Hyperglycemia Has a Greater Impact on Left Ventricle Function in South Asians Than in Europeans

Chloe M. Park,[1] Therese Tillin,[1] Katherine March,[1] Arjun K. Ghosh,[1] Siana Jones,[1] Andrew Wright,[1] John Heasman,[1] Darrel Francis,[1] Naveed Sattar,[2] Jamil Mayet,[1] Nish Chaturvedi,[1] and Alun D. Hughes[1]

OBJECTIVE

Diabetes is associated with left ventricular (LV) diastolic and systolic dysfunction. South Asians may be at particular risk of developing LV dysfunction owing to a high prevalence of diabetes. We investigated the role of diabetes and hyperglycemia in LV dysfunction in a community-based cohort of older South Asians and white Europeans.

RESEARCH DESIGN AND METHODS

Conventional and Doppler echocardiography was performed in 999 participants (542 Europeans and 457 South Asians aged 58–86 years) in a population-based study. Anthropometry, fasting bloods, coronary artery calcification scoring, blood pressure, and renal function were measured.

RESULTS

Diabetes and hyperglycemia across the spectrum of HbA_{1c} had a greater adverse effect on LV function in South Asians than Europeans (N-terminal-probrain natriuretic peptide β ± SE 0.09 ± 0.04, $P = 0.01$, vs. −0.04 ± 0.05, $P = 0.4$, P for HbA_{1c}/ethnicity interaction 0.02), diastolic function (E/e′ 0.69 ± 0.12, $P < 0.0001$, vs. 0.09 ± 0.2, $P = 0.6$, P for interaction 0.005), and systolic function (s′ −0.11 ± 0.06, $P = 0.04$, vs. 0.14 ± 0.09, $P = 0.1$, P for interaction 0.2). Multivariable adjustment for hypertension, microvascular disease, LV mass, coronary disease, and dyslipidemia only partially accounted for the ethnic differences. Adverse LV function in diabetic South Asians could not be accounted for by poorer glycemic control or longer diabetes duration.

CONCLUSIONS

Diabetes and hyperglycemia have a greater adverse effect on LV function in South Asians than Europeans, incompletely explained by adverse risk factors. South Asians may require earlier and more aggressive treatment of their cardiometabolic risk factors to reduce risks of LV dysfunction.

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[1]National Heart and Lung Institute, Faculty of Medicine, Imperial College Academic Health Sciences Centre, London, U.K.
[2]Metabolic Medicine, University of Glasgow School of Medicine, Glasgow, U.K.

Corresponding author: Chloe M. Park, chloe.park@imperial.ac.uk.

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Diabetes is a major risk factor for cardiovascular disease (CVD) and heart failure (1), which is of increasing importance as a consequence of increasing diabetes prevalence and aging populations. However the existence of a distinct diabetes-related cardiomyopathy, specifically as a consequence of hyperglycemia, is controversial (2–4). Understanding the underlying mechanisms driving the association between diabetes and left ventricular (LV) function is greatly assisted by studying ethnic minority groups where risk factor clustering markedly differs.

South Asians across the world have a substantially elevated risk of diabetes. In comparison with European-origin populations, diabetes prevalence is fourfold greater; by the age of 80 years, one in two South Asians will have developed diabetes compared with only one in five Europeans (5). We have reported that diabetes increases the risk of stroke and ischemic heart disease to a greater extent in South Asians than Europeans (6) for reasons that are unclear. It is unknown whether diabetes also exerts a more adverse impact of LV function and risk of heart failure in South Asians.

The comparative risk of heart failure has not been measured directly but could be as much as fivefold higher in South Asians (7), and there is growing evidence that survival, severity, and etiology of heart failure also differ by ethnicity (8). Both LV systolic dysfunction (LVSD) and diastolic dysfunction (LVDD) are independent risk factors for development of heart failure and cardiac death (9,10). Heart failure in middle-age is rare but emerges with older age and with population aging. Studying risk factor associations with subclinical disease may shed light on underlying risks and mechanisms and avoid the problem of medication for heart failure altering the nature of their outcomes.

Ethnic differences in prevalence and severity of LV dysfunction have been reported (8,11–13); however, these reports are from selected populations with established disease or with all morbidities excluded and therefore cannot fully explore the role of diabetes and hyperglycemia in accounting for ethnic differences in risk (14–17). Given the elevated rates of diabetes and adverse CVD risk factors in South Asians, previous studies excluding individuals with known CVD or risk factors (13) may have therefore resulted in biased comparisons.

We therefore aimed to test the hypotheses that diabetes and the spectrum of hyperglycemia would be associated with measures of LV dysfunction and that these relationships would differ by ethnicity. We also sought to establish whether established risk factors could account for any ethnic differences observed in these associations.

RESEARCH DESIGN AND METHODS

Study Population

A population-based sample of 1,206 men and women of white European and South Asian ethnicity was recruited from the Southall and Brent REvisited (SABRE) cohort. SABRE recruited between 1988 and 1991 between the ages of 40 and 69 years from West London primary care registers (18). Random selection of participants was made from 5-year age- and sex-stratified primary care physician lists and workplaces in the London districts of Southall and Brent. This article presents a cross-sectional analysis derived from the 20-year follow-up data. All surviving participants were invited to participate in the follow-up study; the only exclusion criterion was if patients were not able to give informed consent. At the follow-up clinic in 2008–2011, participants were aged 59–86 years. Ethics committee approval was obtained, and all participants gave written informed consent. Ethnicity was assigned by clinic staff and confirmed by participants. All South Asians were first-generation migrants from the Indian subcontinent, and the majority were of Punjabi origin. Participants were fasted for 12 h and refrained from medication on the morning of their visit. They completed a questionnaire detailing health behaviors, morbidity, and medications.

Clinic Data and Blood/Urine Measurements

Height, weight, waist and hip circumference, and blood pressure were measured under standardized conditions (18), and the waist-to-hip circumference ratio (WHR) was calculated. Fasting samples were analyzed for blood glucose, glycosylated hemoglobin (HbA_{1c}), insulin, triglycerides, and total and HDL cholesterol, and the total cholesterol–to–HDL cholesterol ratio was calculated. Serum N-terminal-probrain natriuretic peptide (NT-proBNP) was measured using an Elecsys 2010 electrochemiluminescence analyzer (Roche Diagnostics, Burgess Hill, U.K.) calibrated using the manufacturer's reagents. A spot early-morning urine sample was measured for albumin and creatinine. Microalbuminuria was defined as an albumin-to-creatinine ratio $>$2.5 mg/mol for men and $>$3.5 mg/mol for women. Established diabetes was diagnosed as patient or GP reported and defined according to the 1999 World Health Organization guidelines (19). Those without known diabetes underwent an oral glucose tolerance test. Diabetes duration was established by questionnaire. Hypertension was defined as physician-diagnosed hypertension or participant-reported hypertension in people receiving blood pressure–lowering medication.

Two-Dimensional and Conventional and Tissue Doppler Echocardiography

Transthoracic two-dimensional (2D) and Doppler echocardiography was performed as previously described (20) to assess both systolic and diastolic function on 602 Europeans (88%) and 480 South Asians (92%). Left atrial diameter was measured and indexed to $height^{2.7}$ (LADi). Full Doppler echocardiography could not be performed on 84 individuals with poor acoustic windows (8%) or 40 individuals in atrial fibrillation (4%). Transmitral flow velocity during the early filling phase (E), its deceleration time (DT) (a measure of LV relaxation), and the late filling phase (A) was acquired by pulsed Doppler and averaged from three consecutive cycles. Tissue Doppler echocardiography was performed on the lateral and septal LV wall. Peak velocities during systole (s′) early diastole (e′) and late diastole (a′) were averaged from three consecutive cycles. The s′, e′, and a′ wave velocities taken

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from the lateral and septal walls were averaged. Intra- and interobserver reproducibility of echocardiographic measures was assessed by separate scans (on different days) performed in 10 participants selected at random. Intra- and interobserver reproducibility was excellent for all key measures (intraclass correlation coefficients >0.80).

Calculated Variables

Doppler Variables

The ratio of the transmitral early and late filling phases (E:A) was calculated as a measure of diastolic function. The ratio of early filling and early myocardial velocity (E/e′) was calculated as a noninvasive index of LV filling pressure.

2D Echocardiography Variables

LV mass was calculated as previously described (21).

$$\text{LV mass} = 0.8\times\left(1.04\times\left((\text{IVS}(d)+\text{LVID}(d)+\text{PWT}(d)\right)^3\text{-}\text{LVID}(d)\right)^3+0.6$$

LV mass and left atrial diameter were indexed to height$^{2.7}$ (LV mass index [LVMI]) (22). Ejection fraction (EF) was calculated as a measure of systolic function.

$$\text{EF}=(\text{stroke volume}/\text{end-diastolic volume})\times 100$$

LV Dysfunction

To establish the burden of prevalent disease for cross-study comparison, systolic dysfunction was defined as EF <50%. Diastolic dysfunction was assessed on the basis of the tissue Doppler mitral annular velocities and the Doppler measures of mitral inflow. Cutoffs conformed to guidelines for diastolic function (23).

Key Measures of Function

Key measures were selected a priori and analyzed as continuous variables. With use of newer echocardiographic measures, which are more precise and less prone to pseudonormalization, our key comparator was s′ for longitudinal systolic function and E/e′ for diastolic function. NT-proBNP levels indicated LV global dysfunction (24).

Coronary Artery Calcification Score and Coronary Heart Disease

Coronary artery calcification score (CACS) was acquired using a Philips 64 slice CT scanner as previously described (25). Scans were read by an experienced radiographer blinded to participant ethnicity and other characteristics. The intraclass correlation coefficient was >0.9. CACS were combined with coronary heart disease (CHD) information to create a combined clinical/subclinical CHD variable, labeled CACS/CHD. Categories were based on previously accepted cut points. Category 1 included individuals with minimal CACS (<10 arbitrary units [AU]) and no CHD, category 2 included individuals with moderate CACS (10–400 AU) and no CHD, and category 3 included individuals with severe CACS (>400 AU) or prevalent CHD, defined as a coronary event or revascularization identified by medical record review and adjudicated by an independent committee (6).

Data Analysis

Statistical analyses were performed using Stata 12.0. Of the 1,206 (684 Europeans and 522 South Asians) attending clinic, 1,082 (602 Europeans and 480 South Asians) underwent 2D and Doppler echocardiography. Of these, 999 (542 Europeans and 457

Table 1—Participant demographics and LV functional measures

	European	South Asian	*P*
n	542	457	
Male, *n* (%)	419 (77)	387 (85)	0.003
Age (years)	69.8 ± 6.3	68.9 ± 6.1	0.03
BMI (kg/m^2)	27.6 ± 4.6	26.2 ± 3.7	<0.0001
WHR	0.97 ± 0.07	1.00 ± 0.07	<0.0001
CHD/CACS >400 AU	76 (14)	132 (29)	<0.0001
Microalbuminuria, *n* (%)	76 (14)	100 (22)	0.001
Hypertension, *n* (%)	295 (54)	341 (75)	<0.0001
SBP (mmHg)	138 ± 17	142 ± 18	0.001
DBP (mmHg	77 ± 10	76 ± 10	0.2
HR	68 ± 12	67 ± 13	0.09
NGT, *n* (%)	310 (57)	179 (40)	<0.0001
IGT/IFG, *n* (%)	133 (25)	89 (19)	<0.0001
Diabetes, *n* (%)	99 (18)	189 (41)	<0.0001
Diabetes duration (years)	4.5 (0, 9)	9.0 (2, 19)	0.001
Fasting glucose (mmol/L)	5.1 (4.8, 5.6)	5.3 (4.8, 6.1)	0.0001
HbA_{1c} (%)	5.9 (5.6, 6.2)	6.2 (5.9, 6.9)	<0.0001
HbA_{1c} (mmol/mol)	41 (38, 44)	44 (41, 52)	<0.0001
Insulin (pmol/L)	8.4 (5.4, 13)	9.7 (6.2, 15)	0.01
Fasting triglycerides (mmol/L)	1.14 (0.9, 1.5)	1.21 (0.9, 1.7)	0.02
Cholesterol:HDL (mmol/L)	3.5 (2.9, 4.2)	3.4 (2.8, 4.2)	0.6
LVMI-2D (g/m$^{2.7}$)	43.7 ± 12	42.0 ± 11	0.02
LVSD (%)	118 (22)	93 (20)	0.6
EF (%)	61 ± 10	62 ± 9	0.4
Peak s′ (cm/s)	7.80 ± 1.4	7.46 ± 1.4	<0.0001
LVDD, *n* (%)	511 (94)	422 (92)	0.2
E:A	0.84 ± 0.2	0.89 ± 0.3	0.005
DT (ms)	245 ± 51	236 ± 50	0.006
Peak e′ (cm/s)	7.21 ± 1.8	7.20 ± 1.8	0.9
E/e′	8.75 ± 2.8	9.85 ± 3.1	<0.0001
LADi (cm/ m$^{2.7}$)	0.96 ± 0.2	0.99 ± 0.2	0.0007
NT-proBNP (pg/mL)	134 (123–149)	150 (136–164)	0.2
NT-proBNP adjusted for LV mass	131 (118–144)	156 (141–170)	0.02

Data are mean ± SD, median (interquartile range) for skewed data, *n* (%) for categorical data, and mean (95% CI) for NT-proBNP. DBP, diastolic blood pressure; HR heart rate; IGT impaired glucose tolerance; IFG, impaired fasting glucose; NGT, normal glucose tolerance; peak e′, mitral annular early peak diastolic velocity; peak s′, mitral annular peak systolic velocity; SBP, brachial systolic blood pressure.

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South Asians) had full covariate data. Participant characteristics are reported as mean ± SD, median (interquartile range) for skewed data, and *n* (%) for categorical data. Ethnic group comparisons were made using ANOVA or covariance (ANCOVA). Covariates (age, sex, heart rate, hypertension, ratio of total cholesterol to HDL, WHR, microalbuminuria, clinical/subclinical CHD, and LV mass) were chosen a priori based on their known influence on LV function (26). For related variables (e.g., BMI and WHR), the single variable that most attenuated the ethnic difference was retained in the final model. Significance was assigned at $P < 0.05$. We previously showed important ethnicity × diabetes interactions for clinical end points (CVD events and stroke) (6) and hypothesized that these would be present for subclinical disease. Ethnic differences in systolic and diastolic function were similar in men and women, so sexes were combined for analysis.

RESULTS

Participant Characteristics

Mean age was ~69 years (Table 1). South Asians had a greater prevalence and duration of type 2 diabetes ($P < 0.0001$), and more frequent clinical plus subclinical CHD ($P < 0.0001$), microalbuminuria ($P = 0.001$), and hypertension ($P < 0.0001$) than Europeans. They also had more adverse lipid profiles (triglycerides, $P = 0.02$), were hyperinsulinemic ($P = 0.01$), and were more centrally obese (WHR, $P < 0.0001$).

LV Measures

NT-proBNP was nonsignificantly higher in South Asians than Europeans ($P = 0.2$). On adjustment for LV mass, this ethnic difference increased and became statistically significant ($P = 0.02$) (Table 1).

South Asians had reduced LVMI compared with Europeans ($P = 0.02$). While there was no ethnic difference in prevalence of systolic dysfunction (LVSD, $P = 0.6$) as assessed by EF, peak s′ was significantly lower in South Asians than Europeans ($P < 0.0001$) (Table 1). Diastolic dysfunction, largely mild, was common in both ethnic groups ($P = 0.2$) (Table 1). E:A and E/e′ were significantly higher in South Asians than Europeans (E:A, $P = 0.005$; E/e′, $P < 0.0001$). DT was significantly reduced in South Asians ($P = 0.006$) and LADi was significantly larger ($P = 0.0007$) (Table 1).

LV Function and HbA_{1c} Within Ethnic Groups

Statistically significant interactions between glycemic status and ethnicity on key measures of LV function were observed, and therefore associations between glycemia and function were analyzed separately by ethnicity.

Glycated hemoglobin was not related to any measure of LV function in Europeans (NT-proBNP β [SE] −0.04 [0.05], $P = 0.4$; E/e′ 0.09 [0.2], $P = 0.6$; and peak s′ 0.14 [0.09], $P = 0.1$) (Table 2) but was strongly and adversely associated with functional measures in South Asians (NT-proBNP 0.09 [0.04], $P = 0.01$; E/e′ 0.69 [0.12], $P < 0.0001$; and peak s′ −0.11 (0.06), $P = 0.04$). After further adjustment for key cardiometabolic risk factors (heart rate, hypertension, total cholesterol–to–HDL ratio, WHR, microalbuminuria, CHD/CACS, and LV mass), the significant association between HbA_{1c} and E/e′ in South Asians remained (0.52 [0.12], $P < 0.0001$); however, the associations with peak s′ (−0.06 [0.05], $P = 0.3$) and NT-proBNP (0.02 [0.04], $P = 0.5$) were attenuated. Full regression results are presented in Supplementary Table 1 for Europeans and Supplementary Table 2 for South Asians.

Exploration of Interactions Between Ethnic Group and HbA_{1c}/Glucose Tolerance Categories

For most measures of LV function, worsening glycemic status had a more adverse effect on LV function in South Asians than Europeans, which was statistically significant when tested as an interaction. Across glucose tolerance categories, interaction tests were β (SE) 0.14 (0.06), $P = 0.02$, for NT-proBNP; 0.46 (0.22), $P = 0.03$, for E/e′; and −0.05 (0.10), $P = 0.6$, for s′ (Fig. 1*A*–*C*). Multivariable adjustment for age, sex, heart rate, hypertension, total cholesterol–to–HDL ratio, WHR, microalbuminuria, CHD/CACS, and LV mass did not abolish the statistically significant interaction for NT-proBNP (β [SE] 0.14 [0.06], $P = 0.02$) but did slightly attenuate the E/e′ interaction (0.39 [0.21], $P = 0.06$).

Similarly, HbA_{1c} also had a significantly greater adverse impact on all three measures of LV function in South Asians than Europeans (NT-proBNP interaction β [SE] 0.14 [0.06], $P = 0.02$; E/e′ 0.58 [0.21], $P = 0.005$; and s′ −0.24 [0.10], $P = 0.02$) (Fig. 1*D*–*F*). These interactions remained statistically significant on multivariate adjustment (NT-proBNP 0.14 [0.06], $P = 0.01$; E/e′ 0.62 [0.20], $P = 0.002$; and s′ −0.21 [0.10], $P = 0.03$). Full interaction details are presented in Supplementary Table 3.

The greater adverse effect of hyperglycemia on LV function in South Asians could be due to their longer duration of exposure. Diabetes duration was almost twofold greater in South Asians (Table 1). In people with diabetes, diabetes duration associated significantly with higher NT-proBNP (β [SE] 4.4 [1.2], $P < 0.0001$) and E/e′ (0.08 [0.2], $P = 0.001$) and with slightly poorer s′ (−0.01 [0.01] cm/s, $P = 0.3$). These associations were independent of the

Table 2—Association between measures of LV function and HbA_{1c} stratified by ethnicity

	European (*n* = 542)		South Asian (*n* = 457)	
	β (SE)	*P*	β (SE)	*P*
NT-proBNP (pg/mL)				
Model 1	−0.04 (0.05)	0.4	0.09 (0.04)	0.01
Model 2	−0.08 (0.05)	0.08	0.02 (0.04)	0.5
E/e′				
Model 1	0.09 (0.2)	0.6	0.69 (0.12)	<0.0001
Model 2	−0.13 (0.17)	0.4	0.52 (0.12)	<0.0001
Peak s′ (cm/s)				
Model 1	0.14 (0.09)	0.1	−0.11 (0.06)	0.04
Model 2	0.16 (0.09)	0.06	−0.06 (0.05)	0.3

Data are β (SE). Model 1, adjusted for age and sex; model 2, adjusted for age, sex, heart rate, hypertension, ratio of total cholesterol to HDL, WHR, microalbuminuria, clinical/subclinical CHD, and LV mass.

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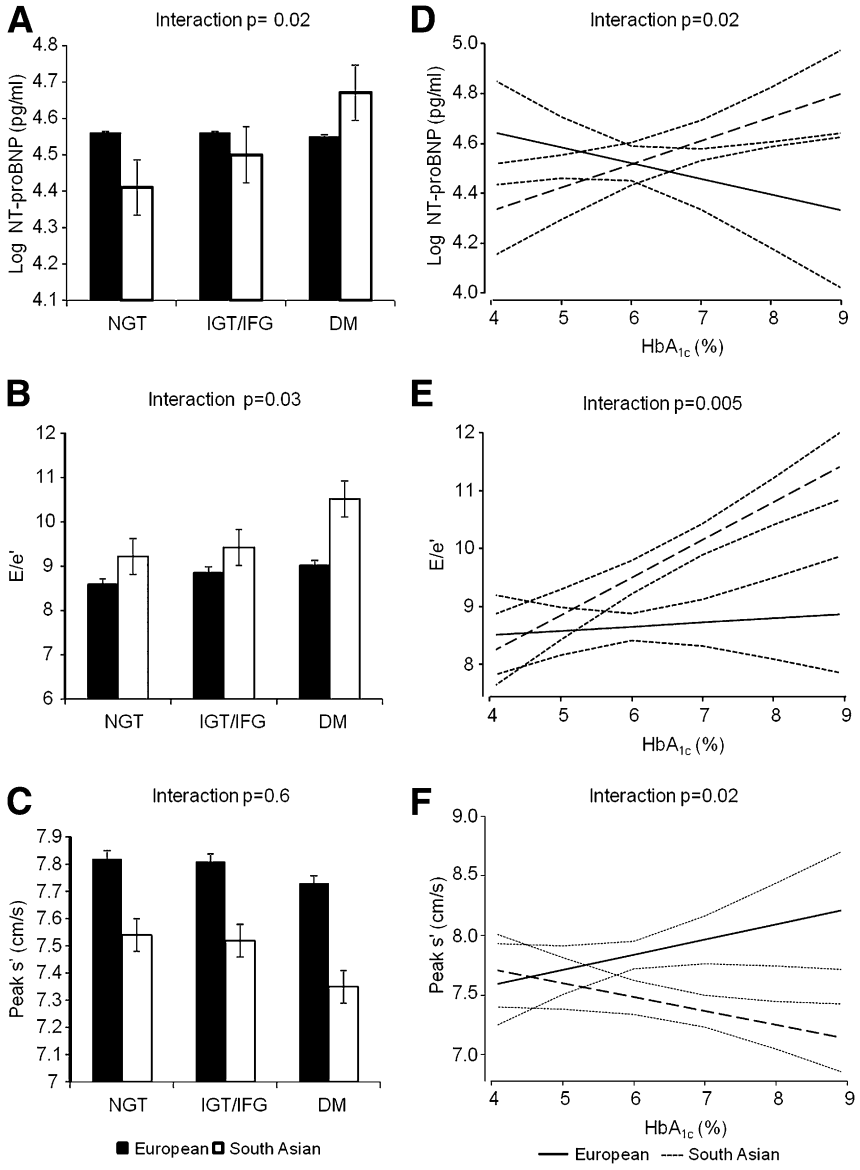

Figure 1—*A–C*: Bar charts showing mean values for LV functional measures divided by diabetes status and ethnicity. NT-proBNP (*A*), E/e′ (*B*), and peak s′ (*C*) (age and sex adjusted). *P* values are for ethnicity × glucose tolerance category interactions. *D–F*: Predicted LV function (95% CI) by HbA_{1c} in South Asians and Europeans. All values adjusted for age and sex. Log-transformed NT-proBNP (*D*), E/e′ (*E*), and peak s′ (*F*). *P* values are for ethnicity × HbA_{1c} interactions. DM, diabetes.

effect of HbA_{1c} for NT-proBNP ($P = 0.001$) and E/e′ ($P = 0.004$). However, when we compared NT-proBNP, E/e′, and s′ by ethnicity in those with established diabetes (where diabetes duration can be estimated), we found that adjustment for diabetes duration, and for HbA_{1c}, could account for little of the ethnic difference in observed function (Table 3 and Supplementary Table 4). In those with established diabetes, we also found that the interactions between glycemic status and ethnicity on key measures of LV function (NT-proBNP 0.24, $P = 0.05$; E/e′ 0.59, $P = 0.2$; and s′ −0.38, $P = 0.04$) remained after further adjustment for diabetes duration (NT-proBNP 0.26, $P = 0.04$; E/e′ 0.77, $P = 0.1$; and s′ −0.45, $P = 0.02$).

CONCLUSIONS

Diabetes and hyperglycemia across the spectrum of HbA_{1c} into the normal range have a far more adverse effect on global (NT-proBNP), diastolic (E/e′), and systolic (s′) ventricular function in South Asians than Europeans; hyperglycemia appeared to have little relationship with LV function in Europeans. The association between worse glycemic status and LV function in South Asians could largely (particularly for systolic and global function) be accounted for by concomitant cardiometabolic risk factors such as hypertension, presence of clinical and subclinical CHD, microalbuminuria, dyslipidemia, and central obesity. Previous studies have shown that systolic or diastolic LV dysfunction are relatively common in older people (10) and independently predict heart failure (9,27) and total mortality (10,28) in European general population samples; e.g., mild diastolic dysfunction was associated with a more than eightfold increase in hazard of all-cause mortality in people aged 45 years or older (10). To our knowledge, no previous study has investigated ethnic differences in the relationship between glycemic status and LV function, but our findings could help to explain the increased risk of heart failure and cardiovascular events in South Asians.

Our finding of poorer longitudinal systolic and diastolic function in South Asians compared with Europeans is in accordance with a smaller previous study, although this latter was restricted to individuals with no abnormal risk factors, disease, or medication (28) and therefore could not explore the role of glycemic status on LV function.

In Europeans, there was little association between glycated hemoglobin and LV dysfunction and only a modest decline in people with diabetes. Previous studies in European origin populations are conflicting, with some showing marked functional LV impairment when comparing people with and without diabetes (29) and across the glycemic spectrum (30), whereas others show no differences between people with and without diabetes (31,32) and mixed associations across the glycemic spectrum (13). A detailed study of the effect of diabetes on LV function noted that while longitudinal systolic function was impaired, radial function was increased compared with those without diabetes (33). These conflicting findings in part could be explained by choice of study population, e.g., clearer associations are

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Table 3—Ethnic differences (South Asian vs. European) in LV function in people with known diabetes

	Mean ethnic difference (95% CI)	*P*
NT-proBNP (pg/mL)		
Unadjusted	59.8 (2.72–116.9)	0.04
Model 1	75.6 (22.4–128.8)	0.006
Model 2	62.0 (5.1–118.9)	0.03
E/e′		
Unadjusted	1.92 (0.88–2.96)	<0.0001
Model 1	2.16 (1.15–3.17)	<0.0001
Model 2	1.91 (0.86–2.96)	<0.0001
Peak s′ (cm/s)		
Unadjusted	−0.41 (−0.81 to −0.01)	0.05
Model 1	−0.47 (−0.87 to −0.07)	0.02
Model 2	−0.45 (−0.87 to −0.03)	0.04

Model 1, adjusted for age and sex; model 2, adjusted for age, sex, HbA_{1c}, and diabetes duration.

observed in younger than older age groups; exclusions or restrictions to the study population, e.g., by disease, risk factor, or medication status; and the functional measures used. Few studies have explored the role of associated confounders, and many were too small for detailed analysis.

The greater adverse effect of hyperglycemia on LV function in South Asians is in keeping with our findings of a greater effect on CVD events (6). This may be a consequence of a longer exposure to hyperglycemia. We show that diabetes duration is greater in South Asians, but in the absence of repeated longitudinal measures of HbA_{1c} this proposal is speculative. Certainly, in people with established diabetes, we show as others do that a longer diabetes duration is associated with adverse LV function; this appears independent of hypertension and CHD (16). Long-standing hyperglycemia is associated with multiple adverse effects including increased oxidative stress, altered energy metabolism, accelerated fibrosis, and accumulation of advanced glycation end products in the myocardium and aorta (34,35) that may adversely affect LV function. However, when we took account of the greater diabetes duration in South Asians, acting as a proxy for duration of exposure, we found that neither it nor the greater level of hyperglycemia could account for the more adverse LV function in this ethnic group. This may suggest on the one hand that duration of exposure has little to do with the greater impact of hyperglycemia on function in South Asians or, alternatively, reflect the marked imprecision inherent in estimating diabetes duration.

NT-proBNP is an accepted measure of LV global dysfunction (16) that predicts CVD (36). We are unaware of previous comparisons of NT-proBNP between South Asians and Europeans and show that unadjusted values are elevated in South Asians. Since NT-proBNP is produced by the ventricles and LV mass differs by ethnicity (20), we additionally adjusted for LV mass (24,37). This further enhanced the ethnic difference in NT-proBNP. Conventionally, EF is often used as a measure of systolic function; however, the association between diabetes and EF is inconsistent. While some report lower EF in patients with diabetes (38), numerous studies have found no significant adverse effect of diabetes (39,40), probably because diminished longitudinal function is compensated for by an increase in radial function (41,42). For this reason, we used tissue Doppler s′ as a more sensitive index of systolic function that also predicts future CVD (28). For diastolic function, E/e′ was used, as unlike E/A ratio, it is not subject to pseudonormalization and also predicts future CVD (43,44). Based on ethnic differences in the relationship between HbA_{1c} and s′ and E/e′, respectively, and previously reported associations between these measures and future CVD (28,44,45), a 1% increment in HbA_{1c} would increase CVD risk in South Asians by 7–10% more than that observed in Europeans.

There are several strengths to this study. The SABRE cohort recruited from primary care without exclusion. As registration with primary care is free, and the gateway to comprehensive health care, it forms a representative sampling frame. Previous studies have either focused on those admitted to hospital, decisions for which may be biased by ethnicity, or excluded people with clinical and subclinical disease, risk factors, and medication. If we had excluded such individuals in this study, only 10.3% of Europeans and 5.5% of South Asians would have been eligible. As CVD and risk factors differ by ethnicity, such exclusion likely biases the comparison and results in highly selected, unrepresentative samples, making it difficult to generalize findings. Our measures of LV dysfunction and risk factors are relatively comprehensive, enabling detailed exploration of pathways.

Study Limitations

Our study has several limitations: sample sizes were relatively small, and consequently we may have insufficient power to detect some clinical important differences. We only studied older-age survivors; this may have introduced a survivor bias. However, detectable subclinical LV disease emerges in older age (10), and we have shown that overall survival rates in this cohort are equivalent by ethnicity (46). While those who survived and attended clinic were healthier at baseline compared with those who did not, these differences were also similar by ethnicity and are therefore unlikely to have seriously biased comparisons (6). Another limitation is that the majority of South Asians in this study were first-generation migrants of Punjabi Sikh origin, and although most South Asian populations worldwide have an increased prevalence of both diabetes and CVD, our findings may not necessarily apply to all people of South Asian ethnicity. Last, the data presented in this article are based on cross-sectional analyses made at follow-up and cannot address issues of causality.

In conclusion, hyperglycemia may be more detrimental to global, systolic, and diastolic LV function in South Asians

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than Europeans. This does not just apply to diabetes but occurs across the glycemic range. Understanding why South Asians are particularly sensitive to the effects of hyperglycemia and associated risk factors, such as hypertension, dyslipidemia, and microvascular disease, on LV function would help elucidate mechanisms and inform strategies for prevention and treatment. These may need to be implemented earlier in the course of disease in South Asians than Europeans, or South Asian people may require more aggressive treatment for a given cardiometabolic risk factor level. Given the predicted marked increase in diabetes prevalence in South Asians worldwide, further studies on this question are urgently required.

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