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DOI:
10.1038/jhh.2016.68

Document Version
Peer reviewed version

Citation for published version (Harvard):
Shantsila, A, Shantsila, E, Gill, P & Lip, G 2016, 'Renal dysfunction and diastolic impairment amongst British ethnic minorities with hypertension: The Ethnic-Echocardiographic Heart of England Screening Study (E-ECHOES)', *Journal of Human Hypertension*. https://doi.org/10.1038/jhh.2016.68

Renal dysfunction and diastolic impairment amongst British ethnic minorities with hypertension: The Ethnic-Echocardiographic Heart of England Screening Study (E-ECHOES)

Running title: Diastolic dysfunction in ethnic groups

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Conflict of Interest: none declared

Abstract

Renal dysfunction is frequently associated with LV hypertrophy and diastolic dysfunction in hypertensive patients. Limited data exist on renal dysfunction and diastolic impairment amongst British ethnic minorities with hypertension. We studied associations between renal impairment and diastolic dysfunction in hypertensive subjects of African-Caribbean and South Asian origin. 510 hypertensive subjects with ejection fraction ≥55%, no history of ischemic heart disease/valve pathology were included from the original population of the Ethnic - Echocardiographic Heart of England Screening Study (E-ECHOES). Diastolic function and cardiac remodeling were measured by echocardiography.

Left ventricular (LV) hypertrophy was common and present in 62% of patients with normal estimated glomerular filtration rate (eGFR, >90 ml/min/1.73m^2), 73% in those with eGFR 60-89 and 87% with eGFR <60. On both univariate and multivariable linear regression, reduced eGFR was associated with higher LV mass index (LVMI, p=0.01 and p=0.039, respectively). On multivariable analyses, increased LVMI (but not eGFR) was an independent predictor of echocardiographic parameters of diastolic dysfunction. Higher LVMI was an independent predictor of all cause or cardiovascular death on multivariable analyses (both p=0.002), but not eGFR.

LV hypertrophy is common in minority ethnic groups with hypertension, especially in presence of renal dysfunction. Increased LVMI rather than renal impairment per se is a major determinant of diastolic dysfunction and increased risk of cardiovascular or all cause death amongst hypertensive patients without end-stage renal failure.

Introduction

Hypertension is a major cause of diastolic dysfunction and heart failure with preserved ejection fraction, with a significant contribution to cardiovascular and overall mortality.(1) Hypertension also frequently leads to renal dysfunction, which increases the risk of cardiovascular complications and death.(2, 3) However, renal dysfunction is frequently associated with LV hypertrophy and diastolic impairment.(4, 5), although studies assessing role of renal failure in diastolic dysfunction in hypertension have been mostly conducted on subjects of White origin with advanced or end-stage renal failure. Limited data exist on renal dysfunction and diastolic impairment amongst minority ethnic groups with hypertension.

The Ethnic-Echocardiographic Heart of England Screening Study (E-ECHOES) study was a cross-sectional population survey of subjects of South Asian and African-Caribbean origin aged ≥45 years. The study participants were recruited from 20 primary care centres in Birmingham, United Kingdom between September 2006 to August 2009 and had comprehensive clinical assessment and echocardiography performed.(6) In this analysis, we aimed to study the associations between renal impairment and diastolic dysfunction in hypertensive subjects of African-Caribbean and South Asian origin.

Methods

We included participants of the E-ECHOES study who had history of hypertension with normal left ventricular (LV) systolic function (i.e., LV ejection fraction ≥55% by echocardiography), no history of ischemic heart disease (i.e., no angina, previous coronary revascularization or myocardial infarction or use of nitrates) and measured plasma creatinine. Other exclusion criteria were abnormalities of cardiac valves (i.e., stenosis or more than mild regurgitation of any valve or previous valve surgery), history of peripheral artery disease, cancer, chronic obstructive pulmonary disease, atrial fibrillation, current treatment with digoxin, warfarin, ADP (adenosine diphosphate receptor) antagonists or antiarrhythmic agents (except beta-blockers or calcium antagonists). The E-ECHOES database had 5353 entries including 2675 patients with hypertension. From this population, 510 patients consented to have serum creatinine measured at the time of the recruitment.

The E-ECHOES study was approved by Walsall Local Research Ethics Committee (05/Q2708/45) with all participants 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). LV ejection fraction, dimensions of cardiac chambers, LV mass index and parameters of diastolic function (mitral valve E/A ratio; E wave deceleration time; and isovolumic relaxation time (IVRT), tissue Doppler imaging of lateral and septal mitral valve annulus to

quantify E/e' ratio) were also measured in accordance with current recommendations.(7) Diastolic dysfunction was determined based on E/A ratio and average septal-lateral E/e' as main criteria and additional criteria of abnormal deceleration time (<130 msec or >230 msec), reduced e' velocity (e' septal <8 cm/sec or e' lateral <10 cm/sec) and increased LA diameter (>4.0 cm in men and >3.8 cm in women). Diastolic dysfunction was defined as (i) E/A <1 (in patients older 60 years only in presence of ≥1 additional factor); (ii) E/A ≥1, E/e' 8-13 and ≥1 additional factor, or (iii) E/A ≥1 and E/e' ≥13. Coding was done by an independent physician who was not involved in any analyses or writing of the manuscript (MD, see acknowledgments).

Increased LV filling pressure was defined based on average septal/lateral E/e' ≥13).(8) In order to assess the separate components of diastolic function, average septal/lateral e' velocity (as a measure of active relaxation) and the ratio of E/e' ratio: LV diastolic volume index (as an index of passive diastolic stiffness). LV hypertrophy was defined as LV mass index >95 g/m2 in women and 115 g/m2 in men.(7) Concentric hypertrophy was defined as the relative wall thickness was ≤0.42; eccentric hypertrophy as the relative wall thickness >0.42 (both in presence of increased LV mass index). Concentric remodelling was defined as a normal LV mass index with relative wall thickness >0.42.(7) Intra- and interobserver variability of measurements of standard parameters of diastolic function in the department was <10%.(9)

Statistical analysis

Normal data are presented as mean ± standard deviation and compared using independent sample T-test. Forward stepwise regression was used to establish predictors of parameters of diastolic dysfunction with the following predictor variables tested: age, gender, history of

diabetes and smoking, systolic and diastolic blood pressure, heart rate, body mass index, waist circumference, use of angiotensin enzyme inhibitors or angiotensin receptor antagonists, aldosterone antagonist, alpha-blocker, calcium channel blocker, diuretic, aspirin, statin, LV mass index (the last parameter was not used in analyses of predictors of LV mass index itself). The variables for the regression analysis have been chosen based on previous literature on diastolic dysfunction and its predictors. Linear regression was used to establish predictors of continues variable and logistic regression was used to find predictors of diastolic dysfunction and increased LV filling pressure). Cox regression analysis was used to establish predictors of all-cause mortality in the study population. For logistic regression and Cox regression analyses, patients were categorised based on eGFR level ($\geq$90 ml/min/1.73m^2, 60-89 ml/min/1.73m^2, and < 60 ml/min/1.73m^2). IBM SPSS Statistics 21 (IBM Inc, USA) was used for statistical analyses. P-values of <0.05 were considered as statistically significant.

Results

A total of 510 patients (239 of South Asian origin and 271 of African Caribbean origin) met the analysis criteria and had information on eGFR. eGFR was normal (≥90 ml/min/1.73m^2) in 352 (69%) subjects (*Group 1*), 128 (25%) had eGFR 60-89 ml/min/1.73m^2 (*Group* 2), 30 (6%) had eGFR <60 ml/min/1.73m^2 (*Group 3*, included 25 patients with eGFR 30-59 ml/min/1.73m^2, 2 with eGFR 15-29 ml/min/1.73m^2 and 3 with eGFR <15 ml/min/1.73m^2).

Patients with reduced eGFR were older than those with normal eGFR (p<0.001), had lower diastolic blood pressure (p<0.001), were more often prescribed aspirin (p=0.007) and statins (p=0.001) (Table 1). Calcium channel blockers were more often used in the Group 2 than in Group 1 (p=0.039) and Group 3 (p=0.016). Diuretics were more often used in Group 3 than in Group 1 (p=0.024). Otherwise demographic and clinical parameters were similar in the study groups.

Cardiac remodelling and diastolic dysfunction

LV hypertrophy was common and present in 62% of patients in Group 1, 73% in Group 2 and 87% in Group 3 (Figure 1). Patients with reduced eGFR were more likely to have abnormal LV geometry (i.e., LV hypertrophy or concentric LV remodelling) compared to those with normal eGFR (p=0.0498 for the Group 2 and p=0.046 for the Group 3). None of the Group 3 patients had normal LV geometry. Concentric LV hypertrophy was the predominant type of LV geometry in patients with reduced eGFR (50% of Group 2 and 59% of Group 3) (Table 1). Diastolic dysfunction was present in 67% of Group 1 and it was more common in Group 3 (87%, p=0.023) with similar trend for Group 2 (75%, p=0.075) (Table

1). Increased LV filing pressure was seen in 6% of Group 1 compared to 20% of Group 3 (p=0.003) with similar trend Group 2 (10%, p=0.075) (Table 1).

Both on univariate and multivariable linear regression, reduced eGFR was associated with higher LV mass index (p=0.01 and p=0.039, respectively). On univariate regression analysis reduced eGFR was associated with presence diastolic dysfunction (p=0.029), increased LV filling pressure (p=0.011), increased LA diameter index (p=0.002) and e' velocity (p=0.001) (Tables 2 and 3). On multivariable analyses including adjustment for LV mass index, eGFR was not independently predictive of these parameters, nor E/e' ratio : LV diastolic volume index (p>0.05 for all) (Tables 2 and 3). In contrast, increased LV mass index was independently associated with all echocardiographic parameters of diastolic dysfunction above.

Mortality

Twenty nine deaths (6%) including 12 cardiovascular deaths occurred during follow up of 71±10 months. On univariate Cox regression eGFR <60 ml/min/1.73m^2 was associated with increased risk of all cause death (hazard ratio (HR) 3.24, 95% confidence interval 1.08-9.78, p=0.037) (Table 4). A nonsignificant trend was seen for the risk of cardiovascular death (HR 4.09, 95%CI 0.83-20.3, p=0.085). On multivariable Cox analyses, higher LV mass index was independently associated with increased risk of both all cause (HR 1.09, 95%CI 1.03-1.14, p=0.002) and cardiovascular death (HR 1.11, 95%CI 1.04-1.19, p=0.002) (Table 4), but eGFR was non-predictive.

Discussion

The study shows for the first time a significant independent association between relatively mild renal impairment and unfavorable LV remodeling in minority ethnic groups with hypertension without end-stage renal failure. In this population, reduced eGFR had an independent liner relationship with increased LV mass index after accounting for known contributors to development of LV hypertrophy.

Association of renal dysfunction with LV hypertrophy is well established in predominantly White populations.(10) Reported frequency of LV hypertrophy varies depending on severity of renal dysfunction, being in the range of 16-31% in patients with chronic kidney disease stage 3 or better, 60–75% of predialysis subjects and over 90% in dialysis patients.(4) However, the present study shows a higher than expected occurrence of LV hypertrophy amongst ethnic minority groups in the UK. Indeed, LV hypertrophy was evident in 62% of patients with normal eGFR and reached 87% in those with eGFR <60 ml/min/1.73m^2. Establishment of the precise causes for the frequent occurrence of LV hypertrophy in this population would require further research but may be due to suboptimal compliance with treatments, ethnicity related factors or relatively elderly study population.

We show that LV hypertrophy is the pivotal factor of developing of diastolic dysfunction and increased LV filling pressure. Indeed, non-end-stage renal dysfunction lost its predictive value for these parameters after adjustment for LV mass index. In contrast, elevated LV mass index was independently associated with presence of both diastolic dysfunction and increased LV filling pressure. Indeed, left atrial diameter index (a marker of chronic diastolic dysfunction), isovolumic relaxation time (a measure of overall relaxation), e' velocity (a

measure of active relaxation) and E/e' ratio : LV diastolic volume index (an index of passive diastolic stiffness) showed no independent association with eGFR in an analysis adjusted for LV mass index. Again, high LV mass index was an independent predictor of all these characteristics of diastolic dysfunction, thus confirming the key role of LV hypertrophy in diastolic dysfunction in hypertension.

Previous studies indicate that several types of myocardial changes contribute to diastolic dysfunction in hypertension including LV hypertrophy, delayed relaxation and increased stiffness of cardiomyocytes and LV fibrosis.(11-13) In the Framingham study in the population free from any cardiovascular disease and aged 40 years or older, the LV hypertrophy was present in 16% of man and 21% of women. (14) This study of the ethic groups in the UK shows considerably higher prevalence of LV hypertrophy, which could be due to age effect. To account the analyses for the age effect we included age in all multivariate models in this study. LV hypertrophy is primarily driven by cardiac remodeling in response to high blood pressure, but the magnitude of LV hypertrophy is also affected by extracardiac target organ damage, such as abnormal arterial stiffness, impaired cardiac-vascular coupling and renal dysfunction.(15) Chronic kidney disease is a frequent complication of hypertension and it does contribute to poor outcome in such patients.

Myocardial hypertrophy and associated cardiac remodeling parallel increase in extracellular matrix production leading to fibrosis.(16) Cardiac fibrosis is also promoted by activation of renin-angiotensin-aldosterone system, typical of hypertension and renal dysfunciton.(17) Pathological cardiac fibrosis increases cardiac stiffness and impairs LV contractility, leading to both systolic and diastolic dysfunction and congestive heart failure.(18) However increased LV hypertrophy rather than cardiac fibrosis appear to be the principal factor

leading to diastolic dysfunction in patients with preserved LV contractility and without end-stage renal failure, as seen in our analysis.

The clinical significance of LV hypertrophy rather than eGFR reduction per se in hypertensive patients without end-stage failure is further supported by increased LV mass index (but not eGFR) being independently predictive of mortality in this study. This observation accords well with previous data from White populations, including those with end-stage renal disease.(19) In advanced renal failure, almost half of deaths have been related to cardiovascular events but risk of such events was much lower in predialysis cohorts.(2, 3, 20) These data have clinical implication as 10% decrease in LV mass has been translated into a 28% reduction in cardiovascular mortality in patients receiving hemodialysis, highlighting the role of LV mass index as a useful marker of effectiveness of blood pressure control.(21)

Limitations

The study population mostly included patients with normal or mildly-to-moderately impaired renal function and the results may not be applicable to patients with end-stage renal failure. Kidney function assessment was based only on eGFR estimation. Lack of comparison group of White origin prevents generalization of the findings to all ethnic groups. Associations between renal function and systolic dysfunction should ideally be analyzed in prospective cohort studies but this was beyond the scope of the current analysis.

Conclusions

LV hypertrophy is common in ethnic minority groups with hypertension, especially so in presence of renal dysfunction. Increased LVMI rather than renal impairment per se is a major

determinant of diastolic dysfunction and increased risk of cardiovascular or all cause death amongst hypertensive patients without end-stage renal failure.

Acknowledgments

We are grateful to all the subjects, practice staff including receptionists, nurses, managers, and general practitioners for taking part in this study. We are grateful to Dr Mikhail Dzeshka for coding of diastolic function.

General Practice Centres: Rotton Park Medical Centre, City Road Medical Practice, Cavendish Medical Practice, Ann Jones Family Health Centre, Shanklin House Surgery, Burbury Street Surgery, Heathford Group Practice, Broadway Health Centre, Victoria Road Medical Centre, Churchill Medical Centre, St Clements Surgery, Handsworth Medical Centre, Soho Health Centre, Church Road Surgery, Bloomsbury Health Centre, Al-Shafa Medical Practice, Enki Medical Practice, Aston Pride Health Centre, Newtown Health Centre, Hockley Medical Centre.

Sources of Funding: This work was supported by the British Heart Foundation (PG/05/036), Heart of Birmingham Teaching Primary Care Trust, and through the National Health Service R&D support funding (Primary Care Research Network-Central England). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

Conflict of Interest: none declared

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Summary Table.

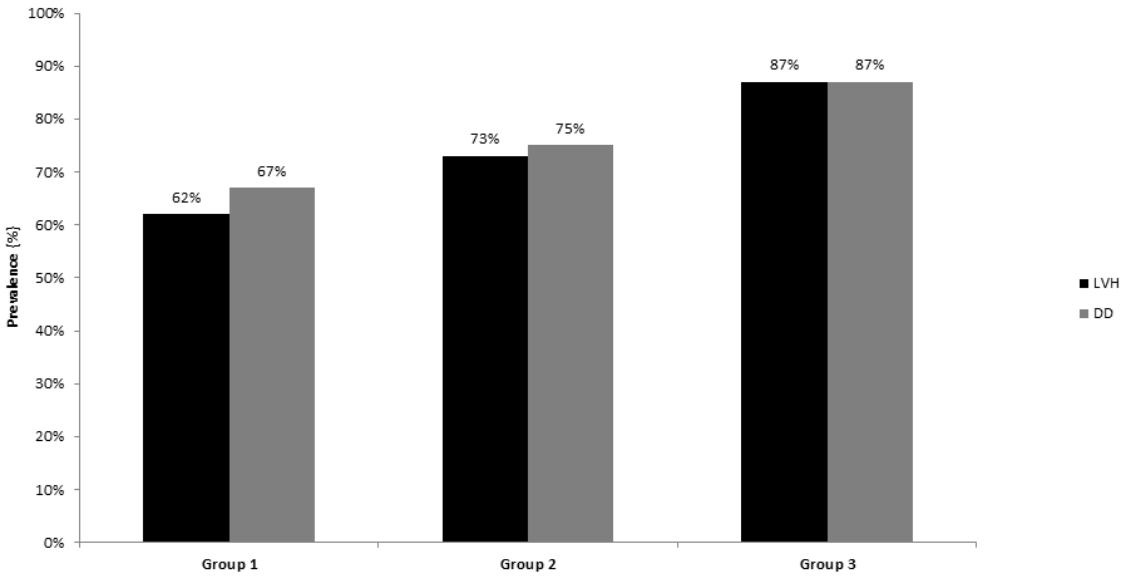
What is known about topic

- Hypertension is a major cause of diastolic dysfunction and heart failure with preserved ejection fraction, with a significant contribution to cardiovascular and overall mortality
- Hypertension also frequently leads to renal dysfunction, which increases the risk of cardiovascular complications and death
- Renal dysfunction is frequently associated with left ventricular hypertrophy and diastolic dysfunction in hypertensive patients

What this study adds

- Increased left ventricular mass index rather than non-end stage renal impairment per se is a major determinant of diastolic dysfunction in ethnic minority groups with hypertension.
- Increased left ventricular mass index is associated with high risk of cardiovascular and all cause death amongst hypertensive patients without end-stage renal failure.

Figure 1. The prevalence of left ventricular hypertrophy and diastolic dysfunction across the categories of renal function.



DD, diastolic dysfunction; LVH, left ventricle hypertrophy; Group 1, eGFR ≥90 ml/min/1.73m^2; Group 2 eGFR 60-89 ml/min/1.73m^2 ; Group 3 eGFR <60 ml/min/1.73m^2.