Ethnic Differences in Arterial Wave Reflections and Normative Equations for Augmentation Index


See Editorial Commentary, pp XX–XX

Abstract—Data regarding ethnic differences in wave reflections, which markedly affect the central pressure profile, are very limited. Furthermore, because age, heart rate, and body height are strong determinants of augmentation index, relating single measurements to normative data (in which augmentation index values correspond with average population values of its determinants) is challenging. We studied subject-level data from 10 550 adults enrolled in large population-based studies. In a healthy reference sample (n=3497), we assessed ethnic differences in augmentation index (ratio of second/first systolic peaks) and generated equations for adjusted z scores, allowing for a standardized comparison between individual augmentation index measurements and the normative population mean from subjects of the same age, sex, ethnic population, body height, and heart rate. After adjustment for age, body height, heart rate, and mean arterial pressure, African blacks (women: 154%; men: 138%) and Andean Hispanics (women: 152%; men: 133%) demonstrated higher central (aortic) augmentation index values than British whites (women: 140%; men: 128%), whereas American Indians (women: 133%; men: 122%) demonstrated lower augmentation index (all P<0.0001), without significant differences between Chinese and British whites. Similar results were found for radial augmentation index. Nonlinear ethnic/sex-specific equations for z scores were successfully generated to adjust individual augmentation index values for age, body height, and heart rate. Marked ethnic differences in augmentation index exist, which may contribute to ethnic differences in hypertensive organ damage. Our study provides normative data that can be used to complement the interpretation of individual hemodynamic assessments among men and women of various ethnic populations, after removing the effect of various physiological determinants. (Hypertension. 2011;57:00-00.) • Online Data Supplement

Key Words: wave reflections ● augmentation index ● ethnicity

A rterial wave reflections have emerged as important markers of vascular health and predict cardiovascular risk independent of blood pressure in various populations. Studies assessing the effects of aging and various physiological parameters on wave reflections in healthy individuals have been performed predominantly in white subjects. Given potential ethnic differences in arterial function and the importance of central hemodynamics in cardiovascular disease, there is a need for a systematic assessment of ethnic differences in late systolic pressure augmentation from wave reflections, which, in turn, markedly affect the central pressure profile for any given level of brachial pressures.

The central augmentation index (AIx; cAIx) is the most widely used index of wave reflections. This index is often assessed noninvasively with use of a generalized transfer function applied to the radial pressure waveform. In addition, the untransformed radial AIx (rAIx) is correlated with cAIx obtained via a generalized transfer function. Therefore, rAIx has also been proposed as a useful index of vascular aging and risk. AIx is an attractive biomarker because it is dimensionless and, therefore, independent of waveform calibration with noninvasive blood pressure values, which is limited by measurement error.

Availability of reference or normative values is important to apply epidemiological findings from populations to hemo-
dynamic assessments in individuals. In addition to potential ethnic differences, the population variability in Alx among healthy individuals is heavily influenced by various physiological determinants, including sex, age, body size, and heart rate. Therefore, it is challenging to assess Alx values obtained from single individuals with varying characteristics and compare them with normative data obtained from groups of individuals in which values of Alx reflect average population values of its physiological determinants. Furthermore, as stated above, ethnicity may be an independent determinant of wave reflections, and, therefore, efforts to determine ethnic-specific normative data are required.

The aims of our study are as follows: (1) to assess interethnic differences in Alx; (2) to establish normative values for Alx that can be applied to assess measurements from various ethnic groups, adjusting individual measurements for chronologic age, sex, body size, and heart rate, via the use of adjusted z scores; and (3) to assess the relation between adjusted z scores and classic cardiovascular risk factors.

Methods

Study Population

We analyzed data from large population-based studies throughout the world that obtained arterial tonometry recordings, including the following (in alphabetic order): the Anglo-Cardiff Collaborative Trial (ACCT), which enrolled individuals selected at random from local general practice lists and open-access cardiovascular risk assessment clinics across East Anglia and Wales; the PREVENCION Study (Spanish acronym for Peruvian Study of the Prevalence of Cardiovascular Disease and Coronary Risk Factors), which enrolled randomly selected community-dwelling adults aged 20 to 80 years of Andean-American ethnicity from Arequipa, Peru; the Strong Heart Study, which enrolled members of 13 American Indian communities in Arizona, North and South Dakota, and Oklahoma and recorded radial tonometry data during the third examination; the study by Li et al. from Shanghai, China, which enrolled community-dwelling subjects over a wide age range; and the African Project on Genes in Hypertension Study in which nuclear families of black African descent were randomly recruited from the South West Township of Johannesburg, South Africa. A total of 10,550 adults with tonometry measurements and covariate data were available, including British whites enrolled in ACCT (n = 3,753), North American Indians from the Strong Heart Study (n = 2,594), Andean Hispanics from the PREVENCION Study (n = 1,949), Chinese adults from the Shanghai study (n = 1,311), and black Africans from the African Project on Genes in Hypertension Study (n = 943). To generate normative data for Alx in various ethnic populations (and assess ethnic differences in Alx), we selected a reference subsample composed of subjects that did not meet any of the following criteria: (1) hypertension (systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or antihypertensive medication use); (2) diabetes mellitus (fasting glucose ≥ 126 mg/dL or antidiabetic medication use); (3) serum cholesterol ≥ 250 mg/dL; (4) serum creatinine ≥ 1.5 mg/dL; (5) history of coronary heart disease or myocardial infarction; (6) peripheral vascular disease; (7) previous stroke; (8) congestive heart failure; (9) atrial fibrillation; (10) body mass index > 30 kg/m²; and (11) current smoking. The resulting reference sample was composed of 3,497 subjects (2,113 women and 1,384 men), including 1,607 British whites enrolled in ACCT (877 women and 730 men), 816 Andean Hispanics from the PREVENCION Study (456 women and 360 men), 612 Chinese from the Shanghai study (483 women and 129 men), 249 black Africans from the African Project on Genes in Hypertension Study (168 women and 81 men), and 213 American Indians from the Strong Heart Study (129 women and 84 men).

Arterial Tonometry

The radial arterial pressure waveform was recorded noninvasively in all of the studies as described previously with the SphygmoCor device (Atcor Medical, Sydney, Australia), which uses a high-fidelity Millar strain-gauge transducer (Millar Instruments, Houston, TX). The radial waveform was converted to a calculated aortic waveform using the generalized transfer function of the SphygmoCor device. The first and second systolic peaks (P1 and P2) of the radial and the derived aortic pressure waveforms were identified automatically by the SphygmoCor software in all of the studies. Given that the relationship between Alx and body size is nonlinear, statistical modeling based on nonlinear methods was deemed appropriate for our analyses. In this regard, expression of cAlx as the ratio of augmented pressure/pulse pressure, which often results in 0 or negative values, poses an incompatibility for such analyses. Therefore, we expressed both rAlx and cAlx as the amplitude of the second systolic peak divided by the amplitude of the first systolic peak (P2/P1) multiplied by 100 (Figure S1, available in the online Data Supplement at http://hyper.ahajournals.org). To define normative values for Alx from the reference populations after accounting for demographic and anthropometric determinants of these parameters, we generated regression equations to compute “expected” values of Alx for any given age, sex, ethnicity, body height, and heart rate. Because significant interactions among ethnicity, sex, and other predictors of Alx were found, ethnic- and sex-specific equations were generated. Estimation of predictive equations was performed with nonlinear regression, in which an iterative technique is applied to estimate model parameters while maximizing data fit. We used the following mathematical construct for nonlinear regression: Alx = a·age + b·HR + c·ht, where “HR” indicates heart rate; “ht” indicates body height; and “a” through “d” are estimated parameters. Because body weight was found to independently account for very little variability in Alx (0% to 1%), it was not included in models for simplicity. Based on these equations, expected Alx values were computed for each individual, which allowed for computation of a ratio of observed/predicted Alx. This ratio was standardized, defining a z score, which indicates the number of SDs above or below the population mean in which an individual observation lies. The independence of the z score from age, body height, and heart rate was ascertained by constructing models in which these variables were used as predictors of the z score; near-0 R² values for

Seated Versus Supine Radial Recordings

In the Strong Heart, Shanghai, and African Project on Genes in Hypertension studies, radial tonometry was performed in the supine position. In the PREVENCION Study, radial tonometry was performed in the seated position. In ACCT, radial tonometry was performed in both supine and seated positions. Therefore, British whites enrolled in ACCT served as a reference population to compare seated Alx values obtained from Andean Hispanics, whereas supine Alx values from British whites in ACCT were used as reference for comparison against supine Alx values from American Indian, Chinese, and African participants. Ethnic-specific predictive equations were generated for supine and/or seated measurements as permitted by all of the available data from each ethnic group. Data for cAlx values were available for all of the studies, whereas data for rAlx values were available for all of the studies, except for the Strong Heart Study.

Statistical Analysis

Subject-level data from the original studies were used for all of the analyses. Once the reference population was selected, the effect of ethnicity on Alx was assessed after adjustment for age, heart rate, body height, and mean arterial pressure. Given that relationships between some of these predictors and Alx are known to be exponential, log-linear modeling was used, and adjusted geometric means for Alx were compared between ethnic groups (white, North Amerindian, Andean Hispanic, African, and Chinese) using ANCOVA; post hoc pairwise comparisons were performed with the Scheffé method.

To define normative values for Alx from the reference populations after accounting for demographic and anthropometric determinants of these parameters, we generated regression equations to compute ‘expected’ values of Alx for any given age, sex, ethnicity, body height, and heart rate. Because significant interactions among ethnicity, sex, and other predictors of Alx were found, ethnic- and sex-specific equations were generated. Estimation of predictive equations was performed with nonlinear regression, in which an iterative technique is applied to estimate model parameters while maximizing data fit. We used the following mathematical construct for nonlinear regression: Alx = a·age + b·HR + c·ht, where “HR” indicates heart rate; “ht” indicates body height; and “a” through “d” are estimated parameters. Because body weight was found to independently account for very little variability in Alx (0% to 1%), it was not included in models for simplicity. Based on these equations, expected Alx values were computed for each individual, which allowed for computation of a ratio of observed/predicted Alx. This ratio was standardized, defining a z score, which indicates the number of SDs above or below the population mean in which an individual observation lies. The independence of the z score from age, body height, and heart rate was ascertained by constructing models in which these variables were used as predictors of the z score; near-0 R² values for...
these models indicate the absence of residual relationships. After formulas to compute z scores were derived from reference samples within each ethnic group, stepwise regression was used to test the association of classic cardiovascular risk factors with the z score in the entire sample for each ethnic group. Statistical significance was defined as 2-tailed \( P < 0.05 \). Analyses were performed using SPSS for Windows version 17 (SPSS Inc, Chicago, IL).

### Results

Table 1 shows general characteristics of subjects enrolled in the various studies, as well as the reference subsamples from each study.

### Ethnic Differences in AIx

Figure 1A and 1B shows mean values of cAIx among women and men of various ethnicities included in the reference sample according to age. Figure 1C and 1D shows corresponding values of rAIx. A consistent marked age-related increase in AIx in early adulthood with a less pronounced increase (or even a decrease) in late adulthood was apparent for both cAIx and rAIx. It was also apparent that Africans and Andean Hispanics demonstrated much higher values of rAIx and cAIx than British whites of similar age.
Figure 2 compares geometric mean values and 95% CIs of cAIx and rAIx among men and women of various ethnicities included in the reference sample, after adjustment for age, body height, mean arterial pressure, and heart rate. Both cAIx and rAIx were significantly higher in African and Andean Hispanic than in white men and women (ANCOVA $P<0.0001$ for all comparisons). Central AIx was significantly lower in American Indian than in white men and women (ANCOVA $P<0.0001$ for both comparisons). Data regarding rAIx among American Indians were not available for analysis. No significant differences were seen between white and Chinese men or women in rAIx or cAIx. These results did not change appreciably when further adjustment for body weight, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and fasting glucose were performed in sensitivity analyses (Figure S2).

Predictive Equations and Normative Values for AIx

Ethnic- and sex-specific equations derived from nonlinear regression for expected AIx among men and women of various ethnicities are shown in Table 2, along with corresponding $R^2$ values. It can be seen that age, body height, and heart rate account for important proportions of the variability in AIx in the studied populations. Mean values of the observed/expected ratio (calculated for each individual) in the reference population were consistently 1, as expected (data not shown). Formulas used to obtain $z$ scores for the observed/expected ratio are shown in Table 2. Table 2 also shows $R^2$ values of models that included age, body height, and heart rate as predictors of the observed/expected ratio (or the $z$ score). In contrast to “crude” AIx, these adjusted observed/expected ratios and $z$ scores were completely independent of age, heart rate, and body height (all $R^2$ values $\approx 0.004$). The $z$ scores in reference samples of various ethnic/sex groups (computed using formulas shown in Table 2) were normally distributed, with essentially identical relative distribution curves in all of the ethnic/sex groups, corresponding with the $z$ distribution (data not shown).

Classic Risk Factors as Determinants of the $Z$ Score

Results of stepwise regression assessing correlates of the standardized observed/predicted ratio ($z$ score) in the entire populations (ie, subjects included and not included in reference samples) are shown in Table 3. Higher mean arterial pressure and current smoking were consistently associated with higher $z$ scores. Diabetes mellitus was associated with a lower $z$ score among British whites, Africans, and Hispanics. However, these models accounted for small proportions of the variability in $z$ scores ($\approx 5\%$ to $11\%$).

Discussion

We compare, for the first time, AIx between adults of various ethnic populations using subject-level data from large population-based studies. We demonstrate pronounced ethnic differences between and among various ethnic populations.
differences in cAIx and rAIx, a novel finding with important implications. We also present ethnic-specific normative equations that allow a standardized comparison between individual AIx measurements and the normative population mean from subjects of the same age, sex and ethnicity, body height, and heart rate.

Our study addresses the remarkable paucity of published data regarding ethnic differences in AIx. One study reported differences in late systolic pressure augmentation between 25 healthy black and 30 white young men, whereas no differences could be demonstrated between 30 black and 30 white habitual smokers. Another study found no differences between 94 East-Asian and 47 age-matched white adults. Most previous studies regarding normative data for AIx were derived from white populations, including a recent study that generated normative equations to compute AIx from a large sample of whites. The results of this study appear to be consistent with those reported previously from the ACCT population but are not directly comparable with our predictive equations given differences in the method to compute AIx and the criteria used to select the reference sample from which normative data were acquired.

We found that, after adjustment for age, heart rate, mean arterial pressure, and body size, black Africans and Andean Hispanics had markedly higher cAIx and rAIx than British whites, whereas North American Indians demonstrated lower cAIx than British whites. These findings indicate that important ethnic differences in central hemodynamics exist, which cannot be assessed with conventional sphygmomanometry. Our finding of greater AIx in blacks is important considering the well-known higher rates of hypertensive target organ damage (particularly left ventricular hypertrophy) in black populations, which cannot be accounted for by resting or ambulatory brachial blood pressure or other conventional risk factors. Importantly, previous experimental data strongly suggest a direct causal effect of wave reflections on left ventricular hypertrophy. The potential role of greater late systolic pressure augmentation on the development of cardiac and other forms of target organ damage in black populations should be investigated. Similarly, the potential determinants of the observed ethnic differences in AIx, such as genetic, cultural, and geographic factors (eg, altitude above sea level for the case of Andean Hispanics), should be the focus of further research.
In research studies that involve many subjects, results from numerous individual AIx measurements can be modeled statistically to assess their relationships with specific end points. Statistical modeling allows investigators to adjust for covariates that affect AIx, such as chronologic age, sex, heart rate, and body size. Such modeling, however, cannot be applied to individually measured values of AIx. Because individuals may have highly variable age, heart rate, and body size, single absolute thresholds of these indices are unlikely to optimally define abnormalities across the range of age, body height, and heart rate seen in adult populations. Furthermore, given the ethnic differences demonstrated in our study, reference values for AIx differ according to the subject’s ethnic background. To aid in the interpretation of individual values while accounting for these factors, we developed mathematical formulas using nonlinear modeling to establish sex- and ethnic-specific predictive equations to calculate expected values of AIx that adjust individual observations for age, heart rate, and body height. Predicted AIx can be used to compute a ratio of observed/predicted AIx, which, in contrast to crude AIx, is completely independent of age, heart rate, and body height. The observed/predicted ratio is normally distributed and can be expressed as an easily interpretable \( z \) score, which compares the individual’s value to average values among normal subjects from the same sex and ethnic population. The \( z \) score expresses the number of SDs that an individual observation falls above or below the normative population mean. Therefore, \( z \) scores are easily interpretable, because values corresponding with the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles are always \(-1.65, -1.28, -0.68, 0, 0.68, 1.28, \) and \( 1.65 \), respectively. The \( z \) score reflects the interindividual variability in AIx not explained by age, heart rate, body height, sex, and ethnicity.

We found that increasing mean arterial pressure and current smoking were consistently associated with a higher \( z \) score in the various ethnic populations. These data are in line with the known effect of mean arterial pressure on wave reflections and previous experimental data that demonstrated a causal effect of smoking on wave reflections.\(^{20,27} \) Interestingly, one study indicated that blacks may be more sensitive to the acute effect on smoking on wave reflections than whites,\(^{20} \) although this cannot explain the markedly elevated AIx among blacks in our reference sample, from which smokers were excluded. We found an association between diabetes mellitus and a lower \( z \) score in British whites, blacks, and Andean Hispanics. Further studies should assess the

### Table 2. Predictive Normative Equations for Radial Augmentation Index and Central Augmentation Index Generated With Nonlinear Regression

<table>
<thead>
<tr>
<th>Group</th>
<th>Predictive Equation</th>
<th>( R^2 )</th>
<th>( P )</th>
<th>Formula for ( Z ) Score</th>
<th>( R^2 ) for ( Z ) Score*</th>
<th>( P )</th>
</tr>
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<tbody>
<tr>
<td><strong>Central augmentation index, supine</strong></td>
<td></td>
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<tr>
<td>British white men</td>
<td>148<em>Age0.267</em>HR-0.576+HR-0.215</td>
<td>0.69</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.11)</td>
<td>0.002</td>
<td>0.65</td>
</tr>
<tr>
<td>British white women</td>
<td>121<em>Age0.319</em>HR-0.094+HR-0.196</td>
<td>0.68</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.12)</td>
<td>0.002</td>
<td>0.61</td>
</tr>
<tr>
<td>Chinese men</td>
<td>628<em>Age0.205</em>HR-1.16+HR-0.434</td>
<td>0.48</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.12)</td>
<td>&lt;0.001</td>
<td>0.99</td>
</tr>
<tr>
<td>Chinese women</td>
<td>281<em>Age0.267</em>HR-0.311+HR-0.383</td>
<td>0.48</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.11)</td>
<td>0.001</td>
<td>0.94</td>
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<td>American Indian men</td>
<td>619<em>Age0.234</em>HR-1.117+HR-0.467</td>
<td>0.41</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.12)</td>
<td>0.001</td>
<td>0.99</td>
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<td>American Indian women</td>
<td>1402<em>Age-0.034</em>HR-0.577+HR-0.45</td>
<td>0.21</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.10)</td>
<td>0.005</td>
<td>0.90</td>
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<td>African men</td>
<td>500<em>Age0.208</em>HR-0.753+HR-0.42</td>
<td>0.39</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.11)</td>
<td>0.004</td>
<td>0.96</td>
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<tr>
<td>African women</td>
<td>422<em>Age0.254</em>HR-1.064+HR-0.368</td>
<td>0.42</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.13)</td>
<td>0.001</td>
<td>0.98</td>
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<td><strong>Central augmentation index, seated</strong></td>
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<tr>
<td>British white men</td>
<td>250<em>Age0.223</em>HR-0.622+HR-0.298</td>
<td>0.69</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.10)</td>
<td>0.003</td>
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<td>British white women</td>
<td>212<em>Age0.274</em>HR-0.746+HR-0.27</td>
<td>0.66</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.12)</td>
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<td>Andean-Hispanic men</td>
<td>232<em>Age0.256</em>HR-0.694+HR-0.333</td>
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<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.10)</td>
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<td>Andean-Hispanic women</td>
<td>395<em>Age0.217</em>HR-0.608+HR-0.362</td>
<td>0.49</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.12)</td>
<td>&lt;0.001</td>
<td>0.98</td>
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<td><strong>Radial augmentation index, supine</strong></td>
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<td>British white men</td>
<td>67<em>Age0.563</em>HR-0.763+HR-0.428</td>
<td>0.73</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.26)</td>
<td>0.002</td>
<td>0.62</td>
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<td>British white women</td>
<td>127<em>Age0.535</em>HR-1.769+HR-0.41</td>
<td>0.68</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.24)</td>
<td>0.002</td>
<td>0.61</td>
</tr>
<tr>
<td>Chinese men</td>
<td>419<em>Age0.378</em>HR-1.455+HR-0.604</td>
<td>0.47</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.21)</td>
<td>0.004</td>
<td>0.91</td>
</tr>
<tr>
<td>Chinese women</td>
<td>180<em>Age0.429</em>HR-0.475+HR-0.54</td>
<td>0.47</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.18)</td>
<td>0.003</td>
<td>0.69</td>
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<tr>
<td>African men</td>
<td>455<em>Age0.346</em>HR-1.159+HR-0.606</td>
<td>0.47</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.16)</td>
<td>0.006</td>
<td>0.92</td>
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<td>African women</td>
<td>441<em>Age0.408</em>HR-1.328+HR-0.607</td>
<td>0.46</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.19)</td>
<td>0.002</td>
<td>0.96</td>
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<tr>
<td><strong>Radial augmentation index, seated</strong></td>
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<tr>
<td>British white men</td>
<td>235<em>Age0.408</em>HR-1.534+HR-0.522</td>
<td>0.68</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.23)</td>
<td>0.001</td>
<td>0.82</td>
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<td>British white women</td>
<td>136<em>Age0.471</em>HR-1.297+HR-0.413</td>
<td>0.66</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.22)</td>
<td>0.005</td>
<td>0.23</td>
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<td>Andean-Hispanic men</td>
<td>84<em>Age0.546</em>HR-0.758+HR-0.3</td>
<td>0.57</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.16)</td>
<td>0.003</td>
<td>0.76</td>
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<tr>
<td>Andean-Hispanic women</td>
<td>204<em>Age0.529</em>HR-0.766+HR-0.42</td>
<td>0.47</td>
<td>&lt;0.0001</td>
<td>([\text{Observed}/\text{Predicted}]-1)/0.17)</td>
<td>0.001</td>
<td>0.89</td>
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HR indicates heart rate; ht, body height.

*Predictors included in the model were age, heart rate, and body height.

The \( z \) score reflects the interindividual variability in AIx not explained by age, heart rate, body height, sex, and ethnicity.

**Table 2. Predictive Normative Equations for Radial Augmentation Index and Central Augmentation Index Generated With Nonlinear Regression**
mechanisms of this perhaps counterintuitive association, which may potentially include the following: (1) preferential stiffening of large (central) arteries with a decrease in the impedance mismatch with more distal muscular arteries resulting in a lower reflection magnitude; (2) increased intra-abdominal pressure because of accompanying obesity with a resultant decrease in the abdominal aortic transmural pressure gradient and consequent lowering of the operating stiffness point (with lower local pulse wave velocity and, hence, delayed return of the reflected waves); (3) subclinical left ventricular dysfunction manifesting as a lower degree of pressure augmentation for any given reflection magnitude; or (4) unknown ethnic-dependent mechanisms and/or a combination of mechanisms described above. This should be the focus of further research.

Our approach to computing a z score should be considered complementary to, rather than a replacement for, assessment of crude AIx. For instance, a normotensive person with a short body height and a slow heart rate is likely to have a high AIx even in the presence of healthy arteries. A high AIx, although in this case being purely related to body height and heart rate, may still suggest adverse central hemodynamic phenomena. Computation of a z score of ≈0 in this situation would essentially indicate that the high observed value of AIx in such an individual is purely the result of a short body height and a slow heart rate (the individual’s observed value would fall in the population mean after removing the effect of body height and heart rate). In a different short person with slow heart rate, a high crude AIx and a high z score (ie, >1.65) would be interpreted as not purely the result of a short body height and slow heart rate, therefore pointing to additional factors contributing to the observed AIx, which is abnormally high when compared with normal individuals of the same age, sex, ethnicity, body height, and heart rate. These 2 approaches used together have the potential to enhance our ability to understand central hemodynamics in individuals with various conditions. Furthermore, this approach enables the rapid identification of individuals at the extremes of population distributions in AIx when the effect of age, body height, and heart rate are eliminated, which may facilitate the discovery of novel clues regarding the biological determinants of wave reflections in humans, because novel

Table 3. Selected Predictors of the Z Score in Stepwise Regression

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Transfer Function–Derived Central Augmentation Index</th>
<th>Radial Augmentation Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (Standard β)*</td>
<td>95% CI</td>
</tr>
<tr>
<td>British whites, supine</td>
<td>Model $R^2=0.052$</td>
<td>0.17 (0.22)</td>
</tr>
<tr>
<td>MAP (10 mm Hg)</td>
<td>0.20 (−0.05)</td>
<td>−0.32 to −0.07</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.19 (0.07)</td>
<td>0.10 to 0.29</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>−0.20 (−0.05)</td>
<td>−0.32 to −0.07</td>
</tr>
<tr>
<td>British whites, seated</td>
<td>Model $R^2=0.071$</td>
<td>0.20 (0.25)</td>
</tr>
<tr>
<td>MAP (10 mm Hg)</td>
<td>0.24 (0.08)</td>
<td>0.15 to 0.34</td>
</tr>
<tr>
<td>Current smoking</td>
<td>−0.17 (−0.04)</td>
<td>−0.29 to −0.04</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>−0.17 (−0.04)</td>
<td>−0.29 to −0.04</td>
</tr>
<tr>
<td>Andean Hispanics, seated</td>
<td>Model $R^2=0.038$</td>
<td>0.15 (0.18)</td>
</tr>
<tr>
<td>MAP (10 mm Hg)</td>
<td>0.25 (0.09)</td>
<td>0.13 to 0.37</td>
</tr>
<tr>
<td>Current smoking</td>
<td>−0.25 (−0.06)</td>
<td>−0.46 to −0.05</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>−0.25 (−0.06)</td>
<td>−0.46 to −0.05</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(per 10 mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese, supine</td>
<td>Model $R^2=0.09$</td>
<td>0.22 (0.28)</td>
</tr>
<tr>
<td>Mean arterial pressure (10 mm Hg)</td>
<td>0.25 (0.10)</td>
<td>0.11 to 0.38</td>
</tr>
<tr>
<td>Current smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indians, supine</td>
<td>Model $R^2=0.094$</td>
<td>0.25 (0.28)</td>
</tr>
<tr>
<td>Mean arterial pressure (10 mm Hg)</td>
<td>0.38 (0.15)</td>
<td>0.28 to 0.47</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.04 (0.05)</td>
<td>0.00 to 0.07</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(per 10 mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blacks, supine</td>
<td>Model $R^2=0.11$</td>
<td>0.16 (0.24)</td>
</tr>
<tr>
<td>Mean arterial pressure (10 mm Hg)</td>
<td>0.48 (0.17)</td>
<td>0.30 to 0.66</td>
</tr>
<tr>
<td>Current smoking</td>
<td>−0.41 (−0.13)</td>
<td>−0.60 to −0.22</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>−0.41 (−0.13)</td>
<td>−0.60 to −0.22</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>−0.619 (0.09)</td>
<td>−0.03 to 0.006</td>
</tr>
<tr>
<td>(per 10 mg/dL)</td>
<td>−0.619 (0.09)</td>
<td>−0.03 to 0.006</td>
</tr>
</tbody>
</table>

*Standard β indicates standardized regression coefficient.
discoveries are often triggered by astute observations from individuals with extreme phenotypes. This approach may also prove useful to identify probands with extreme phenotypes of wave reflections for genetic association studies and to interpret the progression of AIx with aging in single subjects, because the adjusted z scores are age independent and, therefore, directly comparable across adulthood. Finally, the statistical properties of the z score may aid in the quantification and reporting of the effect size of interventions in research studies.

Our study has limitations. The use of mathematical formulas to compute z scores may appear complicated, although in reality, such computations can be easily automated in tonometry device software or simple tools such as an online calculator or a spreadsheet. We did not assess the potential effect of environment across populations of similar ethnic backgrounds. For instance, altitude above sea level may be related to the higher AIx values in Andean Hispanics. Although the individual parent studies were designed to select representative probabilistic samples from the populations under study, sampling frames/strategies and inclusion/exclusion criteria were not standardized across the studies. Our study is also limited by its cross-sectional nature. Normative equations are derived from subsamples that have blood pressure and other risk factors below arbitrary thresholds rather than prospective outcome data. Although we examined a large number of participants from a wide age range in the various cohorts, the normative equations presented here should strictly be applied within the age range of the studied populations used to derive these equations. We did not assess pulse pressure amplification because of heterogeneity among cohorts regarding methods to calibrate the radial pressure waveform from brachial pressures, which impacts computed central pulse pressure and pulse pressure amplification. Future studies should directly assess interethnic differences in pulse pressure amplification. Finally, AIx is an imperfect index of wave reflections, and some data suggest that it is strongly influenced by other factors, such as the aortic reservoir function, although this does not impact the validity of the reported ethnic differences in AIx.

Perspectives
We found marked ethnic differences in AIx that have important implications. Our study also establishes normative data for AIx among adult men and women of various ethnic populations and provides a readily applicable method that allow the interpretation of individual values of AIx while accounting for age, sex, ethnicity, body size, and heart rate. This approach will facilitate application of findings from populations to individual subjects. Although this approach has immediate applicability as an adjunct to crude AIx for the interpretation of AIx values from individuals, future studies should assess whether the z score, because of its unique statistical properties, has any advantages relative to crude AIx as a predictor of cardiovascular outcomes, particularly to assess long-term cardiovascular risk among young adults.

Future studies should assess the role of genetic versus geographic and other environmental influences in AIx in various populations and should compare different racial/ethnic groups living under identical geographic conditions. In the meantime, our normative data should be considered strictly population specific.

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Disclosures
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References


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ONLINE SUPPLEMENT

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Figure S1. Examples of radial (A) and transfer-function-derived (B) central pressure wave forms along with Alx computations based on the amplitude of the 1\textsuperscript{st} and 2\textsuperscript{nd} systolic peaks. Computation of Alx as P1 amplitude / P2 amplitude always results in positive values, rather than negative or zero values.

A. Radial pressure wave form (Alx=66).

B. TF-derived central pressure wave form (Alx=123).
Figure S2. Sensitivity analyses regarding ethnic differences in supine and seated central (A-B) and radial (C-D) augmentation index in women (A,C) and men (B,D). Point estimates and 95% CIs are shown after adjustment for age, heart rate, body height, mean arterial pressure, body weight, LDL-cholesterol, HDL-cholesterol, triglycerides and fasting glucose.
Caucasian Chinese African Caucasian Hispanic

ANCOVA $P<0.0001$

C. ANCOVA $P<0.0001$

Supine Seated

Radial AIx (%)

Caucasian
$n=877$
Chinese
$n=481$
African
$n=168$
Caucasian
$n=858$
Hispanic
$n=454$

$n=730$
$n=686$
$n=79$
$n=686$
$n=350$

$P=0.99$

$P=0.91$

D. ANCOVA $P<0.0001$

RADIAL AIx (%)