Ethnicity and Left Ventricular Diastolic Function in Hypertension
An ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) Substudy

Andrew Sharp, MBCitB,† Robyn Tapp, PtID,*† Darrel P. Francis, MD,* Simon A. McC. Thom, MD,* Alun D. Hughes, MD, PtID,* Alice V. Stanton, MD, PtID,‡ Andrew Zambanini, MD,* Nish Chaturvedi, MD,* Sheila Byrd, BSc,* Neil R. Poulter, MD,* Peter S. Sever, MD,* Jamil Mayet, MD*

London, United Kingdom; Melbourne, Australia; and Dublin, Ireland

Objectives
We investigated whether diastolic function differs between hypertensive patients of African-Caribbean or white European origin and established whether differences could be explained by confounding variables.

Background
African Caribbeans are known to have a higher prevalence of heart failure than white Europeans but it is unclear whether this is a result of known risk factors. Tissue Doppler technology now allows accurate quantification of diastolic function, which is recognized as an important factor in the development of heart failure.

Methods
Participants from a single center participating in the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), composed of patients with hypertension but no evidence of heart failure, were studied. Left ventricular structure and function were measured in 509 patients using conventional and tissue Doppler echocardiography. Diastolic function was assessed using the tissue Doppler early diastolic velocity E (averaged from 3 left ventricular segments) and the ratio of this and the transmitral early filling velocity E (E/E).

Results
In African-Caribbean patients, mean E was significantly lower (7.7 cm/s vs. 8.6 cm/s, p = 0.003) and mean E/E was significantly higher (8.85 vs. 7.93, p = 0.003). After adjustment for confounding variables—age, gender, systolic blood pressure, pulse pressure, cholesterol, smoking, ejection fraction, left ventricular mass index, and diabetes mellitus—the effect of African-Caribbean ethnicity on diastolic function remained highly significant (E: 7.52 vs. 8.51; p = 0.001; E/E: 8.89 vs. 7.93; p = 0.003; African Caribbeans vs. white Europeans for both comparisons).

Conclusions
Diastolic function is significantly worse in hypertensive patients of African-Caribbean origin than in white Europeans. This difference in diastolic performance is not due to known confounding variables. (J Am Coll Cardiol 2008;52:1015–21) © 2008 by the American College of Cardiology Foundation

Persons of black African descent in the Western world (African Americans in the U.S. and African Caribbeans in the United Kingdom) have a greater risk of heart failure (1). It is not known whether this cardiac dysfunction occurs because of an ethnic difference in myocardial susceptibility, or because of an increased prevalence of factors that contribute to ventricular dysfunction among African Caribbeans, such as left ventricular hypertrophy (LVH), type 2 diabetes mellitus, obesity, and high blood pressure (BP) (2–4). In addition, interpretation of comparator studies performed in patients with established end organ failure is made more difficult by possible differential effects of complex treatment regimes. What is required is a study performed at an earlier stage of disease, with stratification or adjustment for risk factors.
The earliest cardiac consequence of hypertension is diastolic dysfunction, which is part of a continuum of ventricular impairment ending in systolic heart failure. However, until relatively recently it has been difficult to reliably quantify diastolic dysfunction.

The advent of tissue Doppler technology has provided a solution to some of the problems associated with traditional Doppler echocardiography. Rather than interpreting patterns of blood flow, it measures myocardial velocities directly and is more reproducible than historically used echocardiographic methods for assessing diastolic function, such as the Valsalva maneuver or pulmonary vein flow. It provides measures that are less affected by volume status or vasoconstrictor drug therapy than are conventional techniques (5-7), and when combined with the transmitral early filling wave (E) to form a ratio (E/E'), provides an estimate of left atrial filling pressures (5,8,9).

In this study, tissue Doppler was used to investigate whether diastolic function differs between hypertensive persons of African-Caribbean origin and white Europeans, and whether any differences observed could be explained by potential confounding variables.

Methods

The population, methods, and response rate for the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) are found in detail elsewhere (10). In brief, ASCOT was a clinical trial of antihypertensive therapy (amlodipine ± perindopril vs. atenolol ± bendroflumethiazide) for 19,342 men and women ages 40 to 79 years with hypertension. Detailed cardiovascular phenotypic data were collected on a subset of 579 participants recruited at St. Mary’s Hospital, London. Participants were asked to categorize their own ethnicity, and 509 declared themselves to be of white European or African-Caribbean origin. The remaining 70 participants were of Oriental, South Asian, or mixed ethnicities and were excluded from this substudy on the grounds of insufficient numbers within each of those ethnic groups to allow analysis.

All participants in the study were hypertensive. They had either untreated hypertension (systolic BP ≥160 mm Hg and/or diastolic BP ≥100 mm Hg at both screening and randomization) or treated hypertension (systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg at randomization), with at least 3 of the following cardiovascular risk factors: previously identified LVH on echocardiography or electrocardiography (ECG [identified before enrollment in ASCOT through previous investigations]), other previously identified specific ECG abnormalities, type 2 diabetes mellitus, peripheral vascular disease, previous transient ischemic attack or stroke, male gender, age ≥55 years, microalbuminuria/proteinuria, smoking, plasma total cholesterol/high-density lipoprotein ratio ≥6, and family history of ischemic heart disease in a first-degree relative (male relative <55 years old at the time, female <60 years old). Diabetes was diagnosed on the basis of fasting plasma glucose ≥7.0 mmol/l or previous diagnosis of diabetes mellitus. Demographic data shown are those at baseline for categorical variables and those at the time of echocardiography for continuous data. Patients with pre-existing ischemic heart disease or heart failure were excluded (10).

Echocardiography. After a 1-year period of standardized antihypertensive therapy according to the ASCOT study protocol, all patients underwent echocardiography using an ATL HDI 5000 ultrasound machine (Phillips, Bothell, Washington) equipped with a 7-4 MHz broadband linear array transducer. All scans were performed by 1 of 2 experienced echocardiographers, with the patient semirecumbent in the left lateral position. Left ventricular measurements were performed using M-mode from the parasternal long axis according to the American Society of Echocardiography guidelines (11). Where on-axis M-mode measures were not possible, measurements were made from 2D. Left ventricular mass was calculated according to the Devereux formula (12). This was then indexed for body surface area to give the left ventricular mass index (LVMI). Relative wall thickness (RWT) was calculated according to the standard formula of $\text{RWT} = (2 \times \text{posterior wall thickness in diastole}/\text{left ventricular internal diameter in diastole})$. Midwall fractional shortening was calculated using formulas detailed elsewhere (13).

Transmitral Doppler flow velocity was measured using a 5-mm sample volume placed at the tips of the mitral leaflets in passive end expiration. A standardized loop of 10 cardiac cycles was downloaded to a computer for off-line analysis of the early filling phase (E-wave) and the late filling phase (A-wave). Tissue Doppler was performed in the apical 4-chamber view, with the 5-mm sample volume placed over the myocardium on the septum at the level of the mitral annulus. Using minimalized gain settings, a series of 10 cardiac cycles was recorded. These were then downloaded for off-line analysis, with measurements made of systolic motion (S’-wave), early diastolic motion (E’-wave), and late diastolic motion (A’-wave). The E’-wave velocities from the septal, lateral, and inferior walls were averaged and the ratio of the transmitral E-wave to E’ velocity (E/E’ ratio) calculated. Analysis was performed using the HDI Laboratory software (Phillips) by a single researcher (A.S.), who was masked to all patient details, and each value represents the mean of 3 measurements taken from 3 consecutive, representative cardiac cycles. Interobserver reproducibility
data were acquired for the 2 echocardiographers involved at the single site used in this study and showed a variation for all echocardiographic measurements of between 3.5% and 7.5%. This variation is within acceptable limits as per previous studies (14).

**Statistical analysis.** Statistical analysis was performed using SPSS version 14.0 for Windows (SPSS Inc., Chicago, Illinois). Data are presented as mean ± SD or median (interquartile range) for skewed data. Skewed data were normalized by log10 transformation before statistical analysis. Continuous data were analyzed according to ethnicity using 1-way analysis of variance (ANOVA), and categorical data were analyzed using chi-square tests.

**Multivariate analysis.** Three multivariate models (ANCOVA), applied separately to each of the 2 measures of diastolic function, were built to allow tiered analysis of the effect of ethnicity on cardiac function: model 1, adjusted for age and gender only; model 2, adjusted for age, gender, systolic BP, pulse pressure, diabetes, smoking, total cholesterol, ejection fraction, and LVMI.

Further analyses were undertaken separately to assess whether any measures of left ventricular (LV) geometry other than LVMI would better explain ethnic differences in diastolic function (RWT, RWT/height2, left ventricular mass [LVMI/height2]) when incorporated into model 3. Additionally, substituting midwall fractional shortening for ejection fraction within an alternate model 3 was performed.

Models were also constructed incorporating drug treatment arm (calcium-channel blocker vs. beta blocker) into model 3. As almost all of the subjects were receiving combination therapy (calcium-channel blocker [CCB] plus angiotensin-converting enzyme [ACE] inhibitor or beta-blocker and diuretic), a separate analysis for ACE inhibitors and diuretics was not undertaken. Marginal means are quoted, representing the mean values for both E’ and for E/E’ after adjustment for covariates. A p value of <0.05 was considered statistically significant.

### Results

The overall patient characteristics are shown in Table 1 and are comparable to the population from the ASCOT parent study (15). There were several differences between the African-Caribbean and white European groups; white Europeans were older, had lower diastolic BP, higher total cholesterol, and higher triglycerides. African Caribbeans had a higher prevalence of diabetes.

#### LV Structural Data

<table>
<thead>
<tr>
<th></th>
<th>White European</th>
<th>African Caribbean</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventricular septum, diastole (cm)</td>
<td>1.25 ± 0.20</td>
<td>1.32 ± 0.21</td>
<td>0.100</td>
</tr>
<tr>
<td>LV internal dimension, diastole (cm)</td>
<td>4.81 ± 0.53</td>
<td>4.67 ± 0.51</td>
<td>0.059</td>
</tr>
<tr>
<td>Posterior wall thickness, diastole (cm)</td>
<td>1.16 ± 0.17</td>
<td>1.24 ± 0.18</td>
<td>0.003</td>
</tr>
<tr>
<td>Interventricular septum, systole (cm)</td>
<td>1.61 ± 0.23</td>
<td>1.75 ± 0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV internal dimension, systole (cm)</td>
<td>3.30 ± 0.57</td>
<td>3.00 ± 0.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posterior wall thickness, systole (cm)</td>
<td>1.56 ± 0.20</td>
<td>1.68 ± 0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>66.28 ± 13.16</td>
<td>71.08 ± 14.62</td>
<td>0.010</td>
</tr>
<tr>
<td>LVMI (g/m2)</td>
<td>114.02 ± 27.93</td>
<td>118.44 ± 26.69</td>
<td>0.250</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.49 ± 0.09</td>
<td>0.54 ± 0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial size (cm)</td>
<td>4.34 ± 0.62</td>
<td>4.16 ± 0.50</td>
<td>0.081</td>
</tr>
</tbody>
</table>

All values are mean ± standard deviation.
LV = left ventricular; LVMI = left ventricular mass index.

### Conventional and Tissue Doppler Echocardiographic Data

<table>
<thead>
<tr>
<th></th>
<th>White European</th>
<th>African Caribbean</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmirtal Doppler</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-wave (cm/s)</td>
<td>63.41 ± 13.99</td>
<td>63.15 ± 14.78</td>
<td>0.895</td>
</tr>
<tr>
<td>A-wave (cm/s)</td>
<td>73.85 ± 15.84</td>
<td>74.51 ± 16.53</td>
<td>0.762</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.89 ± 0.26</td>
<td>0.87 ± 0.22</td>
<td>0.623</td>
</tr>
<tr>
<td>E-wave deceleration time (ms)</td>
<td>201.40 ± 5.20</td>
<td>199.00 ± 4.60</td>
<td>0.685</td>
</tr>
<tr>
<td>Tissue Doppler (cm/s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean E’ (cm/s)</td>
<td>8.57 ± 1.84</td>
<td>7.77 ± 1.63</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean E/E’ ratio</td>
<td>7.93 ± 2.07</td>
<td>8.85 ± 2.39</td>
<td>0.003</td>
</tr>
</tbody>
</table>

E’ = tissue Doppler early diastolic velocity.
Differences in ventricular structure were due to the greater ventricular internal diameters in white Europeans on the one hand and to thicker ventricular walls in African Caribbeans on the other.

**Diastolic function in the African Caribbeans and white Europeans.** Tissue Doppler echocardiography revealed clear differences between the 2 ethnic groups (Table 3). African Caribbeans had lower mean E’ velocity and higher E/E' values than white Europeans. Transmitral Doppler flow did not differ by ethnicity.

**Multivariate analysis for relationship between E’ and ethnicity.** African Caribbeans had a significantly lower mean E’ velocity than White Europeans, and that difference remained statistically significant after adjustment for age, diabetes, systolic BP, pulse pressure, smoking, cholesterol, and structural LV differences (7.52 cm/s vs. 8.51 cm/s, respectively; p < 0.001) (Table 4). Additional models substituting other measures of LV geometry for LVMI (RWT, RWT/height², and LVM/height²) were also performed, but these did not significantly alter the findings. Using midwall fractional shortening as an alternate measure of LV function to ejection fraction also did not significantly alter the findings (data not shown).

**Multivariate analysis for relationship between E/E’ and ethnicity.** African Caribbeans had a significantly higher mean E/E’ ratio than White Europeans, which similarly remained statistically significant after adjustment for risk factors and confounding variables (8.89 vs. 7.93, respectively; p = 0.003) (Table 4). Additional models substituting other measures of LV structure and function for LVMI (RWT, RWT/height², and LVM/height²) or ejection fraction (midwall fractional shortening) were again performed, but these did not significantly alter the findings (data not shown).

As an imbalance in known diabetes prevalence by ethnicity could have affected our observations through some unforeseen interaction, all models were rerun after excluding all patients with diabetes. The magnitude of the ethnic differences seen in both diastolic measures was essentially unchanged and remained statistically significant (E’ 8.59 vs. 7.60, p = 0.003; and E/E’ 7.87 vs. 8.77; p = 0.021). An antihypertensive treatment arm (CCB ± ACE inhibitor vs. beta-blocker ± diuretic) was added to the model as an additional variable and also did not significantly change the findings (data not shown).

Figure 1 demonstrates the magnitude of the ethnic difference in these markers of diastolic function in comparison with that of each decade of aging.

**Discussion**

This study shows that African Caribbeans in our study had a greater degree of diastolic impairment than white Europeans, either measured directly through reduced E’ or through implied higher left atrial filling pressures, as represented by an increased E/E’ ratio. This ethnic effect was large, and using regression coefficients was calculated to be equivalent to 18 years of aging.

African Caribbeans have a significantly greater risk of heart failure, renal failure, and stroke compared with white Europeans (16–19). In these later stages of disease, the adverse risk factor profile of African Caribbeans, such as a greater prevalence of diabetes and hypertension, accounts for some of the excess risk; however, a considerable amount remains unexplained. In the U.S., it is thought that inequitable access to health care, and therefore poorer treatment for risk factors, may also contribute to this excess risk. We have shown, however, that this excess risk persists even at quite early stages of disease, independent of other major risk factors, in a health care and clinical trial setting where care provision is equitable. This finding implies that other explanations for this excess risk must be sought.

Diastolic function has been compared between ethnicities in 2 previous studies, with equivocal results. One study of 24 subjects found a lower transmitral E/A ratio in African Caribbeans (20). Another study investigating 29 African Caribbeans and 29 white Europeans found no such difference in transmitral E/A ratio, but did find a longer isovolumic relaxation time in the African Caribbeans (21).

As neither study employed tissue Doppler, these conflicting findings may be attributable to the limitations of conventional Doppler in terms of its ability to distinguish normal function from “pseudonormalization.” Left atrial diameters were mildly increased in both ethnic groups but were not significantly different. This finding is consistent with the

### Table 4 Multivariate Analysis: Adjusted Values for E/E’ According to Ethnicity

<table>
<thead>
<tr>
<th>Model 1 (factors included age, gender)</th>
<th>White European</th>
<th>African Caribbean</th>
<th>Difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted E’</td>
<td>8.60</td>
<td>7.59</td>
<td>-1.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted E/E’</td>
<td>7.92</td>
<td>9.00</td>
<td>1.08</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 2 (factors included age, gender, diabetes, systolic BP)</th>
<th>White European</th>
<th>African Caribbean</th>
<th>Difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted E’</td>
<td>8.60</td>
<td>7.65</td>
<td>-0.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted E/E’</td>
<td>7.94</td>
<td>8.86</td>
<td>0.92</td>
<td>0.003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 3 (factors included age, gender, diabetes, systolic BP, pulse pressure, EF, cholesterol, smoking, LVMI)</th>
<th>White European</th>
<th>African Caribbean</th>
<th>Difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted E’</td>
<td>8.51</td>
<td>7.52</td>
<td>-0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted E/E’</td>
<td>7.93</td>
<td>8.89</td>
<td>0.96</td>
<td>0.003</td>
</tr>
</tbody>
</table>

BP = blood pressure; CI = confidence interval; E = transmitral early filling velocity; E’ = tissue Doppler early diastolic velocity; EF = ejection fraction; LVMI = left ventricular mass index.
LV mass measurements that were also elevated to a similar degree in both groups. Neither of these 2 structural measures was able to detect differences between these groups at this stage of the disease process. In contrast, tissue Doppler provided unambiguous evidence of early impaired diastolic function in the African-Caribbean group.

Age affects diastolic function regardless of the method of measurement (22). In the present study, the age difference between the groups was small, and ethnic differences in diastolic function remained after statistical adjustment for age. Differences in BP might also contribute to differences in diastolic function, as African Caribbeans are not only known to have an increased prevalence of hypertension but also an increased severity (23). However, in the present study (by design), BP differences in white Europeans and African Caribbeans were small, and statistical adjustment for BP had little impact on the ethnic difference in diastolic function.

Left ventricular hypertrophy is another cause of diastolic dysfunction. Previous studies exploring ethnic differences in LV structure have generally found an increased relative wall thickness in people of black African descent (24), sometimes in association with an increase in LV mass (25–27), although not consistently (28). In our study, LVMI was similar in both ethnic groups, probably as a result of previously identified LVH being one of several entry criteria for the study and the close similarity in BP (again as a consequence of the entry criteria). Statistical adjustment for differences in LVMI did not attenuate ethnic differences in diastolic function nor did other methods of adjusting for LV geometry. It seems unlikely, therefore, that LV geometry fully explains the more impaired diastolic function seen in African Caribbeans.

Diabetes mellitus is known to be more common in the African-Caribbean population and may be associated with diastolic dysfunction (29). However, in the present study, excluding patients with a diagnosis of diabetes from the analysis did not alter the strong association between ethnicity and diastolic function.

Inequality of access to health care and treatments has also been suggested as a factor mediating poorer outcomes in some ethnic groups (1,2). From the onset of randomization within the ASCOT study, all hypertension treatment decisions were strictly protocol based, being uniformly managed throughout the trial in a “treat to target” fashion. Also, before entry into the trial, all patients within this substudy received their general medical care and hypertension treatment through the United Kingdom National Health Service, which provides free “at the point of delivery” access to health care for all. Prescription medicines are given free to persons of low incomes and heavily subsidized for others. Recruitment also took place through local primary care facilities in a small geographical area, with large numbers from the same practices. These factors limit the effects of differences in access and the proposed inequalities of care seen in other health care systems. This is an important difference from several previous studies looking at the consequences of hypertension in different ethnic groups and is a strength of the present study.

A study of this nature can identify ethnic differences in disease patterns but cannot establish underlying mechanisms. Our observations exclude previously proposed mechanisms, such as those related to comorbidity burden or LV structural differences. However, there remain several possible reasons for the observation of greater diastolic dysfunction in African Caribbeans. First, it may represent an
increased susceptibility to myocardial impairment in response to the same degree of hypertension for reasons unknown. Second, ethnic differences in renin (30), aldosterone (31), and salt sensitivity (32) are well established, but the relationship of these factors to diastolic dysfunction remains unclear and therefore we did not adjust for these. Such factors might have a direct bearing on myocardial function. If such factors were to affect our results simply through plasma volume status, this might have an impact on left atrial filling pressure, but less so on the tissue Doppler E′ velocity, as this is a direct myocardial velocity measurement and is relatively independent of preload variation (7,33,34). Finally, as these findings are entirely in African-Caribbean subjects, further work is also required to examine other African populations or those with African heritage such as the African-American population.

Clinical implications. The relatively impaired diastolic function found in this study suggests that the greater burden of heart failure seen in the African-Caribbean hypertensive population may begin to develop from an earlier stage than previously thought, in this case well before symptoms have developed. Tissue Doppler E′ velocities are a measure of early diastolic relaxation and have been shown to progressively deteriorate with increasing diastolic dysfunction and be closely related to symptoms of heart failure in those with preserved systolic function (35). The E/E′ ratio is also a marker of left atrial filling pressure, and a higher ratio has been shown to be an adverse prognostic marker in cardiovascular disease (36).

Conclusions

African Caribbeans with treated hypertension have a greater degree of myocardial dysfunction than their white European counterparts, despite good BP control. This difference could not be accounted for by known confounding variables and may partly explain the increased burden of heart failure in the African-Caribbean population.

Reprint requests and correspondence: Dr. Andrew Sharp, International Centre for Circulatory Health, St. Mary's Hospital and Imperial College London, 59–61 North Wharf Road, Paddington, London W2 1LA, United Kingdom. E-mail: andrewsharp@doctors.org.uk.

REFERENCES


Key Words: tissue Doppler • diastolic dysfunction • ethnicity • echocardiography • hypertension • left ventricle.