaluate for carotid atherosclerosis (carotid plaque, maximum plaque thickness and carotid intima media thickness).**

Results **We included 994 participants with available Doppler and magnetic resonance angiography data (mean age 63 years, 60% female). Any dolichoectasia was reported in 16% of participants, 54% had at least one carotid plaque and the mean carotid intima media thickness was 0·92 ± 0·09 mm. After adjusting for demographic and clinical characteristics, there was no association between markers of carotid atherosclerosis and dolichoectasia. However, stratifying by collaterals, it was observed that dolichoectasia was more likely in the anterior and posterior circulations when collaterals were available among participants with carotid atherosclerosis. These associations were confirmed by noting an increment in arterial diameters in the corresponding arteries ipsilateral and contralateral to each carotid as well as in the posterior circulation.**

Conclusions **We did not find an association of extracranial carotid atherosclerosis with dolichoectasia. However, we found that dolichoectasia is more frequent when intracranial collaterals are available suggesting a compensatory process that needs further investigation.**

Key words: atherosclerosis, carotid ultrasound, Circle of Willis, dolichoectasia, magnetic resonance imaging

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Received: 29 January 2015; Accepted: 6 January 2015; Published online 05 March 2015

Conflict of interest: Gutierrez, Gomez-Schneider, Cheung, DeRosa, Bagci, Sacco, Wright, Rundek disclosures: None. Dr. Alperin reports income from alperin noninvasive diagnostics, Inc. Dr. Elkind reports grants from BMS-Sanofi partnership and diaDexus, personal fees from BMS-Pfizer, Biogen IDEC, Organon, outside the submitted work.

Funding: NINDS R37 NS029993 (Sacco/Elkind); NINDS K24 NS 062737-03 (Rundek).

DOI: 10.1111/ijs.12464

Introduction

Arterial dolichoectasia (DE) has been described in the setting of cerebrovascular disease and is characterized by arterial dilatation and elongation (1). Some investigators consider DE an end result of severe atherosclerosis (2). However, DE can also occur in the absence of vascular risk factors (VRF) or atherosclerosis, suggesting heterogeneity of mechanisms (3). Atherosclerosis is a systemic process simultaneously affecting multiple vascular beds (4,5). Carotid intima media thickness (cIMT) and carotid plaque are frequent markers of atherosclerosis. Both have been associated with vascular risks, but carotid plaques are considered more reliable predictors of atherosclerosis and vascular events than cIMT (6). Although the relationship between DE and extracranial carotid atherosclerosis has been investigated before, we were unable to find studies that also examined the configuration of the Circle of Willis (CoW) in this context (7). Furthermore, the growth of the intima into the lumen, or inward remodeling, is typical in atherosclerosis, while outward remodeling is more characteristic of the dilatation in DE, raising further doubts about the hypothesis that DE and atherosclerosis share the same physiopathology.

Based on prior results that demonstrated the importance of the configuration of the CoW as a predictors of DE (8), we tested the hypothesis that intracranial DE is more prevalent among individuals with extracranial atherosclerosis and that the effects of carotid atherosclerosis vary depending on the CoW configuration.

Methods

Study population

The Northern Manhattan Study (NOMAS) cohort enrolled stroke-free participants identified using random digit dialing as previously described (9). All stroke-free surviving members of the cohort were invited to participate in the MRI substudy initiated in 2003. Recruited subjects were administered informed consent and screened for MRI scanning eligibility at the initial in-person visit (subjects were pre-screened by telephone during the recruitment phone interview). Additionally, we asked during the telephone follow up of the original NOMAS cohort if there were other stroke-free household members, 50 years or older who wish to join the NOMAS MRI substudy ($n = 199$ enrolled). Definitions

for vascular risk factors can be found in the supplementary data. The study was approved by the local Institutional Review Board.

Brain MRA protocol

Imaging was performed on a 1·5-T MRI system (Philips Medical Systems) at the Hatch Research Center using 3-dimensional time-of-flight (TOF) MRA (see supplementary data for MRI protocol). Diameters were obtained from the petrous segment of the internal carotid artery (ICA), from the first 10 mm of the fourth segment of the vertebral arteries (VA), and from the first 5 mm of the origins of the basilar artery (BA), posterior communicating artery (Pcomm), anterior, middle and posterior cerebral arteries (ACA, MCA, and PCA, respectively). If the artery to be evaluated was too small to be reconstructed into the 3-D model used for arterial measurement but it was observed in axial images, its status was recorded as hypoplastic. If the artery was not observed in axial images, it was recorded as absent. Collaterals were defined as present or absent for each ICA if their ipsilateral Pcomm was absent and the anterior communicating artery (Acomm) was absent. Absent collaterals between the BA and the anterior circulation was defined as lack of Pcomm on both sides. A fetal PCA was considered absent Pcomm in the categorization of collaterals for the anterior or posterior circulation because of the missing link with the BA. The methods, definitions and reliability of the measurements used here have been reported before (8).

Dolichoectasia was defined as a head-adjusted diameter >2 SD of a given artery. The cutoff was obtained from the distribution of the diameters per artery for this population. Defining DE as an arterial diameter >2 SD has been previously used (7,10). However, we further adjusted for head size because participants with larger heads are expected to have larger arteries. Because men have bigger heads than women, and head size is an important predictors of brain arterial diameters, the main effect after adjusting for head size is that women, rather than men, are more likely to have intracranial DE and larger head-size adjusted diameters (supplementary data) (11).

Extracranial carotid Doppler protocol

Carotid assessments were carried out with high-resolution B-mode ultrasound using a GE LogIQ 700 system with a multi-frequency 9 to 13 MHz linear-array transducer close to the time of MRI. Standardized carotid ultrasonography protocol was performed by trained personnel. Carotid plaque was defined as a thickening of 50% or greater than the thickness of the surrounding intima-media complex. Maximum carotid plaque thickness (MCPT) was measured from the base of a plaque to its greatest peak. Total carotid IMT was calculated as an average of 12 sites combining the near and the far wall of the maximal IMT in CCA, bifurcation, and ICA in both sides of the neck. MCPT was categorized to the median for the purpose of this analysis. The reliability of this method is good to excellent (12).

Statistical analysis

The differences in characteristics among those included in this analysis compared to global NOMAS cohort were assessed with Student's *t*-test or χ^2 tests as appropriate. The outcome for this analysis was the number of dolichoectatic arteries per subject (i.e. a count). Separate stratified analyses were performed to evaluate if the association of markers of carotid atherosclerosis varied by the degree of collateral to the anterior (i.e. the ICA, MCA, ACA and Pcomm) or posterior circulations [i.e. the BA, VA PCA (fetal or not)]. We assessed diameters continuously in relation to markers of extracranial carotid atherosclerosis and the collaterals. Age, gender, race-ethnicity, height, hypertension, diabetes, hypercholesterolemia, smoking, and prior cardiac disease were used as covariates. Because we previously demonstrated that height, the number of hypoplastic and/or absent arteries are important determinants of DE, we included these variables as covariates (13). Generalized linear models were used with a Poisson distribution (DE count mean 0·02, variance 0·02) and log link function with an exchange covariate matrix. For arterial diameters as continuous variables, we used mixed models with random effects and clustering by subject. Chi-square for Poisson regressions and type II effects were used to obtain beta coefficients, their standard errors (B ± SE) and P values. Statistical significance was set at a P value of $< 0{\cdot}05$. The analysis was carried out with SAS software, version 9·3 (SAS Institute Inc., Cary, NC).

Results

Sample characteristics

All intracranial large arteries were assessed in 1,077 with available MRA data, but data from only 994 subjects were included in the analysis (43 subjects were excluded due to motion artifact and Doppler data were missing in 40). Compared to the NOMAS cohort, the subjects included in this analysis were younger (63 vs. 71 years, $P < 0{\cdot}001$), and more likely to be men (40 % vs. 36 %, $P = 0{\cdot}02$) and Hispanic (66 % vs. 48%, $P < 0{\cdot}001$), but less likely to have HTN (67 % vs. 75%, $P < 0{\cdot}001$), prior cardiac disease (16 % vs. 27 %, $P < 0{\cdot}001$), or history of MI (3 % vs. 9%, $P < 0{\cdot}001$; Table S1).

The prevalence of DE of one or more arteries was 16% (9% in the anterior circulation, 4% in the posterior circulation, and 3% in both circulation systems). Among those with at least one dolichoectatic artery, 38% had two or more arteries involved. The mean ± SD cIMT in the sample was 0·92 ± 0·09 mm (median 0·91, range 0·62–1·41). The majority of participants had one or more carotid plaques (54 %). Among those with carotid plaques, the mean maximum plaque thickness was 2·04 ± 0·59 mm (median 2·09, range 1·12–6·52 mm). Stenosis greater than 40% in either carotid was noted in 32 subjects (40–59% stenosis in 15, 60 to 79% stenosis in 15, and >80% stenosis in 2).

Intracranial DE, extracranial carotid atherosclerosis, and CoW variants

There was no significant association between markers of extracranial carotid atherosclerosis and the number of arteries with DE (Table S2). However, intracranial DE was more likely in the setting of extracranial carotid atherosclerosis ipsilateral to the affected carotid when intracranial collaterals were available (Table 1). To further confirm the dilatatory changes suggested by DE, we used arterial diameters continuously. The increments in arterial diameters appeared greater and more consistent when collaterals were available (Table 2).

Table 1 Association of intracranial dolichoectasia (DE) with extracranial carotid atherosclerosis depending on Circle of Willis collaterals

		Ipsilateral anterior circulation DE		Contralateral anterior circulation DE	
		B coefficient ± SE* Collaterals +	B coefficient ± SE* Collaterals –	B coefficient ± SE* Collaterals +	B coefficient ± SE* Collaterals –
Extracranial right carotid	cIMT > 1 mm	0·40 ± 0·29 $P = 0·18$	–0·47 ± 0·95 $P = 0·62$	0·90 ± 0·24 $P = 0·003$	–0·47 ± 0·98 $P = 0·63$
	≥2 plaques	0·18 ± 0·11 $P = 0·11$	–0·62 ± 0·55 $P = 0·26$	0·26 ± 0·10 $P = 0·01$	–0·63 ± 0·55 $P = 0·25$
	MCPT > 2 mm	0·62 ± 0·27 $P = 0·02$	–0·16 ± 0·99 $P = 0·86$	0·63 ± 0·28 $P = 0·03$	–0·15 ± 0·96 $P = 0·89$
Extracranial left carotid	cIMT > 1 mm	0·44 ± 0·32 $P = 0·16$	–0·31 ± 1·01 $P = 0·76$	0·19 ± 0·32 $P = 0·54$	–0·31 ± 0·97 $P = 0·74$
	≥2 plaques	0·20 ± 0·33 $P = 0·54$	0·09 ± 0·11 $P = 0·42$	0·20 ± 0·07 $P = 0·48$	0·06 ± 0·11 $P = 0·55$
	MCPT > 2 mm	0·80 ± 0·62 $P = 0·19$	0·18 ± 0·30 $P = 0·55$	0·11 ± 0·99 $P = 0·91$	–0·04 ± 0·31 $P = 0·88$

*All Beta coefficients were adjusted for age, gender, race-ethnicity, height, hypertension, diabetes, hypercholesterolemia, current smoking, and prior cardiac disease.
mm, millimeters; SE, standard error; DE, dolichoectasia.

Table 2 Association of extracranial carotid atherosclerosis with intracranial arterial diameters

		Ipsilateral intracranial TCV-adjusted diameters (ICA, ACA and MCA)		Contralateral intracranial TCV-adjusted diameters (ICA, ACA and MCA)	
		B coefficient ± SE* Collaterals +	B coefficient ± SE* Collaterals –	B coefficient ± SE* Collaterals +	B coefficient ± SE* Collaterals –
Extracranial right carotid	cIMT > 1 mm	0·74 ± 0·06 $P < 0·001$	0·63 ± 0·15 $P < 0·001$	0·68 ± 0·09 $P < 0·001$	0·45 ± 0·15 $P = 0·002$
	Two or more plaques	0·62 ± 0·07 $P < 0·001$	0·43 ± 0·19 $P = 0·03$	0·56 ± 0·09 $P < 0·001$	0·51 ± 0·11 $P = 0·003$
	MCPT > 2 mm	0·72 ± 0·07 $P < 0·001$	0·66 ± 0·16 $P < 0·001$	0·57 ± 0·08 $P < 0·001$	0·52 ± 0·10 $P = 0·003$
Extracranial left carotid	cIMT > 1 mm	0·58 ± 0·07 $P < 0·001$	0·54 ± 0·16 $P = 0·008$	0·67 ± 0·07 $P < 0·001$	0·61 ± 0·09 $P < 0·001$
	Two or more plaques	0·70 ± 0·07 $P < 0·0001$	0·51 ± 0·16 $P = 0·001$	0·60 ± 0·07 $P < 0·001$	0·48 ± 0·15 $P = 0·001$
	MCPT > 2 mm	0·60 ± 0·15 $P = 0·001$	0·50 ± 0·06 $P < 0·001$	0·62 ± 0·09 $P < 0·001$	0·57 ± 0·07 P < 0·001

*All Beta coefficients were adjusted for age, gender, race-ethnicity, height, hypertension, diabetes, hypercholesterolemia, current smoking, prior cardiac disease.
ICA, intracranial internal carotid artery; ACA, anterior carotid artery; MCA, middle cerebral artery; SE, standard error; mm, millimeters; TCV, total cranial volume; cIMT carotid intima media thickness; MCPT, maximum carotid plaque thickness.

We tested the association of extracranial carotid atherosclerosis on vertebrobasilar diameters. In the setting of available collaterals between the vertebrobasilar system and the anterior circulation, cIMT ($B = 0·57 \pm 0·15$, $P = 0·002$), the number of carotid plaques ($B = 0·10 \pm 0·01$, $P < 0·001$), and the maximum carotid plaque thickness ($B = 0·15 \pm 0·02$, $P < 0·001$) were associated with increased vertebrobasilar diameters independent of demographic and VRF. Among those without collaterals, the beta coefficients were negative and non-significant. Furthermore, when both the left and right carotid arteries had 2 or more plaques ($B = 0·29 \pm 0·01$) or when both carotids had at least one plaque with maximum thickness ≥ 2 mm ($B = 0·35 \pm 0·10$, $P = 0·001$; Fig. 1), the effects on the BA diameter tripled in comparison to plaques in either carotid artery alone.

Predictors of dolichoectasia and carotid atherosclerosis

In a model excluding markers of extracranial carotid atherosclerosis, age (0·03, 95% CI 0·01 to 0·05, $P = 0·02$), female gender (0·92, 95% CI 0·40 to 1·44, $P < 0·001$) and height ($B = –0·08$ per inch, 95% CI –0·13 to –0·02, $P = 0·005$) were the independent predictors of DE. Further adjustment for markers of extracranial carotid atherosclerosis only slightly modified these associations

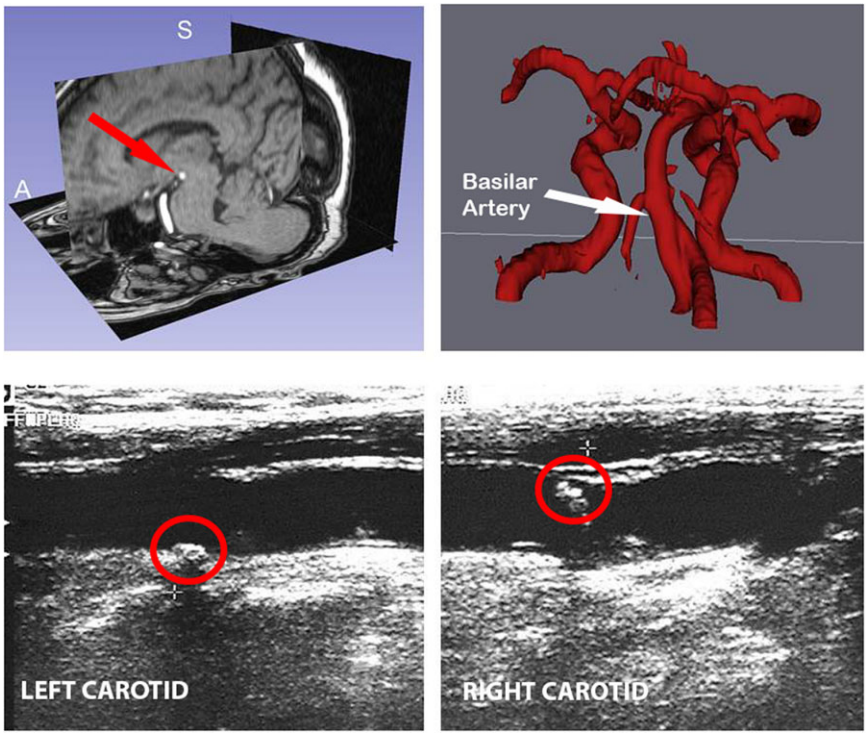

Fig. 1 Top row demonstrates a dilated and tortuous basilar artery [its height of bifurcation reaches the floor of the third ventricles posterior to the midbrain (red arrow)]. The bottom row shows the presence of carotid plaques in both extracranial carotid arteries (red circles).

and their statistical significance with the exception that an independent association between DE and a prior history of MI was disclosed (B = 0·73, 95% CI 0·01 to 1·47, $P = 0·05$). Older participants (B = 0·04, 95% CI 0·02–0·07, $P = 0·001$), Hispanics (B = 0·70, 95% CI 0·04–1·36, $P = 0·04$) and those with prior MI (B = 0·83, 0·08 to 1·58, $P = 0·03$) were more likely to have DE in the anterior circulation, while only participants with HTN were more likely to have DE in the posterior circulation (B = 0·90, 95 % CI 0·11 to 1·70, $P = 0·03$: Table S3).

Discussion

Our results from a population-based, prospective stroke-free sample call into question the previous concept that DE is a form of atherosclerotic disease. This concept is based on studies of selected subjects, often with strokes (1). Because of the shared demographics and VRF between atherosclerosis and DE, we initially hypothesized that atherosclerosis would be, in many cases, the underlying physiopathology in both arteriopathies. We could not find an association, however, between cIMT, number of extracranial carotid plaques, or MCPT with the number of dolichoectatic arteries in the brain. However, further stratification of our cohort by the degree of intracranial collaterals at the level of the CoW disclosed that in some cases extracranial carotid atherosclerosis was associated with ipsilateral DE and increased arterial diameters of the anterior circulation, or in case of bilateral advanced extracranial carotid disease, to posterior circulation DE. This is surprising to us because most of the participants in our sample had non-stenotic plaques. Even cIMT, which by definition is non-stenotic, was strongly associated with larger arterial diameters in both ipsilateral and contralateral vessels when collaterals were present. These results suggest that in a subset of individuals with extracranial atherosclerosis, DE represents a compensatory dilatation rather than a distal extension of atherosclerosis into the intracranial arteries.

These results add to what we previously reported as 'compensatory DE' in intracranial brain arteries in the setting of hypoplastic or absent components of the CoW (8). Because we do not have information on the arterial wall characteristics of the dolichoectatic arteries, we cannot totally exclude atherosclerosis in these vessels. There is evidence, however, that flow-induced arterial remodeling is not typically accompanied by atherosclerosis. For example, in animal models of increased arterial flow, investigators have reported that the pathological correlates of progressive dilatation of the investigated arteries were internal elastic lamina (IEL) disruption with gap formation (14,15). An experiment in rabbits in which one or both common carotid arteries were occluded demonstrated that (1) the occlusion of one carotid did not significantly alter the BA diameters, but the occlusion of both led to flow-induced BA dilatation and tortuosity, and (2) the pathology of the resultant dolichoectatic BA showed IEL disruption, with eventual IEL disruption (16). In this study, the increased BA diameter must have been supplemented from extracranial collaterals since both common carotid arteries were occluded. Together, these results support our findings that there is a dose-dependent interaction between carotid artery disease and posterior circulation DE and also suggest that atherosclerosis may not be the underlying pathology of DE. In this context, we pos-

tulate that in some cases, the identification of large intracranial arteries may be a surrogate of good collaterals, thus rendering DE a desired arterial phenotype in the setting of an acute stroke, for example.

We also found that posterior circulation DE is more frequent among those with HTN, as reported by others (7). However, we found that HTN was only associated with DE in the posterior circulation, not in the anterior circulation, and that this association was independent of markers of carotid atherosclerosis. This suggests some predisposition of the posterior circulatory system to dilate independently of the possible compensatory stimuli arising from anterior circulation atherosclerosis. The confluence of the VA into the single BA might render the BA susceptible to flow-related dynamics that alter its propensity to dilate (17). Also, the poorer sympathetic innervation of the posterior circulation makes the BA more susceptible to HTN-induced dilatation (18). Older participants, Hispanics and those with prior MI were more likely to have anterior circulation DE, perhaps due to greater susceptibility of the anterior circulation to the vascular effects of aging (5). Furthermore, progressive arterial stiffness due to loss of elastic fibers from arteries and increasing pulse pressure might render the anterior circulation susceptible to the dynamics of the cardiac cycle (19). In fact, we have found greater degrees of carotid stiffness in Hispanics and blacks compared to non-Hispanic whites in this same sample, which might help explain the reported increase of anterior circulation DE in Hispanics (20).

We are unaware of other large, population-based studies of intracranial DE in stroke-free individuals. This is the greatest strength of this study, and also a limitation when comparing our results to other series that are mainly from samples of stroke patients or hospital based-series. An additional caveat when comparing our results to prior studies is that we used semi-automated software to measure arterial diameters and we adjusted for head size and height based on the arguments discussed above. We did not include measures of elongation in the definition of DE because the few prospective studies that have evaluated the vascular risk attributed to DE have shown that arterial diameters convey well the risk of vascular events (21). A limitation to our study concerns the specificity and sensitivity of MRA to identify the presence of intracranial brain arteries compared to digital subtraction angiography (22). It is possible that we rated as absent arteries that might truly be patent and functional, but this seems to be the case in arteries with diameters of <1 mm, which would limit this error to a very small proportion of brain arteries in our sample.

In summary, we did not find an association between markers of extracranial carotid atherosclerosis and intracranial DE. Nonetheless, there was evidence that ipsilateral extracranial carotid atherosclerosis is associated with larger ipsilateral anterior circulation arterial diameters and more frequent DE in the presence of intracranial collaterals. Posterior circulation DE was also more common in subjects with bilateral extracranial carotid plaques but not when only one side was affected. The degree of carotid atherosclerosis did not modify the association between posterior circulation DE with HTN and anterior circulation DE with older age, MI or Hispanic race-ethnicity suggesting an independent, non-atherosclerosis mediated association of these variables with DE.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Characteristic at baseline of the NOMAS cohort.

Table S2. Association between intracranial dolichoectasia and extracranial carotid atherosclerosis.

Table S3. Effects of extracranial carotid atherosclerosis on the strength of association between dolichoectasia (DE) and demographic and clinical characteristics.