Published in final edited form as:

J Neuroimaging. 2014 ; 24(3): 226–231. doi:10.1111/j.1552-6569.2012.00781.x.

Dolichoectasia Diagnostic Methods in a Multi-Ethnic, Stroke-Free Cohort: Results from the Northern Manhattan Study

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Abstract

BACKGROUND AND PURPOSE—Dolichoectasia (DE) is a vasculopathy that consists of abnormal elongation and dilatation of arteries. The objective of this study is to evaluate the frequency of DE in an unselected population and assess different diagnostic methods.

METHODS—The Northern Manhattan Study is a multiethnic population based cohort of stroke-free participants. The definition proposed for DE was total cranial volume (TCV)-adjusted arterial diameter ≥ 2 SD. Other methods studied included visual assessment, unadjusted arterial diameters cutoff, Smoker's criteria and basilar artery (BA) volume.

RESULTS—A total of 718 subjects were included in the analysis (mean age 71.6 ± 8.0 years, 40% men, 61% Hispanic). Using the TCV-adjusted DE definition, 19% of the sample had at least one dolichoectatic artery. In 7% of the subjects, two or more arteries were affected. The BA was the most common dolichoectatic artery. Reproducibility for arterial diameter measurements was good to excellent (.70–.95), while for visual assessment ranged from fair to good (.49–.79).

CONCLUSIONS—A TCV-adjusted intracranial arterial diameter ≥ 2 SD is proposed as a useful DE definition. The variability in the prevalence of DE depending on the methods used underscores the need to agree on a reliable, universal definition of DE.

Keywords

Dolichoectasia; arterial remodeling; MRA methods

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Information presented in this manuscript has been partially reported at the American Heart Association-International Stroke Conference, New Orleans, 2012.

Introduction

Dolichoectasia (DE) is an arteriopathy characterized by vessel dilatation and elongation. The prevalence of this disease varies widely depending upon the population studied and the methods used for its diagnosis.¹ In prospective studies, DE has been identified as an independent risk factor for ischemic and hemorrhagic stroke,^{2,3} underscoring the importance of the study of this condition.

One of the main challenges in the understanding of DE has been the various diagnostic methods used and the diversity of hospital-based samples studied. In general, older reports come from retrospective reviews of postmortem material, neurosurgical series, or single case reports with highly selected, symptomatic populations in which the diagnosis was established by the visual inspection of the expected vessel trajectory and dimension, with no assessment of reproducibility.^{4,5} In 1982, Yu et al suggested using arterial diameters obtained from brain vessel angiograms in normal controls as a reference to diagnose DE.⁶ It is unclear what distribution cutoffs were used to define DE and whether the diameters measured using conventional angiograms would be comparable to less invasive diagnostic modalities. In 1986, Smoker et al proposed criteria to diagnose DE of the basilar artery (BA) based on a semi-quantitative score that evaluated the diameter, the height of the bifurcation, and the laterality of the BA using high-contrast brain CT.⁷ The same criteria have been applied to brain CTA, MRI and/or MRA to diagnose BADE.^{2,8-10} The limitations of using Smoker's criteria are that they exclude other intracranial arteries, were not obtained from an unselected population, and the cutoffs used to determine abnormality in the exceptionally broad age range (0–89 years, 40% younger than 50 years) might not be applicable to other populations. More recently, other authors have used arterial diameters of the anterior circulation,^{2,10} although in one case they were not used to ascertain DE but to confirm the visual assessment,¹⁰ and in the other case, the cutoffs for abnormality were arbitrary.² Although the methods used to study DE have improved with time, the lack of multiethnic, population-based studies raises the question of whether the results so far reported are generalizable to other groups.

The objective of this analysis is to evaluate the prevalence of Dolichoectasia using several methods in an unselected community-based population that is stroke free, and to evaluate the discriminant ability of the different diagnostic methods used. We used methods that incorporated arterial diameters, in keeping with prior attempts to define Dolichoectasia. We also used an unbiased approach by including definitions of Dolichoectasia that are derived from a normal distribution of arterial diameters in the population.

Methods

The Northern Manhattan Study includes participants identified using random digit dialing. The methods used for this study have been previously described.^{11,12} All members of the cohort remaining stroke-free were invited to participate in an MRI Substudy between 2003 and 2008. Participants were eligible if >55 years of age and had no contra-indication to MRI. All participants signed written informed consent and the study was approved by the IRBs at Columbia and the University of Miami. Imaging was performed on a 1.5-T MRI

system (Philips Medical Systems) at the Columbia University Medical Center following a standardized protocol. We used 3-dimensional time-of-flight (TOF) MRA with the following parameters: FOV of 15 cm, 1 mm effective slice thickness, acquisition matrix was interpolated to 256×228 matrix, Flip angle of 25 degrees, TR/TE are 20 and 2.7 ms, respectively, and one average. Sociodemographic data, including age, sex, and race/ethnicity, were recorded as reported elsewhere.^{11,12}

Arterial Diameter Measurement

Quantitation of the effective diameter was obtained using a validated in-house software tool.¹³ Automated tracking of the vessel centerline used a distance field transform.¹⁴ Calculation of the local vessel cross-sectional area and diameter includes an iterative refinement of the local center line to assure that the area is derived using a plane that is most perpendicular to the centerline (shown as a disk in Fig. 1, row 1). The diameters of the individual vessels were calculated at the level where the cross-sectional area was largest, as determined by operator-guided measurements along the vessel segment of interest (see supplementary methods).

Basilar Artery Volume and Length

The volume of the basilar artery was estimated from the total number of voxels included in the section between the manually marked vessel origin and bifurcation to account for tapering of the vessel lumen as it gives off branches (Fig. 1, row 2). The complete basilar artery volume and length were obtained in the majority of the participants. However, incomplete volumes and lengths were recorded in a few instances where the origin of the basilar artery was not included in the MRA sequences or when the basilar artery proximal segment was technically difficult to measure (due to an inclined rather than vertical pathway). For these reason, we standardized BA volume (measured in mm^3) by the length (measured in cm) to be able to use all the scans.

Proposed DE Definition

As demonstrated in prior reports from our sample, women have larger arterial diameters than men after adjusting for differences in head size.¹⁵ As a consequence, the proposed new definition for DE in this study is a total cranial volume (TCV)-adjusted arterial diameter ≥ 2 SD above the population mean. To justify this decision, a linear regression model including age, sex, height and ethnicity was created to predict internal carotid artery and basilar artery diameters. TCV was the most important parameter predicting larger diameters. TCV was obtained using a custom-designed image analysis package (QUANTA 6.2 using a Sun Microsystems Ultra 5 workstation).¹⁶ All scans were assessed by one operator (J.G.).

Other DE Definitions

Two other definitions were explored in all arteries. One was based on visual inspection of the artery trajectory and its association with surrounding structures. This method has been previously reported (see supplementary file).^{17,18} The second DE definition consisted of unadjusted arterial diameters ≥ 2 SD. For the BA, two additional methods were used. A Smoker's criteria-based BADE was defined as BA diameters ≥ 4.6 mm at the level of the mid

pons, a laterality score ≥ 3 , and/or a height of BA bifurcation score ≥ 3 and TCV-adjusted, standardized (by BA length) BA volume ≥ 2 SD.

Statistical Analysis

Sample characteristics were assessed in relation to the presence of DE by comparing means and proportions using ANOVA or χ^2 tests as appropriate. Normality in the distribution for continuous variables was assessed with the Kolmogorov–Smirnov test. Adjustment of the arterial diameters by head size was carried out dividing the diameters by the TCV. A 10% random sample was selected for intra-reader agreement. To assess reproducibility, kappa values were used for categorical variables and intra-class correlation coefficient (ICC) for continuous measurements. Sensitivity, specificity, positive and negative predictive values (NPV), and area under the receiver operating curve (AUROC) were obtained comparing all methods used against the TCV-adjusted arterial diameters ≥ 2 SD definition of DE. A two-tailed alpha value of .05 was considered significant for all comparisons. The statistical software used for the analysis was PASW Statistics 18 (Release 18.0.0, IBM Corporation, 2010).

Results

There were 718 NOMAS MRI substudy participants with good quality head MRA data available included in this analysis (23 were excluded due to severe motion artifact). Compared to the original NOMAS cohort, participants included in this study were more likely to be Hispanic (61% vs. 51%, $P = .001$), but less likely to be diabetic (19% vs. 22%, $P = .049$), hypertensive (68 vs. 74%, $P = .002$) or to have prior cardiac disease (16% vs. 25%, $P = .001$). The mean age of the group was 71.6 ± 8.0 years, 40% were men, 61% Hispanic, 20% black, 19% white, 68% had HTN, 19% had DM, and 16% had history of any cardiac disease.

Frequency of DE in All Intracranial Arteries

Arterial diameters were available for 6,863 intracranial arteries (Table S1). Using the TCV-adjusted arterial diameters, 19% of the sample had DE in at least one artery and more than a third of those diagnosed with DE (38%) had two or more affected arteries. The most commonly involved territory was the anterior circulation, but the BA was the single most common dolichoectatic artery. Using arterial diameters unadjusted for TCV, the prevalence of DE varied minimally. On the contrary, using visual assessment increased the prevalence of DE to almost half of the sample (Table S2). Nonetheless, greater unadjusted arterial diameters were observed in arteries classified as dolichoectatic by visual inspection compared to those classified as not dolichoectatic (Table S3).

Basilar Artery Assessment

Basilar artery DE was present in 18.8% by visual assessment only. Using Smoker's criteria, BADE was found in 15.5% of the cases (supplementary material). Using the 3D tool, the mean length of the completely measured BA ($N = 476$) was 2.7 cm and mean volume 262 ± 11 mm³. After adjusting for BA length and TCV in all participants, 2.4% of the sample had BA volume ≥ 2 SD.

Reproducibility Measures and Tests Characteristics

The ICC for arterial diameters was good to excellent while the visual assessment kappa values ranged from fair to good (Tables S1 and S3). The ICC for Smoker's criteria score was good (ICC .66) and the ICC for BA volume was excellent (ICC = .98). The visual assessment method performed worse than the arterial diameter definition of DE. The unadjusted arterial diameters failed to detect almost half of the subjects detected with head size-adjusted DE definition as demonstrated with a sensitivity of roughly 50%.

Focusing on the BA, four different methods were evaluated against the definition of DE using 2 SD above the TCV-adjusted mean BA diameter. Overall, the best method was Smoker's criteria as manifested by the highest AUROC, sensitivity and specificity. However when looking at the PPV and NPV, the discriminant capacity of Smoker's criteria was poor as it correctly predicted the presence of DE in less than one out of five cases. The best discriminant capacity for BADE was seen with the adjusted BA volume followed by the unadjusted BA diameters (Table 1).

Discussion

The results of our analysis showed that approximately one out of five stroke-free, Northern Manhattan community dwellers above the age of 55 had at least one arterial diameter above a threshold of 2 SD, and one out of ten have more than one artery in that category. We suggest that arterial dilatation may thus be a more common finding than traditional studies of Dolichoectasia would suggest, and that Dolichoectasia may simply be considered an extreme in the normal spectrum of arterial dilatation. We further suggest that, in the absence of accepted or definitive criteria to define DE, this more quantitative approach to the definition, categorization and study of arterial diameters provides a more objective method to further research associations with risk factors for clinical outcomes, despite the lack of a gold standard to definitively define DE *ante mortem*.

Using our definition of DE, we found a greater DE prevalence compared to previous reports.¹ The high prevalence of cardiovascular risk factors in the sample could partially explain this finding and will be the subjects of future analyses. As evidenced by our results, the definition of DE is crucial to its study, since the results vary greatly by method. This presents an important challenge to the comparison of results among populations and there is no consensus on a DE definition. An arterial diameter-based definition has been the most commonly used study method for the last 20 years.^{6,7,10,19} However, the demographic composition of the studied population, the diseases or circumstance leading to the DE diagnosis, and the different radiological modalities used to measure the diameters pose a problem when arterial parameters from these studies are applied to other groups.

Previous investigators have recommended the use of 2 SD cutoffs based on arterial diameters to define DE, and most subsequent studies have replicated these methods.^{6,7,10} Arterial diameters vary depending on the age range, the composition of the sample, the reference population from which the sample is obtained, and the imaging methods used for measurements.^{6-8,20,21} Based on these findings, we believe that for research purposes, the measurements used to define abnormality must come from the studied population, if large

enough, rather than a cutoff obtained from other samples. For example, the arterial cutoffs from this study are not applicable to younger and healthier populations. An arterial diameter-based definition of DE is supported by reports suggesting that arterial diameters are the feature most associated with increased cardiovascular events and other clinical outcomes.^{2,3}

We did not include tortuosity in our definition of DE. It is uncertain if tortuosity without elongation has the same biological significance as isolated dilatation. In younger populations with inherited disorders of collagen, an increased risk of cardiovascular events has been predicted by greater tortuosity.²²

These findings might not be applicable to older adults with atherosclerosis-prone vessels, and since arterial diameters were not measured in the younger samples, it is still possible that the arterial diameters could be better predictors of cardiovascular events even in the younger age group.

Another factor affecting the proposed definition of DE is the benefit of adjusting arterial measurements for TCV. Behind this lies the presumption that the dimensions of the intracranial structures (eg, arteries) vary depending on the head size. This logic was used in other studies that have controlled for TCV differences among individuals in studies of other intracranial quantitative measurements.²³⁻²⁶ To our knowledge, we are the first group to normalize arterial diameters by TCV. The major difference noted with TCV adjustment was that women have larger TCV-adjusted arterial diameters compared to men,¹⁵ which is opposite to the greater proportion of men with DE reported in some studies.^{10,27,28} The association of greater arterial diameters and arterial stiffness in women compared to men has been reported in extracranial arteries,^{29,30} but it appears that the intracranial arteries might be involved as well. An alternative approach would be to stratify by sex. A problem with this approach is that the power of the study would be diminished by creating strata, and that sex strata would fail to account for other factors contributing to the head size among individuals.

Visual assessment seems to provide greater discriminant capacity in ruling out BADE than in the rest of the supratentorial vessels. This supports our previous argument that there is a bias toward over-diagnosing BADE because it is easier to identify tortuosity due to the smaller dimensions of the posterior fossa, as well as a relatively midline BA configuration.¹ Our results showed that brain arteries impinging the parenchyma are more likely to have larger diameters compared to those that do not impinge upon the parenchyma (Table S3). This method over-calls DE as manifested by the PPV of less than 10%, but it might work well to exclude cases without DE (NPV 98%). A utility of the visual assessment method can be foreseen if it can be demonstrated that outward arterial remodeling occurs as a continuous spectrum of disease such that this method will capture the arteries with larger overall diameters, and can be easy to implement in clinical practice.

We found that the anterior circulation more commonly has dilated arteries than the posterior circulation. The results in the literature are mixed, with some reports suggesting the posterior circulation is more prone to develop DE,^{2,10} and others supporting our findings.^{6,31}

An alternative explanation could be that we included 6 arteries from the anterior circulation and only 5 from the posterior circulation (excluding Pcomm), resulting in a smaller proportion of DE in the posterior circulation.

The distribution of BA diameters was within the statistically normal range, but the curve was shifted to the right with a greater proportion of larger diameters in the upper percentiles (kurtosis .6). This is noticeable in the proportion of subjects with a dolichoectatic BA (4.7% vs. approximately 2.5% if obtained from a perfectly normal distribution). This elevated proportion of BADE suggests a predisposition of the BA to dilate. This is consistent with multiple reports, although the reasons remain elusive.^{2,7,32-35} Ichikaga et al demonstrated that DM and higher glycosylated hemoglobin were associated with greater BA/ICA ratios rather than HTN suggesting a differential interaction of the BA with cardiovascular risk factors.³⁶ Another hypothesis is that the posterior circulation is less well innervated by sympathetic nerves than the anterior circulation, rendering it unprotected from the trophic effect that the sympathetic innervation exerts on the arterial wall, particularly the muscularis layer.³⁷

To ascertain BADE, we used a TCV-adjusted arterial diameter ± 2 SD. Compared to this definition, the visual assessment diagnosis of DE is the second most sensitivity method but it has the poorest PPV. This suggests that although the visual assessment method for the BA captures most of the cases with adjusted arterial dilatation, it will identify a very high proportion of false positives. Smoker's criteria resulted in the greatest AUROC from all tested methods, but the low PPV underscores the inappropriateness of using an arterial diameter cutoff from a different reference population (Smoker's ± 2 SD cutoff was 4.6 mm compared to 5.1 mm in our sample).⁷ A novel method studied here consisted of the length-standardized, TCV-adjusted BA volume. Although it is likely that the arterial diameters have a direct relationship with the arterial volume, standardization by arterial length might integrate other aspects (eg, elongation) of the arterial configuration distinct from measures of dilatation. This issue should be further clarified in the future.

The strength of our results relies on the good to excellent reproducibility of the diameter measurements, the inclusion of objective data from all intracranial arteries, the systematic data collection, and the derivation of diameters from vessel cross-sectional areas that have been associated with blood flow.^{38,39} The comparison of methods allowed us to examine the performance of each one and make a case for systematic measurements of arterial diameters with adjustment for head size to account for expected size-dependent differences in arterial dimensions. The results are more generalizable to similar urban-dwelling, stroke-free, multiethnic populations than results previously reported due to the relatively unbiased sample.

There are limitations to our results. There is no gold standard for DE. As a consequence, this and other studies on DE lack proper validation. The binary categorization of the dilatative process increases the chances of missing important biological information and patterns of disease that should be further reevaluated with continuous data. The cross-sectional design of this sample precludes inferences about etiology or natural history of the dilatation process. Our sample included stroke-free people from the original NOMAS cohort (ie, a healthier

group), which limits the generalizability of these data. The lack of a second operator to evaluate inter-reader reliability in all but a small sample limits our confidence regarding the reproducibility of our measurements. However, the software's original validations confirmed the good intra- and inter reader agreement of this method.¹³ Although the software used to measure arterial diameters is precise and reproducible, it remains largely a research tool that might not be easily applicable in clinical settings.

Conclusions

We propose that TCV-adjusted intracranial arterial diameters ± 2 SD provide a useful working definition of DE that accounts for differences in head size across individuals. Using this definition, DE is present in roughly a fifth of this urban, multiethnic, stroke free sample. The variability in the prevalence of DE depending on the methods used underscores the need to use a reliable, more universal definition of DE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: NINDS R37 NS029993 (Sacco/Elkind).

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Fig 1. Demonstration of the software used for arterial morphometric evaluation. Row one shows the tool used to measure the arterial diameters in different arteries. Row 2 exemplifies the steps to measure the volume and length of the BA. Abbreviations: BA = basilar artery, LPCA = left posterior cerebral artery, LMCA = left middle cerebral artery (mm), millimeters

Table 1

Test characteristics of DE methods compared to DE defined as 2 SD TCV-adjusted arterial diameters

	DE Defined as 2SD Unadjusted Arterial Diameters (%)	DE by Visual Assessment (%)	BADE by Smoker's Criteria (%)	BADE as TCV- and Length-Adjusted Volume (%)
All intracranial arteries				
Sensitivity	53.0	61.5	Not applicable	Not applicable
Specificity	90.0	50.2		
PPV	50.8	19.4		
NPV	90.8	87.0		
AUROC	71.5	55.9		
Basilar artery only				
Sensitivity	19	52.4	81	33.3
Specificity	98.4	82.2	86.5	98.6
PPV	26.6	8.1	15.3	41.2
NPV	97.6	97.2	99.3	98.0
AUROC	58.7	67.3	83.7	65.9

TCV = total cranial volume, DE = dolichoectasia, SD = standard deviation, BADE = basilar artery Dolichoectasia, PPV = positive predictive value, NPV = negative predictive value, AUROC = area under the receiver operating curve.