Ethnic Differences in Arterial Responses, Inflammation, and Metabolic Profiles
Possible Insights into Ethnic Differences in Cardiovascular Disease and Stroke

Gregory Y.H. Lip, Christopher J. Boos

Despite enormous strides in our understanding of the potential risk factors implicated in cardiovascular disease (CVD), there has been a marked underrepresentation of data among ethnic minority groups in the published studies to date. It is critically important that this imbalance is addressed because it is clear that there are considerable variations in the rate of cardiovascular events and mortality among the differing ethnic groups, at least in the United Kingdom.

Compared with Caucasians, Afro-Caribbeans and people of African descent have an elevated risk (>1.5 to 2.5 times greater) of hypertension and diabetes mellitus, as well as related complications such as stroke, insulin resistance, and end-stage renal failure.1-6 Yet paradoxically, they have a far lower incidence of coronary artery disease than both south Asians (originating in the Indian subcontinent) and white Caucasians. The reasons for this apparent disparity are not clear but may relate to the clustering of known cardiovascular risk factors among the different ethnic groups. For example, when compared with Caucasians, Afro-Caribbeans are noted (in some studies) to have an increased incidence of obesity as well as lower levels of low-density lipoprotein cholesterol (yet higher high-density lipoprotein cholesterol) and of smoking rates and abnormal levels of adhesion molecules (which are implicated in coronary atheromatous plaque formation), such as vascular cell adhesion molecule-1, intracellular adhesion molecule-1, and soluble P-selectin.2,3,5,7-11 In the Table we present an overview of some of the key studies that have compared the known cardiovascular risk factors and CVD among the two groups.

Atherosclerosis beginning in the arterial wall and in the related endothelial damage/dysfunction is the hallmark of CVD. In recent years, increasing emphasis has been placed on the noninvasive identification of patients at future risk of CVD so that preventative measures can be introduced before the establishment of overt disease. Among the noninvasive risk profiles that have taken center stage are the assessment of carotid intimal-medial thickness (CIMT), coronary artery calcium scoring, arterial stiffness, flow-mediated dilatation (a surrogate marker of endothelial function), and the quantification of known vascular risk markers, such as homocysteine, fibrinogen, cholesterol, and inflammatory parameters (eg, C-reactive protein [CRP]).12-14 Adverse re-arrangement in any one of these indices has been linked to increased risk of future cardiovascular events.

The identification of increased arterial stiffness is important because it precedes a rise in systolic blood pressure and arterial pulse pressure, which in themselves are strongly linked to adverse cardiovascular events.15 Indeed, structural changes in the larger, more proximal conduit elastic arteries result in increased wall thickness (intimal-medial thickness), increased arterial pulse wave velocity, a reduction in arterial capacitance, and consequent increased arterial stiffness. It is also increasingly clear that the distal arterial tree and microvascular network is a vital determinant of long-term vascular resistance and itself is subject to increased stiffening as a consequence of atherosclerosis.16

In this issue of Atherosclerosis, Thrombosis, and Vascular Biology, Kalra et al attempt to further address the issues of cardiovascular risk and ethnicity, with a detailed and comprehensive assessment of ethnicity and CVD profiling.17 In this cross-sectional study, the authors compared a cohort of 78 apparently healthy Afro-Caribbeans (aged 35 to ≤75 years) with 82 age- and sex-matched Caucasian controls to ascertain whether important differences in known metabolic, vascular, and inflammatory markers as well as differences in physiological responses between large and small arteries might help to explain the excess of small vessel pathology among Afro-Caribbeans. Metabolic status was assessed by fasting measurements of blood glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, homocysteine, insulin sensitivity, and insulin levels. Inflammatory status was assessed by quantification of CRP, tumor necrosis factor (TNF)-α, and interleukin (IL)-6. Vascular assessment included the measurement of CIMT, using B-mode ultrasound, as well as assessment of small vessel reactivity and large artery stiffness, using digital volume pulse photoplethysmography. Genotyping for important β2-adrenoceptor polymorphisms, such as Arg16Gly and Gln27Glu, controversially linked to an increased risk of hypertension and coronary disease (with increased allele frequencies among Africans) was also performed. Overall, this was a most impressive and comprehensive attempt at cardiovascular risk profiling.
Kalra et al\textsuperscript{17} found that Afro-Caribbean patients had increased diastolic blood pressure, Arg16Gly and Gln27Glu polymorphisms, body mass index, and fasting insulin levels, but these results were unsurprising and somewhat consistent with previously published data. However, demonstration of higher levels of TNF-\(\alpha\) and IL-6 despite equivalent CRP levels among the Afro-Caribbeans was interesting because this is in contrast with a previous article by Heald et al\textsuperscript{18} which showed reduced CRP levels in Afro-Caribbeans (compared with both Europeans and Pakistanis) and noted that CRP was independently associated with an increased risk of having the metabolic syndrome (by homeostasis model assessment of insulin sensitivity). Kalra et al\textsuperscript{17} found a nonsignificant trend to lower homocysteine levels among the Afro-Caribbean patients in support of previous data.\textsuperscript{19} After adjustments for potential confounders, CIMT was greater among Afro-Caribbeans when compared with Caucasians,\textsuperscript{17} again consistent with two previously published articles on the subject\textsuperscript{20,21}; this might help explain the comparative increase in stroke risk among Afro-Caribbeans. However, despite the increased CIMT among Afro-Caribbeans, there was no significant difference in arterial stiffness (by quantification of stiffness index) between the two groups, which is contrary to previously published work.\textsuperscript{22,23}

The reason for the disparity between the study by Kalra et al\textsuperscript{17} and previously published work is uncertain—perhaps

### TABLE 1. A Summary of Key Articles Comparing Cardiovascular Risk Factors Among Afro-Caribbeans Compared With Caucasians

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Patient Population</th>
<th>Afro-Caribbean/White/Other</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heald et al\textsuperscript{18}</td>
<td>2005</td>
<td>Population-based community survey looking into CRP levels among differing ethnic groups</td>
<td>177/155/108</td>
<td>CRP was significantly lower in Afro-Caribbean groups than among the other two ethnic groups other groups.</td>
</tr>
<tr>
<td>Strain et al\textsuperscript{6}</td>
<td>2005</td>
<td>Cross-sectional study of patients in general Practice register</td>
<td>88/93/Nil</td>
<td>Poorer microvascular structure and function, higher resting and ambulatory BP, BMI and rates of insulin resistance, yet lower total cholesterol and fasting triglycerides among Afro-Caribbeans compared with Caucasians.</td>
</tr>
<tr>
<td>Hajat et al\textsuperscript{7}</td>
<td>2004</td>
<td>Cross-sectional comparison of ethnic differences in risk factors for ischemic stroke</td>
<td>416/820/144</td>
<td>Higher (PAR) for hypertension and DM but lower PAR for smoking and ischemic heart disease among Afro-Caribbeans compared with Caucasians.</td>
</tr>
<tr>
<td>Chaturvedi et al\textsuperscript{22}</td>
<td>2003</td>
<td>Cross-sectional study comparing the degree of vascular stiffness and relationship to vascular damage</td>
<td>99/103/Nil</td>
<td>Increased Aortic stiffness among Afro-Caribbeans, even after adjustment for blood pressure.</td>
</tr>
<tr>
<td>Whitty et al\textsuperscript{9}</td>
<td>2003</td>
<td>Comparison of CVD risk factors among three ethnic groups as part of the Whitehall II cohort study</td>
<td>360/8973/577</td>
<td>Higher systolic and diastolic BP and rate of DM among the Afro-Caribbean group compared with Caucasians. Afro-Caribbeans also had lower total cholesterol and triglyceride levels despite higher HDL cholesterol levels.</td>
</tr>
<tr>
<td>Wolfe et al\textsuperscript{6}</td>
<td>2002</td>
<td>Retrospective analysis of stroke register in London</td>
<td>203/995/52</td>
<td>The black group had a significantly higher incidence of all and unclassified strokes compared to whites (adjusted incidence rate ratio: 2.18; 95% CI 1.86 to 2.56, (P&lt;0.0001)).</td>
</tr>
<tr>
<td>Lane et al\textsuperscript{3}</td>
<td>2002</td>
<td>Cross-sectional community study of in the West Midlands, UK</td>
<td>453/2169/231</td>
<td>Prevalence of hypertension was greater in both Afro-Caribbean men (31%) and women (34%) (both (P&lt;0.001)), compared with Caucasians (19% and 13% respectively), and South-Asian men (16%).</td>
</tr>
<tr>
<td>Markus et al\textsuperscript{21}</td>
<td>2001</td>
<td>Cross-sectional study of Afro-Caribbean and Caucasian patients in two General Practices in South London</td>
<td>202/89/Nil</td>
<td>CIMT was increased in Afro-Caribbeans, even after controlling for cardiovascular risk factors, including homocysteine and social class (95% CI 0.036 to 0.189, (P=0.004)).</td>
</tr>
<tr>
<td>Khattar et al\textsuperscript{2}</td>
<td>1999/2000</td>
<td>Longitudinal comparison of morbidity and mortality among white, South Asian and Afro-Caribbean hypertensives</td>
<td>54/528/106</td>
<td>Afro-Caribbeans had the lowest all cause cardiovascular event rate, which was predominantly driven by a significantly lower rate of coronary events compared with the other groups.</td>
</tr>
<tr>
<td>Cappucio et al\textsuperscript{10}</td>
<td>1997</td>
<td>Population survey during 1994–1996 in South London</td>
<td>549/524/505</td>
<td>Afro-Caribbeans had higher rates of obesity (particularly women) but lower cholesterol levels and smoking rates compared with Caucasians.</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; BMI, body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein; PAR, population attributable risk.
differences in the patient populations studied, techniques used, and the increased statistical adjustments for additional confounders (beyond simply age and blood pressure) in this study versus the other published reports are possible causes. The great biological diversity of life also means that statistical adjustments can never fully adjust for all pathophysiological processes.

One novel observation by Kalra et al.\(^{17}\) merits further discussion. Although there was a significant relationship between Caucasians, CIMT, and arterial stiffness, this relationship did not hold true for Afro-Caribbeans.\(^{17}\) Unlike Caucasians, Afro-Caribbeans also had selectively reduced small artery, but not large artery, function, as quantified by a change in reflectance index from baseline in response to stimuli, even after adjustment for potential confounders; however, there was a consistent and independent association between increasing CIMT and reducing small artery function among the Caucasian but not Afro-Caribbean patients.

Although large artery stiffness has been well studied,\(^{15}\) the situation with small artery stiffness is quite the opposite. Given the importance of small arteries in contributing to vascular resistance and blood pressure, as well as the consequent ventricular remodeling, it is plausible to suggest that some of the differences in CVD between Caucasians and Afro-Caribbeans may relate to the propensity for small artery dysfunction among Afro-Caribbeans. It is also increasingly understood that arterial stiffness varies throughout the arterial tree, with likely variations in functional and structural changes in response to a host of hemodynamic and inflammatory insults.\(^{12}\)

Nonetheless, the relationship between ethnicity and CVD is a highly complex one and is further compounded by a number of confounders, such as the effects of migration, generation gaps, and the clustering of ethnic minorities among the lower socioeconomic classes, which in itself is strongly linked to an increased CVD.\(^{9}\) Furthermore, the risk factors for CVD are only partly known, with an increasing number of CVD risk markers being recognized in recent years. The additive role of genes and genetic pleiotropisms to such CVD risk assessment is also uncertain but remains an active area of research.

In conclusion, Kalra et al.\(^{17}\) have identified an association between small artery disease and a constellation of cardiovascular risk factors, such as increased TNF-\(\alpha\) and IL-6 (proinflammatory markers), fasting insulin, body mass index, and diastolic blood pressure. Statistical association does not necessarily equate to causation, especially in a cross-sectional analysis, and this interesting article certainly raises more questions and research hypotheses that should ignite further research efforts toward a better understanding of the relationships between ethnicity and CVD so that we might be in a better position to prevent disease, rather than treat established disease, in the future.

References


Ethnic Differences in Arterial Responses, Inflammation, and Metabolic Profiles: Possible Insights into Ethnic Differences in Cardiovascular Disease and Stroke

Gregory Y.H. Lip and Christopher J. Boos

doi: 10.1161/01.ATV.0000188507.89134.ef

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/25/11/2240

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/