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26 **Abstract**

27 The study aimed to establish a relationship of ethnicity to diastolic dysfunction in subjects of
28 African-Caribbean and South Asian origins and the impact of diastolic dysfunction and
29 ethnicity on all-cause and cardiovascular mortality.

30 Hypertensive subjects with ejection fraction $\geq 55\%$ and no history of ischemic heart
31 disease/valve pathology (n=1546, 830 South Asians and 716 African-Caribbeans) were
32 identified from the Ethnic - Echocardiographic Heart of England Screening Study (E-
33 ECHOES). Diastolic function and cardiac remodelling were measured by echocardiography.

34 African-Caribbean ethnicity was associated with lower prevalence of having diastolic
35 dysfunction (odds ratio 0.67, 95% confidence interval 0.51-0.87, p=0.003) and increased left
36 ventricular filling pressure (odds ratio 0.48, 95% confidence interval 0.34-0.69, p<0.001) as
37 well as lower left atrial index (p<0.001). This was the case despite the fact that African-
38 Caribbean ethnicity was independently associated with higher left ventricular mass index
39 (p<0.001). Ninety-two deaths (6%) occurred during 68±21 months follow up. On Cox
40 regression analysis, South Asian ethnicity (p=0.024) was predictive of all-cause death before
41 adjustment for parameters of diastolic dysfunction, but it was no longer predictive of death
42 after accounting for these variables.

43 South Asian ethnicity is independently associated with worse parameters of diastolic function
44 in hypertension, despite African-Caribbeans having more prominent hypertrophy.

45

46 **Introduction**

47

48 Hypertension is a major cause of heart failure with preserved ejection fraction (HFpEF),
49 which is commonly associated with poor quality of life and poor outcomes.(1, 2) Diastolic
50 dysfunction and increased myocardial stiffness are recognised pathogenic factors contributing
51 to the development of HFpEF in hypertension.(3, 4)

52 There are significant ethnic differences in prevalence and outcome of hypertension, with
53 overall cardiovascular morbidity and mortality being substantially higher in South Asian and
54 African-Caribbean ethnic groups than in the white population. Adults of African-Caribbean
55 origin have higher blood pressure and are more prone to develop hypertension than white
56 subjects, with more controversial data regarding people of South Asian origin.(5-7) Whilst
57 the impact of different factors on the development of diastolic dysfunction has been
58 extensively studied in white subjects, limited information is available on the occurrence of
59 diastolic dysfunction in hypertensive patients of African-Caribbean and South Asian origin,
60 and the factors associated with progression to diastolic dysfunction in these ethnic groups.

61 The Ethnic-Echocardiographic Heart of England Screening Study (E-ECHOES) was a cross-
62 sectional community-based survey of subjects of South Asian origin (i.e. from India, Pakistan
63 or Bangladesh) and African-Caribbean origin aged ≥ 45 years. The two ethnic groups were
64 recruited in parallel. All individuals living in the recruitment area and belonging to these
65 ethnic groups were included if they were agreeable to participate in the study. The study
66 individuals were recruited from September 2006 to August 2009 from 20 primary care
67 centres in Birmingham, United Kingdom and the collected data included comprehensive
68 clinical assessment and echocardiography.(8) The present ancillary E-ECHOES analysis
69 assesses the prevalence of diastolic dysfunction and factors predicting its occurrence in a
70 well-characterized population of adult African-Caribbean and South Asian hypertensive

71 subjects. The study also evaluates the impact of diastolic dysfunction and ethnicity on all-
72 cause and cardiovascular mortality.

73

74 **Methods**

75

76 We included participants of the E-ECHOES study who had a history of hypertension with
77 normal left ventricular (LV) systolic function (i.e., LV ejection fraction $\geq 55\%$ by
78 echocardiography) and no history of ischemic heart disease (i.e., no angina, previous
79 coronary revascularization or myocardial infarction or use of nitrates) (Figure 1). Other
80 exclusion criteria were abnormalities of cardiac valves (i.e., stenosis or more than mild
81 regurgitation of any valve or previous valve surgery), history of peripheral artery disease,
82 cancer, chronic obstructive pulmonary disease, atrial fibrillation, current treatment with
83 digoxin, warfarin, ADP (adenosine diphosphate receptor) antagonists or antiarrhythmic
84 agents (except beta-blockers or calcium antagonists). The E-ECHOES database has 5353
85 entries including 2675 patients with hypertension. A total of 1546 subjects were analysed,
86 after all exclusion criteria were applied.

87 The E-ECHOES study was approved by Walsall Local Research Ethics Committee
88 (05/Q2708/45) with all participants provided written informed consent for data collection and
89 analysis. Following patient recruitment data on outcomes (i.e. mortality) have been collected
90 prospectively. This is provided by the Health and Social Care Information Centre
91 (www.hscic.gov.uk).

92

93 *Echocardiography*

94 All study participants underwent detailed echocardiographic analysis with images reviewed
95 by a consultant cardiologist with expertise in echocardiography. Echocardiography was done
96 in primary care settings using a portable VIVID i machine (GE Healthcare, Chalfont St Giles,
97 UK). LV ejection fraction, dimensions of the cardiac chambers, LV mass index and
98 parameters of the diastolic function (mitral valve E/A ratio; E wave deceleration time; tissue

99 Doppler imaging of lateral and septal mitral valve annulus to quantify average septal-lateral
100 E/e' ratio) were also measured following current recommendations.(9)

101

102 Presence of diastolic dysfunction was determined based on E/A ratio and average septal-
103 lateral E/e' as main criteria and additional criteria of abnormal deceleration time (<130 msec
104 or >230 msec), reduced e' velocity (e' septal <8 cm/sec or e' lateral <10 cm/sec) and
105 increased LA diameter (>4.0 cm in men and >3.8 cm in women). Diastolic dysfunction was
106 defined as (i) E/A <1 (in patients older 60 years only in presence of ≥ 1 additional factor); (ii)
107 E/A ≥ 1 , E/e' 8-13 and ≥ 1 additional factor, or (iii) E/A ≥ 1 and E/e' ≥ 13 . The coding was
108 done by an independent colleague who was not involved in any analyses or writing of the
109 manuscript (MD, please see acknowledgement). Increased LV filling pressure was defined
110 based on average septal-lateral E/e' ≥ 13).(10) To assess the separate components of diastolic
111 function, average septal-lateral e' velocity (as a measure of active relaxation) and the ratio of
112 E/e' ratio : LV diastolic volume index (as an index of passive diastolic stiffness) were
113 calculated. LV hypertrophy was defined as LV mass index >95 g/m² in women and 115 g/m²
114 in men (concentric hypertrophy if relative wall thickness was ≤ 0.42 and eccentric
115 hypertrophy if relative wall thickness >0.42). Concentric remodelling was defined as a
116 normal LV mass index with relative wall thickness >0.42.(9) Echocardiographic
117 measurements and measurements of blood pressure and heart rate were performed in
118 triplicates and their averages were used for the analysis.

119

120 *Statistical analysis*

121 Data were tested for normality graphically by histogram plotting and using Kolmogorov-
122 Smirnov test. Normal data are presented as mean \pm standard deviation and compared using
123 independent sample T-test. Regression analysis was used to establish predictors of

124 parameters of diastolic dysfunction with the following predictor variables tested: age, gender,
125 ethnicity, history of diabetes and smoking, systolic and diastolic blood pressure, heart rate,
126 body mass index, waist circumference, use of angiotensin enzyme inhibitors or angiotensin
127 receptor antagonists, aldosterone antagonists, beta-blockers, calcium channel blockers,
128 diuretics, aspirin, statins, LV mass index (NB. the last parameter was not used in analyses of
129 predictors of the LV mass index itself). Linear regression was used to establish predictors of
130 continues variables and logistic regression was used to identify predictors of diastolic
131 dysfunction and increased LV filling pressure). To further assess a possibility that observed
132 higher LV stiffness in South Asian individuals may be related to higher prevalence of
133 diabetes a sensitivity analysis was performed excluding people with a history of diabetes.
134 Stepwise Cox regression analysis was used to establish predictors of all-cause and
135 cardiovascular mortality in the study population. LA diameter index quartiles were coded as
136 quartile 1 (i.e., less 1.51 cm/m²), quartile 2 (i.e., from 1.51 to less 1.69 cm/m²), quartile 3
137 (i.e., from 1.69 to less 1.88 cm/m²), and quartile 4 (i.e., 1.88 cm/m² or more) with dummy
138 variables used to assess contrasts. Proportional hazards assumption for Cox models was
139 graphically checked by plotting partial residuals against time for continues variables and
140 using log minus log plots for categorical variables. P-values of <0.05 were considered as
141 statistically significant. IBM SPSS Statistics 21 (IBM Inc, USA) software was used for
142 statistical analyses. Figure 2 was prepared using STATA 13, marginsplot command package
143 (StataCorp, USA). The figure presents adjusted linear regression lines with standard errors
144 for individual age categories. The adjustment was made for the same parameters as described
145 for the multivariable linear regression analysis above.

146

147 **Results**

148

149 A total of 1546 subjects were included (830 of South Asian origin and 716 of African-
150 Caribbean origin). Among the 830 South Asian patients 772 (93%) were born in India,
151 Pakistan or Bangladesh, only 6 (0.7%) patients were born in the UK and 3 in other parts of
152 Europe, with the rest 49 (6%) patients born in other parts of the world (mostly from countries
153 of East Africa). The mean age of coming to the UK was 26 ± 13 years and the mean duration
154 since coming to the UK was 36 ± 12 years. Among the 716 participants of African-Caribbean
155 origin 621 (87%) were born on the Caribbean islands (majority – 547 (76%) in Jamaica), 70
156 (9.8%) in the UK and 25 (3.5%) in other countries. The mean age of coming to the UK was
157 24 ± 11 years and the mean duration since coming to the UK was 43 ± 13 years.

158 Compared to participants of South Asian origin, African-Caribbeans were older ($p<0.001$),
159 had a higher body mass index ($p<0.001$), and higher systolic blood pressure ($p=0.002$), but
160 smaller waist circumference ($p<0.001$), lower heart rate ($p<0.001$) (Table 1). There were no
161 statistical differences in gender, LV ejection fraction, diastolic blood pressure and history of
162 smoking.

163 South Asian patients had higher rates of diabetes (47% vs. 35%, $p<0.001$) and more
164 frequently received angiotensin converting enzyme inhibitors or angiotensin receptor
165 blockers, aldosterone antagonists and statins, but less often amlodipine, diuretics and alpha-
166 blockers. There was no significant difference in utilisation of aspirin or beta-blockers
167 between the two ethnic groups.

168

169 *Diastolic dysfunction*

170 Overall 73% of South Asian subjects and 72% of African-Caribbean participants had
171 diastolic dysfunction ($p=0.74$). On logistic regression analysis, independent predictors of

172 diastolic dysfunction were more advanced age, female gender, South Asian ethnicity, higher
173 LV mass index, diastolic blood pressure, heart rate, waist circumference and use aldosterone
174 antagonists (Table 2).

175

176 *Increased left ventricular filling pressure*

177 Increased LV filling pressure was found in 14% of South Asian patients and 11% of African-
178 Caribbean patients (p=0.09). On logistic regression analysis, independent predictors of
179 increased LV filling pressure were advanced age, female gender, South Asian ethnicity,
180 higher LV mass index and systolic blood pressure (p<0.001 for all).

181

182 *e' velocity*

183 On linear regression analysis, independent predictors of lower e' velocity were advanced age,
184 female gender, history of diabetes, higher LV mass index and lower waist circumference and
185 diastolic blood pressure (p<0.001), but not the ethnicity (Table 3, Figure 2).

186

187 *Ratio of E/e' ratio: LV diastolic volume index*

188 On linear regression analysis, independent predictors of higher ratio of E/e' ratio: LV
189 diastolic volume index were advanced age, female gender, higher LV mass index, systolic
190 blood pressure, South Asian ethnicity (p<0.001 for all), history of diabetes (p=0.01) and
191 smoking (p=0.027), higher body mass index (p=0.004) and heart rate (p=0.024). South Asian
192 ethnicity remained independently associated with higher LV stiffness in a sensitivity analysis
193 excluding individuals with history of diabetes (Table 3).

194

195 *LV mass index*

196 On linear regression analysis, predictors of LV mass index were advanced age, male gender,
197 African-Caribbean ethnicity, higher waist circumference and systolic blood pressure
198 ($p<0.001$), history of diabetes ($p=0.02$), use of beta-blockers ($p=0.01$) or calcium channel
199 blockers ($p=0.04$).

200

201 *LA diameter index*

202 On linear regression, independent predictors of higher LA diameter index were advanced age,
203 female gender, South Asian origin, higher values of body mass index, LV mass index, heart
204 rate ($p<0.001$ for all), diastolic blood pressure ($p=0.002$) and history of smoking ($p=0.003$).

205

206 *All-cause and cardiovascular death*

207 Ninety-two deaths (6%) including 26 cardiovascular deaths occurred during a follow up of
208 68 ± 21 months. On Cox regression analysis without adjustment for parameters of diastolic
209 dysfunction, independent predictors of all-cause death were advanced age ($p<0.001$), history
210 of smoking ($p<0.001$), South Asian ethnicity ($p=0.024$) and higher heart rate ($p=0.009$)
211 (Table 4). After additional adjustment for parameters of diastolic dysfunction (i.e., LV mass
212 index, e' velocity, E/e' ratio : LV diastolic volume index, quartiles of LA diameter index,
213 presence of diastolic dysfunction and increased LV filling pressure [$E/e' \geq 13$]) independent
214 predictors of all-cause death were advanced age ($p<0.001$), male gender ($p=0.049$), history of
215 smoking ($p=0.012$), higher heart rate ($p=0.003$) as well as presence of diastolic dysfunction
216 ($p=0.035$) and the top quartile of LA index ($p=0.002$, vs. 1st quartile). After adjustment for
217 parameters of diastolic dysfunction, ethnicity was no longer an independent predictor of all-
218 cause death.

219

220 Only advanced age ($p<0.004$) was the independent predictor of cardiovascular death. After

221 additional adjustment for parameters of diastolic dysfunction above, independent predictors
222 of cardiovascular death were increased LV filling pressure ($p < 0.001$), history of smoking
223 ($p = 0.008$) and the top quartile of the LA diameter index ($p = 0.045$, vs. 1st quartile).
224

225 **Discussion**

226 In this study we showed, for the first time, significant differences in characteristics of
227 diastolic dysfunction in ethnic minority groups in the United Kingdom. South Asian ethnicity
228 was independently associated with the presence of diastolic dysfunction and increased LV
229 filling pressure, which paralleled a higher overall mortality associated with this ethnic group.
230 Of interest, this was despite African-Caribbeans having more prominent LV hypertrophy. In
231 contrast, South Asian ethnicity was associated with higher LA diameter index, a recognised
232 marker of chronic diastolic dysfunction and higher E/e' ratio : LV diastolic volume index as
233 an index of passive diastolic stiffness.

234 The pathophysiology of diastolic dysfunction is complex and still poorly understood. Under
235 physiological conditions, LV pressure rapidly decays after systole, allowing low filling
236 pressures and adequate diastolic filling. In diastolic dysfunction LV filling is compromised as
237 a result of impairment in active (i.e., myocardial relaxation) and/or passive stiffness
238 (increased cardiac stiffness).(11, 12) This ventricular filling defect, in turn, might reduce
239 cardiac output contributing to heart failure symptoms in HFpEF patients. This is supported by
240 both interventional experiments and by large population-based studies carried out using a
241 non-invasive approach to measure diastolic stiffness.(13-15)

242 The present study suggests that African-Caribbeans are less likely to have diastolic
243 dysfunction despite higher myocardial mass and thickness and more extensive concentric
244 myocardial remodelling. The fact that African-Caribbean vs. South Asian ethnicity was not
245 associated with higher e' velocity may suggest that the intrinsic velocity of myocardial
246 relaxation might be preserved in these patients despite myocardial thickening. This indicates
247 relatively benign nature of LV hypertrophy in African-Caribbean, which poses a relatively
248 low risk of diastolic dysfunction. This observation also calls for the presence of increased
249 passive diastolic stiffness in South Asian people that lead to diastolic dysfunction despite

250 lower myocardial mass and thickness. This possibility is supported by higher E/e' ratio: LV
251 diastolic volume index (an index of passive diastolic stiffness) associated with South Asian
252 ethnicity. Excessive myocardial fibrosis is a plausible explanation, although its assessment
253 was beyond the scope of this population-based study.

254 The present study does not give a direct answer on how the ethnicity-related differences in
255 diastolic dysfunction are translated into clinical outcomes. However, it provides evidence that
256 the ethnic differences extend beyond mild changes in diastolic dysfunction and are associated
257 to progression towards increased LV filling pressure. Published evidence, although mostly
258 derived from white population shows that such changes are not benign and are strongly
259 related to increased risk of cardiovascular events.(16, 17) Indeed, ethnic minorities may
260 represent an independent predictor of increased mortality in HFpEF.(18, 19)

261 The factors causing increased LV mass in African-Caribbean subjects are not clear but they
262 may have a genetic predisposition. Although children of African-Caribbean origin might
263 even have lower blood pressure compared to white children, African-Caribbeans have higher
264 blood pressure and more often develop hypertension later in their adult life.(20, 21) Ethnic
265 differences in blood pressure begin to emerge in adolescence and early adulthood.(22-24)
266 The Health Surveys for England showed a crossover in blood pressure (i.e., African-
267 Caribbeans higher than whites) somewhat later, at 30-40 years of age.(25) Even after
268 adjustment for age, body mass index, smoking, and alcohol intake African-Caribbeans still
269 have higher odds of having hypertension.(26) Smaller nocturnal blood pressure falls and a
270 higher prevalence of non-dipping seen in African-Caribbeans may contribute to the higher
271 levels of hypertension-related complications seen in African-Caribbeans.(27) No such
272 phenomenon was seen in South Asians.

273 In a UK-based study of highly trained nationally ranked athletes black sportsmen had greater
274 LV wall thickness and LV mass compared to white athletes thus indicating a possibility of

275 genetic predisposition to LV hypertrophy.(28) Large meta-analyses of genome-wide studies
276 have found many loci significantly associated with higher blood pressure.(29) Of the 34 loci
277 identified in the meta-analyses, 26 loci showed ethnic variations and they could be implicated
278 in ethnic differences in hypertension.

279 Which factors could predispose to diastolic dysfunction in South Asian individuals despite
280 lower LV mass? Genetic or acquired predisposition to LV fibrosis may play a role. For
281 example, diabetes is more common in South Asians and it has a negative impact on LV
282 diastolic function in this ethnic group.(30) Microalbuminuria is more frequent in the UK
283 South Asians compared with white people, being associated with South Asian origin even
284 after adjustment for hypertension, diabetes and age.(31) This may indicate higher
285 susceptibility of South Asians to target organ damage (e.g., endothelial dysfunction). The
286 enlarged LA could predispose to increased risk of developing atrial fibrillation that would
287 further negatively impact diastolic function, but such analysis was beyond the scope of this
288 study.

289 Hypertension was shown to be one of the leading attributable risk factors for mortality in
290 South Asians but some controversy exists in this regard.(5) For example, South Asians were
291 less likely to be adherent to antihypertensive medications, which contributed to excess in
292 mortality.(32) In a large registry of patients with newly diagnosed hypertension, South
293 Asians were reported to have lower mortality and risk of cardiovascular disease outcomes
294 compared to whites.(6) The clinical implication of ethnic differences in diastolic dysfunction
295 in South Asians thus merits further investigation.

296 The study shows that South Asian ethnicity is independently associated with higher all-cause
297 death in patients with hypertension, before the adjustment for parameters of diastolic
298 function. This parallels to the independent association of South Asian ethnicity with diastolic
299 dysfunction in this population of hypertensive subjects (dilated left atrial can be considered a

300 marker of longer-term abnormalities of diastolic dysfunction in patients without valvular
301 pathology and atrial fibrillation).(10) Ethnicity was no longer independently predictive of
302 mortality after adjustment for parameters of diastolic dysfunction.

303

304 *Limitations*

305 The analysis does not cover white population, but our group previously showed in a subset of
306 the participants of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) trial that
307 African-Caribbean origin was linked to higher E/e' ratio vs. white subjects.(33) This much
308 bigger study with more detailed assessment of diastolic dysfunction and cardiac geometry
309 expands those observations in relation to South Asian cohort and it sheds some light on
310 cardiac changes contributing to diastolic dysfunction in ethnic groups. LA size was assessed
311 based on its diameter rather than volume. The ethnic differences observed in the analysis
312 could be, at least partly, related to body composition, which was not assessed in the E-
313 ECHOES study.(34, 35) The generalizability of the findings to ethnic groups in other regions
314 (e.g., Asia or Africa) may be limited since both studied ethnic groups were recruited in the
315 UK. Finally, the study does not provide mechanistic insight into pathways linking the
316 observed differences and these need to be addressed by separate studies.

317

318 *Conclusions*

319 In ethnic groups recruited in the UK, South Asian ethnicity is associated with worse
320 characteristics of diastolic function in hypertension, which parallels a higher mortality
321 associated with this ethnic group. This occurs despite the fact that African-Caribbeans have
322 more prominent LV hypertrophy. The findings likely reflect higher myocardial stiffness in
323 South Asians possibly due to excessive fibrosis.

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342

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453

454 **Figure legends:**

455 **Figure 1. Study analysis flow chart.**

456 E-ECHOES, The Ethnic-Echocardiographic Heart of England Screening Study; COPD,
457 chronic obstructive pulmonary disease; GTN, glycerol trinitrate; IHD, ischemic heart disease;
458 LV, left ventricular; PAD, peripheral artery disease.

459

460 **Figure 2. Relationship between ethnicity and echocardiographic measured of diastolic**
461 **dysfunction on multivariable linear regression models.**

462 The plots present adjusted regression lines with standard errors for specific age categories.

463 **Summary Table.**

464 What is known about topic

- 465 • Hypertension is a major cause of heart failure with preserved ejection fraction, which
- 466 is commonly associated with poor quality of life and poor outcomes.
- 467 • Diastolic dysfunction and increased myocardial stiffness are recognised pathogenic
- 468 factors contributing to the development of heart failure.
- 469 • Ethnic differences play a major role in coronary artery disease and hypertension.

470

471 What this study adds

- 472 • The present study shows for the first time that South Asian ethnicity is independently
- 473 associated with worse parameters of diastolic function in hypertension, which
- 474 parallels a higher mortality associated with this ethnic group.
- 475 • This occurs despite the fact that African-Caribbeans have more prominent
- 476 hypertrophy and more distinct concentric remodelling.
- 477 • The findings are likely reflecting higher myocardial stiffness in South Asians possibly
- 478 due to excessive fibrosis.

Table 1. Patient characteristics

| Parameter | South Asian | | African-Caribbean | | p value |
|---|-------------|-----------|-------------------|-----------|---------|
| | n | value | n | value | |
| Demographic and clinical characteristics | | | | | |
| Age, years | 830 | 62±10 | 716 | 65±11 | <0.001 |
| Male gender | 830 | 357 [43%] | 716 | 302 [42%] | 0.74 |
| Diabetes | 830 | 392 [47%] | 716 | 250 [35%] | <0.001 |
| Smoking | 830 | 71 [9%] | 716 | 110 [15%] | 0.26 |
| Body mass index, kg/m ² | 825 | 29±5 | 715 | 30±6 | <0.001 |
| Waist circumference, cm | 830 | 100.2±13 | 716 | 99.8±13 | <0.001 |
| Systolic blood pressure, mmHg | 830 | 147±20 | 716 | 150±19 | 0.002 |
| Diastolic blood pressure, mmHg | 830 | 84±11 | 716 | 84±10 | 0.86 |
| Heart rate, bpm | 830 | 81±14 | 716 | 78±13 | <0.001 |
| Echocardiography | | | | | |
| Left ventricular ejection fraction, % | 830 | 66±6 | 716 | 66±6 | 0.22 |
| End-diastolic diameter index, cm/m ² | 830 | 2.46±0.3 | 716 | 2.38±0.30 | <0.001 |
| Left ventricular mass index, g/m ² | 815 | 115±38 | 713 | 131±43 | <0.001 |
| Left atrial diameter index, cm/m ² | 820 | 1.74±0.3 | 715 | 1.67±0.27 | <0.001 |
| E/e' (medial-lateral) | 809 | 8.19±2.41 | 701 | 7.77±2.31 | 0.001 |
| E/e' ratio : LV diastolic volume index | 794 | 0.21±0.10 | 694 | 0.20±0.09 | 0.064 |
| Isovolumic relaxation time, msec | 825 | 94±16 | 705 | 98±15 | <0.001 |
| Diastolic dysfunction | 830 | 583 [73%] | 716 | 501 [72%] | 0.74 |
| Increased left ventricular filling pressure | 799 | 109 [14%] | 695 | 75 [11%] | 0.09 |

| | | | | |
|----------------------------|-------------------------------|-----------|-----------|--------|
| Left ventricular geometry: | <i>Normal</i> | 127 [16%] | 67 [9%] | <0.001 |
| | <i>Concentric remodelling</i> | 211 [26%] | 126 [18%] | |
| | <i>Eccentric hypertrophy</i> | 122 [15%] | 110 [15%] | |
| | <i>Concentric hypertrophy</i> | 347 [43%] | 409 [57%] | |

Medications

| | | | | | |
|--------------------------|-----|-----------|-----|-----------|--------|
| ACEIs or ARAs | 830 | 363 [44%] | 716 | 243 [34%] | <0.001 |
| Aldosterone antagonists | 830 | 182 [22%] | 716 | 127 [18%] | 0.040 |
| Alpha-blockers | 830 | 37 [4%] | 716 | 74 [10%] | <0.001 |
| Aspirin | 830 | 334 [40%] | 716 | 274 [38%] | 0.43 |
| Beta-blockers | 830 | 131 [16%] | 716 | 108 [15%] | 0.70 |
| Calcium channel blockers | 830 | 295 [36%] | 716 | 424 [59%] | <0.001 |
| Diuretics | 830 | 299 [36%] | 716 | 350 [49%] | <0.001 |
| Statins | 830 | 488 [59%] | 716 | 360 [50%] | 0.001 |

ACEI, angiotensin converting enzyme inhibitors; ARA, angiotensin receptor antagonists.

Table 2. Logistic regression analysis of factors associated with diastolic dysfunction and increased left ventricular filling pressure

| | Odds ratio [95% confidence interval] | p value |
|---|--------------------------------------|---------|
| Diastolic dysfunction (n=1473), Chi-Square statistic 302, p<0.001 | | |
| Age, per 1 year | 1.10 [1.08-1.12] | <0.001 |
| Female gender | 1.72 [1.32-2.24] | <0.001 |
| African-Caribbean origin | 0.67 [0.51-0.87] | 0.003 |
| Diastolic blood pressure, per 1 mmHg | 1.03 [1.02-1.04] | <0.001 |
| Heart rate, per 1 bpm | 1.03 [1.02-1.04] | <0.001 |
| Waist circumference, per 1 cm | 1.03 [1.02-1.04] | <0.001 |
| Aldosterone antagonist use | 1.41 [1.01-1.97] | 0.04 |
| Left ventricular mass index, per 1 g/m ² | 1.01 [1.00-1.01] | <0.001 |
| Increased left ventricular filling pressure (n=1476), Chi-Square 128, p<0.001 | | |
| Age, per 1 year | 1.06 [1.04-1.07] | <0.001 |
| Female gender | 2.48 [1.73-3.56] | <0.001 |
| African-Caribbean origin | 0.48 [0.34-0.69] | <0.001 |
| Systolic blood pressure, per 1 mmHg | 1.02 [1.01-1.03] | <0.001 |
| Left ventricular mass index, per 1 g/m ² | 1.01 [1.00-1.01] | <0.001 |

Table 3. Linear regression analysis of factors associated with parameters of diastolic dysfunction, cardiac remodelling

| | B ± standard error | Beta | P value |
|---|--------------------|--------|---------|
| Left ventricular mass index (n=1528, overall r²=0.15) | | | |
| Age, per 1 year | 0.49±0.09 | 0.13 | <0.001 |
| Female gender | -14.2±1.97 | -0.17 | <0.001 |
| African-Caribbean origin | 12.9±2.05 | 0.16 | <0.001 |
| Waist, per 1 cm | 0.45±0.08 | 0.14 | <0.001 |
| Systolic blood pressure, per mmHg | 0.31±0.05 | 0.15 | <0.001 |
| Beta-blocker | 6.90±2.69 | 0.06 | 0.01 |
| History of diabetes | 4.62±2.04 | 0.06 | 0.02 |
| Calcium channel blocker | 4.23±2.01 | 0.05 | 0.04 |
| Left atrial diameter index (n=1523, overall r²=0.21) | | | |
| Body mass index, per kg/m ² | -0.014±<0.01 | -0.29 | <0.001 |
| Left ventricular mass index, per g/m ² | 0.002±<0.01 | 0.23 | <0.001 |
| Female gender | 0.088±0.02 | 0.16 | <0.001 |
| African-Caribbean origin | -0.082±0.01 | -0.15 | <0.001 |
| Age, per 1 year | 0.003±<0.01 | 0.11 | <0.001 |
| Heart rate, per 1 bpm | -0.002±<0.01 | -0.10 | <0.001 |
| Diastolic blood pressure, per mmHg | -0.002±<0.01 | -0.08 | 0.002 |
| History of smoking | -0.046±0.02 | -0.077 | 0.003 |
| e' velocity (n=1492, overall r²=0.27) | | | |
| Age, per 1 year | -0.10±<0.01 | -0.46 | <0.001 |
| Waist, per 1 cm | <0.01±<0.01 | -0.13 | <0.001 |
| Diastolic blood pressure, per mmHg | <0.01±<0.01 | -0.16 | <0.001 |

| | | | |
|---|--------------|--------|--------|
| Left ventricular mass index, per g/m ² | -0.01±<0.01 | -0.14 | <0.001 |
| Female gender | -0.50±0.10 | -0.11 | <0.001 |
| History of diabetes | -0.40±0.10 | -0.08 | 0.001 |
| E/e' ratio : LV diastolic volume index (n=1476, overall r²=0.15) | | | |
| Age, per year | <0.01±<0.01 | 0.265 | <0.001 |
| Female gender | 0.04±0.01 | 0.203 | <0.001 |
| Systolic blood pressure, per mmHg | <0.01±<0.01 | 0.131 | <0.001 |
| Left ventricular mass index, per g/m ² | <0.01±<0.01 | -0.107 | <0.001 |
| History of diabetes | 0.01±0.01 | 0.065 | 0.010 |
| African-Caribbean origin | -0.02±0.01 | -0.097 | <0.001 |
| Body mass index, kg/m ² | 0.00±<0.01 | 0.075 | 0.004 |
| Heart rate, per 1 bpm | <0.01±<0.01 | 0.056 | 0.024 |
| History of smoking | 0.01±0.01 | 0.061 | 0.027 |
| E/e' ratio : LV diastolic volume index (only patients without diabetes included) | | | |
| (n=870, overall r²=0.15) | | | |
| Age, per year | 0.002±<0.001 | 0.244 | <0.001 |
| Female gender | 0.047±0.006 | 0.256 | <0.001 |
| Systolic blood pressure, per mmHg | 0.01±<0.001 | 0.106 | 0.001 |
| Heart rate | 0.001±<0.001 | 0.085 | 0.007 |
| African-Caribbean origin | -0.018±0.006 | -0.100 | 0.002 |

Table 4. Stepwise forward Cox regression analysis of factors associated with any death and cardiovascular death (n=1546)

| | Hazard ratio | |
|---|---------------------------|---------|
| | [95% confidence interval] | p value |
| Any death (without adjustment for parameters of diastolic function*), Chi-Square 102, p<0.001 | | |
| Age, per 1 year | 1.11 [1.08-1.13] | p<0.001 |
| History of smoking | 2.33 [1.50-3.63] | p<0.001 |
| African-Caribbean origin | 0.60 [0.39-0.93] | 0.024 |
| Heart rate, per 1 bpm | 1.02 [1.01-1.03] | 0.009 |
| Any death (with adjustment for parameters of diastolic function*), Chi-Square 111, p<0.001 | | |
| Age, per 1 year | 1.09 [1.06-1.12] | p<0.001 |
| Female gender | 0.61 [0.38-1.00] | 0.049 |
| History of smoking | 1.89 [1.15-3.10] | 0.012 |
| Heart rate, per 1 bpm | 1.02 [1.01-1.04] | 0.003 |
| Presence of diastolic dysfunction | 2.25 [1.06-4.78] | 0.035 |
| Increased LA diameter index vs. 1 quartile | | 0.003 |
| 4 quartile | 2.92 [1.51-5.66] | 0.002 |
| Cardiovascular death (without adjustment for parameters of diastolic function*), Chi-Square 8.5, p=0.004 | | |
| Age, per 1 year | 1.06 [1.02-1.10] | 0.004 |
| Cardiovascular death (with adjustment for parameters of diastolic function*), Chi-Square 27, p<0.001 | | |
| Increased LV filling pressure | 4.99 [2.09-11.9] | p<0.001 |

| | | |
|--|------------------|-------|
| History of smoking | 3.03 [1.33-6.91] | 0.008 |
| Increased LA diameter index vs. 1 quartile | | 0.045 |
| 4 quartile | 4.39 [1.21-15.9] | 0.024 |

*Parameters of diastolic dysfunction included LV mass index, e' velocity, E/e' ratio : LV diastolic volume index, quartiles of LA diameter index, presence of diastolic dysfunction and increased LV filling pressure ($E/e' \geq 13$). LA, left atrial; LV, left ventricular.

5353 entries in the E-ECHOES database

Excluded:
2678 patients with no history of hypertension

2675 patients with hypertension

Excluded (>1 criteria in some patients) :

- LV ejection fraction <55% – 114
- history of angina – 385, previous MI – 260
- percutaneous or surgical revascularisation – 201
- use of: GTN– 59, and/or oral nitrates – 150
- lack of echocardiogram of adequate quality – 73
- mitral stenosis – 6, aortic stenosis – 71, moderate-severe mitral regurgitation – 36, aortic regurgitation – 40, tricuspid regurgitation – 19
- valve surgery – 15
- significant arrhythmia (predominantly AF) – 80
- use of: antiarrhythmic agents other than beta-blockers and calcium channel blockers – 12,
- use of: clopidogrel – 77, digoxin – 20, warfarin – 50
- PAD– 36, significant COPD– 35,
- cancer – 89

1546 hypertensive patients included with:

- normal LV function
- and no history of IHD

