Heritability of Carotid Artery Distensibility in Hispanics The Northern Manhattan Family Study

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Abstract

Background and Purpose—Reduced arterial distensibility has been introduced as a novel risk factor for atherosclerosis. The importance of the genetic contribution to variation in distensibility is largely unknown. The purpose of this study was to estimate heritability of carotid distensibility.

Methods—The ongoing Northern Manhattan Family Study recruits high-risk Caribbean Hispanic families to study genetic effects on stroke/cardiovascular risk factors. The distensibility metrics (strain, stiffness, distensibility, and elastic modulus) were measured from the right common carotid artery, and the heritability for each was estimated. Variance component methods were used to estimate age- and sex-adjusted heritability. Correlations were calculated to evaluate the relationship between distensibility phenotypes and intimamedia thickness (IMT) at each carotid segment.

Results—The current data included 88 probands and 605 relatives from 88 families. Age- and sex-adjusted heritability was 25% for strain, 17% for distensibility, 20% for stiffness, and 20% for elastic modulus. Without adjustment for covariates, strong correlations were found between distensibility metrics and IMT: the absolute values of correlation coefficients were between 0.2 and 0.5, and all *P* values were <0.001. However, the correlation coefficients were reduced substantially after adjusting for age and sex.

Conclusions—These results suggested that genetic factors explained a moderate proportion of the variability of carotid distensibility. The correlations between distensibility and IMT were mainly attributable to age and sex effects. The regulation of carotid distensibility and IMT may reflect different underlying genetic and environmental mechanisms.

Keywords

atherosclerosis; carotid arteries; genetics

Arterial distensibility is a measure of arterial ability to expand and contract with cardiac contraction and relaxation. A decrease of arterial distensibility (ie, increased artery wall stiffness) seems to be a common pathological mechanism for many factors that lead to atherosclerosis.[1,2] A decrease of arterial distensibility has been introduced as a novel risk

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factor for atherosclerosis in epidemiologic studies.[3,4] Furthermore, decreased distensibility of the common carotid artery was associated with stroke and cardiovascular risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, and myocardial infarction.[3,5–7] Arterial stiffness has been shown to be an independent predictor of cardiovascular morbidity and mortality in patients with essential hypertension[8] and end-stage renal disease.[9]

Distensibility of an artery segment is a reflection of the mechanical stress affecting the arterial wall during the cardiac cycle. The stress can be defined as the difference in systolic and diastolic blood pressure (BP) and strain as the response of the artery system. This stress-strain relationship (defined as distensibility) has been investigated in the aorta and peripheral arteries, including the femoral and brachial artery, for many years. Because of the technological development of a high-resolution B-mode ultrasound, distensibility in the carotid arteries has been explored only recently. Several large, prospective epidemiological studies currently are evaluating carotid distensibility and the risk of myocardial infarction, stroke, or death.[4,10–12]

Although arterial distensibility can be influenced by known factors, much of its variability is unexplained and may be attributable to genetic factors. However, the importance of the genetic contribution to variation in distensibility is largely unknown. We performed genetic analyses on Caribbean Hispanic families to estimate the heritabilities of four distensibility metrics: strain, stiffness, distensibility, and elastic modulus. In addition, we investigated the correlation between the distensibility metrics and carotid intimamedia thickness (IMT), because both of these traits may represent distinctive subclinical atherosclerotic phenotypes.

Methods

Subjects

The subjects in the present study were from the ongoing Northern Manhattan Family Study (NOMAFS). NOMAFS was designed to investigate genetic factors conferring susceptibility to stroke and cardiovascular risk factors in Caribbean Hispanic families. The probands of NOMAFS were selected from high-risk members enrolled in a prospective community-based cohort: the Northern Manhattan Study.[13] A high-risk proband was defined by 1 of the following criteria: (1) reporting a sibling with a history of myocardial infarction or stroke; or (2) having 2 of 3 quantitative risk phenotypes (maximal carotid plaque thickness, left ventricle mass divided by the body surface area, or homocysteine level above the 75th percentile in the Northern Manhattan Study cohort). Families of the eligible probands were considered for enrollment provided that the proband was able to provide a family history, obtain the family member's permission for the research staff to contact them, and had ≥3 primary relatives able to participate. After the proband made the first contact, we followed up with the relatives to explain the study and solicited participation. All of the participants gave informed consent. The study was approved by the Columbia University Medical Center institutional review board.

Data Collection

Baseline data were collected through interviews of the subjects by trained bilingual research assistants using standardized data collection instruments. Standardized questions were adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System. Brachial BP recordings were obtained after ≥5 minutes rest in a supine position. Fasting blood specimens were drawn.

Carotid Distensibility and IMT Measurement

High-resolution B-mode carotid ultrasound (GE LogIQ 700 with an 11/13 MHz transducer) scanning was performed according to a standardized protocol.[14,15] In brief, the transducer was placed on the neck with the least possible pressure so as not to compress the overlying

jugular vein and to allow expansion of the carotid artery in all directions. The 10 mm of the right common carotid artery (CCA) below the origin of the carotid bulb was imaged. Both the near and far wall interfaces defining the blood-intima boundaries were maximized and clearly imaged in B-mode. M-mode images were obtained in orientations perpendicular to the CCA walls throughout the cardiac cycle. Two wall interfaces were tracked on B/D and M-mode images for ≤10 consecutive cardiac cycles. The off-line measurement was performed by the IMAGE-Pro V 5.1 (Microsoft) analysis software. The best visualized blood-intima boundaries from the 5 mol/L-mode cardiac cycles were marked, and the systolic and diastolic CCA diameters were computed and averaged. Brachial artery BP measurements were taken with a semiautomated oscillometric BP recorder (Dinamap Pro 100; Criticon, LLC) before and after each ultrasound examination and averaged. BP measurements were made in both arms, and the greater measurement was used.

The 4 carotid distensibility metrics were calculated using the following equations: (1) strain= (SD−DD)/DD, where SD is the systolic and DD diastolic intraluminal CCA diameter (mm); strain is a percentage change of the CCA diameter during the cardiac cycle; (2) stiffness=ln (SBP/DBP)/strain, where SBP and DBP are brachial BPs measured in the systolic and diastolic cardiac cycle, respectively; (3) distensibility (DIST)=(DD/IMT)/[ln (SBP/DBP)/strain]; and (4) pressure-strain elastic modulus (EM)=K(SBP−DBP)/strain, where K=133.3 is the conversion factor for mm Hg to Nm^{-2}.

Assessments of carotid diameters and distensibility based on ultrasound measurements were shown to be reproducible in several studies.[16–19] In our laboratory, the reliability was excellent with an interreader reliability correlation coefficient of 0.96 for systolic and 0.95 for the diastolic diameter of CCA.[15]

The ultrasound IMT protocol is described previously.[14,20] The total carotid IMT was calculated as a composite measure (mean of the 12 carotid sites) of the near and far wall IMT in CCA, the bifurcation, and the internal carotid artery bilaterally. Total IMT was expressed in the following 2 ways: (1) as a mean of the means of the 12 carotid sites; and (2) as a mean of the maximums of the 12 carotid sites (M-IMT). In our laboratory, the intrareader mean absolute IMT difference was 0.07±0.04 mm, with a variation coefficient of 5.4%, a correlation coefficient of 0.94, and a percent error of 5.6%.[14]

Statistics

The mean and SDs of the quantitative phenotypes were evaluated. Log transformations were used for nonnormally distributed variables. We used the Sequential Oligogenic Linkage Analysis Routines package[21] to fit a variance-components model for estimating heritability. Maximum-likelihood estimation was applied to a mixed-effects model, which incorporates fixed-covariate effects, random-additive genetic effects, and residual error. The random-additive genetic effects and residual error are assumed to be normally distributed and to be mutually independent. Heritability in the narrow sense is calculated as the proportion of phenotypic variance explained by the additive genetic effects while accounting for covariates. Ascertainment correction was performed for all of the heritability analyses by conditioning on the proband in each family.

A Pearson correlation was computed to evaluate the relationship between 2 continuous variables. Because genetic and environmental contributions to IMT are different in each carotid segment,[20] correlation coefficients were calculated between distensibility metrics and total IMT, as well as IMT in each carotid segment. To investigate how much of the heritability of one metric is attributable to the heritability of another, we partitioned phenotypic correlation (ρ_p) between 2 metrics into genetic (ρ_G) and environmental correlations (ρ_E) using the

following formula: $\rho_p = \rho_G \times \sqrt{h_1^2 \times h_2^2} + \rho_E \sqrt{(1 - h_1^2) \times (1 - h_2^2)}$ where h_1^2 and h_2^2 are the heritabilities for each metric.

Results

The current study consisted of a total of 693 subjects (88 probands and 605 relatives among 88 families) with distensibility data. Table 1 shows the characteristics of the study participants. Men accounted for 37% of the study subjects. The mean age was 47 years, with a range of 18 to 95 years. The mean family size was 9 members, ranging from 3 to 53. Thirty-four percent of the families had ≥10 family members enrolled. The number of major pair-wise relationships is shown in Table 2.

Heritabilities of carotid distensibility metrics are shown in Table 3. We first included age and sex as covariates while calculating heritability. Although sex was not a significant covariate, age explained a significant proportion of the variance. In general, the age- and sex-adjusted heritability of either distensibility metric was ≈20%: 25% ($P=0.001$) for strain, 17% ($P=0.007$) for DIST, 20% ($P=0.003$) for stiffness, and 20% ($P=0.003$) for EM. Because distensibility is strongly correlated with mean arterial pressure (MAP),[22] we also calculated heritability with adjustment for MAP and other potential covariates (smoking, diabetes, and hypertension) in addition to age and sex. The estimates of heritability were essentially the same after adding more covariates (model 2 in Table 3). The individual distensibility metrics were highly correlated with each other (all absolute values of coefficients were between 0.75 and 0.98; all P values were <0.001; Table 4). Based on the genetic and environmental correlations, the results indicated that both common genetic and environmental factors contributed substantially to the correlations of any 2 distensibility metrics. Among the 4 metrics, strain was less correlated with the other 3 metrics. The correlations between distensibility metrics and IMT in various carotid segments were substantial and very significant before adjusting for age and sex (all absolute values of coefficients were between 0.2 and 0.5; all P values were <0.001). However, the correlation coefficient was generally not significant (or became weakly correlated) after adjusting for age and sex (data now shown).

Discussion

We found that all of the carotid distensibility metrics had moderate but significant heritabilities of ≈20%. Distensibility metrics analyzed in this study represent various expressions of the carotid artery wall function. Strain is a measure of the distension of the CCA, whereas both stiffness and EM are derived from strain after adjustment for pulse pressure of the brachial artery. In addition, we have calculated a distensibility coefficient, DIST, defined as an inverse measure of stiffness with the IMT component in the formula. Although both distensibility and IMT are considered to be surrogate markers of subclinical atherosclerosis, they may not be closely related to each other after adjusting for sex and age. Measurement of both traits may improve the power to predict the risk for stroke and coronary heart disease. To the best of our knowledge, there is only 1 published article reporting the heritability of carotid distensibility.[23] The Strong Heart Family Study investigated 32 American Indian extended families and estimated a heritability of 23% for carotid stiffness and 18% for augmentation index.[23] The heritability estimates for carotid stiffness in the Strong Heart Family Study are comparable with our results.

Although distensibility is an indicator of arterial wall function and IMT is a measure of wall structure, they are weakly correlated when covariates are adjusted. Using stiffness and EM, no significant correlation between distensibility and IMT was reported in a small sample of 58 healthy men.[24] In the Atherosclerosis Risk in Communities cohort,[25] carotid strain remained nearly constant or increased slightly for any IMT values below the 90th percentile. However,

strain decreased above the 90th percentile of IMT. Another study reported a significant correlation between EM and M-IMT at CCA in vascular patients with M-IMT >0.88 mm and with plaques but not in normal subjects.[26] There is no previous report of the correlations between carotid distensibility and carotid IMT in different segments as we examined in this study. We recently demonstrated significant genetic contribution to IMT and genetic correlation between IMT and obesity in a subset (n=440) of the current cohort.[20] However, we did not find a substantial phenotypic or genetic correlation (data not shown) between IMT and distensibility metrics in the present study. It is unlikely that carotid distensibility and IMT are closely correlated in general, suggesting an existence of different underlying mechanisms for these 2 markers of subclinical atherosclerosis.

The pathophysiological mechanism influencing carotid distensibility impairment is not fully understood. Age is the most important risk factor for arterial stiffness.[27] Fracture and fragmentation of the elastin fibers after repetitive stress cycles, with consequent dilation and stiffening, may contribute to stiffness.[28] Cellular ionic changes during aging may also be one of the contributors to arterial distensibility impairment.[29] The concept that early changes in the functional properties of the arterial wall precede the clinical stage of atherosclerosis has been investigated in peripheral arteries (femoral and brachial) and the aorta. This area is of great importance in the noninvasive evaluation of lesion-prone arteries, such as carotids, which respond to the various shear stress changes by the mechanisms of compensatory remodeling. [30] Indeed, recent attention has been focused on the carotid arteries.

Several limitations need to be noted. The calculations of the carotid distensibility metrics are adjusted for the pulse pressure of the brachial artery. We thereby assume that pulse pressure measured in the brachial artery is tightly correlated with pulse pressure in the carotid arteries. However, despite the fact that the arterial pressure waves undergo transformation in the arterial tree, studies showed the validity of brachial pressure to measure pulse pressure.[31,32] Another limitation is that the distensibility metrics are strongly correlated with MAP.[22] A higher MAP in the artery stretches the elastin and collagen fibers in the arterial wall, making the arteries less distensible. To correct for this, we repeated the heritability analysis after adjustment for MAP, and the results did not change. Although female participants outnumber male participants, the different participation rates between women and men are not likely to be biased by the subjects' understanding of the carotid distensibility test results. Most participants are unaware of the definition of distensibility, and many are less aware about their own BP, glucose, or lipid levels in this underserved community. Other limitations exist, including the fact that cardiac output remains unknown in the distensibility assessments. Under normal circumstances, however, pulse pressure generated by ventricular ejection is low and does not significantly influence the measurements of distensibility.[33] When the myocardium weakens and the heart fails, the heart starts to behave like a pressure source with ventricular output being very sensitive to pressure. In this situation, the measurement of carotid distensibility may be problematic. However, none of the subjects in our study had severe heart failure, which could influence the distensibility assessments. Finally, because heritability is a population-specific parameter, our results may not be applicable to other ethnic groups.

In conclusion, we found moderate heritabilities for the 4 carotid distensibility metrics. Regardless of the formula to derive distensibility metrics, they have similar heritability estimates. The lack of substantial age- and sex-adjusted correlations between distensibility metrics and IMT indicate that the functional and structural traits may be determined by different mechanisms. The current results warrant our long-term efforts to map susceptibility genes to carotid distensibility.

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TABLE 1

Characteristics of Study Participants

Characteristic	Mean±SD
Family size	9±8
Proband, male/female	18/70
Age, y	46.9±17.7
Gender, % male	37.3
Hypertension, %	40.6
Diabetes, %	14.6
Low-density lipoprotein cholesterol, mg/dL	112.3±35.4
High-density lipoprotein cholesterol, mg/dL	48.3±14.1
Current smoking, %	15.5
Past smoking, %	22.8
Body mass index, kg/m^2	29.2±5.8
Total M-IMT	0.81±0.08
Total m-IMT	0.61±0.07

Hypertension indicates systolic BP ≥140/90 mm Hg, the patient's self-report of hypertension or use of antihypertensive medications; diabetes, fasting blood glucose ≥126 mg/dL, the patient's self-report of diabetes, insulin, or hypoglycemic use; current smoker, smoking at the time of enrollment or within the last year; past smoker, smoked >1 year ago; m-IMT, mean of the means of the 12 carotid sites.

TABLE 2

No. of Pair-Wise Relationships Among Participants

Pair-Wise Relationship	No.
Parent–offspring	500
Siblings	498
Grandparent–grandchild	107
Avuncular	664
Half siblings	133
Grand avuncular	262
First cousins	417
First cousins, once removed	307
First cousins, twice removed	58
Half-first cousins	117
Second cousins	179
Second cousins, once removed	140
Third cousins	20

TABLE 3

Heritability of Carotid Distensibility (DIST) Metrics

Variable	Mean±SD	Heritability (model 1)	Heritability (model 2)	Variance Explained by the Covariates in Model 2
Strain	0.11±0.06	0.25 (*P*=0.001)	0.25 (*P*=0.001)	0.26
DIST	1.64±1.03	0.17 (*P*=0.007) *	0.17 (*P*=0.007) *	0.42
Stiffness	6.48±5.59	0.20 (*P*=0.003) *	0.20 (*P*=0.003) *	0.30
EM×10⁻³	86.96±80.89	0.20 (*P*=0.003)	0.20 (*P*=0.002) *	0.40

Model 1, adjusting for age and sex; model 2, adjusting for age, sex, MAP, diabetes, hypertension, and smoking status.

*
Heritability of DIST, stiffness, and EM was estimated from log-transformed data.

TABLE 4

Phenotypic (ρ), Genetic (ρ_G), and Environmental (ρ_E) Correlations Between 2 Distensibility Metrics

Metric 1	Metric 2	ρ	ρ_G	ρ_E
Strain	DIST	0.75 ($P<0.001$)	0.71 ($P=0.03$)	0.79 ($P<0.001$)
Strain	Stiffness	−0.80 ($P<0.001$)	−0.84 ($P=0.01$)	−0.79 ($P<0.001$)
Strain	EM	−0.78 ($P<0.001$)	−0.79 ($P=0.02$)	−0.78 ($P<0.001$)
DIST	Stiffness	−0.97 ($P<0.001$)	−0.96 ($P<0.001$)	−0.98 ($P<0.001$)
DIST	EM	−0.95 ($P<0.001$)	−0.95 ($P=0.004$)	−0.95 ($P<0.001$)
Stiffness	EM	0.98 ($P<0.001$)	0.97 ($P=0.007$)	0.98 ($P<0.001$)