Premature Cardiac Aging in South Asian Compared to Afro-Caribbean Subjects in a Community-Based Screening Study

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Background—People of South Asian (SAs) and African Caribbean (AC) origin have increased cardiovascular morbidity, but underlying mechanisms are poorly understood. Aging is the key predictor of deterioration in diastolic function, which can be assessed by echocardiography using E/e′ ratio as a surrogate of left ventricular (LV) filling pressure. The study aimed to assess a possibility of premature cardiac aging in SA and AC subjects.

Methods and Results—We studied 4540 subjects: 2880 SA and 1660 AC subjects. All participants underwent detailed echocardiography, including LV ejection fraction, average septal-lateral E/e′, and LV mass index (LVMI). When compared to ACs, SAs were younger, with lower mean LVMI, systolic blood pressure (BP), diastolic BP, and body mass index (BMI), as well as a lower prevalence of hypertension and smoking ($P \leq 0.001$ for all). In a multivariate linear regression model including age, sex, ethnicity, BP, heart rate, BMI, waist circumference, LVMI, history of smoking, hypertension, coronary artery disease, diabetes mellitus, medications, SA origin was independently associated with higher E/e′ (regression coefficient±standard error, -0.66 ± 0.10; $P<0.001$, adjusted R^2 for the model 0.21; $P<0.001$). Furthermore, SAs had significantly accelerated age-dependent increase in E/e′ compared to ACs. On multivariable Cox regression analysis without adjustment for E/e′, SA ethnicity was independently predictive of mortality ($P=0.04$). After additional adjustment for E/e′, the ethnicity lost its significance value, whereas E/e′ was independently predictive of higher risk of death ($P=0.008$).

Conclusions—Premature cardiac aging is evident in SAs and may contribute to high cardiovascular morbidity in this ethnic group, compared to ACs. (*J Am Heart Assoc*. 2016;5:e004110 doi: 10.1161/JAHA.116.004110)

Key Words: aging • diastolic dysfunction • ethnicity • hypertension • left ventricular mass index

S
outh Asians (SAs) comprise one quarter of the world's population and represent a major minority ethnic group in many Western countries. Both native and migrant SAs have a high prevalence of cardiovascular disease and increased cardiovascular mortality.[1–5] This is partly attributable to high frequency of cardiovascular risk factors, particularly diabetes mellitus.[6] In the UK, SAs have a higher risk of coronary artery disease (CAD), compared to white Europeans, but an opposite trend is observed in people of African-Caribbean (AC) origin.[7] Of note, excess in cardiac morbidity in SAs is evident despite

adjustment for conventional cardiovascular risk factors, and they typically present with heart failure and require coronary interventions at a younger age compared to white subjects.[8,9] Also, the Framingham score, which developed in the white US population, failed to predict excess in cardiovascular mortality in SAs in the UK.[10,11] Initially, this was deemed attributable to lack of socioeconomic adjustment in the score.[12] However, a new QRISK2 score developed in the UK that accounts for deprivation was equally unreliable in ethnic minority groups.[13] Whereas the Framingham score underestimates risk among SAs, it overestimates outcome in the AC community, thus indicating intrinsic ethnic differences in prognostication beyond conventional risk factors.[13]

E/e′, a ratio of peak early diastolic mitral flow velocity and peak early diastolic mitral annulus tissue velocity, has been established as a noninvasive surrogate for left ventricular (LV) diastolic pressures.[14] E/e′ is widely used for grading LV diastolic function, and it has been uniformly shown to be reproducible in daily practice.[15] Numerous clinical studies have produced convincing evidence of a positive, linear relation of E/e′ and invasively measured mean LV diastolic pressure regardless of heart rhythm, heart rate, and LV ejection fraction (LVEF).[16–21] Indeed, E/e′ was more accurate

than natriuretic peptides for noninvasively determining LV diastolic pressures.[20] Also, E/e′ parallels changes in LV diastolic pressures during exercise.[22]

In addition to its relationship with filling pressure, E/e′ has a clear association with aging, even in healthy individuals, and can serve as a surrogate measure of cardiac aging.[23–25] However, no information is currently available on differences of age-related changes in E/e′ and presence of accelerated ageing in ethnic minority groups, as well as its role in prognostication.

The Ethnic-Echocardiographic Heart of England Screening Study (E-ECHOES) study was a cross-sectional population survey of subjects of SA origin (ie, from India, Pakistan, or Bangladesh) and AC origin age ≥45 years.[26] Study individuals were recruited from September 2006 to August 2009 from 20 primary care centers in Birmingham, UK, and the collected data included comprehensive clinical assessment and echocardiography.[26] In the present ancillary analysis to the E-ECHOES study, we assessed the presence of accelerated cardiac aging in SAs using E/e′ as a surrogate and its role in all-cause mortality, compared to AC subjects.

Methods

The analysis was performed using the E-ECHOES study population. Exclusion criteria were conditions known to affect utility of E/e′ ratio as an estimate of LV filling pressure: (1) moderate-severe aortic or mitral valve disease (stenosis or regurgitation), significant cardiac dyssynchrony attributed to LV conduction abnormalities (ie, QRS ≥140 ms). The analysis only included patients who had no missing data in the parameters used to establish the regression model described below. The E-ECHOES database has 5353 entries, of whom 813 met the exclusion criteria and 4540 patients have been included in the analysis.

The vast majority of the study participants were first-generation migrants who lived most of their life in the UK. Among the 2880 South Asian patients, 2625 (91%) were born in India, Pakistan, or Bangladesh, only 50 (1.7%) were born in the UK, with the rest (205; 7%) of the patients born in other parts of the world (mostly from East Africa). Mean age of settling in the UK was 26±13 years, and mean duration since coming to the UK was 35±12 years. Among the 1660 participants of AC origin, 1293 (78%) were born in the Caribbean islands (majority, 1104 [67%] in Jamaica), 291 (18%) in the UK, and 76 (5%) in other countries. Mean age of settling in the UK was 23±12 years, and mean duration since coming to the UK was 41±14 years.

The E-ECHOES study was approved by Walsall Local Research Ethics Committee (05/Q2708/45), with all participants having provided written informed consent for data collection and analysis. Cases of deaths and their causes were provided by the Office of National Statistics.

Echocardiography

All study participants underwent detailed echocardiographic analysis with images reviewed by a consultant cardiologist with expertise in echocardiography. Echocardiography was done in primary care settings using a portable VIVID i machine (GE Healthcare, Chalfont St Giles, UK). LVEF, dimensions of cardiac chambers, LV mass index (LVMI), and parameters of diastolic function (mitral valve E/A ratio; E-wave deceleration time; and isovolumic relaxation time, tissue Doppler imaging of lateral, and septal mitral valve annulus) were also measured in accord with current recommendations.[27] An average of septal and lateral E/e′ was calculated and used in the analysis.

Statistical Analysis

Descriptive data are presented as median (interquartile range; IQR) and compared using the Kruskal–Wallis test. Linear regression was used to establish predictors of E/e′ and left atrial diameter index (LADI) with the following predictor variables tested: age, sex, history of diabetes mellitus and smoking, systolic and diastolic blood pressure (BP), heart rate, body mass index (BMI), waist circumference, and LVMI. Cox regression analysis was used to establish predictors of all-cause mortality in the study population using the predictor variables above. *P* values of <0.05 were considered as statistically significant. STATA software (version 13; StatCorp LP, College Station, TX) was used for statistical analyses.

Results

Demographic characteristics of participants reflect distribution of ethnic minority groups in Birmingham (Table 1). When compared to ACs, SAs were younger, had lower systolic BP, diastolic BP, and BMI, as well as lower prevalence of hypertension and smoking (*P*≤0.001 for all). Diabetes mellitus was more common in SAs (30% vs 27%; *P*=0.005). Calcium-channel blockers and diuretics were more often used in ACs (*P*<0.001 for both). Consistently with lower rates of hypertension and blood pressure values, SAs had lower LVMI (117 [93–143] vs 103 [85–125] g/m^2 in ACs). ACs and SAs had similar low rates of reduced LVEF (<55%; 2% in both groups), and E/e′ was nonsignificantly different from ACs (*P*=0.85) in a nonunadjusted analysis.

The strongest predictors of E/e′ on multivariable regression analysis were high systolic BP (standardized β=0.22), advanced age (standardized β=0.20), higher LVMI

Table 1. Demographic Characteristics of the Study Population

	South Asians (n=2880)	African Caribbeans (n=1660)	P Value
Demographic and clinical characteristics			
Age, y	56 [51–66]	61 [50–72]	<0.001
Male	1380 [48%]	747 [44%]	0.02
SBP, mm Hg	138 [126–152]	143 [131–157]	<0.001
DBP, mm Hg	81 [74–88]	82 [75–90]	0.001
Heart rate, bits/min	78 [70–87]	76 [68–85]	<0.001
BMI, kg/m^2	28 [25–31]	29 [26–33]	<0.001
Waist circumference, cm	97 [90–104]	97 [88–105]	0.58
Hypertension, n	1254 [44%]	944 [57%]	<0.001
CAD, n	311 [11%]	86 [5%]	<0.001
Diabetes mellitus, n	878 [30%]	441 [27%]	0.005
History of heart failure	25 [1%]	18 [1%]	0.47
Chronic obstructive pulmonary disease, n	25 [1%]	15 [1%]	0.90
AF, n	17 [1%]	14 [1%]	0.32
History of smoking, n	653 [23%]	721 [43%]	<0.001
Medications			
Angiotensin conversion enzyme inhibitors or angiotensin receptor antagonists, n	651 [23%]	391 [24%]	0.46
Calcium-channel blockers, n	487 [17%]	599 [36%]	<0.001
Aldosterone antagonists, n	280 [10%]	180 [11%]	0.23
Beta-blockers, n	370 [13%]	199 [12%]	0.40
Diuretics, n	475 [16%]	506 [30%]	<0.001
Echocardiographic data			
Reduced ejection fraction <55%	70 [2%]	34 [2%]	0.41
E/e′ ratio	8.0 [6.3–10.2]	8.0 [6.5–9.9]	0.85
LVMI, g/m^2	103 [85–125]	117 [93–143]	<0.001
End-diastolic diameter index, cm/m^2	2.46 [2.26–2.69]	2.37 [2.17–2.59]	<0.001
LADI, cm/m^2	1.73 [1.55–1.91]	1.65 [1.46–1.85]	<0.001
Diastolic dysfunction, n	1683 [59%]	1023 [62%]	0.03

AF indicates atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; LADI, left atrial diameter index; LVMI, left ventricular mass index; SBP, systolic blood pressure.

(standardized β=0.19), and SA ethnicity (standardized β=0.10; $P<0.001$ for all; adjusted R^2 for the model, 0.21; Table 2). Relationship between age and E/e′ was polynomial with linear (F statistics, 124; $P<0.001$) and quadratic (F statistics, 22; $P<0.001$) components. On polynomial regression, SA ethnicity was associated with higher E/e′ for the whole model and for all age groups presented ($P<0.001$ for all; Figure 1).

There was a significant interaction between age and ethnicity in their relation to E/e′ (standardized β=0.36 for interaction; $P<0.001$; Figure 2). This interaction is suggestive that SA had a steeper age-related increase in adjusted regression slope of age-E/e′ relationship. Based on the

adjusted model, E/e′=8 is reached at age 46.3 years in SAs and at 53.4 years in ACs (ie, 7.1-year difference with South Asians). Further increase in 1 unit of E/e′ (ie, E/e=9) was reached at age 62.7 years in SAs and at 78.1 years in ACs (ie, 15.4 years later).

The model was additionally tested for possible interactions between ethnicity and presence of diabetes or CAD, but no such significant interactions were found (standardized β=0.04; $P=0.10$ for diabetes mellitus; standardized β=−0.03; $P=0.32$ for CAD). In this model, interactions between SA ethnicity and age remain highly significant (standardized β=0.42; $P<0.001$), supporting the presence of accelerated E/e′ increase in this ethnic group. The role of

Table 2. Independent Predictors of E/e′ in Multivariable Analysis (n=4540)

Parameter	Regression Coefficient±SE	Standardized β	P Value
SBP	0.04±0.003	0.22	<0.001
Age	0.06±0.01	0.20	<0.001
Female	1.27±0.11	0.19	<0.001
LVMI	0.01±0.001	0.11	<0.001
South Asian origin	0.66±0.10	0.10	<0.001
Diabetes mellitus	0.68±0.11	0.09	<0.001
DBP	−0.03±0.01	0.09	<0.001
History of smoking	0.37±0.11	0.05	0.001
Waist	0.01±0.01	0.04	0.04
CAD	0.38±0.18	0.03	0.03
Beta-blockers	0.32±0.16	0.03	0.04

CAD indicates coronary artery disease; DBP, diastolic blood pressure; LVMI, Left ventricular mass index; SBP, systolic blood pressure.
For the model, adjusted R^2=0.21, P<0.001.

ethnicity in predicting E/e′ was further tested in separate subgroups of subjects with and without diabetes mellitus and CAD. Independent association of SA ethnicity with higher E/e′ was evident in all 4 subgroups (Table 3). Analysis of interactions between ethnicity and age in patients had limited power in patients with diabetes mellitus (n=441 for AC patients with diabetes mellitus and n=86 of AC patients with CAD), especially given the ethnic difference in age distributions. Interactions between SA ethnicity and age were highly
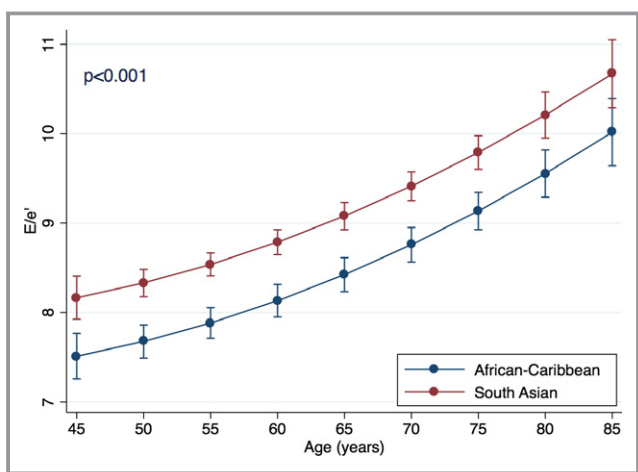

Figure 1. Relationship between age and E/e′ in ethnic groups. The figure presents multivariable polynomial regression showing predictive value of ethnicity for E/e′ across the different age groups. The analysis is based on the model presented in Table 2, with an additional adjustment of the polynomial component of age-related effects. Also, age was categorized by groups with 5-year increments, which are presented as the graph points. Error bars are 95% CIs for the correspondent graph points.
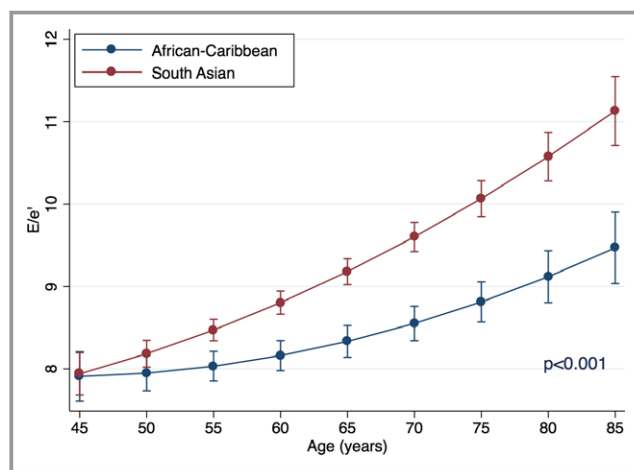

Figure 2. Interactions of age and ethnicity for prediction for E/e′. Point estimates are values of the regression line at age groups categorized by 5-year increments. Error bars are 95% CIs for the correspondent graph points.

significant in subjects without diabetes mellitus (standardized β=0.39; P<0.001) and without CAD (standardized β=0.42; P<0.001), but such interactions were not significant in patients with diabetes mellitus (standardized β=0.21; P=0.18) and CAD (standardized β=−0.47; P=0.17; Figure 3).

Also, on multivariable regression, SA ethnicity was the strongest significant predictor of increased LADI among all variables (standardized β=0.20; P<0.001). Similar to E/e′, the relationship between age and LADI was polynomial, with linear (F statistics 91; P<0.001) and quadratic (F statistics 4; P=0.04) components. On polynomial regression, SA ethnicity was associated with higher LADI for the whole model (standardized β=0.20; P<0.001) and for all age groups presented (P<0.001 for all; Figure 4). There was no significant interaction between age and ethnicity in their relation to LADI (standardized β=0.07 for interaction; P=0.41; Figure 5). SA ethnicity was strongly associated with increased LADI already at the youngest test age (ie, 45 years), and the association remain throughout the whole included age range.

After a median follow-up of 5.8 years (IQR, 5.2–6.5), 241 (5.3%) participants died from any cause. On multivariable Cox regression analysis without adjustment for E/e′, independent predictions of mortality were SA ethnicity, advanced age, history of CAD and smoking, higher heart rate, BMI, and use of diuretics (Table 4). After additional adjustment for E/e′, ethnicity lost its statistical significance, whereas E/e′ was independently predictive of higher risk of death (other significant predictors remained unchanged). When the same model was fitted with dichotomized E/e′, values of E/e′ ≥10 were independently associated with higher risk of death (hazard ratio [HR], 1.34; 95% CI, 1.04–1.83; P=0.027; Figure 6).

Table 3. Subgroup Analysis of Predictive Value of South Asian Ethnicity for E/e′ (Multivariable Linear Regression)

	South Asian Subjects (n)	African Caribbean Subjects (n)	Regression Coefficient±Standard Error	Standardized β	P Value
Diabetes mellitus*					
Present	878	441	1.53±0.23	0.19	<0.001
Not present	2002	1219	0.35±0.20	0.57	<0.001
CAD†					
Present	311	86	1.26±0.54	0.12	0.02
Not present	2569	1574	0.61±10	0.09	<0.001

CAD indicates coronary artery disease.

*Variables included in the multivariable analysis: age, sex, history of smoking, systolic and diastolic blood pressure, heart rate, body mass index, waist circumference, and left ventricular mass index.

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Discussion

The study shows, for the first time, that SAs have accelerated cardiac aging, as suggested by changes in E/e′. When E/e′ is used as a surrogate of premature aging after adjustment for risk factors, diastolic dysfunction, and chronological aging, the study findings provide some explanation on why people of SA origin have increased cardiovascular risk even after
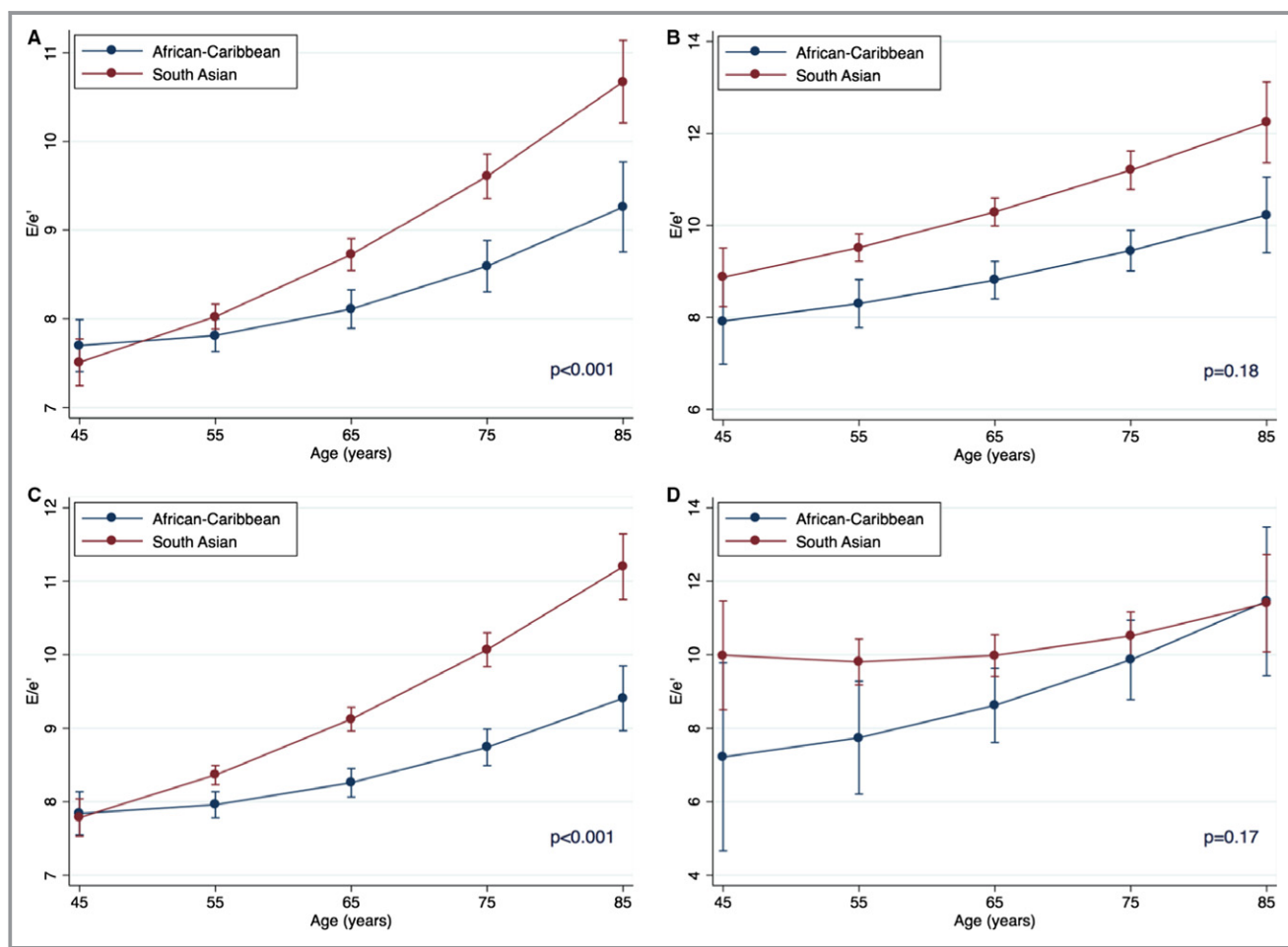

Figure 3. Interactions of age and ethnicity for prediction for E/e′ in subgroups. A, Without diabetes mellitus (SA, n=2002; AC, n=1219). B, With diabetes mellitus (SA, n=878; AC, n=441). C, Without coronary artery disease (SA, n=2569; AC, n=1574). D, With coronary artery disease (SA, n=311; AC, n=86). Point estimates are values of the regression line at age groups categorized by 5-year increments. Error bars are 95% CIs for the correspondent graph points. AS indicates African-Caribbean origin; SA, South Asian origin.
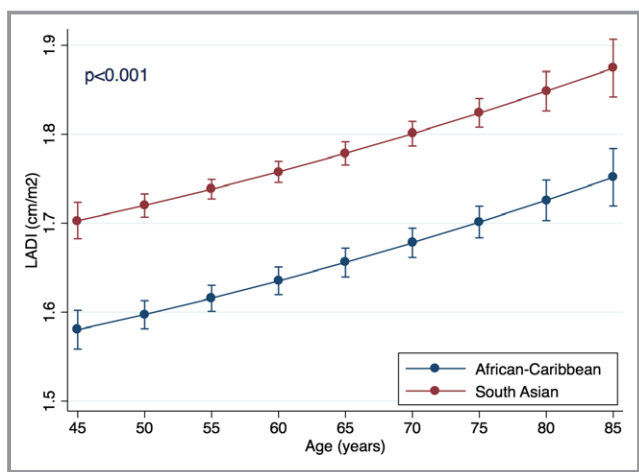
Figure 4. Relationship between age and left atrial diameter index (LADI) in ethnic groups. Point estimates are values of the regression line at age groups categorized by 5-year increments. Error bars are 95% CIs for the correspondent graph points.
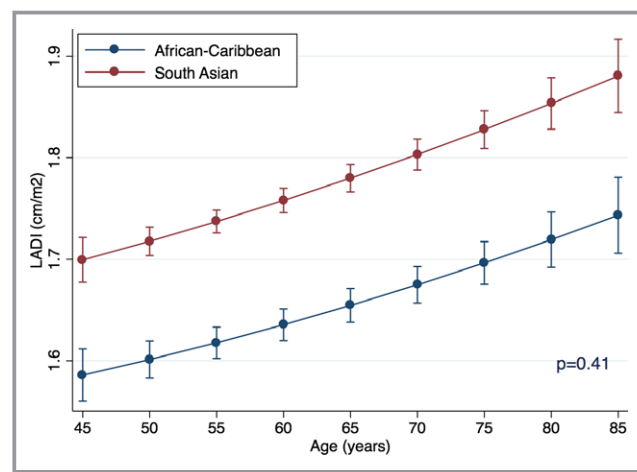

Figure 5. Interactions of age and ethnicity for prediction for left atrial diameter index (LADI). *P* value for interaction. Point estimates are values of the regression line at age groups categorized by 5-year increments. Error bars are 95% CIs for the correspondent graph points.

accounting for standard cardiovascular risk factors.[10,11] Indeed, SAs reached E/e′ of 8, a value commonly considered as a cutoff for normal range, at a younger mean age of 7.1 years compared to ACs (ie, an ethnic group with an excellent longevity profile in the UK).[13]

Evidence of high clinical significance of even mild diastolic dysfunction with relatively low E/e′ comes from the Olmsted population-based study of subjects aged ≥45 years, where mild diastolic dysfunction with E/e′ <10 was present in 21% of participants and was strongly and independently predictive of all-cause mortality (HR, 8.31; 95% CI, 3.00–23.1; *P*<0.001).[28] In our study, there was a highly significant interaction between SA ethnicity and the age-related increase in E/e′. This means than SA had much more prominent acceleration in the E/e′ elevation with advanced age compared to ACs. In fact, E/e′ of 9 was reached, on average, 15.4 years younger than ACs. Although these relatively low E/e′ values may not signify a clinically relevant increase in LV filling pressure in healthy subjects, they may significantly contribute to development of cardiac complications in people with predisposing factors, such as hypertension and CAD.

Moreover, E/e′ was independently predictive of an increased risk of death, and SA ethnicity lost its independent predictive value for mortality after adjustment for E/e′. This, again, supports clinical relevance of accelerated aging in SAs reflected by E/e′ as a prognosticator.

At present, there are no universally accepted clinical markers of cardiac aging. Although many cardiac parameters show changes in with age (eg, increase in LV dimensions and wall thickness), it is difficult to distinguish contributions of aging per se from those related to age-related changes in blood pressure or hemoglobin levels, given that the observed age-related changes are usually small. Among all age-related cardiac changes, shifts in parameters of diastolic function (eg, E/A mitral flow ratio) are most prominent and widely acknowledged. However, many parameters of diastolic dysfunction change bidirectionally with progression of diastolic dysfunction. For example, E/A decreases and isovolumic relaxation time and early mitral inflow deceleration time increase in mild diastolic dysfunction, whereas opposite changes are observed in more-advanced stages. This makes analysis of continuity of the changes problematic. E/e′ offers the advantage of unidirectional, relatively linear changes with increase in LV filling pressure, and E/e′ has a clear relation to aging in healthy subjects.[29]

In order to minimize the effect of age-related hemodymanic changes (eg, gradual increase in BP even in healthy subjects), we constructed regression models adjusted for history of hypertension, BP, and, most important, LVMI. Unsurprisingly, LVMI itself was strongly predictive for higher E/e′ and mortality, but adjustment for this parameter lets us speculate that the observed ethnic differences occurred attributed to other mechanisms that result in delayed myocardial relaxation secondary to thickened myocardium. Indeed, this observation points toward age-related modulation of cardiac extracellular matrix (ie, fibrosis) or diminished elastic properties/relaxation speed of cardiomyocytes.

Although there were no significant interactions between ethnicity and diabetes mellitus or CAD in prediction of E/e′ on regression analysis, and SA origin was uniformly linked to higher E/e′ in people with or without diabetes mellitus or CAD, subgroup analyses showed that interactions between ethnicity and age were largely confined to subjects without diabetes mellitus or CAD. It is likely (and not unexpected) that the magnitude of diabetes mellitus/CAD-induced cardiac

Table 4. Independent Predictors of All-Cause Mortality (Cox Regression)

Independent Predictors	Without Adjustment for E/e′		With Adjustment for E/e′	
	HR [95% CI]	*P* Value	HR [95% CI]	*P* Value
South Asian ethnicity	1.38 [1.02–1.88]	0.04		
E/e′			1.04 [1.01–1.07]	0.008
Age, per y	1.08 [1.06–1.09]	<0.001	1.08 [1.06–1.09]	<0.001
CAD	1.59 [1.10–2.29]	0.01	1.58 [1.10–2.28]	0.01
Smoking	1.60 [1.18–2.17]	0.003	1.55 [1.14–2.11]	0.005
Heart rate, per 1 bpm	1.02 [1.01–1.03]	<0.001	1.02 [1.01–1.03]	<0.001
BMI, per kg/m^2	0.95 [0.91–0.99]	0.02	0.95 [0.91–0.99]	0.02
LVMI, per g/m^2	1.01 [1.00–1.01]	<0.001	1.00 [1.00–1.01]	0.002
Diuretics	1.56 [1.15–2.11]	0.004	1.56 [1.15–2.11]	0.004

BMI indicates body mass index; bpm, beats per minute; CAD, coronary artery disease; HR, hazard ratio; LVMI, left ventricular mass index.

changes reflected by E/e′ was more substantial compared to more-subtle effects of aging. A substantially bigger population would be required to specifically assess contribution of aging to cardiac changes in individuals with overt heart disease or diabetes mellitus.

In support of E/e′-based conclusions, SA origin was a strong independent predictor of larger left atrial size across all tested age groups. However, the pattern of age-related effects was different from those observed for E/e′. Whereas ethnic difference in E/e′ was relatively modest at the youngest tested age and SAs had a clear acceleration of E/e′ elevation with more-advanced age, prominent ethnic differences were already observed for LADI age 45 years and the magnitude of these changes remained constant in older people. The precise explanations of differences are not clear, but they could be attributed to a larger number of hemodynamic influences for atrial size.
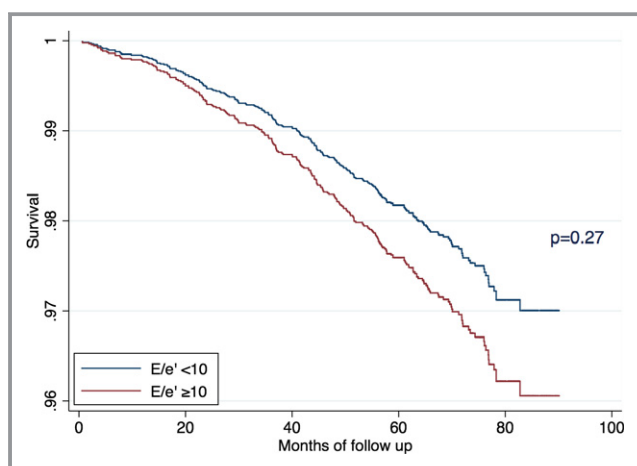

Figure 6. Predictive value of E/e′ ≥10 for all-cause mortality in a multivariable Cox regression analysis.

Limitations

Because of lack of accepted clinical markers of cardiac aging, E/e′ was used as a surrogate measure of aging. It was beyond the scope of the present work to provide mechanistic insights into the background processes of aging. The analysis of association of SA ethnicity with premature aging was based on observational study, and a prospective analysis would ideally be required. Although E/e′ is accepted as a noninvasive measure of LV filling pressures, recent studies found that the correlation between E/e′ and pulmonary capillary wedge pressure may be worse than previously reported, and a novel, more-advanced echocardiographic technique may be a preferable choice for future research.[30–33]

Perspectives

People of SA origin are at increased risk of cardiovascular morbidity and mortality. This cannot be fully explained by their profile of standard cardiovascular risk factors. SAs often present with cardiac pathology at a younger age than other ethnic groups. Premature cardiac aging is evident in SAs and may contribute to high cardiovascular morbidity in this ethnic group, compared to ACs. This opens a new direction in the understanding of "unexplained" excess in cardiac morbidity in certain populations. Further mechanistic studies are needed to provide insights into mechanisms of cardiac aging in SAs. Scarce methods for quantification of cardiac senescence are available at present, and this study encourages further development in the field.

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Disclosures

None.

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