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Do arterial stiffness and wave reflection underlie cardiovascular risk in ethnic minorities?

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Abstract

Increasing evidence indicates that remarkable differences in cardiovascular risk between ethnic groups cannot be fully explained by traditional risk factors such as hypertension, diabetes or dyslipidemia measured in midlife. Therefore, the underlying pathophysiology leading to this “excess risk” in ethnic minority groups is still poorly understood, and one way to address this issue is to shift the focus from “risk” to examine target organs, particularly blood vessels and their arterial properties more directly. In fact, structural and functional changes of the vascular system may be identifiable at very early stages of life when traditional factors are not yet developed. Arterial stiffening, measured as aortic pulse wave velocity, and wave reflection parameters, especially augmentation index, seem to be an important pathophysiological mechanism for the development of cardiovascular disease and predict mortality independent of other risk factors. However, data regarding these arterial indices in ethnic minorities are relatively rare and the heterogeneity between populations, techniques and statistical methods make it difficult to fully understand their role.

Keywords

Pulse wave velocity, augmentation index, risk factors, atherosclerosis, cardiology, ethnicity

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Introduction

Europe’s population is undergoing a significant and rapid growth in its ethnic diversity. As an example, latest updated census data in the UK¹ showed that the White European ethnic group accounted for 86.0% of the usual resident population in England and Wales in 2011, a decrease from 91.3% in 2001 and 94.1% compared to 25 years before. Meanwhile over the last decades, ethnic minority groups (South Asian, African-Caribbean and Black African) continued to rise, and in metropolitan areas like London, proportions increased up to 40% of the total. These population data may continue to have long-term influences on health profiles, particularly ethnic differences in cardiovascular (CV) and metabolic diseases, noted over the last 40 years.

CV disease (CVD) is the leading cause of death worldwide with the burden of stroke and coronary heart disease (CHD) most relevant. Both are the major continuing, yet preventable, causes of morbidity and mortality in the Western world and are rapidly reaching or have reached epidemic proportions in

modernizing countries. Stroke and CHD clearly show ethnic differences and a particular pattern of incidence between resident and migrant populations from different backgrounds; therefore, evaluation and management of CV risk have become essential globally.

Examples studied over several decades which include mortality from CHD and stroke in South Asian migrants to the UK show that it is between 50% and 100% higher than the White British population.² Interestingly, stroke was and is not more common in resident South Asians, but its incidence is now higher for migrants coming from that area and living in the UK.³ At the same time, people of Black African and African Caribbean origin are still significantly

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protected from CHD, although mortality from stroke is even more relevant than in South Asians.²

Higher CV risk in migrant populations is not just a British issue; similar results have occurred in different European countries like Norway, Sweden or the Netherlands. Prevalence and incidence of CVD have also long varied in the US between African-Americans, in whom hypertension and subsequent stroke are notably more frequent but where the cross-over from lower to gradually higher rates of CHD than in White Americans occurred in the mid-1960s, indicating its environmental origins. However, here our discussion is mainly restricted to European data.

Increasing evidence indicates that these remarkable differences between ethnic groups cannot be fully explained by traditional CV and metabolic risk factors, such as hypertension, dyslipidemia, central adiposity or insulin resistance, measured in midlife.⁴ In fact, the underlying pathophysiology leading to this “excess risk” in ethnic minority groups is still poorly understood.

There are different rates of hypertension, type 2 diabetes and dyslipidemia, among ethnic groups, with diabetes greatest in South Asians, marginally less in Black Caribbeans or (west) Africans and vice versa for hypertension, compared with White Europeans.⁵ Recent emphasis that cultural and socio-economic factors might account, at least in part, for excess of both CVD itself and these risk factors is still a matter of debate. Socio-economic circumstances is an umbrella term for many lifestyle and living conditions that can be seen as risk factors per se⁶ or which can contribute to marginalization and perpetuate a vicious cycle of increasing CV risk through changes in health behaviors.⁷

Therefore, one way to address the issue of ethnic variability in CV risk is to shift the focus from “risk” to examine target organs, particularly blood vessels and their arterial properties more directly. Structural and functional changes of the vascular system may be identifiable at very early stages of life when traditional factors are not yet developed.

Arterial stiffness in ethnic minorities

Arterial stiffening, measured as aortic pulse wave velocity (PWV), seems to be an important pathophysiological mechanism for the development of CVD. When the artery wall is stiffer, the forward pulse wave travels faster, and the arterial waves reflected from the periphery reach the heart early during systole leading to an increase in systolic blood pressure (BP), augmentation pressure and cardiac workload, whereas diastolic BP decreases resulting in reduced diastolic coronary perfusion. Furthermore, arterial stiffness contributes to increase in the transmission of pulsatile energy into smaller arteries and peripheral microcirculation, thus

causing microvascular damage in parenchymal organs such as heart, kidney and the brain.⁸ Nowadays, PWV is recognized as the most useful and robust index of arterial stiffness and independent predictor of vascular morbidity and mortality in the general population or in patients with hypertension, diabetes mellitus or end-stage renal disease.⁹ At the same time, other arterial properties are becoming important: arterial wave reflection parameters¹⁰ have emerged as important markers of vascular health and predict CV risk independent of conventional risk factors including BP.

Consequently, knowledge on ethnic differences in these other arterial properties may help to understand better the pathophysiology of underlying ethnic differences in CV risk. As yet, data regarding these arterial indices in ethnic minorities are relatively rare, and the heterogeneity between populations, techniques and statistical methods makes it difficult to fully understand their role.

A relative small number of studies have investigated ethnicity-related differences in PWV taking into account the well-established conventional risk factors (particularly age and BP, the most important determinants of arterial stiffness¹¹) (Table 1). Two small UK studies offer some evidence that South Asians have higher PWVs than Europeans, after adjustment for CV risk factors.^{12,13} Both studies found higher PWVs in the ethnic minority compared to the resident population at similar age and brachial/central distending pressures (or after adjusting for confounding factors); limitations included the first cohort being made up of male volunteers only, and the other study was limited to participants of a diabetes screening program. Another tri-ethnic population-based study conducted in the UK¹⁴ found differences in arterial function between European, South Asians and African Caribbeans at similar level of brachial BP. Particularly, South Asians show unfavorable arterial function (measured as ratio between central pulse pressure and stroke volume) compared to Europeans and African Caribbeans. However, carotid-femoral PWV measured with Doppler probe did not differ between ethnic groups, and the follow-up studies were limited to survivors who were willing and able to attend the clinic. In a small cohort of South Asians older adults (>60 years) living in Canada, local carotid stiffness was higher compared to White Caucasian peers and it was related with diabetic parameters. However, the differences in brachial-ankle PWV (as a measure of global stiffness) were not statistically significant after adjusting for mean BP.¹⁵ Data on populations of African origin are inconsistent to date in the UK. In an early North-West London study, baseline PWV measured by Doppler did not differ between local Europeans, Gujarati Indians and African-Caribbeans (only) but

Table 1. Summary of the studies regarding arterial stiffness.

References	Population	Aim	Arterial stiffness parameters	Findings	Conclusions
Cruickshank et al. ⁶	Subsample (n = 666) of young multi-ethnic cohort (21–23 years) from DASH study	Ethnic differences and childhood determinant of arterial stiffness	PWV: Arteriograph	Unadjusted PWV in Black Caribbean and White UK young men similar and lower in other groups at similar systolic BP and BMI. In fully adjusted regression models, Black Caribbean, Black African and Indian young women lower stiffness than did White British women	Increased waist/height ratios, lower physical activity, blood pressure and psychosocial variables (e.g., perceived racism) independently increase arterial stiffness
Rezai et al. ¹²	198 British male: South Asians (n = 68) African Caribbeans (n = 67) Europeans (n = 63)	To investigate the role of vitamin D and aldosterone in aortic stiffness	Aortic PWV (aPWV): Arteriograph device. Local PWV in a subsample (n = 47) (aortic arch and descending aorta) MRI	aPWV in South Asians higher compared to African Caribbeans and Europeans (adjusted for age, BP and diabetes). PWV over descending aorta in South Asians higher than in African Caribbeans and Europeans; no differences in PWVs over the aortic arch	PWV parallels with coronary disease risk in ethnic groups, descending aortic but not arch PWV has this feature.
Webb et al. ¹³	132 South Asians (55.7 years) and 125 age-matched White Europeans (56 years)	To investigate the role of vitamin D deficiency in vascular wall senescence	Carotid-femoral PWV (cfPWV)	Unadjusted cfPWV higher (9.32 vs. 8.68 p = 0.001) in South Asians compared to White Europeans a similar level of BP	Aortic stiffness is increased in British Indo-Asians without vascular disease despite conventional risk profiles, which are comparable to age-matched White Europeans.
Park et al. ¹⁴	Tri-ethnic UK cohort (n = 1312, age 70 years)	To investigate differences in arterial central hemodynamics and stiffness	Pulse pressure (PP), augmentation index (AIx) (SphygmoCor). cfPWV (Doppler probe) in n = 960). Elasticity coefficient, cPP/stroke volume (SV) with echocardiography.	cPP/SV higher in South Asians and lower in African Caribbeans compared to Europeans. cfPWV slightly lower in African Caribbeans but not significantly. Results did not differ after adjustments for confounding factors (including BP)	Compared to Europeans, South Asians have unfavorable arterial function. In contrast, African Caribbeans have more favorable arterial function than Europeans and South Asians. These differences may contribute to the differential ethnic rates of cardiovascular disease.
Brar et al. ¹⁵	22 South Asians (SA) and 22 White Caucasians (CA) older adults	Association between arterial stiffness and cerebral flow hemodynamic	Brachial-ankle pulse wave velocity (baPWV), common carotid artery (CCA), pulse pressure (cPP) and CCA compliance coefficient (CC)	SA had greater local arterial stiffness compared with CA, (higher cPP and lower CC). baPWV did not significantly differ between the two (p = 0.080).	Stronger associations between pulsatile cerebrovascular hemodynamics and structural and functional alterations in central arteries in SA that may underlie the elevated risk for cerebrovascular disease.

(continued)

Table 1. Continued

References	Population	Aim	Arterial stiffness parameters	Findings	Conclusions
Cruickshank et al. ¹⁶	Gujaratis (<i>n</i> = 20), African-Caribbeans (<i>n</i> = 101) and White Europeans (<i>n</i> = 232)	aPWV predicts cardiovascular and all-cause mortality in type 2 diabetes and glucose-tolerance-tested (GTT)	Doppler-derived aortic PWV	For all groups combined, age, sex and systolic BP predicted mortality; the addition of PWV independently predicted all-cause and cardiovascular mortality	Aortic PWV is a powerful independent predictor of mortality in both diabetes and GTT population samples.
Chaturvedi et al. ¹⁷	103 Europeans and 99 African Caribbeans aged 40–64 years	Arterial stiffness may further account for ethnic differences in risk of hypertensive target organ damage	cfPWV	cfPWV higher in African Caribbeans (12.7 m/s) compared to Europeans (11.2 m/s, <i>p</i> < 0.001). This difference persisted on adjustment for resting and ambulatory BP (<i>p</i> = 0.003).	Aortic PWV differs between African Caribbean and European
Mackey et al. ¹⁸	356 participants (53.4% women, 25.3% African American), aged 70–96 years	To examine risk factors associated with arterial stiffness in elderly individuals.	PWV: pencil-type Doppler probe	Mean aortic PWV (850 cm/s, range 365 to 1863) not differ by ethnicity or sex.	Aortic stiffness was positively associated with risk factors.
Snijder et al. ¹⁹	1797 White European, 1846 SA Surinamese, 1840 African Surinamese and 1673 Ghanaian (aged 18–70 years)	To assess ethnic differences in arterial stiffness	PWV: Arteriograph	South-Asian Surinamese higher PWVs compared with Whites African Surinamese. Ghanaians higher PWVs compared with Whites across the entire age range. These differences disappeared or reversed after adjustment for risk factors.	After adjustment for CV risk factors ethnic differences in PWV largely disappear. Higher PWV in South-Asian and African ethnic groups develops due to higher exposure to cardiovascular risk factors.
Zhang et al. ²⁰	Multi-ethnic type 2 diabetes Asian cohort: Chinese (<i>n</i> = 1045), Malays (<i>n</i> = 458) and Indians (<i>n</i> = 468).	Ethnic disparity in arterial stiffness	PWV applanation tonometry	PWV higher in Malays (10.1 ± 3.0 m/s) than Chinese (9.7 ± 2.8 m/s) and Indians (9.6 ± 3.1 m/s)	Malays and Indians with diabetes have higher central arterial stiffness, which may explain their higher risk for adverse outcomes.

BP: blood pressure; BMI: body mass index; CV: cardiovascular.

was higher in people with type 2 diabetes at any level of BP. These groups were sampled from the local population, but those with diabetes were supplemented by clinic patients; PWV had a powerful effect at 11-year follow-up on mortality displacing BP, with lower mortality in Caribbeans.¹⁶

In another later study of a middle-aged population (202 subjects, 40–64 years) in west London, carotid-femoral PWV in African-origin subjects (both Black African and African Caribbean) showed higher values compared to Europeans (12.7 m/s vs. 11.2 m/s). That difference was statistically significant after adjusting for confounding factors, particularly mean arterial pressure which was considerably higher in the African-origin groups (102 mmHg vs. 95 mmHg).¹⁷

The US Cardiovascular Health Study¹⁸ collected data of a longitudinal study designed to describe the relationship between aortic stiffness and CV risk factors in 356 elderly individuals. In that cohort, no ethnicity or sex effects were detected on PWV. However, the lack of correlation in this case could have been due to a survivor effect as the mean age in the cohort was 78 years; therefore, individuals with elevated values of PWV may have not survived up to that age.

Interestingly, cross-sectional data in a Dutch multi-ethnic population-based sample (more than 7000 subjects) with a wide age range (18–70 years) from HELIUS study¹⁹ found that unadjusted PWVs in African and South Asian-origin groups were higher as compared with those of resident population (Dutch descent), but these differences largely disappeared after adjustment for conventional CV risk factors. These results support the hypothesis that early exposure to CV risk factors, including in utero, may be the main driving force for differences in arterial stiffness.

Similar conclusions can be derived by the analysis of “DASH study,”⁶ which collected data on PWV in a multi-ethnic cohort of young adults (aged 21–23 years) in the UK where unadjusted values and regression models for PWVs were similar or lower in ethnic minorities than in White Europeans. At similar BPs (120 mmHg), Black Caribbean and White UK young men had similar PWV values while South Asians had lower PWVs. Fully adjusted models for gender, age, BP, ethnicity, waist–height ratio (an index of body “fat”) showed that none of the ethnic minorities increased PWVs compared to White UK. Therefore, PWV at least in early adulthood seemed not to provide additional information for evaluating CV risk. Interestingly, earlier BP had no predictive value for current PWV, which was only related to current (“distending”) BP.

That observation is still a matter of debate, however data from an older European cohort suggest that BP does not cause the progressive increase in arterial

stiffening but rather vice versa, arterial wall properties modulate BP change over time.²¹

Taking all these results into account, the role of arterial stiffness as “predictor” of CV risk in ethnic minorities remains largely unclear, especially after considering the role of BP.

Wave reflection in ethnic minorities

Very limited evidence can be used to clarify if augmentation index (AIx), considered a robust index of wave reflection rather than arterial stiffness,²² can help to account for the variability in CV risk in ethnic minorities groups (Table 2).

The arterial pulse wave form is the sum of the forward pressure wave and the backward wave that is reflected from the peripheral sites. AIx is calculated as the ratio of the central augmented pressure to the central pulse pressure and, because of its nature, it is a complex composite measurement influenced by age, gender, height, BP, reflectance points, and left ventricular ejection characteristics (such as heart rate and contractility).⁸

In a small cohort of healthy young African-American men in the US, AIx was greater, despite comparable brachial BP, compared with White comparators.²³ Similarly, a Belgian study reported that smoking acutely increased arterial stiffness and wave reflection in Black people (mainly directly of African origin) more than in Whites.²⁴

However, no studies considered all confounding factors, especially anthropometric data, in their regression analysis. In another large US, multi-ethnic cohort ($n=951$), average AIx values were higher for African-Americans compared to Whites (23 vs. 20%); and in regression models (in subjects without metabolic syndrome), ethnicity was an independent predictor of AIx.²⁵ The final model included waist circumference (as a parameter of “fat”) and not height, and this approach may lead to misleading results, because shorter individuals have a “shortened return time” for reflected waves, leading to increased central pressure augmentation. For example, another study found no significant differences in AIx between 94 East-Asian and 47 age-matched White peers after adjusting for height.²⁶

Conversely, in a composite of five large population-based studies from Britain, American Indian, Peruvian highlanders, South Africa and China (total > 10,000 participants), after standardized adjustment with z -scores for confounding factors (age, heart rate, BP and body size), Black South Africans had markedly higher AIx than British Whites,²⁷ using the same (“Sphygmocor”-based) methods. The study concluded that marked ethnic effects on AIx do exist and may

Table 2. Summary of the studies regarding wave reflection parameters.

References	Population	Aim	Wave reflection parameters	Findings	Conclusions
Heffernan et al. ²³	55 healthy men (25 African American, 30 Whites)	Ethnic differences in arterial function related to central pressure	Alx and transit time (Tr) with applanation tonometry	African-American men had greater aortic stiffness and Alx; reduced aortic Tr compared with White men ($P < 0.05$) with similar level of brachial BP (but greater central BP).	African-American men have greater central BP and wave reflection, despite comparable brachial BP, compared with young White men.
Lemogoum et al. ²⁴	Black ($n = 30$) and White ($n = 30$) smokers	Ethnic differences in smoking effects on PWV and augmentation index (Alx).	Alx with Complior device	Smoking increase Alx and PWV. Blacks disclose larger increases in Alx adjusted for heart rate and PWV normalized for BP.	Smoking acutely increases PWV and Alx in Blacks more than in Whites.
Shen et al. ²⁵	Community-middle age cohort $n = 951$ African Americans (AAs) and White	To evaluate the relationship between metabolic syndrome (MetS) and vascular function	Alx with Sphygmocor	MetS is associated with increased PWV and Alx in both races. In subjects without MetS, AAs had higher PWV and Alx compared with White subjects. Adding BP effect racial differences disappear	MetS is associated with increased arterial stiffness in both racial groups, AAs without MetS have greater vascular dysfunction but additional weighting for hypertension attenuated the racial differences
Sugawara et al. ²⁶	47 White adults (45 years) and 94 age-matched Asian adults	Ethnic differences in central (cAlx) and peripheral Alx (pAlx).	Radial Alx: tonometry-based automated radial AI measurement device. Carotid arterial waveforms	cAlx and pAlx tend to be lower in White compared with Asian adults ($P < 0.10$ for both). Such tendency disappears when height is taken into account.	pAlx may provide a surrogate measure of cAlx irrespective of difference in race
Chirinos et al. ²⁷	10,550 adults multi-ethnic cohort	Ethnic differences in wave reflections. Reference values.	Alx with Sphygmocor	Black African and Andean Hispanics have higher central Alx compared to White British whereas American Indians had lower, no significant differences between Chinese and British Whites.	Marked ethnic differences in augmentation index exist, which may contribute to ethnic differences in hypertensive organ damage.
Sibiya et al. ²⁸	808 cohort of Black African ancestry (283 men)	Influence of gender in the relationship between wave reflection	Alx with Sphygmocor	In men, but not in women, Alx derived from aortic augmentation pressure/central aortic pulse pressure and Alx	Radial applanation tonometry-derived Alx may account for less of the variation in end-

(continued)

Table 2. Continued

References	Population	Aim	Wave reflection parameters	Findings	Conclusions
Zhang et al. ²⁰	Multi-ethnic type 2 diabetes Asian cohort: Chinese (n = 1045), Malays (n = 458) and Indians (n = 468).	parameters and target organ damage Ethnic disparity in arterial stiffness	Aix appplanation tonometry	derived from the second peak/first peak of the aortic pulse wave are associated with left ventricular mass index (LVMI). Aix higher in Indians (28.1 ± 10.8%) than Malays (25.9 ± 10.1%) and Chinese (26.1 ± 10.7%) (P < 0.001). In fully adjusted models (age, gender, BMI, SBP, DBP and height), Indians remain associated with higher AI (β = 2.776, P < 0.001).	organ changes in women as compared with men. Malays and Indians with diabetes have higher Aix which may explain their higher risk for adverse outcomes.

contribute to the well-established ethnic differences in hypertensive organ damage. Similarly, in a wide age range (21–90 years) diabetic population in multi-ethnic Singapore, Aix was significantly higher in Indians (28.1 ± 10.8%) compared to Chinese (26.1 ± 10.7%) and Malays (25.9 ± 10.1%) while PWV showed an opposite trend.²⁰ Of note, in regression analysis, Indians remained associated with higher Aix after adjustment for confounding (age, gender, BMI, BP, height) which also independently predicted Aix itself. Interestingly, epidemiological data in the same area found that mortality related to CVD was higher in the Indian and Malay population compared to the Chinese one supporting the idea that wave reflection (and arterial stiffness) may contribute to differences in outcome.²⁹ In that sample, systolic BP was lower for Indians compared to Chinese (132.3 mmHg vs. 135.8 mmHg), stressing the concept that some ethnic differences in central hemodynamics may not be fully assessed with conventional sphygmomanometry by BP alone.

Therefore, it does seem possible that wave reflection may act as an independent contributing factor to development of organ damage like left ventricular hypertrophy (LVH) and that this relationship could explain higher rates of hypertensive target organ damage in some ethnic minorities (as it was found in African-Americans as above, and in African-Caribbeans in Britain).³⁰

In this scenario, increased central wave reflection since early adulthood in ethnic minorities groups could determine target organ damage before the onset of other well-established risk factors, particularly BP. In such context, discrepancy between the results of PWV and Aix is not surprising since Aix is not a surrogate marker of arterial stiffness.²²

There are still aspects which need further investigation. For example, Aix derived from radial appplanation tonometry was independently associated with LVH in a sample of 808 subjects of Black African descent²⁸ only among men and not in women, suggesting the origin of gender differences need attention. In the long-term follow-up of the UK “SABRE” study above, the latter’s 3-D echo analysis showed that cardiac remodeling rather than hypertrophy per se was the main issue in prognosis.³⁰

Finally, it is still unclear whether Aix should be considered a genuine marker of wave reflection because both amplified Windkessel-like effects and excess (aortic) “reservoir” pressure may be additional, or even replacement, causes of these apparent wave reflections

Conclusions

To summarize, CV risk between ethnic groups varies and is unaccounted for by traditional CV or metabolic risk factors measured in midlife. Increasing evidence suggests that arterial stiffness and central

hemodynamics could be important contributing risk factors especially in early stages of life when other well-established conventional risk factor, like BP fail to predict further burden of CV disease. Of note AIx, the most widely used index for wave reflection, *rather than* PWV, which indicates arterial stiffness, appears to provide the best additional information. However, the evidence is still very limited and mainly based on cross-sectional data with no long-term follow-up available.

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