Carotid distensibility characterized via the isometric exercise pressor response

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Myers, Christopher W., William B. Farquhar, Daniel E. Forman, Todd D. Williams, Dustin L. Dierks, and J. Andrew Taylor. Carotid distensibility characterized via the isometric exercise pressor response. Am J Physiol Heart Circ Physiol 283: H2592–H2598, 2002. First published August 15, 2002; 10.1152/ajpheart.00309.2002.—Distensibility of the large elastic arteries is a key index for cardiovascular health. Distensibility, usually estimated from resting values in humans, is not a static characteristic but a negative curvilinear function of pressure. We hypothesized that differences in vascular function with gender and age may only be recognized if distensibility is quantified over a range of pressures. We used isometric handgrip exercise to induce progressive increases in pressures and carotid diameters, thereby enhancing the characterization of distensibility. In 30 volunteers, evenly distributed by gender and age across the third to fifth decades of life, we derived pulsatile distensibility slopes as a function of arterial pressure for a dynamic distensibility index and compared it with a traditional static index at a reference pressure of 95 mmHg. We also assessed intima-media thickness (IMT). We found that women had greater distensibility slopes within each decade, despite comparable IMT. Furthermore, declines in distensibility slope with increasing age were correlated to increased IMT. The static distensibility index failed to show gender-related differences in distensibility but did show age-related differences. Our results indicate that gender- and age-related differences can be manifest even in young, healthy adults and may only be identified with techniques that assess carotid distensibility across a range of pressures.

carotid arteries; ultrasonography; compliance; vascular

THICKENED WALLS AND DIMINISHED DISTENSIBILITY of large elastic arteries occur with usual aging and are found in hypertension, atherosclerosis, and diabetes (4, 17, 34, 39). Both intima-medial thickening and distensibility of the carotid and aortic arteries are now widely viewed as clinically important, both as prognostic indicators and as important pathophysiological precursors to cardiovascular disease (12, 35). Reduced distensibility may also blunt vagal baroreflex responses (8). Therefore, reduced arterial distensibility heightens cardiovascular risk and increases clinical instability.

Techniques to assess distensibility typically use resting blood pressures and vessel diameters to extrapolate distensibility curves that infer values across the range of pressures from diastole to systole (6). To compare distensibility between groups, a single intermediate distensibility value, usually 100 mmHg, is used. However, distensibility is not a static measure but rather is a dynamic characteristic of elastic vessels that decreases as a negative curvilinear function of increasing pressure. Therefore, distensibility could be more meaningfully represented if derived from a continuum of pressure-diameter relations over a physiological range. For example, distensibility estimated from resting pressures and diameters may not discriminate between increased transmural distending pressure and altered arterial structure (e.g., reduced elastin-to-collagen ratio) (16). In the former condition, reduced resting (i.e., static) distensibility would be the manifestation of elevated pressure driving distensibility into the range of collagen recruitment. In the latter, reduced static distensibility would evidence an actual downward shift in the entire distensibility slope. Values of distensibility derived from static indexes could provide the very same value for both conditions, obscuring important differences. Other indexes commonly used in humans, such as the β-stiffness index (19), are also confounded, but by the lack of distinction between systemic pressure and the actual distending variable, the pulsatile volume ejected in the arterial tree.

We hypothesized that differences in distensibility between individuals may be more distinct if characterized across a range of physiological arterial pressures. Therefore, we induced progressive increases in arterial pressures and vessel diameters in volunteers via sustained isometric handgrip exercise to derive a complete distensibility curve and to assess differences relative to gender and age. Pulsatile carotid distensibility was plotted as a function of mean arterial pressure; the average slope across all pressures and the value at a...
reference pressure provided a broad measure and the more customary static index of distensibility. Comparisons between the distensibility slope and the static index were made, and relations to concurrently measured carotid intima-media thickness (IMT) were determined. We hypothesized that distensibility would correlate inversely to vessel thickening, possibly indicating a mechanism by which gender and age alter arterial vessel characteristics.

METHODS

Subjects. Thirty volunteers evenly distributed both by gender and across the third, fourth, and fifth decades of life participated. Subjects had no history of cardiovascular or other diseases, and females were premenopausal. All subjects refrained from alcohol, caffeine, and strenuous physical activity for 12 h before the study. The Institutional Review Board of the Hebrew Rehabilitation Center for Aged approved the protocol, and all subjects gave verbal and written informed consent.

Measurements and protocol. Subjects were studied in the supine position. Initially, ultrasound images were acquired with a 7.5-MHz linear array transducer (Hewlett-Packard Sonos 2500) focused on the far wall of the left common carotid artery (~1 cm proximal to the carotid bulb). Fifteen seconds of images were acquired by a computer on a beat-by-beat basis at 15 images/cardiac cycle triggered by the R-wave. This provided over 150 digitized bitmap images for off-line assessment of IMT. Subsequently, maximal voluntary handgrip force was determined from three maximal contractions on a handgrip dynamometer with both the right and left hands. Subjects were then instrumented with a four-lead electrocardiograph for a R-wave trigger, digital photoplethysmograph (model 2300 Finapres, Ohmeda) on the middle finger of the left hand for beat-by-beat arterial pressures (electrocardiograph and Finapres blood pressure were digitized to computer at 500 Hz with Windaq software) and an oscillometric device (Dinamap, Critikon) on the left arm for brachial arterial pressures. Photoplethysmographic pressures were compared and calibrated against oscillometric pressures to insure accuracy in beat-by-beat measures. The left carotid artery was insonated for B-mode images at ~30 Hz (15 images/R-wave trigger, capturing the initial 500 ms of the cardiac cycle). After a 30-s resting baseline, subjects performed 60 s of sustained isometric handgrip exercise with the right hand (40% of maximum). Sympathetic microneurography studies in humans have demonstrated that there is an approximate 60-s delay before nerve traffic increases with static exercise (26, 28, 43). Therefore, this paradigm was designed to avoid sympathetically mediated changes in distensibility. In addition, in humans, unlike dogs, the carotid artery contains little smooth muscle and is considered almost purely elastic (3, 7); thus sympathetic activation would likely have minimal influence on carotid distensibility. Target force was displayed on an oscilloscope and set at 40% of the mean of the two greatest maximal contractions for that hand. Continuous visual and auditory feedback (from the investigator) was provided to subjects to ensure maintenance of target force. During a 10-min recovery period, the photoplethysmograph and oscillometric device were placed on the right hand and arm, and the right carotid artery was insonated for a second bout of sustained isometric handgrip exercise with the left hand (identical protocol).

Data analysis. Resting systolic and diastolic blood pressures were derived from the average of oscillometric values recorded before the two exercise trials. Arterial pressures during isometric exercise were derived from the systolic maximum and diastolic minimum of the beat-to-beat pressure waveform. Mean arterial pressure for each cardiac cycle was computed as two-thirds diastolic plus one-third systolic blood pressure.

The common carotid artery, IMT, and diameters were determined from digitized B-mode ultrasound images by custom software as published previously (37, 38). Analysis for both the IMT and vessel diameter utilized similar techniques. For IMT, several points along the proximal aspect of the intima and distal aspect of the media in the posterior vessel wall were selected. For diameter measurements, several points in proximity to the edges of the near and far walls were selected. Subsequently, the computer fit a spline containing 100 points to each set of preliminary edge points. The direction locally perpendicular to each spline point was calculated, and the image was interpolated for six pixels in either direction perpendicular to the spline. The location along the interpolated line, with the largest mean arterial pressure, and second derivatives was chosen as the best edge point. This process was repeated for each spline point along the two edges. Edge points representing weak edges (e.g., points selected at edges with <20% of the maximum sum of the intensity derivatives of all edge points) were replaced by linear interpolation between the nearest strong edge points. The two sets of edge points extracted by the above procedure were modeled as a pair of parabolas, according to a least-square error fit, where the two parabolas are constrained to have the same curvature. Either the IMT or diameter of the artery was then estimated by the distance between the two parabolas. We associated maximum and minimum carotid diameters with the appropriate systolic and diastolic blood pressures acquired simultaneously via photoplethysmograph. The spatial resolution of the images was 0.1 mm/pixel.

Distensibility model. Pulsatile distensibility values (Dist) were derived (6) from each beat as twice the ratio of diameter change (\(\Delta D = D_s - D_d\), where \(D_s\) and \(D_d\) are the systolic and diastolic diameters, respectively) to pulse pressure change (\(\Delta P = P_s - P_d\), where \(P_s\) and \(P_d\) are the systolic and diastolic pressures, respectively) relative to \(D_d\): \(\text{Dist} = 2\Delta D/(\Delta P \times D_d)\). Beat-by-beat data were averaged over 1-mmHg increments for the entire data set. The plot of these binned distensibility values against mean arterial pressure provided distensibility curves across the range of pressures provided by the isometric handgrip exercise. Each data point on the plot thus represents distensibility calculated directly from measured pressure and diameter within a beat at a given mean arterial pressure. This method accounts for the distinct distending effects of pulsatile pressure at different mean arterial pressures. This is in contrast to commonly used approaches that extrapolate distensibility to different mean arterial pressures based on relations measured within a narrow pulsatile range, where several beats are observed to estimate distensibility parameters. Such approaches fail to distinguish between the distending effects of mean and pulsatile pressures, and the values derive from a very narrow range, because physiological variation in mean arterial pressure is typically small over a few continuous cardiac cycles.

To derive parameters reflecting the salient characteristics of the distensibility curves for quantitative analysis, data from each subject were assessed as separate two parameter models (inverse and exponential). Letting \(y\) denote distensibility and \(x\) denote mean arterial pressure, these models took the form:

\[
y = \frac{A}{1 + B x^n}
\]

where \(A\) and \(B\) are parameters to be determined, \(n\) is a power law exponent, and \(x\) is mean arterial pressure.
the form $y = (a + bx)^{-1}$ and $y = ae^{bx}$, where $a$ is the intercept and $b$ is the slope parameter. From these models, we derived distensibility values at a reference pressure of 95 mmHg ($\text{Dist}_{95}$) and an average slope across the range of pressures achieved ($\text{Distslope}$) (equal to $\frac{x}{(\frac{dy}{dx})_x}$), the average of the first derivative of the model distensibility curve, where $x$ is the mean $x$ value). Both models yielded comparable results, so only the parameters from the inverse model are presented.

$\text{Dist}_{95}$ is a static measure indicating pressure-diameter relations at a given point on the curve, whereas $\text{Distslope}$, given by the average of the first derivatives at each value of mean arterial pressure, is a broader measure of vessel distension. It reflects the amount of distension possible before a vessel reaches the collagen-imposed limits on its diameter. Thus a vessel with a large negative slope (steepest curve) moves through a large range in distensibility before reaching the limit where further pressure increases yield negligible diameter changes. Conversely, a small negative slope (flat curve) corresponds to a vessel that sits near its elastic limits even at rest. The reproducibility of the distensibility slope was estimated by comparing the slope parameters derived from the right and left carotid artery. The trials varied from the mean by $10 \pm 6\%$, on average, and a Levene test for homogeneity indicated there was no difference between trials.

$\beta$-Stiffness index. To assess the effect of changes in pulsatile volume (i.e., stroke volume) ejected in the arterial tree in the absence of significant systemic pressure changes, static indexes were assessed in a group of eight additional subjects (6 women and 2 men, aged 21–44 yr) before and after head-up and head-down tilts at 20°. Beat-to-beat pressures and carotid ultrasound images were acquired as described above for 1 min of supine rest before each tilt and for 1 min during each tilt in random order. Arterial pressures from the Finapres were corrected for the hydrostatic pressure gradient associated with tilt. The $\beta$-stiffness index was calculated from $\ln(P_d/P_a)\left[D_s - D_a/D_s\right]$, and pulsatile distensibility was calculated as above.

Statistics. Hemodynamic and carotid artery parameters were compared for gender and age by a two-way ANOVA using the Student-Newman-Keuls test for multiple comparisons. Pearson’s correlation coefficients ($r$) were calculated between age and hemodynamic (resting arterial pressures) and carotid artery (resting diastolic diameter, resting diameter change, and IMT) parameters. Supine and tilt values were compared with a two-tailed, paired t-test. Differences were considered significant at $P < 0.05$. Measurements are reported as means $\pm$ SE.

### RESULTS

For five subjects, we used data from only one trial due to either poor ultrasound image quality ($n = 2$) or lack of relations between distensibility and pressure ($n = 3$). For the other 25 subjects, the distensibility parameters $\text{Dist}_{95}$ and $\text{Distslope}$ were computed as an average of two trials. Only two subjects had maximal mean arterial pressures that failed to exceed 95 mmHg on both runs; likewise, two subjects had minimal mean arterial pressures that exceeded 95 mmHg on both runs. For these subjects, $\text{Dist}_{95}$ represents an extrapolation from the model; for the remaining subjects, mean arterial pressure actually passed through 95 mmHg on at least one trial.

Table 1 lists hemodynamic and carotid vessel parameters grouped by gender and decade. Resting arterial pressures showed a significant effect of gender but not age ($P = 0.18$), although diastolic and mean pressure tended to increase with age in men. Across genders, age correlated positively to IMT ($r = 0.83$, $P < 0.01$) and resting diastolic diameter ($r = 0.44$, $P < 0.05$) and correlated negatively to resting pulsatile diameter change ($r = -0.58$, $P < 0.01$).

Isometric handgrip exercise raised arterial pressure by an average of 30 ± 11 mmHg systolic and 20 ± 7 mmHg diastolic. Figure 1 illustrates raw systolic and diastolic pressures and diameters before and during exercise in one subject. Isometric handgrip produced a consistent, linear increase in arterial pressures and, consequently, carotid diameters. Figure 2 is the corresponding distensibility curve derived from the pressor response in this representative subject; both raw and binned data are shown. The average $r$ for the best fitting trial from each subject was 0.75.

Figure 3 shows the fits to the distensibility data pooled by gender and decade. The line through each group indicates the model fit for that group extrapolated to the pressure range for the entire study population. Whereas $\text{Dist}_{95}$ showed a significant age-related decline ($P = 0.013$) but no gender-related difference ($P = 0.23$), $\text{Distslope}$ showed significant relations to both age ($P = 0.013$) and gender ($P = 0.035$). On average, women had steeper (more negative) slopes than men.

### Table 1. Blood pressure and carotid artery parameters by decade and gender

<table>
<thead>
<tr>
<th></th>
<th>Third Decade</th>
<th>Fourth Decade</th>
<th>Fifth Decade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Age, yr</td>
<td>27.4 ± 0.68</td>
<td>25.8 ± 1.28</td>
<td>33.4 ± 1.4</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>67 ± 3</td>
<td>68 ± 4.3</td>
<td>69 ± 2.5</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>105 ± 5</td>
<td>121 ± 3.8*</td>
<td>119 ± 3.8*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>79 ± 4</td>
<td>86 ± 3.9</td>
<td>79 ± 2</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.5 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>Ds, mm</td>
<td>6.3 ± 0.1</td>
<td>6.4 ± 0.4</td>
<td>6.7 ± 0.3</td>
</tr>
<tr>
<td>Dd, mm</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>Dslope</td>
<td>-0.88 ± 0.19</td>
<td>-0.65 ± 0.12*</td>
<td>-0.56 ± 0.11</td>
</tr>
<tr>
<td>Dist50</td>
<td>3.24 ± 0.68</td>
<td>3.06 ± 0.41</td>
<td>2.67 ± 0.43</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SE. Arterial pressure are resting brachial. DBP, diastolic blood pressure; SBP, systolic blood pressure; MAP, mean arterial pressure; IMT, intima-media thickness; Ds, diastolic diameter; Dd, change in diameter; Distslope, slope of the distensibility curve; Dist50, distensibility at the reference pressure of 95 mmHg. *$P < 0.05$ vs. women within decade.

AJP-Heart Circ Physiol • VOL 283 • DECEMBER 2002 • www.ajpheart.org
and both genders demonstrated progressive flattening of distensibility curves with age. In women, the largest change in slope appeared between the third and fourth decades, whereas in men the decrements in slope were similar in each age strata. Across all subjects, Distslope and Dist95 correlated significantly with IMT (r = 0.41 and 0.40, P < 0.05).

Figure 4 shows the individual β-stiffness index values for the supine, +20° head-up, and −20° head-down tilt positions in the eight subjects that were tilted. The β-stiffness index increased 22% (P < 0.05) with head-up tilt but was more variable in the head-down position, where four subjects demonstrated a 12% decrease and four subjects demonstrated a 19% increase. Pulsatile distensibility tended to demonstrate similar but nonsignificant changes (P > 0.10).

DISCUSSION

Our analysis reveals progressively reduced carotid artery distensibility in association with advancing middle age among healthy, normotensive adults. We also demonstrate significant gender differences, with women showing greater distensibility slopes than men at every age. Such robust vascular aging and gender differences among relatively young adults have not been previously demonstrated. Our results not only provide physiological insights to vascular aging but also demonstrate the utility of characterizing distensibility as a dynamic index across a range of blood pressures. For example, our examination of static indexes derived from resting pulsatile values clearly shows that pulsatile pressure may not adequately gauge the assumed input of distending volume ejected into the arterial tree.

Age-related changes. A primary finding of this investigation is the demonstration that aging is associated with diminished carotid artery distensibility even among healthy young to middle-aged adults between 20 and 50. Although this finding is consistent with other investigations (9), it expands upon previous literature by demonstrating age-stratified distensibility curves in relatively young adults. Differences in distensibility slopes and intercepts indicate that even slightly older vessels are intrinsically stiffer, particularly among males. Such age-associated constitutive differences are supported by histomorphological evidence of age-related increases in stiff extracellular matrix proteins (particularly collagen), cellular apoptosis, and fragmentation of elastin (23). Our ability to assess and stratify distensibility suggests that similar measurements may provide a convenient and effective tool to study therapeutic interventions such as exercise, diet, and medications.

Surprisingly, despite a plethora of investigations focused on carotid IMT (10, 29, 31) and carotid stiffening (24), few investigations have explored the relationship of IMT to distensibility. A previous report (33) concludes there is no relationship between IMT and carotid artery elasticity estimated from resting data in middle-aged subjects except in those with the most pronounced increases in IMT. In contrast, we found a significant relationship between IMT and both distensibility slope and the static distensibility index across all subjects. These findings are in agreement with a more recent investigation in older subjects (42).

Gender-related differences. Previous studies using a variety of techniques reported lower (17, 22), similar (5, 21, 36), and higher (41) carotid stiffness in women...
compared with men. We found a greater distensibility in women than men, which was not apparent from the more customary static index of distensibility. This might explain conflicting conclusions of previous investigations, because none evaluated distensibility over a range of blood pressures. A gender effect may not be surprising because estrogen increases mesenteric artery distensibility (49) and coronary artery distensibility in rats (48). Moreover, in humans, premenopausal women have greater static carotid distensibility than age-matched postmenopausal women (44). Thus estrogen may confer beneficial effects on vessel distensibility. Interestingly, when comparing women and men within each decade (see Table 1), carotid distensibility was greater in women despite similar IMT. If estrogen reduces collagen formation and deposition in the arterial wall (13, 47), and because collagen is located predominately in the outer most adventitia layer (32), then higher distensibility despite similar IMT might be expected in women compared with men.

Methodology. The mechanical properties of large vessels are mainly determined by the elastic behavior of their structural constituents (1). This is depicted best by examining stress-strain relations of artery segments, allowing elastin and collagen contributions to be determined (2). However, direct measurement of these variables remains beyond traditional scopes of evaluation. Instead, noninvasive indexes of systemic pressure and ultrasound-derived diameters are used to provide surrogate measures of vessel mechanics. A common approach is to derive a distensibility curve from continuous recordings of pressure and diameter over several cardiac cycles (18, 24), generally coupling continuous Finapres blood pressure data to ultrasound-derived diameters in the carotid (20, 40) and radial (24) vessels. However, the restricted range of basal pressures may be insufficient to fully characterize the distensibility curve. For example, diastolic pressure is high in hypertensives and systolic blood pressure tends to be low in normotensives; thus only the collagen component of the distensibility curve may be assessed in the former and the elastin component in the latter. Some have pooled distensibility relations with populations to overcome this deficit (18, 24), but this ignores important intersubject variability and therefore may be misleading.

The $\beta$-stiffness index has been proposed to account for pressure differences and is quantified from systolic and diastolic pressure-diameter relations (19). However, the $\beta$-stiffness index is not actually independent of pressure; this index treats the relation between pressure and relative cross-sectional diameter change logarithmically (11). In addition, this index requires that measured $D_d$ equal unstrained diameter, which may not be correct (11). Figure 4 demonstrates that this index can be acutely changed with tilt. For example, when moving from a supine to a $+20^\circ$ head-up tilt position, the $\beta$-stiffness index increases. Because arterial pressure is tightly regulated, maintained arterial
pressure in the head-up position masks probable decrements in stroke volume. In these eight subjects, pulse pressure remained unchanged, but pulsatile diameter declined, causing the calculated $\beta$-stiffness index to increase 22%. The more variable responses with head-down tilt probably reflect a combination of increased stroke volume (causing a decrease in this index) vs. increased distending pressure from the cephalad shift in blood volume (causing an increase in this index). Nevertheless, calculated $\beta$-stiffness can be acutely changed, even though the inherent structure of the carotid artery does not change with tilt. In short, static assessments of vessel stiffness may not provide an accurate index of carotid artery structure.

Limitations. This study did not standardize analysis to a single point in each woman's menstrual cycle. Although radial artery distensibility may be affected by menstrual phase (15), static carotid distensibility appears unaffected by either menstrual phase or oral contraceptive use (45, 46). Thus this may not be a confound for our results. Our analysis of distensibility entailed use of Finapres data, i.e., blood pressure values recorded at the finger. Although Finapres values have been shown to be highly related to direct intraarterial blood pressure (30), such peripheral measurements are often criticized for distorting (i.e., elevating) values in the central vessels. However, because calculations of distensibility depend primarily on differences in pulse pressure at specific points in time, and not absolute blood pressure values, the tendency for this technique to provide elevated absolute blood pressure values is less significant for this work. As we indicate, stroke volume may play an important role in determining the carotid distensibility derived from pulsatile pressures and diameters. Our method assumes that stroke volume is minimally changed by 60 s of isometric exercise (14, 25, 27). However, it is possible that changes in stroke volume resulted in the lack of relation between distensibility and pressure in three trials. Future work may be improved if beat-by-beat stroke volume can be incorporated into the model.

In conclusion, our results indicate that gender-related differences and age-related declines in carotid distensibility can be manifest even in relatively young, healthy adults. Moreover, our findings suggest that assessing arterial distensibility across a range of pressures in humans may identify differences in vascular function that would otherwise be overlooked and that static indexes of arterial vascular function can be misleading.

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AJP-Heart Circ Physiol • VOL 283 • DECEMBER 2002 • www.ajpheart.org