Intima-Media Thickness and Regional Cerebral Blood Flow in Older Adults

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Background and Purpose—The relationship between the thickness of the carotid intima (IMT) and brain function remains unclear in those without clinical manifestations of cerebrovascular disease. Understanding the neural correlates of this vascular measure is important in view of emerging evidence linking poorer cognitive performance with increased IMT in individuals without clinical cerebrovascular disease.

Methods—Seventy-three participants in the Baltimore Longitudinal Study of Aging (70.9 years; SD, 7.3) were evaluated with carotid artery ultrasound and resting [15O]H2O positron emission tomography.

Results—After adjusting for age, gender, and gray and white matter volumes in the regions where IMT is related to regional cerebral blood flow (rCBF), we found that higher IMT was associated with lower rCBF in lingual, inferior occipital, and superior temporal regions. Higher IMT was also associated with higher rCBF in medial frontal gyrus, putamen, and hippocampal–uncal regions (P=0.001). Whereas women had lower IMT (P=0.01) and mean arterial pressure (P=0.05) than men, they showed more robust associations between IMT and rCBF. The relationship between IMT and rCBF was only minimally affected by additional adjustment for mean arterial pressure.

Conclusions—IMT is related to patterns of resting rCBF in older adults without clinical manifestations of cerebrovascular disease, suggesting that there are regional differences in CBF that are associated with subclinical vascular disease. (Stroke. 2010;41:273-279.)

Key Words: aging ■ brain ■ carotid artery ■ common carotid artery ■ positron emission tomography ■ regional blood flow

Increased carotid intima-media thickness (IMT) is a marker of accelerated arterial aging.1 Because many of the factors influencing arterial wall thickness are also implicated in the pathogenesis of atherosclerosis, it is not surprising that increased IMT not only is a risk factor for stroke2 but also is associated with MRI-defined cerebral infarcts and white matter disease, as well as sulcal and ventricular widening.4,5 Relatively little is known, however, about the relationship between IMT and resting regional cerebral blood flow (rCBF) in older adults without clinical manifestations of cerebrovascular disease.

It has been shown that IMT is an independent predictor of reduced cognitive speed and poorer performance on tests of verbal and nonverbal memory, semantic fluency, and executive function, even in individuals without clinical manifestations of cerebrovascular disease.2,6,7 These findings suggest that accelerated arterial aging is associated with global alterations in brain function. Because rCBF is a marker of brain function and IMT is a modifier of rCBF changes that occur as individuals age, we hypothesized that rCBF and IMT may be directly related in older individuals, even in the absence of cerebrovascular disease symptoms. Given that preventative measures and treatment may decrease or even arrest progression of atherosclerosis at early stages, understanding of accelerated aging and its cerebral correlates is important.

In the present study, we examined the cross-sectional relationship of IMT and rCBF in 73 older adults without overt cerebrovascular disease from the neuroimaging study of the Baltimore Longitudinal Study of Aging.8 We hypothesized that rCBF patterns would differ in individuals with higher IMT compared with lower IMT, even in the absence of clinically diagnosed cerebrovascular disease. Given that there are differences between men and women in both IMT9 and rCBF,10 gender differences in the relationships between IMT and rCBF were examined. We also evaluated the effects of mean arterial pressure (MAP) on the relationship between IMT and rCBF, because pathophysiological circulatory changes affecting arterial tone might be related to the association between IMT and rCBF. Finally, to better characterize the degree of vascular disease in this sample, we quantified the white matter lesion (WML) load and examined how it relates to IMT.
Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>Demographic information</th>
<th>All, N=73</th>
<th>Males, N=42</th>
<th>Females, N=31</th>
<th>Statistical Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70.9 (7.3)</td>
<td>71.7 (7.3)</td>
<td>70 (7.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Race</td>
<td>62 white, 11 black</td>
<td>37 white, 5 black</td>
<td>25 white, 6 black</td>
<td>NS</td>
</tr>
<tr>
<td>Education, yr</td>
<td>17.0 (2.4)</td>
<td>17 (2.6)</td>
<td>16.8 (2.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Cognitive status</td>
<td>MMSE</td>
<td>28.9 (1.5)</td>
<td>28.9 (1.7)</td>
<td>29 (1.2)</td>
</tr>
<tr>
<td>Clinical history</td>
<td>Cardiovascular disease</td>
<td>6 (8.2%)</td>
<td>3 (7.1%)</td>
<td>3 (9.7%)</td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>32 (43.8%)</td>
<td>23 (54.8%)</td>
<td>9 (29%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>6 (8.2%)</td>
<td>4 (9.5%)</td>
<td>2 (27%)</td>
<td>NS</td>
</tr>
<tr>
<td>Vascular data</td>
<td>SBP, mm Hg</td>
<td>123.0 (14.8)</td>
<td>125.1 (15.3)</td>
<td>120 (13.8)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>66.3 (8.5)</td>
<td>70.8 (8.6)</td>
<td>66.9 (7.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>85.2 (9.7)</td>
<td>87.1 (9.9)</td>
<td>82.7 (9.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>White matter lesion volume*</td>
<td>1348 (2308.5)</td>
<td>1673.1 (2902.4)</td>
<td>866.3 (699.2)</td>
<td>NS</td>
</tr>
<tr>
<td>White matter lesion load*</td>
<td>0.1 (0.17)</td>
<td>0.12 (0.22)</td>
<td>0.07 (0.06)</td>
<td>NS</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.6 (0.2)</td>
<td>0.7 (0.2)</td>
<td>0.6 (0.2)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*White matter lesion load is white matter lesion volume (WMV) adjusted for intracranial volume (WMV/intracranial volume)*100.

DBP indicates diastolic blood pressure; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure.
Continuous data reported as mean (standard deviation). Group differences evaluated by Student t test (continuous variables) and Fisher exact test (categorical variables).

Materials and Methods

Study Participants

Seventy-three nondemented participants from the neuroimaging study of the Baltimore Longitudinal Study of Aging who underwent resting [15O]H2O positron emission tomography (PET) and carotid ultrasound during the same visit were included in the current analyses. Structural MRI was acquired concurrently with PET in all but 3 individuals who were unable to tolerate MRI at the time of the PET study. For these individuals, MRI obtained 1.3 (SD 0.6) years before PET imaging was used.

Participant demographic, cognitive, and medical history data are shown in Table 1. Neuroimaging study of the Baltimore Longitudinal Study of Aging initially enrolled individuals with no history of central nervous system disease (epilepsy, stroke, bipolar illness), severe cardiac disease (myocardial infarction, coronary artery disease requiring angioplasty or bypass surgery), or diagnosis of dementia. In this investigation, only participants without significant carotid artery disease (ie, those who had not undergone carotid endarterectomy) were included. In addition, participants with dementia or cognitive impairment at the time of imaging were excluded from analyses. Cognitive status was determined by consensus diagnosis according to established procedures. Institutional Review Board approval was obtained for the study, and written informed consent was obtained from each participant.

PET Scanning Parameters and Conditions

[15O]H2O scans were performed on a GE 4096+ scanner (15 slices; in-plane resolution, 6.5 mm full width half maximum; 60-second acquisition). During rest, participants were instructed to focus on a screen covered with black cloth. Attenuation correction using 2-dimensional mode transmission scan (Ge-68 rotating source) was performed.

Carotid Ultrasonography

High-resolution B-mode carotid ultrasound was obtained using a linear array, 5- to 10-Mhz transducer (Ultramark 9 HDI; Advanced Technology Laboratories). Evaluation was performed in the supine position in a dark, quiet room. The IMT was measured on a frozen frame of the region 1.5 cm proximal to the carotid bifurcation after the left common carotid artery was maximized in the longitudinal plane. The IMT measurement was obtained by averaging the distance between the lumen–intima interface and the media–adventitia interface obtained from 5 contiguous sites 1 mm apart. Blood pressure measurements (Critikon1846SX/P, version 085, Dinamap; Critikon) were obtained in a supine position 15 minutes after the onset of testing.

Statistical Parametric Mapping Analysis of PET Scans

Using statistical parametric mapping (SPM2: Wellcome Department of Imaging Neuroscience), [15O]H2O-PET scans were re-aligned, spatially normalized, and smoothed to FWHM of 12 mm. To control for variability in global flow, rCBF values at each voxel were ratio-adjusted to the mean global flow and then multiplied by 50 to scale the data to the range of experimentally derived mean CBF values of 50 mL/100 grams per minute. Using a multiple regression model, the relationship between resting rCBF and IMT was assessed on a voxel-by-voxel basis, adjusting for age and gender. Separate contrasts were used to determine linear associations between IMT and higher rCBF and lower rCBF, respectively. To examine the effects of antihypertensive medications, this analysis was repeated with antihypertensive medication as an additional covariate. The effect of gender on the association between IMT and rCBF was also examined across all participants in the multiple regression model using a gender×IMT interaction. In view of IMT gender differences in our sample (Table 1) and effect of gender on the IMT–rCBF relationship in the multiple regression model, separate age-adjusted regression analyses of IMT and rCBF also were performed in males and females. These analyses were then repeated to include additional adjustments for MAP and for the (gray and white matter) brain volumes of regions showing IMT rCBF associations in the initial analyses. Significant effects for all analyses were based on the peak magnitude (P≤0.001) with a spatial extent of ≥ 100 voxels. We...
chose a relatively large spatial extent threshold to limit spurious correlations because we hypothesized that IMT and rCBF will be related in relatively large brain regions.

MRI
Spoiled gradient recalled MRI (124 slices; matrix, 256×256; pixel size, 0.93×0.93 mm; slice thickness, 1.5 mm), proton density, and T2-weighted images (repetition time, 3000; echo time, 34/100; field of view, 24 cm; matrix, 256×192; number of excitations, 0.5; slice thickness, 5 mm) were obtained on a 1.5 Tesla GE Signa system.

Brain Volumes for Significant Clusters of Interest
After segmentation into gray matter, white matter, and cerebrospinal fluid, the images were spatially normalized using a high-dimensional elastic warping method and a volume-preserving transformation.15 Masks of regions showing significant relationships between IMT and rCBF from the primary statistical parametric mapping regression analyses were then used to extract the total gray and white matter tissue volumes for each region.

WML Quantitation
A computer-assisted WML segmentation method, based on local features extracted from T1-weighted, T2-weighted, and proton density sequences, was used for volumetric assessment of WML volume using a support vector machine classifier.16

Results

Carotid Ultrasound Findings
Overall, the mean IMT was 0.62 mm (SD, 0.18). IMT was higher with increasing age; for every decade, IMT increased by 0.08 mm (SE, 0.03), adjusting for gender. Females had significantly lower mean IMT than males (P=0.01; Table 1, Figure 1).

Vascular Data
Of these 73 individuals, only 6 had systolic blood pressure >140 mm Hg and none had diastolic blood pressure >90 mm Hg (Table 1); 43.8% of the participants were using antihypertensive medications at the time of the study. Although 29% of women as compared to 55% of men were using antihypertensive medications (χ²=4.8; P=0.03), the mean MAP was lower in females than in males (P=0.05; Table 1). MAP did not correlate with IMT (r=0.06; P=0.6). Additionally, IMT did not correlate with WML burden (r=0.06; P=0.6) after removal of a single outlier.

Resting rCBF and IMT
In the group as a whole (Table 2, Figure 2), higher IMT was associated with lower rCBF in the left lingual gyrus (BA19), right inferior occipital gyrus (BA19), and right superior temporal gyrus (BA38). In addition, higher IMT was associated with greater rCBF in the right medial frontal gyrus (BA9) extending bilaterally and inferiorly to the left inferior frontal gyrus, and also in the right putamen and left hippocampal–uncal region. The additional adjustment for antihypertensive medications in the overall analysis did not alter the pattern of results.

Sex Differences in Associations Between IMT and rCBF

Across all participants, the multiple regression model revealed significant effects of gender on the relationship between IMT and rCBF in a number of large regions such as the right middle/inferior occipital gyri (BA18/19), the left middle/inferior (BA19/37) temporal gyri, bilateral anterior cingulate (BA32), and medial frontal (BA10) regions, and the left striatum, and the left superior frontal gyrus (BA10). To

Table 2. Maxima of Regions Showing Significant Correlation Between IMT and rCBF

<table>
<thead>
<tr>
<th>Cluster Maxima**†</th>
<th>Side</th>
<th>Coordinates</th>
<th>Spatial Extent, N of Voxels</th>
<th>Spatial Extent, N of Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x    y    z</td>
<td>t   P</td>
<td>x    y    z</td>
</tr>
<tr>
<td>LU</td>
<td>L</td>
<td>−26  −64  −6</td>
<td>3.7 &lt;0.001 476</td>
<td>−26  −64  −6</td>
</tr>
<tr>
<td>LU</td>
<td>R</td>
<td>42   −86  0</td>
<td>3.73 &lt;0.001 419</td>
<td>42   −86  0</td>
</tr>
<tr>
<td>LU</td>
<td>R</td>
<td>46   18   −20</td>
<td>3.43 0.001 185</td>
<td>46   18   −22</td>
</tr>
<tr>
<td>LU</td>
<td>L</td>
<td>−8   46   28</td>
<td>4.07 &lt;0.001 2126</td>
<td>−6   46   30</td>
</tr>
<tr>
<td>LU</td>
<td>R</td>
<td>32   −14  0</td>
<td>4.89 &lt;0.001 328</td>
<td>32   −14  0</td>
</tr>
<tr>
<td>LU</td>
<td>L</td>
<td>−34  −20  −34</td>
<td>3.68 &lt;0.001 264</td>
<td>−34  −20  −34</td>
</tr>
</tbody>
</table>

**Brodmann areas noted in parenthesis.
†All analyses are adjusted for the combined grey and white matter volume of a given region in which IMT is related to rCBF.
††indicates higher; ††, lower.
define this relationship further, we investigated the relationship between IMT and rCBF separately by gender. In males, higher IMT was associated with lower rCBF in right superior temporal gyrus (BA38) and greater rCBF in the right putamen and right inferior frontal gyrus (BA47) (Table 3, Figure 3). In women, higher IMT was associated with lower rCBF in the right middle temporal gyrus (BA19), left middle occipital gyrus (BA19), and right inferior parietal lobule (BA40).

Table 3. Maxima of Regions Showing Significant Age-Adjusted Relationship Between IMT and rCBF in Men and Women

<table>
<thead>
<tr>
<th>Cluster Maxima*†</th>
<th>Side</th>
<th>Coordinates</th>
<th>t</th>
<th>p</th>
<th>Spatial Extent, N of Voxels</th>
<th>Coordinates</th>
<th>t</th>
<th>p</th>
<th>Spatial Extent, N of Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males: ↑ IMT ↓ rCBF</td>
<td></td>
<td>Superior temporal gyrus (BA38)</td>
<td>R</td>
<td>46</td>
<td>18</td>
<td>-20</td>
<td>3.37</td>
<td>0.001</td>
<td>143</td>
</tr>
<tr>
<td>Males: ↑ IMT ↑ rCBF</td>
<td></td>
<td>Putamen</td>
<td>R</td>
<td>32</td>
<td>-14</td>
<td>0</td>
<td>4.06</td>
<td>&lt;0.001</td>
<td>140</td>
</tr>
<tr>
<td>Males: ↑ IMT ↓ rCBF</td>
<td></td>
<td>Inferior frontal gyrus (BA47)</td>
<td>R</td>
<td>30</td>
<td>26</td>
<td>-16</td>
<td>3.51</td>
<td>0.001</td>
<td>112</td>
</tr>
<tr>
<td>Females: ↑ IMT ↓ rCBF</td>
<td></td>
<td>Middle temporal gyrus (BA19)</td>
<td>R</td>
<td>34</td>
<td>-64</td>
<td>18</td>
<td>7.36</td>
<td>&lt;0.001</td>
<td>4671</td>
</tr>
<tr>
<td>Females: ↑ IMT ↓ rCBF</td>
<td></td>
<td>Middle occipital gyrus (BA19)</td>
<td>L</td>
<td>-38</td>
<td>-62</td>
<td>-2</td>
<td>4.92</td>
<td>&lt;0.001</td>
<td>1509</td>
</tr>
<tr>
<td>Females: ↑ IMT ↓ rCBF</td>
<td></td>
<td>Inferior parietal lobule (BA40)</td>
<td>R</td>
<td>64</td>
<td>-32</td>
<td>40</td>
<td>3.94</td>
<td>&lt;0.001</td>
<td>369</td>
</tr>
<tr>
<td>Females: ↑ IMT ↓ rCBF</td>
<td></td>
<td>Fusiform gyrus (BA37)</td>
<td>L</td>
<td>-46</td>
<td>-48</td>
<td>-12</td>
<td>3.6</td>
<td>0.001</td>
<td>1534</td>
</tr>
<tr>
<td>Females: ↑ IMT ↓ rCBF</td>
<td></td>
<td>Fusiform gyrus (BA21)</td>
<td>L</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>3.6</td>
<td>0.001</td>
<td>1534</td>
</tr>
<tr>
<td>Females: ↑ IMT ↓ rCBF</td>
<td></td>
<td>Middle temporal gyrus (BA21)</td>
<td>R</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

*Brodmann areas noted in parenthesis.
†All analyses are adjusted for the combined grey and white matter volume of a given region in which IMT is related to rCBF.
Higher IMT was also related to greater rCBF in the medial frontal gyri bilaterally, the right insular region, bilateral putamen, and left superior temporal gyrus. Although women comprise only 43% of the participants, the relationship between rCBF and IMT in women more closely resembles the overall pattern in the group as a whole.

Effect of MAP on the Relationship Between IMT and rCBF

The additional adjustment for MAP in the overall analysis resulted in only minimal changes in the correlation patterns, primarily in the spatial extent of the significant clusters (Table 2, Figure 2). When MAP was added to the models evaluating males and females separately, the effect on spatial extent was more pronounced in females than in males, with decreases in spatial extent occurring primarily in the occipitotemporal regions (Table 3, Figure 3).

Discussion

This study investigated whether IMT, a marker of accelerated vascular aging, is associated with differential spatial patterns of rCBF in older adults without clinical manifestations of cerebrovascular disease. We have shown that: (1) IMT is related to resting rCBF patterns; (2) greater IMT is associated with lower rCBF in occipitotemporal regions and with higher rCBF in the frontotemporal regions; (3) there are gender differences in relationship between IMT and rCBF; (4) in individuals with well-controlled blood pressure, MAP only minimally affects the relationship between IMT and rCBF; and (5) WML burden is not associated with IMT in this sample of individuals.

We found that higher IMT is related to lower rCBF in the lingual, inferior occipital, and superior temporal gyri. These findings suggest that accelerated vascular aging may be related to rCBF decreases in occipitotemporal regions. Based on the involvement of these areas in memory function,17,18 decreased rCBF in occipitotemporal regions may be related to previous reports of a relationship between cognitive function and IMT.2 A recent study of Baltimore Longitudinal Study of Aging participants that included the subset of neuroimaging study of the Baltimore Longitudinal Study of Aging participants in our report found that higher IMT was associated with declining verbal and nonverbal memory performance over time,7 supporting this relationship.

We also found that higher IMT was associated with higher rCBF in the medial frontal gyri, putamen, and hippocampal–uncal regions. This anterior medial temporal finding complements that of another recent functional MRI study in which IMT was positively associated with amygdala activation and connectivity.19 Whereas the association of IMT with lower rCBF in the posterior occipitotemporal region suggests that these areas may be negatively impacted during accelerated vascular aging, relative increases in rCBF in frontal and medial temporal regions associated with higher IMT may represent an attempt to preserve function. The findings of both increased and decreased rCBF in relation to IMT support functional compensation theories20,21 and may play a role in the posterior–anterior shift in age-related activation patterns characterized by decreases in occipital activation and increases in prefrontal cortex activation.22 Because the spatial distribution of the rCBF correlates is very similar to
regional differences in vasodilatory capacity during hypercapnia in older adults,\textsuperscript{23} this distribution may reflect regional differences in neuronal vasoresponsivity through nitric oxide, and possibly in angiotensin system expression with subclinical vascular disease.

We further investigated gender differences in the relationship between IMT and rCBF. Although women had lower IMT, they exhibited a robust relationship between IMT and rCBF. Furthermore, the spatial distribution of rCBF correlates with IMT in women was very similar to the pattern seen in the entire group, suggesting that women significantly contributed to the overall relationship between IMT and rCBF. In women, higher IMT correlates with lower rCBF in temporal, occipital, and parietal regions, and the correlates of higher rCBF with higher IMT are seen in medial frontal, superior temporal, and insular regions, and in bilateral putamen. These findings are in contrast with regional correlates in males, in whom higher IMT correlates with lower rCBF only in the superior temporal gyrus and with greater rCBF in the putamen and right inferior frontal gyrus. The differences in location and spatial extent of the rCBF correlates for men and women may reflect gender differences in nitric oxide and angiotensin system expression\textsuperscript{24–28} in the brain and at the common carotid artery.\textsuperscript{29,30} Differential susceptibility to angiotensin induced attenuation in rCBF by neural activity,\textsuperscript{31} and differences in gender hormone levels that may affect other endothelial factors, such as prostanoids and endothelium-derived hyperpolarizing factor,\textsuperscript{27} may further contribute to the gender differences observed here, because many of these factors are related not only to rCBF but also to IMT.

Because increased blood pressure can modify cerebral autoregulation, we also evaluated whether MAP significantly affects the relationship between IMT and rCBF. In this study, additional adjustment for MAP only minimally affected the relationship between rCBF and IMT, primarily influencing the spatial extent of the regional correlations. In females, MAP adjustment had a more pronounced impact on the relationship between IMT and rCBF, with decreased spatial extent primarily in the occipitotemporal region. These findings are of interest because women had, on average, lower MAP, and fewer women in this study were using antihypertensive medications. Overall, however, in this group of older adults, we found that MAP adjustment has a limited effect on the relationship between IMT and CBF when blood pressure is well-controlled. This attenuated effect suggests that, at least in individuals with well-controlled blood pressure, the relationship between carotid IMT and neuronal function is not greatly affected by levels of distending blood pressure.

Finally, the relationship between IMT and WML burden was examined. In a subset of our sample for which WML data were available, we did not observe associations between IMT and WML. Although cross-sectional\textsuperscript{4} and longitudinal studies\textsuperscript{32} have reported strong associations between IMT and WML, recent findings suggest that IMT measured at the internal carotid artery\textsuperscript{33} and presence of arterial plaque in addition to increased IMT\textsuperscript{34} may be stronger predictors of WML load and silent cerebral infarcts than IMT alone. This, in conjunction with lower WML load in our sample than in studies of community-dwelling elderly,\textsuperscript{8} may account for the lack of relationship between IMT and WML load.

A limitation of our study is that participants are not representative of the general population with respect to their vascular health. Individuals who had histories of myocardial infarction, bypass surgery, or angioplasty were not accepted into the neuroimaging study of the Baltimore Longitudinal Study of Aging at the time of initial enrollment. In addition, 44% of the study participants were using antihypertensive therapy and nearly 10% were using statin treatment, which are medication classes shown to decrease IMT.\textsuperscript{35} Finally, we used a statistical threshold of \( P = 0.001 \) with spatial extent of 100 voxels as compromise between type 1 and type 2 errors attributable to the limited power afforded by only a single resting PET scan per individual in these analyses.

**Conclusions**

Although our results require replication in other samples, investigation of associations between carotid IMT and rCBF is important for our understanding of the cumulative effects of subclinical vascular disease in the brain. Our findings will help inform future investigations of the central nervous system effects of therapies targeting markers of subclinical atherosclerosis.

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**Disclosure**

None.

**References**


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