Ethnic Differences in Aortic Pulse Wave Velocity Occur in the Descending Aorta and May Be Related to Vitamin D

Mohammad-Reza Rezai, A. Michael Wallace, Naveed Sattar, Joseph D. Finn, Frederick C.W. Wu, J. Kennedy Cruickshank

Abstract—We studied aortic pulse wave velocity (aPWV), a predictor of cardiovascular events independent of blood pressure, in a multiethnic sample of British men, to investigate the roles for blood levels of vitamin D and aldosterone in total and regional aortic stiffness. Total aPWV was estimated noninvasively by the Arteriograph device (aPWVAG) in 198 men, with its length measure calibrated by magnetic resonance. PWVs over the aortic arch and descending aorta were measured by magnetic resonance in a subsample (n=47). Mean (SE) aPWVAG in South Asians (n=68; age 55±10 years), at known higher coronary disease risk than other groups, was 0.5 m/s (0.2 m/s) higher than in African Caribbeans (n=67; 55±10 years), at lowest coronary disease risk here, and Europeans (n=63; 57±8 years), adjusted for age, systolic blood pressure, and diabetes mellitus (P=0.01). By magnetic resonance, PWV over the descending aorta in South Asians was 0.7 m/s (0.3 m/s) and 0.8 m/s (0.3 m/s) higher than in African Caribbeans and Europeans, respectively; PWV over the aortic arch was not different. South Asians and African Caribbeans had 21 nmol/L (3 nmol/L) and 14 nmol/L (3 nmol/L) lower mean (SE) 25(OH)D than Europeans (P<0.001). Unlike aldosterone, 25(OH)D was negatively correlated with aPWVAG adjusted for age and systolic blood pressure, as well as weakened or removed ethnic differences in aPWVAG in regression models. These data suggest that aortic stiffness as aPWV parallels coronary disease risk in ethnic groups, descending aortic but not arch PWV has this feature, and serum 25(OH)D is an independent negative correlate of aPWV and may partly account for ethnicity-related differences in aPWV and coronary disease risk. (Hypertension. 2011;58:247-253.) • Online Data Supplement

Key Words: vitamin D ■ aorta ■ pulse wave velocity ■ ethnic groups ■ aldosterone

Cardiovascular morbidity and mortality vary among different ethnic groups. People of Indian subcontinental, or South Asian, origin (SA) in Britain and North America have higher coronary heart disease (CHD) prevalence and mortality, experiencing events at a younger age and slower declines in premature CHD mortality than other populations1–4 (Figure S1A, available in the online Data Supplement at http://hyper.ahajournals.org). Conventional risk factors, such as diabetes mellitus, obesity, and hypertension, fail to explain these ethnic differences fully.5 In contrast, African Caribbeans (AfCs) have lower CHD mortality than Europeans despite higher rates of hypertension, diabetes mellitus, and stroke2,6,7 (Figure S1B). Despite sharing excess hypertension and diabetes mellitus, a similar heritage, and genetic background with AfCs, blacks have a different vascular profile further along the epidemiological transition to atheromatous disease than AfCs.7,8

There has been little comparative data on arterial function of these populations. Aortic pulse wave velocity (aPWV), an index of arterial stiffness, is a powerful independent predictor of cardiovascular events and death.9–12 We studied aPWV and its determinants in a sample of men from 3 ethnic groups to investigate the following questions. First, do differences in aPWV across ethnic groups parallel their known coronary risk profiles, and, if so, do proximal and distal aPWVs measured by more precise magnetic resonance (MR) imaging differ similarly? Second, are serum vitamin D or aldosterone concentrations related to aPWV as a risk marker, and do they influence cross-ethnic aPWV differences?

Methods

Participants were 198 men aged 40 to 80 years of AfC, SA, and European origin in Manchester, United Kingdom, who had already been recruited to the European Male Ageing Study.13 The participants had to be free of severe chronic or acute disease of active malignant renal or liver origin. Ethnicity was defined by participants’ self-reporting and 3 of 4 grandparents being of the same ethnic origin. Original recruitment was through volunteers by advertising in community centers and media in Manchester for SA and AfC groups and by general practice register sampling for Europeans.
Main Study
All of the participants had noninvasive oscillometric arterial stiffness and blood pressure (BP) measurement in the morning after avoiding caffeine, tobacco, and heavy meals 3 hours before their visit, as well as alcohol from the night before. Using a standard protocol, BP was measured using a validated Omron semiautomatic device on the left upper arm, sitting, 3 times after 5 minutes rest in a temperature-controlled room. The values from the last 2 measurements were averaged and recorded.

The Arteriograph (TensioMed, Budapest, Hungary) device was used to measure arterial stiffness indices, including total aPWV (aPWV_{AG}), estimated central (aortic) augmentation index (aoAIx), and central systolic BP (SBP). The device records pressure waves in the brachial artery with an arm cuff and estimates the aortic pulse wave transit time between the aortic root and bifurcation from the time interval between the peaks of forward and reflection pressure waves in each cardiac cycle using a commercial algorithm. It assumes that the corresponding aortic path is approximated by sternal notch-to-pubis distance on body surface.

Comparison of the MR-measured total aortic lengths (ie, aortic root lengths) were investigated with robust regression models, with results expressed as unstandardized coefficients (B) and SEs. Multiple-testing errors were corrected for 3 pairwise comparisons by a lower P value, <0.02 (ie, 0.05/3.00). Spearman p was used for correlation between nonparametric variables.

MRI Substudy
A subsample of the men in the main study free from diabetes mellitus and cardiovascular medications and without previous histories of cardiovascular events was invited for the MR study and seen under the same conditions. The MR protocol for PWV measurement used a 1.5-T Philips Intera scanner (Philips Medical Systems, Best, the Netherlands) to acquire 2 consecutive nonbreath-hold, through-plane, velocity-encoded, phase-contrast transverse aortic cine images, one from the aortic arch at the level of pulmonary artery and the other 2 cm above the aortic bifurcation (Figure 1). Image analysis was performed offline with the same analyst blinded to patient identities.

Arrival times of the aortic pulse waves were computed from the 3 flow-time curves recorded at the 3 points: P1, P2, and P3 (Figure 1), from which 3 transit-times could be derived for P1-P2, P2-P3, and P1-P3. The lengths of corresponding aortic paths were measured on MRIs. This enabled measurement of 3 PWV values, over the aortic arch (archPWV_{MR}), descending aorta (desPWV_{MR}k) and the overall segment (aoPWV_{MR}b) (Figure 1). Intraobserver coefficient of variation was 7.8% (0.91) for archPWV_{MR}, 3.4% (0.96) for desPWV_{MR}, and 2.5% (0.98) for aoPWV_{MR}, when MRI analysis was repeated for 10 participants.

Improving aPWV_{AG} Estimation With MRI Aortic Lengths
Comparison of the MR-measured total aortic lengths (ie, aortic root to bifurcation) to the surface sternal notch-pubis length used by Arteriograph (as externally estimated arterial pathway) showed that the latter would overestimate the real aortic path and that it was possible to predict MR-measured total aortic lengths from a regression model derived from age and height. Consequently, the Arteriograph aPWV_{AG} was recalculated using the transit time measured by the device and the length of aortic path estimated by the aforementioned regression model.

Statistical Analysis
Data were analyzed by R statistical package version 2.11.1. ANOVA was used to compare means of parametric (and transformed skewed) variables across ethnic groups. PWV and hormonal corre-
Table 1. General, Hemodynamic, and Metabolic Characteristics of the Participants With Univariate Analysis (n=198) in Mean±SD or Median (Interquartile Range)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (N=198)</th>
<th>MR Subsample (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AIC (N=67)</td>
<td>SA (N=68)</td>
</tr>
<tr>
<td>Age, y</td>
<td>55±10</td>
<td>55±10</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (12%)</td>
<td>24 (35%)</td>
</tr>
<tr>
<td>Hypertension Tx</td>
<td>8 (12%)</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Dyslipidemia Tx</td>
<td>6 (9%)</td>
<td>13 (19%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>12 (19%)</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84±11.0</td>
<td>79±11.0</td>
</tr>
<tr>
<td>Height, cm</td>
<td>174±6</td>
<td>170±6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28±3</td>
<td>27±3</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>130±16</td>
<td>124±14</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>82±11</td>
<td>78±9</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>48±10</td>
<td>46±9</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>98±12</td>
<td>94±11</td>
</tr>
<tr>
<td>cSBP, mm Hg</td>
<td>127±20</td>
<td>125±19</td>
</tr>
<tr>
<td>cPP, mm Hg</td>
<td>46±11</td>
<td>45±11</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>65±8</td>
<td>68±11</td>
</tr>
<tr>
<td>archPW by MRI, m/s</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>desPW by MRI, m/s</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>aPWV AG or MRI, m/s</td>
<td>6.8 (1.7)</td>
<td>7.6 (2.4)</td>
</tr>
<tr>
<td>aAIX, %</td>
<td>27±13</td>
<td>33±13</td>
</tr>
<tr>
<td>cAP, mm Hg</td>
<td>13±9</td>
<td>16±9</td>
</tr>
<tr>
<td>FPG, mmol/L</td>
<td>5.3 (0.9)</td>
<td>5.6 (1.5)</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>95±14</td>
<td>85±14</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>5.0±1.1</td>
<td>4.7±0.8</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.4 (0.5)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>TC/HDL ratio</td>
<td>3.6±0.9</td>
<td>4.4±1.1</td>
</tr>
<tr>
<td>25 (OH)D, nmol/L</td>
<td>30 (16)</td>
<td>18 (15)</td>
</tr>
<tr>
<td>Aldosterone, pmol/L</td>
<td>180 (137)</td>
<td>295 (160)</td>
</tr>
</tbody>
</table>

*Data show significant P values.
†Data show χ² P values.
‡Data show P values from ANOVA on reverse-transformed pulse wave velocity values and log transforms of other marked variables.

Adjusted mean (SE) aPWV AG in SAs was ~0.5 m/s (0.2 m/s) higher than in AfCs and Europeans (Table 2), whereas AIC adjusted aoAIX and central augmentation pressure were 7% (2%) and 3.6 mm Hg (1.0 mm Hg) lower than SAs and 7% (2%) and 2.5 mm Hg (1.0 mm Hg) less than Europeans. Thus, SAs had higher aPWV AG for given levels of age and distending pressures. Excluding diabetes mellitus or replacing SBP with mean arterial pressure did not change the ethnic

Figure 2. Pulse wave velocity (PWV) profiles across ethnic groups; bar charts show mean±95% CI. Note the contrast between A and B and C and compare with coronary heart disease (CHD) risk profile in Figure S1A. AIC indicates African Caribbean; SA, South Asian; WE, European.
effects for \( aPWV_{AG} \) and \( aoAIx \); entering heart rate in the \( aPWV \) model (Model A, Table 2) slightly weakened but did not remove them (data not shown).

Hormones

Vitamin D and aldosterone were significantly different across the groups (Table 1 and Figure 3A and 3B). Adjusted for age, weight, season of blood sampling, and vitamin D supplement use, mean (SE) 25(OH)D in SAs was 21 nmol/L (3 nmol/L) and AfCs 14 nmol/L (3 nmol/L) lower than Europeans and in SAs was lower by 7 nmol/L (2 nmol/L) than AfCs (\( P<0.001 \) for all).

Compared with AfCs, aldosterone was 85 pmol/L (20 pmol/L) higher in SAs (\( P<0.001 \)) and 51 pmol/L (21 pmol/L) higher in Europeans (\( P=0.015 \)) after adjusting for antihypertensive use and body mass index. SAs had 34 pmol/L (22 pmol/L) higher aldosterone than Europeans, but this was not significant (\( P=0.13 \)) after adjustments. There was borderline inverse correlation between aldosterone and 25(OH)D (\( \rho = -0.14; \ P = 0.06 \)).

Arterial Stiffness-Hormonal Relations

Neither hormone was correlated with BPs, \( PWV \), and \( aoAIx \) in univariate analysis. Adjusted for age, SBP, and diabetes mellitus, 25(OH)D was inversely related to \( aPWV_{AG} \) (B [SE]= -0.013 [0.004]; \( P<0.001 \)) but not \( aoAIx \) (data not shown). With similar adjustments, the participants in tertiles 2 and 3 of 25(OH)D had 0.3 m/s (0.2 m/s; \( P=0.1 \)) and 0.5 m/s (0.2 m/s; \( P=0.015 \)) lower \( aPWV_{AG} \) respectively, compared with tertile 1. The correlations between aldosterone and \( aPWV_{AG} \) were insignificant in similar models. Entering 25(OH)D in the model removed statistical ethnic differences in \( aPWV_{AG} \); such results were not observed for aldosterone (Table 2). An interaction term between ethnicity and 25(OH)D had 0.3 m/s (0.2 m/s; \( P=0.14 \)) but not \( aoAIx \) (data not shown). Age adjustment was the main factor making the 25(OH)D-\( aPWV_{AG} \) relationship significant, notably in those >50 years of age (Figure 3C).

MRI Substudy

MRI study participants consisted of 16 Caribbean, 13 Pakistani, and 18 European men whose age, body mass index, brachial BP, or central BP differed significantly with this relatively small sample size (Table 1). After adjusting for age and SBP, mean (SE) \( desPWV_{MR} \) in SAs was 0.7 m/s (0.3 m/s) and 0.8 m/s (0.3 m/s) higher than in AfCs and Europeans, respectively; \( archPWV_{MR} \) was not statistically different (Table 3). This pattern of ethnic difference in \( desPWV_{MR} \) in the MR study replicates the result for the \( aPWV_{AG} \) in the total sample (Figure 2A through 2B), but the pattern for \( archPWV_{MR} \) is different (Figure 2C). Adjusted for age and SBP, higher aldosterone tertiles were associated with greater \( archPWV_{MR} \) but not \( desPWV_{MR} \) (Table 3); this remained significant after adjusting for ethnicity.

Discussion

The results suggest firstly that SA men had higher \( PWV \) than AfCs and Europeans for the same levels of age and brachial/central distending pressures, thus reflecting the known CHD population risk differences across ethnic groups. Despite slightly higher peripheral BPs, AfCs had lower \( PWV \) paralleling currently lower CHD risk in Britain and the Caribbean region. Second, the MR substudy showed that pathology in the more elastic descending aortic segment, but not that of the aortic arch, may be related to CHD risk. Third, serum 25(OH)D was inversely related to \( PWV \) independent of age and SBP; hence, poor vitamin D status may account for some of the ethnic differences in \( PWV \) and, potentially, thereafter, some vascular disease in the population as a whole. Randomized trials to test that hypothesis are scarce.19

Studies comparing arterial stiffness in SAs, AfCs, and Europeans, particularly in community samples, are few. Our previous population-based work focused on comparing risks across glucose tolerance with relatively small numbers of controls found no difference in Doppler-measured \( PWV \) down the descending aorta in AfC (10.1 m/s), Gujarati SA (10.5 m/s), and European (9.7 m/s) groups after adjusting for age and sex.9 However, those data were not adjusted for BPs, which were higher in AfCs. Two studies reported higher arterial stiffness estimated by reflection wave indices among
healthy\textsuperscript{20} and poststroke\textsuperscript{21} SA subjects compared with their European counterparts. Neither measured aPWV.

We found no significant aPWV differences between AfCs and Europeans. Similar results were found in different populations of black and white adults, using Doppler-measured aortic-femoral PWV,\textsuperscript{22} central aPWV,\textsuperscript{23} or arterial compliance by the Windkessel method.\textsuperscript{24} However, 2 other studies using the Complior device reported higher carotid-femoral PWV in younger Brazilians of African descent\textsuperscript{25} and for British AfCs compared with Europeans.\textsuperscript{26} The above inconsistencies may be attributed to different techniques, study populations, statistical approaches, and arterial paths or length estimation methods used for PWV measurement, as we found in a recent European pooling project.\textsuperscript{27} Here we measured aPWV over a central aortic path.

Data on the relationship between vitamin D and PWV is scarce and limited to chronic kidney disease patients, with inverse relationships found.\textsuperscript{28–30} Our study appears to be the first to report such an association in a community-dwelling, multiethnic sample. A recent randomized trial (n=49) found a fall in carotid-femoral PWV among black teenagers given 2000 IU/d of vitamin D\textsubscript{3} compared with those on 400 IU/d.\textsuperscript{31} These pilot results suggest promise for vitamin D as an intervention in black populations. Other data from disease-free or asymptomatic subjects primarily relate to endothelial function measured by brachial flow-mediated dilation,\textsuperscript{32} which was positively correlated with serum 25(OH)D and improved on supplementation in deficient cases.\textsuperscript{33}

In our data, vitamin D was also negatively related to total cholesterol/high-density lipoprotein cholesterol ratio, fasting plasma glucose, and aldosterone. Including these variables in the regressions did not remove the independent correlation of vitamin D and aPWV\textsubscript{AG} (data not shown).

Effects of vitamin D on arterial stiffness may be via a variety of mechanisms, including endothelial function, renin-angiotensin system inhibition, regulation of parathyroid hor-
The "high-aldosterone" SA group in the total sample had higher aPWVAG than the "low-aldosterone" AfCs, but without correlation between aldosterone and aPWVAG. Reports of an aldosterone and aPWV relationship are inconsistent. The circulating levels of aldosterone are variable, may not reflect local aldosterone inside the vascular wall, and are affected by diurnal variations and antihypertensive medications.

Almost all SAs and AfCs and half of Europeans were vitamin D "deficient" (<50 nmol/L) here, as is described in Britain. Lower vitamin D among migrants of SA and African descent resident in temperate climates compared with Europeans is also well established.

### Study Limitations

Although the participants were community-dwelling men, they were recruited as volunteers. The study sample is, therefore, not fully representative, although their BP and metabolic profiles are similar to those reported previously. Similarly, our MR substudy samples were recruited as volunteers. The study sample is, therefore, not fully representative, although their BP and metabolic profiles are free from the University of Manchester and partly supported by Wellcome Trust Clinical Research Facility. The MRI scans were funded by the National Institute for Health Research, Manchester Biomedical Research Centre.

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### Disclosures

None.

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Aortic Stiffness, Vitamin D, and Multiethnicity

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Ethnic differences in aortic pulse wave velocity occur in the descending aorta and may be related to vitamin D

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Short title: Aortic stiffness & vitamin D, a multi-ethnic study

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Figure S1. a) Men’s CHD prevalence by age and three ethnic groups in England, 2008, (adapted from data in ¹) and b) Men’s stroke mortality trends, 1979-2003 by country of birth in England and Wales (adapted from data in ¹, ²)