Elevated Homocysteine and Carotid Plaque Area and Densitometry in the Northern Manhattan Study

Sara Alsulaimani, MD; Hannah Gardener, ScD; Mitchell S.V. Elkind, MD; Ken Cheung, PhD; Ralph L. Sacco, MD; Tatjana Rundek, MD

Background and Purpose—Studies have linked elevated total homocysteine (tHcy) levels to atherosclerotic carotid plaque development, but data are limited to predominantly white populations. We examined the association between tHcy and carotid plaque burden and morphology in a multiethnic cohort.

Methods—In the Northern Manhattan Study, we conducted a cross-sectional analysis among 1327 stroke-free subjects (mean age, 66±9; 41% men; 19% black; 62% Hispanic; 17% white) with serum tHcy and ultrasonographic assessment of plaque morphology measured by gray-scale median (GSM) and total plaque area (TPA). GSM and TPA were examined in 4 categories. High and low GSM categories were considered echodense and echolucent plaque, respectively, and compared with no plaque. Logistic regression models were used to assess the associations of tHcy with GSM and TPA adjusting for demographics, vascular risk factors, renal insufficiency, and B₁₂ deficiency.

Results—The mean tHcy was 9.4±4.8 µmol/L (median=8.6). The prevalence of carotid plaque was 57% (52% among Hispanics, 58% black, and 70% white). Among those with plaque, the mean TPA was 20.3±20.6 mm² (median=13.6) and mean GSM 90.9±28.5 (median=93.0). The top 2 tHcy quartiles (versus quartile 1) had an elevated risk of having either echoluent plaque (tHcy Q3, odds ratio [OR]=1.8; [95% confidence interval {CI} 1.2–2.8]; tHcy Q4, OR=1.9 [95% CI 1.2–3.1]) or echodense plaque (tHcy Q3, OR=1.7 [95% CI, 1.1–2.7]; tHcy Q4, OR=1.9 [95% CI, 1.2–3.2]). The top 2 tHcy quartiles were also more likely to be in the highest TPA category (tHcy Q3, OR=1.8 [95% CI, 1.1–3.0]; tHcy Q4, OR=2.2 [95% CI, 1.3–3.7]).

Conclusions—In this population-based multiethnic cohort, elevated tHcy was independently associated with plaque morphology and increased plaque area, subclinical markers of stroke risk. (Stroke. 2013;44:XX-XX.)

Key Words: atherosclerosis ■ carotid arteries ■ echodense plaque ■ echolucent plaque ■ gray-scale median ■ homocysteine ■ plaque area ■ ultrasonography

Several epidemiological studies have shown that elevated total homocysteine (tHcy) is strongly related to atherosclerosis,¹⁻¹⁰ a leading cause of stroke.¹¹ However, most of the available data are derived from case–control studies with a small number of cases or from cross-sectional studies limited to predominantly white populations. The increased risk of atherosclerosis and stroke among blacks and Hispanics underscores the importance of examining the role of modifiable risk factors in racially and ethnically diverse populations.¹² Therefore, in the multiethnic population-based Northern Manhattan Study (NOMAS), we investigated how tHcy levels are related to carotid plaque area and plaque morphology, 2 novel, distinct, and reliable measures of subclinical atherosclerosis.¹³⁻¹⁵

Total plaque area (TPA) and plaque echogenicity, which correspond to the vulnerable plaque histology, may be useful subclinical measurements to assess the effects of antitherosclerotic treatments.¹⁶⁻¹⁹ The gray-scale median (GSM), an ultrasonographic measure of plaque echogenicity, represents a novel and promising marker of plaque stabilization of potential clinical use because of simplicity of assessment, reliability, and ability to be measured from plaque images collected during a standard clinical B-mode ultrasonography.²⁰ Data on risk factors for these plaque phenotypes in general and multiethnic populations are limited. We hypothesized that tHcy would be associated with high TPA and an increased risk of having either echoluent or echodense carotid plaque.

Methods

Study Population

The NOMAS is a prospective, population-based cohort study with a unique race/ethnic distribution of community residents. The study was designed to study the incidence and risk factors for stroke in...
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a multiethnic urban community. A total of 3298 subjects, identified by random digit dialing using dual frame sampling as previously described, were enrolled between 1993 and 2001.11 Inclusion criteria were (1) age ≥39 years, (2) no prior history of stroke, and (3) had resided in the Northern Manhattan area for at least 3 months with a telephone. The overall response rate was ≥68%. This study was approved by the Columbia University Medical Center and the University of Miami Institutional Review Boards.

Using a primary cross-sectional design, the current study is an analysis of a sample of NOMAS participants who had baseline tHcy measured and a carotid ultrasound evaluation of carotid plaque area and morphology. Among 3298 NOMAS subjects, carotid ultrasound with GSM and TPA measurements was available for 1500, of which 1327 had baseline tHcy measured.

Baseline Evaluation

Data regarding baseline functional status, vascular risk factors, and medical conditions were collected through in-person interviews conducted by trained bilingual research assistants. Physical examinations were conducted by study physicians. Race/ethnicity was based on self-identification using questions modeled after the US census and conforming to standard definitions outlined by Directive 15.24 Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control regarding hypertension, diabetes mellitus, smoking, and cardiovascular conditions. Methods regarding the measurement of blood pressure, collection of fasting blood specimens for glucose, lipids, creatinine, and vitamin B12, and the definitions of vascular risk factor covariates in NOMAS have been described previously.22–25

Assessment of Homocysteine

Blood samples were drawn from the participants after an overnight fast by trained phlebotomists. After venipuncture, the blood samples were immediately put on crushed ice. In the following hour, samples were centrifuged at 3000g for 20 minutes at 4°C and immediately frozen at −70°C until analysis. At the University of Colorado Health Science Center’s research laboratory, tHcy levels were assayed by stable isotope dilution gas chromatography–mass spectrometry that is reported to be a highly sensitive and accurate method for determination of moderate hyperhomocysteinemia in human plasma.26 Homocysteine was examined as a continuous variable and in quartiles.

Assessment of Carotid Atherosclerosis

High-resolution B-mode ultrasounds (GE LogIQ 700, 9- to 13-MHz linear-array transducer) were performed by trained and certified sonographers as previously described.27 The presence of plaque is defined as a focal wall thickening or protrusion in the lumen >50% greater than the surrounding thickness.28 Carotid plaque area (mm²) and plaque echodensity expressed as the GSM index were measured using an automated computerized edge tracking software M’Asth (Paris, France).29 Among those with plaque, low GSM (the first tertile of the GSM distribution) is considered echolucent plaque and high GSM (the top tertile) is considered echodense plaque. TPA was defined as the sum of all plaque areas measured in any of the carotid artery segments within an individual.18 Both TPA and GSM were treated as separate dependent variables and each variable was categorized into 4 categories: for TPA, there were 4 categories: no plaque (reference), mild plaque (tertile 1 TPA), moderate plaque (tertile 2 TPA), and severe plaque (tertile 3 TPA). For GSM, there were 4 categories: no plaque (reference), echolucent plaque (tertile 1 GSM), intermediate density (tertile 2 GSM), and echodense (tertile 3 GSM).

Statistical Analysis

Multinomial logistic regression models with no plaque as the reference were constructed to examine the association between tHcy (continuous and in quartiles) and each plaque phenotype after adjusting for demographics (age, sex, and race/ethnicity) in model 1, demographics and vascular risk factors (diabetes mellitus, hypertension, high-density lipoprotein, low-density lipoprotein, body mass index, smoking, and alcohol use) in model 2, and demographics, vascular risk factors, renal insufficiency, and vitamin B12 deficiency in model 3.

Results

Cohort Characteristics

Baseline cohort characteristics are shown in Table 1. Among the 1327 subjects, the mean age was 66±9 years, 41% were men, 19% non-Hispanic black, 62% Hispanic, and 17% non-Hispanic white. Renal insufficiency (serum creatinine > 1.5 mg/dL) was observed in only 38 participants (3%), whereas vitamin B12 deficiency (methylmalonic acid>271 nmol/L) was observed in 177 participants (13%).

The mean tHcy was 9.4±4.8 µmol/L and the median was 8.6 µmol/L. Figure shows the distribution of tHcy in the study population. tHcy quartiles were 3.0 to 7.0 µmol/L, 7.1 to 8.5 µmol/L, 8.6 to 10.4 µmol/L, and 10.5 to 86.3 µmol/L. In regards to clinically used cut points, 24% had tHcy 10 to 15 µmol/L and 6% had tHcy≥15 µmol/L. Elevated tHcy was greater among men, non-Hispanic blacks, and those with renal insufficiency and B12 deficiency (not shown).

For 40% of the study population, carotid ultrasound was performed at baseline when the homocysteine levels were measured. The other 60% of the study population had their carotid ultrasound after baseline. The mean and median time span between baseline homocysteine measurement and carotid ultrasound was 3 years (range=0–13 years). Carotid plaque was detected in 752 (57%) participants (70% in whites, 52% in Hispanics, and 58% in blacks). Among those with carotid plaque, the mean plaque area was 20.3±20.6 mm² and the median was 13.6 mm² (Tertile 1/mild TPA: N=257, mean area=5.2, range=1.3–9.1; Tertile 2/moderate TPA: N=255, mean area=14.2, range=9.1–21.5; and Tertile 3/severe TPA: N=237, mean area=43.2, range=21.5–155.9).

Among those with carotid plaque, the mean plaque echodensity was 90.9±28.5, and the median was 93.0 (Tertile 1/echoluent plaque: N=250, mean density=58.7, range=17.0–80.7; Tertile 2/intermediate density plaque: N=249, mean density=92.7, range=81.0–103.3; and Tertile 3/echodense plaque: N=250, mean density=121.4, range=103.5–180.0). Among non-Hispanic blacks with plaque, the mean plaque area was 22.7±23.1, median=13.8 mm² and the mean density was 91.8±27.6, median=95.6. Among Hispanics with plaque, the mean plaque area was 18.1±19.5, median=12.0 mm² and the mean density was 90.7±29.1, median=92.0. Among non-Hispanic whites with plaque, the mean plaque area was 23.6±20.4, median=17.4 mm² and the mean density was 90.8±28.0, median=94.8. Table 1 shows the characteristics of the study population stratified by category of GSM.

Association Between Homocysteine and Plaque

Table 2 shows the relationship between homocysteine quartiles and carotid plaque density and plaque area in model 3, and the online-only supplemental Table provides the results from models 1 and 2. When tHcy was examined as a continuous variable, an association between increased levels of tHcy and having echodense plaque was suggested, although a clear dose–response relationship was not observed. In all 3
multivariable-adjusted models, tHcy quartiles 3 and 4 were significantly associated with a greater prevalence of both echo-lucent plaque and echodense plaque. No significant association was observed for the second quartile of tHcy with GSM. Examination of tHcy as a continuous variable suggested that increasing tHcy was associated with an increasing risk of being in the severe category of TPA versus having no plaque. Across all 3 multivariable-adjusted models, those in the third and fourth quartiles of tHcy were more likely to be in the severe TPA category.

Table 1. Demographic and Vascular Risk Factors Overall and in Relation to Mean Plaque Density

<table>
<thead>
<tr>
<th>Variable</th>
<th>All N=1327</th>
<th>No Plaque N=575</th>
<th>Echolucent Plaque (GSM 17.0–80.7) N=250</th>
<th>Intermediate Density Plaque (GSM 81.0–103.3) N=249</th>
<th>Echodense Plaque (GSM 103.5–180.0) N=250</th>
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<tbody>
<tr>
<td>Age, mean (SD)*</td>
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<td>63 (8)</td>
<td>66 (8)</td>
<td>69 (9)</td>
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<tr>
<td>Women</td>
<td>59</td>
<td>63</td>
<td>45</td>
<td>61</td>
<td>61</td>
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<td>Race/ethnicity, %*</td>
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<td></td>
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<tr>
<td>Black</td>
<td>19</td>
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<td>17</td>
<td>12</td>
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<td>59</td>
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<td>22</td>
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<td>Hypertension, %*</td>
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<td>67</td>
<td>72</td>
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<td>78</td>
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<td>HDL, mean (SD)</td>
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<td>46 (14)</td>
<td>45 (14)</td>
<td>46 (14)</td>
<td>47 (15)</td>
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<tr>
<td>LDL, mean (SD)</td>
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<td>127 (33)</td>
<td>132 (35)</td>
<td>131 (35)</td>
<td>127 (36)</td>
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<tr>
<td>BMI, mean (SD)*</td>
<td>28 (5)</td>
<td>29 (5)</td>
<td>28 (5)</td>
<td>28 (5)</td>
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<td>12</td>
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<td>Moderate alcohol use†, %</td>
<td>38</td>
<td>36</td>
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<td>Renal insufficiency†, %</td>
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<td>2</td>
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<td>B12 deficiency†, %</td>
<td>13</td>
<td>10</td>
<td>15</td>
<td>17</td>
<td>15</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; GSM, gray-scale median; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

*P<0.05 across categories of plaque density.
†Moderate alcohol: current drinking of >1 drink per month and ≤2 drinks per day, renal insufficiency: serum creatinine>1.5 mg/dL, B12 deficiency: methylmalonic acid>271 nmol/L.

No significant interactions were observed between tHcy and race/ethnicity, renal insufficiency, and vitamin B12 deficiency in relation to the plaque phenotypes in model 3 (P<0.05).

Discussion

Our study is among the first to evaluate the relationship between tHcy and carotid plaque density measured by the ultrasonographic GSM index. We have observed a U-shaped relationship between tHcy and GSM, such that elevated levels of tHcy are independently associated with both echolucent, low-density plaques with low content of calcification, and echodense, high-density plaques with high content of calcification. Both echolucent plaque as vulnerable plaque prone to ulceration and echodense plaques as a marker of generalized atherosclerosis have been associated with increased risk of stroke. Among patients with asymptomatic carotid stenosis, plasma tHcy was significantly higher in those with microemboli detected by transcranial Doppler. This was confirmed in a later study that showed higher levels of tHcy among subjects with microemboli, but not with ulceration of carotid plaques. These findings suggest that plaque density and its embolic potential may be useful markers of vascular disease and endpoints in future clinical trials examining tHcy because previous trials using recurrent cardiovascular diseases as an outcome have failed to demonstrate clinical benefits of tHcy modification.
Our results support the possibility of an atherogenic role of tHcy. Homocysteine is hypothesized to affect the pathogenesis of atherosclerosis through its involvement in complex pathways of inflammation and calcification.\textsuperscript{27} tHcy may promote plaque formation through various mechanisms that are still not well understood. It is has been postulated that tHcy may increase clotting factors, tissue factor expression, platelet aggregation, and inhibit the anticoagulant protein thrombomodulin. It may also cause abnormalities in the function of fibrinogen and thrombin generation.\textsuperscript{38–43}

We have shown that elevated tHcy is an independent risk factor for greater plaque burden, as measured by total carotid plaque area, confirming the results from previous studies.\textsuperscript{3,10,44} In the Atherosclerosis Risk in Communities Study, participants in the top homocysteine quintile were 3.16x at risk of developing a thickened carotid wall, a distinct yet related atherosclerotic phenotype, as compared with those in the bottom quintile.\textsuperscript{2} tHcy was also positively associated with carotid intima-media thickness and focal plaque formation in a cohort with broad age range from 27 to 77 years and mutation of methylenetetrahydrofolate reductase.\textsuperscript{3} The findings of our study extend this association to a race/ethnic diverse population with a large percentage of blacks and Hispanics at an increased risk of stroke. Also, we used TPA, which is a measure more related to atherosclerosis burden and risk of stroke than intima-media thickness.\textsuperscript{14}

Although effect modification by race/ethnicity was not suggested for the associations between tHcy and plaque burden and echodensity, the power to detect interactions was limited. Our findings did not support a monotonic dose-response relationship, and suggested that an elevation in carotid plaque burden and echodensity was observed at tHcy levels that are not conventionally believed to be pathological (ie, <15 µmol/L). Compared with other observational studies, cut points of tHcy quartiles were lower,\textsuperscript{45–47} which raises an important clinical question: how much should tHcy levels be lowered because the definition of normal tHcy level is based on population means.

Although our current and previous NOMAS results suggest a relationship between elevated tHcy and carotid atherosclerosis, and incidence of stroke, myocardial infarction, and vascular death,\textsuperscript{15} results from large clinical trials (VISP [Vitamin Intervention for Stroke Prevention trial] and VITATOPS [VITAmins TO Prevent Stroke trial]) did not support the use of vitamin B supplements as a secondary preventive measure to reduce the incidence of recurrent stroke and transient ischemic attacks.\textsuperscript{33,36} However, the effect of lowering tHcy on atherosclerotic lesions in primary prevention is still unknown.

Limitations of our study include the primary cross-sectional design that limits inferences about temporality and causality. However, in a previous prospective study in our cohort, we showed that tHcy was associated with an increased risk of vascular events, including ischemic stroke.\textsuperscript{15} The results of the current study suggest that increased plaque burden may be an underlying mechanism through which homocysteine is associated with an elevated risk of vascular events, including ischemic stroke in our cohort. We did not systematically measure folate and vitamin B\textsubscript{12} levels, important predictors of tHcy level, which may bias the association. However, these factors may not be as important as previously thought, since the era of folic acid fortification for the incidence of folate deficiency has dropped from 22% to <2%,\textsuperscript{48} and no well-documented vascular benefits of vitamin B\textsubscript{12} use exist.\textsuperscript{33,36}

In conclusion, the current study builds on existing and consistent evidence that tHcy is a modifiable risk factor for carotid atherosclerosis, now associated with 2 novel imaging biomarkers of atherosclerosis, carotid plaque morphology (echodensity), and total carotid plaque area, in an ethnically diverse population.

Sources of Funding
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Disclosures
None.

References
2. McQuillain MB, Beibly JP, Nidrof M, Thompson PL, Hung J. Hyperhomocysteinemia but not the C677T mutation of methylene


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Table 2. Association between homocysteine and plaque echodensity and area

<table>
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<tr>
<th>Outcome</th>
<th>Model</th>
<th>Quartile 1 (3.0-7.0 (\mu)mol/L)</th>
<th>Quartile 2 (7.1-8.5 (\mu)mol/L)</th>
<th>Quartile 3 (8.6-10.4 (\mu)mol/L)</th>
<th>Quartile 4 (10.5-86.3 (\mu)mol/L)</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
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<td>Echolucent Plaque vs. no plaque</td>
<td>1*</td>
<td>Ref 1.0 (0.6-1.5)</td>
<td>1.7 (1.1-2.6)</td>
<td>1.9 (1.2-3.0)</td>
<td>1.0 (1.0-1.1)</td>
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<tr>
<td></td>
<td>2†</td>
<td>Ref 0.9 (0.6-1.5)</td>
<td>1.85 (1.2-2.9)</td>
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<tr>
<td></td>
<td>3‡</td>
<td>Ref 0.9 (0.6-1.5)</td>
<td>1.8 (1.2-2.8)</td>
<td>1.9 (1.2-3.1)</td>
<td>1.0 (1.0-1.1)</td>
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<tr>
<td>Intermediate density plaque vs. no plaque</td>
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<td>Ref 1.0 (0.7-1.5)</td>
<td>1.0 (0.6-1.5)</td>
<td>1.3 (0.8-2.1)</td>
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<tr>
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<td>2†</td>
<td>Ref 1.1 (0.7-1.6)</td>
<td>1.1 (0.7-1.7)</td>
<td>1.4 (0.9-2.3)</td>
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<tr>
<td>Plaque area</td>
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<td>Mild TPA vs. no plaque</td>
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<td>1.5 (1.0-2.4)</td>
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<td>Severe TPA vs. no plaque</td>
<td>1*</td>
<td>Ref 1.0 (0.6-1.7)</td>
<td>1.7 (1.1-2.7)</td>
<td>2.2 (1.3-3.6)</td>
<td>1.0 (1.0-1.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2†</td>
<td>Ref 1.0 (0.6-1.7)</td>
<td>1.8 (1.1-3.0)</td>
<td>2.2 (1.3-3.7)</td>
<td>1.1 (1.0-1.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3‡</td>
<td>ref 1.0 (0.6-1.7)</td>
<td>1.8 (1.1-3.0)</td>
<td>2.2 (1.3-3.7)</td>
<td>1.0 (1.0-1.1)</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for demographics (age, sex, race/ethnicity)
† Adjusted for demographics and vascular risk factors (diabetes, hypertension, HDL, LDL, BMI, smoking, alcohol use)
‡ Adjusted for demographics, vascular risk factors, renal insufficiency, vitamin B12 deficiency
£ The cutoff thresholds for tHcy quartiles (1-4): 3-7, 7.1-8.5, 8.6-10.4, and 10.5-86.3 µmol/l