Viscoelastic Properties of Normal and Atherosclerotic Carotid Arteries


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Background: remodelling of the arterial wall occurs with ageing, even in the absence of atherosclerotic risk factors. With increasing age, arteries dilate, thicken, and get stiffer. The aim of this study was to correlate carotid artery stiffness with wall thickness and plaque presence between healthy individuals and patients with early and advanced atherosclerosis.

Methods: twenty healthy volunteers, 40 carotid segments and 90 patients, 174 carotid segments, with vascular disease were included in the study. The carotid artery was imaged longitudinally and measurements of the intimal–medial thickness (IMT) and plaque were obtained. Systolic and diastolic blood pressures were taken from each arm. The carotid artery stiffness (pressure–strain elastic modulus, E_p) was calculated in all sites from the changes in pressure and diameter. M-mode was used to detect the diameter change (systolic to diastolic) over five cardiac cycles.

Results: in the healthy volunteers there was no evidence of plaque or increased IMT. The mean IMT was significantly higher in the patients compared to control (0.83 ± 0.27 mm vs. 0.54 ± 0.08 mm, p<0.0001). The IMT had a poor correlation with E_p at lower thickness (r=0.24, p=0.08) but this association became stronger with increasing thickness (r=0.62, p<0.001). Arterial segments with an IMT ≥0.88 mm became significantly stiffer compared to the controls (p<0.001) and to patients with an IMT<0.88 mm (p<0.01). Carotid E_p was markedly greater in arterial segments with plaques than in those with increased IMT (p<0.001) and the controls (p<0.0001).

Conclusions: carotid wall areas with small increase in IMT became significantly stiffer compared to the controls (p<0.001) and to patients with an IMT<0.88 mm (p<0.01). Carotid E_p was markedly greater in arterial segments with plaques than in those with increased IMT (p<0.001) and the controls (p<0.0001).

Conclusions: carotid stiffness increases in areas with marked wall thickening and particularly in segments with plaque. The simultaneous study of vessel-wall elastic behaviour with IMT and plaque changes may increase our understanding of atherosclerotic progression and wall remodelling.

Key Words: Viscoelastic properties; carotid artery; atherosclerosis.

Introduction

Although atherosclerosis is the leading cause of mortality in most industrialised nations, the initiation and progression of pathological changes in arteries attributable to atherosclerosis are not fully understood. Nonetheless, alterations in the structural and mechanical properties of the blood vessels are thought to be early manifestations of the disease process. Such alterations are believed to have an early role in the aetiopathogenesis of atherosclerosis, and may serve as specific markers for future atherosclerotic disease. Using non-invasive techniques such as ultrasound, it has been possible to identify asymptomatic, subclinical cases of atherosclerosis and monitor the progression of the disease in those at risk.

One potential predictor of future atherosclerotic disease is increased arterial stiffness. This is of interest because early arterial stiffness may be reversed pharmacologically and through dietary changes. Furthermore, increased arterial stiffness is associated with many risk factors for vascular disease, including blood cholesterol, male sex, blood pressure, and diabetes. It is well known, however, that arterial stiffness increases with age, beginning in the third decade of life, and that this process is not necessarily pathological. Since the elastic properties of the arterial wall are due to the contributions of elastin and collagen, the relative decrease in elastin content, progressive fraying of elastic lamellae, and increase in collagen content with ageing cause arteries to become stiffer.

Another change that is proposed to be an early indicator of atherosclerosis is an increase in the thickness of the intimal–medial layers of the arterial wall. The intimal–medial thickness (IMT) of the common carotid artery has been shown to be associated with other risk factors for atherosclerosis, including smoking, hypertension, and hyperlipidaemia. These data suggest that non-focal increases in IMT may be the
earliest measurable form of atherosclerosis. Yet an increase in IMT, like the increase in arterial stiffness, is a non-pathological process associated with ageing. Not coincidentally, increased age is a major risk factor in the development of vascular disease. While the increases in arterial stiffness and IMT are associated with the effects of ageing, they are also correlated with atherosclerotic disease. This study was designed to compare the relative differences in arterial stiffness between healthy individuals and patients with early and advanced atherosclerosis.

**Patients and Methods**

Subjects in this study were divided into two groups, 20 healthy volunteers, 12 males and eight females with a mean age of 45 years, range 29–63 and 90 patients with vascular disease, 54 males and 36 females with a mean age of 61 years, range 37–79. All volunteers were free of vascular disease. In the patients group arterial occlusive disease was present in the lower extremities in 72 (ankle to brachial index <0.9), in the left upper extremity in three (brachial pressure difference of >35 mmHg in all cases) and in 31 in the coronaries.

Prior to imaging, systolic and diastolic brachial artery blood pressures were taken from each arm while the patient was in the supine position. Ultrasound imaging was done with either an ATL HDI-3000 or Hewlett Packard Sonos 2000 duplex machine using a 4–7 MHz linear array or 5.5–7.5 MHz trapezoid transducer, respectively. The common carotid artery was imaged longitudinally between 0.5 to 2.0 cm proximal to the carotid bifurcation. During imaging the patient was in the supine position, with the head tilted slightly to the contralateral side. Scans were performed on both right and left common carotid arteries. Measurements of intimal–medial thickness and plaque thickness were taken directly from B-mode ultrasound images, using the thickest section for each carotid segment. The intimal–medial thickness is defined as the lumen–intimal interface to the medial–adventitial border, and plaque was defined as a local irregular structure that protrudes into the lumen more than 1.5 mm. The thickest wall area was obtained by using the anterior view, medial to the sternocleidomastoid muscle (SCM), the anterolateral view, over the SCM and the posterolateral view, behind the SCM. When the highest IMT area or plaque were determined a mean value was obtained from five measurements. Diameter change during the cardiac cycle was determined by M-mode ultrasonography at the exact site where the largest IMT and plaques were obtained. The reproducibility of obtaining values from M-mode ultrasonography has been confirmed previously.

Arterial stiffness was determined by Peterson’s pressure–strain elastic modulus (Ep). Ep is an index of stiffness that relates deformation (strain) to pressure (stress), and is defined as \( \frac{d(\Delta P)}{\Delta d} \). In this equation, \( d \) is the diameter of the artery, \( \Delta d \) is the change in diameter, and \( \Delta P \) is the pulse pressure. These values were calculated from the changes in pressure and diameter by measuring diameter change between systole and diastole over five cardiac cycles. The brachial–artery blood pressure was taken to be equivalent to that of the common carotid artery.

Statistical analysis was performed using a two-tailed t-test for the difference of the means IMT and Ep. All data are expressed as mean and one standard deviation. The correlation coefficient was used to determine the association between IMT, plaque and Ep.

**Results**

Forty carotid segments were imaged from 20 healthy volunteers, and 174 carotid segments from 90 patients. Sixteen carotid sites were excluded from the study for the following reasons: poor wall-imaging due to anterior wall calcification that produced acoustic shadowing (eight), highly pulsatile internal jugular vein (four), occlusion of the common carotid artery (one) and internal carotid artery (three) that affected wall pulsatility.

There was no evidence of plaque or of IMT value of >0.85 mm among the healthy volunteers. The plaque thickness in patients ranged from 2.3 to 4.2 mm, but none of the patients had a residual lumen of less than 2 mm. In patients with vascular disease, the mean IMT was significantly higher than the controls (0.83 mm ± 0.27 mm vs. 0.54 mm ± 0.08 mm, \( p < 0.0001 \)) and healthy aged-matched individuals from the ARIC study (0.83 mm vs. 0.69 mm, \( p < 0.01 \)). The IMT had a poor correlation with Ep at lower thickness (\( r = 0.24, p = 0.08 \)) but this association became stronger with increasing thickness (\( r = 0.62, p < 0.001 \)) (Table 1). Arterial segments with an IMT ≥ 0.88 mm (\( n = 46 \)) became significantly stiffer compared to the controls (\( p < 0.001 \)) and to patients with an IMT <0.88 mm (\( n = 87, p < 0.01 \)) (Table 1). Carotid Ep was markedly greater in arterial segments with plaques (\( n = 41 \)) than in those with increased IMT (\( p < 0.001 \)) and the controls (\( p < 0.0001 \)) (Table 1).
Table 1. Comparison and relationship of IMT and $E_p$ in the different groups.

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>IMT ± s.d. (mm)</th>
<th>$E_p$ ± s.d. (Kpa)</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>40 0.54 ± 0.08</td>
<td>52 ± 7.6</td>
<td>0.19, $p = 0.12$</td>
</tr>
<tr>
<td>Patients</td>
<td>174 0.83 ± 0.27</td>
<td>73 ± 16</td>
<td>0.62, $p &lt; 0.001$</td>
</tr>
<tr>
<td>IMT &lt; 0.88 mm</td>
<td>87 0.7 ± 0.17</td>
<td>61 ± 12</td>
<td>0.24, $p = 0.08$</td>
</tr>
<tr>
<td>IMT &gt; 0.88 mm</td>
<td>46 0.97 ± 0.29</td>
<td>82 ± 15</td>
<td>0.69, $p &lt; 0.001$</td>
</tr>
<tr>
<td>Plaque</td>
<td>41</td>
<td>96 ± 19</td>
<td>0.78, $p &lt; 0.001$</td>
</tr>
</tbody>
</table>

- IMT control vs. patients $p < 0.001$.
- $E_p$ control vs. any other group $p < 0.01$.
- $E_p$ plaque vs. any other group $p < 0.01$.
- $E_p$ of IMT < 0.88 mm vs. $E_p$ of IMT > 0.88 mm $p < 0.01$.

**Discussion**

The current measure of atherosclerosis is percentage of stenosis of an artery, and clinically significant carotid disease is defined as a minimal residual lumen of 2 mm or less. Since this is a relatively late manifestation of the disease process, the degree of stenosis is not helpful as an early index of the disease to monitor patients at risk. Furthermore, relying solely on lumen diameter to measure the progression of atherosclerosis is unreliable, due to the compensatory enlargement of arteries with an increase in IMT. Non-invasive evaluation of the mechanical properties of arteries, however, may be a more reliable measure of atherosclerotic development.

The common carotid artery (CCA) presents many advantages as a site for monitoring the progression of atherosclerotic disease. Alterations in the CCA may generally be taken to be representative of changes occurring in large vessels throughout the body. Indeed, it has been found that among individuals with an IMT value of greater than 0.8 mm in the CCA, 95.5% had plaque present in one of the bifurcations of the common carotid or common femoral arteries. Furthermore, the development of advanced lesions from fatty streaks has been associated with those that are located at eccentric thickenings. Eccentric thickenings of the artery wall are associated with arterial bifurcations, specifically in the half of the circumference opposite the flow-divider wall, and they are associated with bifurcations of the main coronary artery, brachiocephalic artery, and the carotid artery. For purposes of ultrasound imaging, however, it has been found that images are more difficult to obtain at the carotid bifurcation and the internal carotid artery than at the CCA. Furthermore, the CCA has the advantage of most closely approximating a cylinder, allowing the use of mathematical models to calculate stiffness and compliance.

Both an increase in IMT and an increase in arterial stiffness have been associated with early atherosclerosis. The progression of atherosclerotic disease involves increased thickening of the arterial wall with simultaneous dilatation of the lumen to preserve flow. The property of stiffness, however, follows a more complicated course in atherosclerosis. In the initial phase of the disease process, stiffness has been found to remain constant or even decrease, which is later followed by an increase in stiffness. Our data indicate that there is a non-linear progression to increased arterial stiffness with an increase in IMT. The assumption that an increase in IMT would be accompanied by an increase in arterial stiffness is not observed, corroborating the findings of Riley et al., who found a significant increase in arterial stiffness in only the highest decile of IMT values. This is also in agreement with observations from animal models and cross-sectional studies, where moderate increases in IMT were not found to accompany an increase in arterial stiffness. An increase in IMT does not necessarily signify an increase in arterial stiffness; it is the composition of arterial wall, not its thickness, which determines stiffness.

While our data suggest that the IMT value of >0.88 mm marks the threshold of increased arterial stiffness, this figure must not be considered absolute, due to the small sample size of our study. In the ARIC study involving 10,920 participants, a significant increase in arterial stiffness was found in only the upper tenth percentile, corresponding to IMT values greater than 0.8 mm. Because IMT values are so variable in the population at large, it may generally be concluded that the highest 10% of IMT values will show increased arterial stiffness. In a report describing the ARIC cohort, only 2.5% of participants had IMT values greater than 1.1 mm in the CCA, which explains the lower number of carotid segments with IMT values greater than 1.1 mm in our study. Based on the IMT nomograph by Howard et al., the mean IMT values for the controls in this study (0.54 ± 0.08 mm) closely approximated the mean IMT values of the age-matched population (0.6 mm), allowing us to use fewer control subjects. Furthermore, because the mean age of the controls and the patients differed, we confirmed that
the mean IMTs of the patients were significantly higher (0.83 mm ± 0.27 mm) than age-matched healthy individuals (0.69 mm). Thus, by utilising the IMT nomogram compiled by ARIC investigators, we were able to conclude that the high IMT values of the patients were not due to age alone.

Thickening of the intimal-medial layer below the highest decile may represent early stages of atherosclerosis. In histological studies, these early lesion types were found to involve the enlargement and coalescence of separate pools of extracellular lipid particles in the musculo-elastic layer of the intima, contributing to the initial thickening of the vessel wall. Furthermore, surviving structural intimal smooth-muscle cells in the region of the lipid core were found to be widely scattered, weakening the wall. These findings may explain why arterial stiffness is relatively constant, if not decreased, when IMT values increase moderately. Furthermore, gradual thickening of the arterial wall that accompanies lipid core formation does not cause stenosis because the loss of structural smooth-muscle cells, collagen and elastic tissue without scar tissue allows compensatory dilatation.

The high arterial stiffness of advanced atherosclerotic plaques may be due to multiple structural alterations with profound functional effects. Plaques are often characterised by a collagenous cap over the lipid core comprised of an altered proteoglycan layer of the intima, with increased number of smooth-muscle cells embedded in a dense matrix of collagen. Furthermore, the compensatory dilatation of the artery due to increased IMT thickening has the effect of causing collagen fibres to become more load-bearing, increasing overall stiffness. These alterations result in increased arterial stiffness as the elastin to collagen ratio changes. Stiffness can also be augmented by calcification of the collagen cap. Thus, the gradual progression of arterial stiffness from healthy carotid segments to those with increased IMT values, and finally to those with advanced plaques, may possibly reflect a continuum in atherosclerosis. Wada et al., in a study of 60 common carotid arteries found a good correlation between wall stiffness and severity of atherosclerosis ($r=0.68$).

Recently, several studies have investigated the stiffness of carotid arteries in health and disease. In the ARIC study it was demonstrated that arterial stiffness had excellent short-term repeatability. In that study arterial stiffness was termed as emerging important risk factor for cardiovascular disease. Carotid wall-motion velocity, as measured by ultrasound, had a high correlation with distensibility and compliance in a study of 78 individuals with no history of cardiovascular disease. In another study, both carotid IMT and distensibility were found to be acceptable when used in large trials. Carotid stiffness was also shown to have a moderate relationship with aortic stiffness ($r^2=0.42$, $p<0.001$). This association was independent of age, gender and blood pressure. In a prospective follow-up of 6992 normotensive people by the ARIC investigators, one standard deviation decrease in arterial elasticity was associated with 15% greater risk of hypertension. This association was independent of known risk factors for hypertension and the baseline blood pressures. Age-associated increases in carotid stiffness were reduced by oestrogen replacement therapy in postmenopausal women. Finally, in a prospective 6.2-year median follow-up (Cardiovascular Health Study) of 4476 subjects over the age of 65 years and without a history of cardiovascular disease, increases in carotid IMT were directly associated with increased risk of stroke and myocardial infarction. These recent data on carotid IMT and stiffness indicate that both measurements are important in the evaluation of the cardiovascular system. Therefore, the study of these parameters alone or in combination should increase our understanding on the evolution of atherosclerosis and may allow us to improve its management.

Conclusions

This study describes differences in arterial elasticity and compliance in a wide spectrum of carotid segments. We have attempted to correlate functional information with structural observations from ultrasonography, and IMT has been found to have a good correlation with increasing CCA stiffness. $E_p$ increases significantly in areas with marked wall-thickening, and particularly in segments with plaque. These functional differences may correspond to specific structural alterations that have been described by histological studies. The simultaneous evaluation of vessel-wall elastic behaviour with IMT and plaque changes in longitudinal prospective studies may increase our understanding of atherosclerotic progression and wall-remodelling.

References

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