Functional Correlates of Central Arterial Geometric Phenotypes

Angelo Scuteri, Chen-Huan Chen, Frank C.P. Yin, Ting Chih-Tai, Harold A. Spurgeon, Edward G. Lakatta

Abstract—We have assessed the functional correlates of common carotid artery (CCA) arterial geometry, derived by combining a measure of vascular mass (VM) with the wall-to-lumen (W/L) ratio in both untreated hypertensive (HT) and normotensive (NT; blood pressure <140/90 mm Hg) subjects of a broad age span (30 to 79 years) of both genders. Brachial systolic, diastolic, and pulse (SBP, DBP, PP) pressures; CCA SBP and PP; CCA diameter (D); intima-media thickness (IMT); relative distensibility; circumferential wall stress (MBP×W/L); fluid shear stress (FSS); strain; augmentation index (AGIh); and aortic pulse wave velocity (PWV) were measured in 680 NT and 635 untreated HT Taiwanese men and women. Carotid geometric phenotypes (CGPs) were derived from ultrasonographic measures of VM and W/L means. Three “deviant” CGPs were defined as follows: CGP2 or remodeling, ie, a normal VM coupled with an increased W/L; CGP3 or hypertrophy, ie, an increase in both VM and W/L; and CGP4 or hypertrophy with dilation, ie, an increased VM with normal W/L. The prevalence of specific CGPs in the total sample was 83.4% for CGP1, 5.5% for CGP2, 2.2% for CGP3, and 8.9% for CGP4. Compared with CGP1, all deviant CGPs had increased carotid resistance, had higher CCA circumferential wall stress, and varied in blood flow velocity. Compared with CGP1, CGP2 subjects were more likely to be women (69.3% versus 45.9%), were on average 10 years older, and had similar central and brachial BP levels, PWV, and AGIh but had increased strain, higher distensibility, lower flow, and a higher FSS. CGP3 subjects did not differ in age or gender but had a higher prevalence of HT; higher circumferential stress, PWV, and distensibility; and lower flow, as well as a trend toward higher SBP, PP, and AGIh and lower FSS. CGP4 subjects did not differ in age or gender but exhibited higher AGIh and aortic PWV, lower distensibility and FSS, and unchanged strain and flow. CGP4 was the only deviant CGP in which the average brachial or central arterial pressures were significantly increased. CGP4 subjects also had the highest prevalence of HT among all the CGPs (77.8% versus 45% in CGP1). CGPs exhibit some common mechanical or functional properties but each also exhibits a unique profile. Although differing quantitatively in NT and HT and at young and older age, the characteristic functional profile of a given CGP is preserved, regardless of age or BP status. A normal CGP is characterized by a low circumferential wall stress and high FSS. Each deviant CGP is characterized by a unique combination of increased circumferential wall stress, with variable FSS, strain, distensibility, central BP, and late pressure augmentation. The interplay among these factors, particularly circumferential wall and FSS, likely determines the CGP; conversely, the resultant CGP may modulate the FSS and wall stress for a given pressure and flow. (Hypertension. 2001;38:1471-1475.)

Key Words: blood flow velocity ■ blood pressure ■ carotid arteries ■ hypertension ■ arterial remodeling ■ ultrasonography

It is widely recognized that aging in both normotensive (NT) and hypertensive (HT) individuals is associated with marked structural and functional alterations within the central arterial tree.1–3 Specific geometric patterns (phenotypes) that deviate from normal have been identified.4 Although it has been demonstrated that the geometry of small arteries and arterioles affects distensibility and that specific geometric patterns are associated with hypertension,5 the functional correlates of different geometric phenotypes of large arteries have not been characterized in a population of a broad age span comprising both genders and both HT and NT individuals. The goal of the present study was to survey a diverse population with respect to characterization of the distribution of central arterial geometric phenotypes, their functional correlates, and their relationship to...
gender, age, body size, blood pressure (BP), and other measured hemodynamic variables.

Methods
The study population consisted of 1315 Taiwanese subjects (698 men, 617 women) nearly equally distributed across the third through seventh age decades. None of the subjects were receiving antihypertensive therapy, and none had a history of angina pectoris, peripheral vascular disease, or diabetes mellitus. Brachial peripheral pressure (PP) was calculated as sphygmomanometric systolic BP (SBP) minus diastolic BP (DBP). Brachial mean BP (MBP) was calculated as DBP+1/3×PP. Subjects with a brachial SBP >140 and/or a DBP >90 mm Hg were defined as HT. Blood lipids, blood urea nitrogen, creatinine, and uric acid were assayed by standard laboratory techniques. Common carotid artery (CCA) pressure waveforms were obtained by application tonometry. Central SBP and PP, which closely reflect the pressure values in the ascending aorta, were calculated from the CCA waveform calibrated by the brachial MBP and DBP.

CCA diameter (D) at end diastole, intima-media wall thickness (IMT), relative distensibility (by ultrasonography), CCA strain (strain = 100×ΔD/D, where ΔD is the difference in diameter between end systole and end diastole), CCA circumferential stress (defined as MBP times wall/lumen ratio [W/L]), CCA augmentation index (AGI; by applanation tonometry), and aortic pulse wave velocity (PWV; by Doppler velocimetry) were measured as described previously. Of note, CCA distensibility presented in this study was calculated by use of central carotid PP. All vascular recordings were performed by the same sonographer. Values provided are the average of 4 consecutive online recordings for each parameter. CCA AGI was normalized for body height (AGI = AGI×height). Carotid flow was calculated as follows: Q = VT×CSA×HR, where VT is velocity time integral (cm); CSA is carotid cross-sectional area, or πr²; and HR is heart rate. Carotid vascular resistance was calculated as MBP/Q. CCA FSS was defined as Q < πr²/4π², where r is blood viscosity. The W/L ratio was calculated as 2×IMT/D. Vascular mass (VM) was calculated, as previously reported, as πL(πRe²−πri²), where r is the arterial wall density (ρ = 1.06), L is the length of the arterial segment (L = 1 cm), and Re and Ri are the mean external and internal radii, respectively. Normal values of W/L ratio and VM were defined as those within the age- (by decade) and gender-specific 95th percentile of the 680 NT subjects from the studied population. Four common carotid geometric phenotypes (CGPs) were defined: CGP1 = normal W/L ratio and VM; CGP2 = arterial remodeling, ie, increased W/L ratio with normal VM; CGP3 = arterial hypertrophy, ie, increased W/L ratio with increased VM; and CGP4 = arterial hypertrophy with dilation, ie, normal W/L ratio and increased VM.

Data are presented as mean ± SD unless otherwise specified. CGP characteristics were compared by ANOVA, followed by Bonferroni’s test.

Results
Demographics of CGPs
Prevalence in the Total Population
The mean age of the study population was 53 ± 13 years (range, 30 to 79 years), and mean body mass index was 24.7 ± 3.6 kg/m². Six hundred eighty subjects (52%) were NT, and 635 (48%) were HT. As noted, the values of the NT subset of the population by decade and gender were used as the reference for normal values with respect to CGP classification. Among the total study population of 1315 subjects, 1097 (83.4%) exhibited a CGP1 phenotype (normal), 72 (5.5%) showed a CGP2 phenotype, 29 (2.2%) had a CGP3 phenotype, and 117 (8.9%) showed a CGP4 phenotype (the Table).

Prevalence of CGPs by BP Status or Age
The prevalence of HT (BP >140/90 mm Hg) increased with increasing age, ranging from 31% in subjects <40 years of age to 59% in subjects >70 years of age. However, most HT subjects (79%) had a normal CGP. Although the “hypertrophy with dilatation” phenotype (CGP4) was clearly more frequent in HT than in NT (14.2% versus 3.8%, P < 0.05), differences between HT and NT in the prevalence of “remodeling” (CGP2) and “hypertrophy” (CGP3) phenotypes were less evident (4.2% versus 6.0% for CGP2; 3.0% versus 1.5% for CGP3; P = NS for both). CGP2 and CGP4 phenotypes were more frequent in older individuals (6.8% versus 4.0% for CGP2; 10.7% versus 6.9% for CGP4; P < 0.05 for both).

Vascular Function of “Deviant” CGPs Compared With the Normal Phenotype
Compared with CGP1, all deviant phenotypes had an increased circumferential wall stress and an increased carotid resistance (Table). Neither blood lipids nor renal function differed between CGP1 and any deviant CGP or among deviant CGPs (data not shown).

Subjects with CGP2 were on average 10 years older than normal subjects and more likely to be women (69.3% versus 45.9%; Table). Average brachial and central BP levels did not differ between normal subjects and CGP2. Compared with normal subjects, CGP2 was characterized by higher distensibility (51%), circumferential wall stress (62%), and FSS (16%) and lower flow (28%) with no difference in PWV or AGIh (Table).

Subjects with CGP3 did not differ from normal subjects in age or gender distribution but had the highest value of circumferential stress, which was 95% higher than normal subjects. They also had higher distensibility (42%) and PWV (16%) and a trend for a higher prevalence of HT, higher SBP and PP (but not DBP), and AGIh with lower flow and FSS (Table).

Subjects with CGP4 did not differ from normal subjects with respect to age or gender but had a higher body mass index than normal subjects; had significantly higher brachial and central SBP, DBP, and PP; and had the highest prevalence of HT among all the CGPs (77.8% versus 45% in normal subjects; Table). Circumferential wall stress (43%), PWV (10%), and AGIh (76%) were higher than in normal subjects, but FSS (31%) and distensibility (22%) were lower (Table).

CGP Vascular Structure and Function by Age and Hypertension
Figures 1 and 2 illustrate various aspects of CCA structure and function by age (younger or older than the median age of 51 year) or BP status (HT or NT). Note that although absolute values of arterial functional parameters between NT and HT or in younger versus older age groups differed, the vascular profile characteristic of a specific CGP was preserved regardless of age or BP status. Thus, although HT status and age had a quantitative impact on vascular structure and function, the qualitative characteristic functional profile of most CGPs is not largely dependent on age or HT status.
### Demographic and Vascular Profiles of Common CGPs in the Total Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CGP 1, Normal (n=1097; 83.4%)</th>
<th>CGP 2, Remodeling (n=72; 5.5%)</th>
<th>CGP 3, Hypertrophy (n=29; 2.2%)</th>
<th>CGP 4, Hypertrophy With Dilation (n=117; 8.9%)</th>
<th>P&lt;0.05 (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51.8±12.8</td>
<td>61.9±8.7</td>
<td>54.3±15.0</td>
<td>55.2±10.8</td>
<td>2 vs 1</td>
</tr>
<tr>
<td>Female, %</td>
<td>45.9</td>
<td>69.3</td>
<td>38</td>
<td>51.3</td>
<td>2 vs 1</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.5±3.6</td>
<td>25.0±3.0</td>
<td>25.2±3.0</td>
<td>26.5±3.4</td>
<td>4 vs 1</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>45.1</td>
<td>39.0</td>
<td>65.5</td>
<td>77.8</td>
<td>4 vs 1, 2</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>134.4±23.5</td>
<td>133.0±23.5</td>
<td>142.4±24.3</td>
<td>156.3±25.9</td>
<td>4 vs all</td>
</tr>
<tr>
<td>Central SBP, mm Hg</td>
<td>126.4±23.0</td>
<td>125.1±22.5</td>
<td>133.6±23.9</td>
<td>145.8±25.3</td>
<td>4 vs all</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>83.5±13.3</td>
<td>79.4±10.8</td>
<td>84.1±13.0</td>
<td>95.4±16.0</td>
<td>4 vs all</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>100.5±15.7</td>
<td>97.3±14.1</td>
<td>104.2±18.1</td>
<td>115.2±18.6</td>
<td>4 vs all</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>50.8±16.2</td>
<td>53.6±16.9</td>
<td>58.2±17.7</td>
<td>60.9±17.5</td>
<td>4 vs 1</td>
</tr>
<tr>
<td>Central PP, mm Hg</td>
<td>42.8±15.8</td>
<td>45.6±15.6</td>
<td>49.4±17.5</td>
<td>53.1±17.4</td>
<td>4 vs 1, 2</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>73.6±9.9</td>
<td>71.0±10.3</td>
<td>73.0±10.0</td>
<td>74.0±10.4</td>
<td>NS</td>
</tr>
<tr>
<td>CCA diameter, mm</td>
<td>6.4±0.7</td>
<td>5.5±0.5</td>
<td>6.1±0.6</td>
<td>7.4±0.9</td>
<td>4 vs all; 1, 3 vs 2</td>
</tr>
<tr>
<td>CCA IMT, mm</td>
<td>0.96±0.20</td>
<td>1.35±0.16</td>
<td>1.77±0.35</td>
<td>1.37±0.17</td>
<td>3 vs 2, 4 vs 1</td>
</tr>
<tr>
<td>CCA W/L ratio</td>
<td>0.30±0.07</td>
<td>0.51±0.07</td>
<td>0.58±0.13</td>
<td>0.38±0.06</td>
<td>3 vs 2–4 vs 1</td>
</tr>
<tr>
<td>CCA VM, mm³</td>
<td>11.1±2.7</td>
<td>13.6±2.3</td>
<td>20.7±5.3</td>
<td>18.4±3.2</td>
<td>3 vs 2–4 vs 1</td>
</tr>
<tr>
<td>Aortic PWV, cm/s</td>
<td>979±220</td>
<td>981±278</td>
<td>1135±428</td>
<td>1076±282</td>
<td>3, 4 vs 1; 3 vs 2</td>
</tr>
<tr>
<td>CCA AgIH, %</td>
<td>19.1±23.8</td>
<td>19.3±24.3</td>
<td>23.7±22.3</td>
<td>33.7±24.3</td>
<td>4 vs 1, 2</td>
</tr>
<tr>
<td>CCA circumferential stress, mm Hg</td>
<td>30.4±8.4</td>
<td>49.2±7.1</td>
<td>60.0±14.3</td>
<td>43.4±9.3</td>
<td>3 vs 2, 4 vs 1</td>
</tr>
<tr>
<td>CCA FSS, dynes/cm²</td>
<td>1.29±0.44</td>
<td>1.51±0.41</td>
<td>1.05±0.35</td>
<td>0.90±0.35</td>
<td>2 vs all; 1 vs 4</td>
</tr>
<tr>
<td>Strain, %</td>
<td>6.3±3.1</td>
<td>8.9±6.0</td>
<td>9.0±4.0</td>
<td>5.8±3.1</td>
<td>2, 3 vs 1, 4</td>
</tr>
<tr>
<td>CCA distensibility, μm · mm Hg⁻¹ · mm⁻¹</td>
<td>110±65</td>
<td>151±125</td>
<td>156±97</td>
<td>86±58</td>
<td>2, 3 vs 1–4</td>
</tr>
<tr>
<td>Carotid flow, mL/min</td>
<td>938±262</td>
<td>676±204</td>
<td>711±218</td>
<td>979±312</td>
<td>1–4 vs 2, 3</td>
</tr>
<tr>
<td>Carotid resistance, mm Hg⁻¹ · min⁻¹ · L⁻¹</td>
<td>116.5±37.4</td>
<td>161.8±47.3</td>
<td>170.2±51.1</td>
<td>130.1±45.0</td>
<td>2, 3 vs 4–1</td>
</tr>
</tbody>
</table>

*Percentage of total (NT+HT) population.

All probability values are after Bonferroni’s adjustment for multiple comparisons.

**Discussion**

Circumferential wall stress and FSS are considered to be important determinants of the arterial wall structure during development and its remodeling during aging or in response to disease in adults. BP and blood flow are major determinants of these mechanical stresses that act on the arterial wall and lumen. Thus, chronic, experimentally induced, or aging- or disease-induced alterations in BP or flow that perturb the circumferential wall and FSS, respectively, act as stimuli for arterial structural changes that result in altered vascular geometry in an attempt to reduce or normalize the stress. However, for a given change in arterial pressure and flow, the ambient vascular geometry is a determinant of the resulting mechanical stress on the vessel wall. Additionally, a variety of already identified growth factors (angiotensin II, endothelin, and others) can also regulate vascular structure independently of BP, blood flow, or vascular geometry. Thus, arterial pressure and flow, classically measured mechanical wall and FSS, downstream peripheral resistance, less well-studied or measurable growth factors, and the vascular geometric pattern or phenotype are intimately intertwined.

The present study describes the CCA geometric pattern or phenotype (CGP) based on VM and W/L ratio in a large number of NT and HT men and women of a broad age range. A normal CGP was defined on the basis of both a VM and a W/L ratio within the 95% confidence levels of the mean values for age decade and gender. Our main goal was to characterize the distensibility of phenotypes within the study population and determine their functional correlates that could be derived from measured variables. Three deviant CGPs were identified on the basis of an increased VM, an increased W/L, or both.

Although each deviant CGP occurred in the context of increased carotid resistance and was characterized by an increased circumferential wall stress, the deviant CGPs differed in central arterial pressure, flow, FSS, strain, and distensibility. That the IMT, W/L ratio, and VM varied directly among CGPs in a manner identical to that of estimated circumferential wall stress (CGP3>CGP2 or CGP4>CGP1) underscores the importance of circumferential wall stress with respect to CGP.

Prior studies have addressed the functional correlates of the components of CGP. The CCA IMT is associated directly with circumferential wall stress and inversely with FSS and increased SBP. An increased VM was more likely to occur in HT than NT subjects. A lower FSS, inversely related to SBP, a high circumferential wall stress, and reduced strain identify a “cluster” of subjects with risk factors for carotid atherosclerosis. Although in the present study HT status and age had a quantitative impact on vascular structure and function, the qualitative characteristics of the
functional profile of a given CGP were largely independent of age or HT; and most HT patients (79%) had a normal VM and lumen (CGP1). Still, individuals with a CGP characterized by an increased VM (CGP3 and CGP4) were more likely to be HT than NT (the Table), consistent with previous reports.\(^\text{14–16}\)

CGP4, which is a typical vascular profile in patients with long-standing hypertension,\(^\text{18,19}\) may reflect the fatiguing effects of repeated intense cyclic stress that may cause fracture of the load-bearing elastin fibers and thus dilation of the lumen.\(^\text{20}\) In the present study, CGP4 was associated with higher central and brachial BP values than other deviant CGPs or CGP1 and had the highest PWV and late augmentation of the pressure carotid of all the CGPs. That calculated FSS in CGP4 is reduced to levels lower than in normal subjects likely results from lumen dilatation in the presence of a normal flow rate. CGP3 can be interpreted as a transition state between normality and CGP4, because it shares some properties of both. Average central and brachial pressures in CGP 3 were intermediate between those of normal subjects and those with CGP4, as were FSS, PWV, and AGIh. Thus, the deviant CGPs, CGP3 and CGP4, which both have an increase in VM but differ in lumen size and flow, are linked to an increase in central arterial pressure. However, given the interaction of pressure, flow, wall stress, FSS, and vascular geometry, it is not possible to conclude that an increased pressure is a cause of CGP3 or CGP4.

CGP2 is very intriguing and does not readily fit with the idea that arterial pressure is its major determinant. In fact, there are no differences in the systemic hemodynamic parameters between CGP1 and CGP2. Although subjects with CGP2 were, on average, 10 years older than normal subjects, their central and peripheral BPs were similar and their CCA distensibilities were, in fact, greater than those of all other groups. The CGP2 group exhibited the highest FSS, which is attributable to their smallest lumen diameter. Thus, individuals with CGP2 maintained more optimal CCA properties, even in the presence of increased carotid wall stress and resistance (arterioles distal to CCA), which is the apparent cause of an increased circumferential wall stress.

In conclusion, each deviant CGP was associated with functional alterations specific to each. Neither age nor HT status was able to discriminate a given deviant CGP. Whereas hemodynamic factors may underlie some changes in circumferential wall stress and other aspects of arterial function of a given CGP, other factors may also be implicated in the apparent paradoxical relationship between arterial wall stress and arterial structure and function, eg, CGP2. Elucidation of these factors, such as genetic factors or growth factor status within the arterial wall, which were not possible to measure in the present study, requires further study. Finally, whether deviant CGPs in asymptomatic persons without a clinical diagnosis, eg, the volunteer subjects of this study, are cardiovascular risk factors for HT or cardiovascular disease or whether patients who are already labeled with these diagnoses but have differing CGPs have a differential risk for end-organ damage are provocative issues that merit future consideration.

A limitation of the present study is that ultrasound imaging cannot discriminate between the intimal and medial layers of the vessel wall. However, the CCA is usually spared atherosclerosis, in contrast to the carotid bifurcation and proximal internal carotid. In this regard, it is noteworthy that clinical atherosclerosis is not prevalent in this Asian population sample and that plasma lipids were not an independent determinant of IMT (data not shown).

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References


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