New insights into the relationship of left ventricular geometry and left ventricular mass with cardiac function: a population study of hypertensive subjects

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Aims
Remodelling of the left ventricle (LV) is associated with adverse cardiovascular events, but the mechanisms of these effects remain undefined. We investigated the relationship of LV mass and geometry to LV function in a large cohort of hypertensive subjects.

Methods and results
We studied 1074 hypertensive individuals without cardiovascular disease recruited from the London Life Sciences Prospective Population (LOLIPOP) study. All subjects underwent echocardiography for derivation of LV mass index (LVMI), measurement of transmitral filling pattern, and LV ejection fraction (EF). The tissue Doppler parameters of peak myocardial systolic velocity (Sa), diastolic velocity (Ea), and of LV filling pressure (E/Ea) were measured. Left ventricular function was correlated with degree of concentric remodelling, determined by relative wall thickness, and with LV geometric pattern. The presence of LV hypertrophy was independently associated with significantly worse systolic function, diastolic function, and higher LV filling pressure when compared with subjects with normal LV geometry or non-hypertrophic concentric remodelling. After adjustment for covariates including LVMI, peak Sa velocity and EF increased (P < 0.001), whereas peak Ea velocity decreased significantly (P < 0.001) with increasing degrees of concentric remodelling.

Conclusion
In hypertensives, hypertrophic remodelling is independently associated with impaired LV function and increased LV filling pressure. Increasing degrees of non-hypertrophic concentric remodelling are associated with attenuated diastolic function, but augmented systolic function, possibly representing an adaptive response to pressure overload physiology.

Keywords
LV remodelling • LV function • Hypertension • Population study

Introduction
Left ventricular hypertrophy (LVH) is a form of cardiac remodelling strongly associated with major cardiovascular events independent of blood pressure (BP), known risk factors, and coronary artery disease.1–4 However, discerning the independent prognostic value afforded by alterations in left ventricular (LV) shape in the presence or absence of LVH has proved more controversial. Concentric remodelling with normal LV mass has been associated with worse prognosis compared with normal LV geometry.5–8 Conversely, classification by LV geometry has also been shown to provide little incremental prognostic information beyond that offered by LV mass alone.9–12 Longitudinal studies assessing the relationship of abnormal LV geometry with cardiovascular outcomes have tended to combine non-fatal cardiovascular events and death as the outcome measure, and thus have limited our understanding of the potential mechanisms that may be responsible. Recently published follow-up data from a large cohort

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study suggested that LV mass, rather than concentric remodelling, is a better predictor of incident heart failure, yet the effect of different LV geometrical patterns upon LV systolic and diastolic function have still not been adequately defined.

Myocardial longitudinal velocities derived from tissue Doppler (TD) echocardiography have assumed greater importance as prognosticators of cardiovascular risk. Long-axis motion of the LV is an important component of LV systolic and diastolic function and the subendocardial fibres that contribute to long-axis function are particularly sensitive to various diseases and pathologies. Left ventricular filling pressure can also be estimated from TD imaging and conventional transmitral Doppler to derive the E/Ea ratio.

This study investigates the relative importance of cardiac geometry and mass upon the function of the LV in a large population of hypertensive subjects with no prior history of cardiovascular disease.

Methods

Subjects were recruited between August 2004 and November 2007 from the LOLIPOP (London Life Sciences Prospective Population) study. LOLIPOP is an ongoing population-based study of ∼30,000 Indian Asian and European white men and women recruited from the lists of 58 General Practitioners in West London. Assessment of participants is performed by a trained nurse using a standard protocol including questions on medical history, family history, cardiovascular risk factors, alcohol intake, physical activity, and drug history (verified from the practice computerized records). Subsequently, 2293 Indian Asian and European White subjects, aged 35–74 years and free from clinical cardiovascular disease, were selected at random and enrolled into the LOLIPOP atherosclerosis sub-study. The study was approved by the Northwick Park and Ealing Hospitals Research Ethics Committees. Consenting subjects had a physical assessment including BP determination, anthropometric measurements (height, weight, waist-hip ratio), and an electrocardiogram. Subjects were then invited to undergo echocardiography and provide fasting plasma and serum samples for biochemical analysis stored at −80°C.

We identified 1074 subjects with hypertension defined as having a prior history of hypertension or a current prescription of antihypertensive medications or a mean systolic BP ≥140 mmHg or a mean diastolic BP ≥90 mmHg (BP taken from three separate measurements in a seated position).

Echocardiography

Left ventricular dimensions, geometry, and ejection fraction

Transthoracic two-dimensional echocardiography was performed by experienced sonographers using a digital commercial harmonic imaging ultrasound system with an S3 3 MHz phased-array transducer (Philips IE33, Philips Medical Systems, Holland) at a single centre. Left ventricular dimensions were obtained in the parasternal short-axis view with measurement of the interventricular septal thickness in diastole, LV dimension in diastole, LV dimension in systole, and LV posterior wall thickness in diastole. Left ventricular mass was calculated using the Devereux formula and indexed to height (m) to provide left ventricular mass index (LVMI). Relative wall thickness (RWT) was used to measure the degree of concentric remodelling and was calculated as: (interventricular septal thickness in diastole+LV posterior wall thickness in diastole)/LV dimension in diastole. Subjects were stratified according to quintile of RWT and also according to LV geometrical pattern. The RWT and LVMI were used to categorize subjects as having: (i) normal geometry—normal RWT and normal LVMI; (ii) concentric remodelling—increased RWT and normal LVMI; (iii) eccentric hypertrophy—normal RWT and increased LVMI; (iv) concentric hypertrophy—increased LVMI and increased RWT. Internal gender- and ethnicity-specific partition values for increased LVMI and RWT were established from data representing the 95th percentiles in our normotensive population who lacked evidence of manifest cardiovascular disease and other modifiable risk factors (n=453). Partition values for LVMI (g/m²) and RWT were: European white men—137/0.47; European white females—116/0.46, Indian Asian males—118/0.50 and Indian Asian females—107/0.47.

Left ventricular end-diastolic and end-systolic volumes indexed to body surface area were measured using Simpson’s apical biplane rule. Tracing of the LV contour was performed carefully so as to exclude papillary muscles and trabeculations, as recommended by the American Society of Echocardiography. Ejection fraction (EF) was automatically calculated following acquisition of the LV volumes using the Simpson’s method.

Tissue Doppler imaging

Myocardial velocities were measured on-line using a standard pulse-wave Doppler technique acquired during a breath hold over two consecutive cardiac cycles using low-velocity, high-intensity myocardial signals at high frame rate (>150 MHz). The imaging angle was adjusted to ensure as near parallel alignment of the beam as possible with the myocardial segment of interest. The sample volume was placed at the junction of the LV wall with the mitral annulus of the septal and lateral myocardial segments from the apical four-chamber view and inferior and anterior myocardial segments from the apical two-chamber view. Peak velocities (cm/s) during systole (Sa) and early diastole (Ea) were measured on-line from all four mitral annular site segments and averaged.

Transmitral flow and E/Ea ratio

The transmitral flow velocities were recorded using pulsed wave Doppler with the sample volume placed at the tip of the mitral valve leaflets in the apical four-chamber view. From the mitral valve inflow velocity curve, the following measurements were made: peak E-wave velocity (cm/s) and its deceleration time (ms); peak A-wave velocity (cm/s); the ratio of E-wave to A-wave (E/A) velocities and the ratio of transmitral E-wave velocity and averaged Ea velocity (E/Ea).

Statistical analysis

Continuous variables are summarized as the mean ± 1 standard deviation according to quintiles of RWT and also according to LV geometrical pattern. Categorization of RWT into quintiles allowed the relationship between the degree of concentric remodelling with parameters of LV function to be assessed more closely, in particular for evidence of a threshold effect of RWT. Analysis of variance was used to test differences of continuous variables and Bonferroni’s correction for multiple comparisons (with rescaled P-values) was performed when data were stratified by LV geometrical pattern. The chi-squared test was used to test differences among categorical data. Effects of increasing quintiles of RWT and different LV geometry upon parameters of LV function were evaluated by analysis of covariance (ANCOVA) in a main-effects design, using Type III sum of squares. Comparison was adjusted for relevant confounders including age, sex, race, systolic BP, diastolic BP, antihypertensive use, diabetes, BMI, and LVM (adjustments made for LVMI when stratified by quintile of RWT). For post hoc comparisons of least-square means arising in the ANCOVA models, the alpha level for rejection of the null hypothesis
was corrected based on the number of comparisons being made \((P < 0.01 \text{ for four comparisons when stratification by quintile of RWT and } P < 0.02 \text{ for three comparisons when stratification by geometrical pattern})\). Estimated marginal means are given and displayed in figures, after adjustment for covariates. Statistical analyses were performed on SPSS (version 15).

**Reproducibility**

Echocardiographic measurements were repeated by two sonographers in 15 subjects to assess interobserver variability and reliability. The coefficient of variance was 11.5, 5.8, 9.9, and 3.7% for LVMI, end-diastolic volume index, end-systolic volume index, and EF, respectively. For the TD parameters mean Sa velocity, mean Ea velocity, and mean E/Ea ratio, the coefficient of variance was 11.4, 8.7, and 8.0%, respectively. Inter-observer reliability was assessed by calculating the intraclass correlation coefficients (ICC) as 0.88 \((P < 0.001)\) for LVMI, 0.97 \((P < 0.001)\) for end-diastolic volume index, 0.92 \((P < 0.001)\) for end-systolic volume index, and 0.77 \((P = 0.001)\) for EF. For TD parameters, the ICC was 0.72 \((P = 0.003)\) for Sa velocity, 0.98 \((P < 0.001)\) for Ea velocity, and 0.95 \((P < 0.001)\) for E/Ea ratio.

**Results**

The clinical characteristics and echocardiographic features in subjects stratified by quintile of RWT and by LV geometric pattern are displayed in Tables 1 and 2, respectively. Increasing RWT was associated with greater age \((P < 0.001)\), systolic BP \((P = 0.05)\), BMI \((P = 0.01)\), LVMI \((P < 0.001)\), prevalence of diabetes \((P = 0.02)\), and a higher proportion of subjects taking antihypertensive medications \((P = 0.05)\). There was an even distribution of people of European white ethnicity and male gender across RWT quintiles.

Normal LV geometry was present in 61% of the subjects studied, with concentric remodelling present in 13%, eccentric hypertrophy in 20%, and concentric hypertrophy in 6% (Table 2). Subjects with abnormal LV geometry were all older compared with those with normal LV geometry (all \(P < 0.001\)). Significantly higher systolic BP was only observed in subjects with eccentric hypertrophy, compared with controls \((P = 0.005)\). Both LVMI and RWT were highest in subjects with concentric hypertrophy (both \(P < 0.001\) vs. normal geometry).

**Table 1** Clinical characteristics stratified by quintile of relative wall thickness

<table>
<thead>
<tr>
<th>RWT quintile (RWT ranges)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (0.22–0.33)</td>
<td>2 (0.34–0.37)</td>
</tr>
<tr>
<td>(n)</td>
<td>160</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 10</td>
</tr>
<tr>
<td>Male (%)</td>
<td>75</td>
</tr>
<tr>
<td>European white (%)</td>
<td>43</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>142 ± 16</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>85 ± 10</td>
</tr>
<tr>
<td>Treated for HTN (%)</td>
<td>44</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>23</td>
</tr>
<tr>
<td>LVMI (g/m)</td>
<td>96.2 ± 25.4</td>
</tr>
</tbody>
</table>

ANOVA used to test differences of continuous variables and \(\chi^2\) used to test for differences in categorical variables between quintiles of RWT. BP, blood pressure; HTN, hypertension; RWT, relative wall thickness; LVMI, left ventricular mass index.

**Table 2** Clinical and echocardiographic characteristics stratified by left ventricular geometric patterns

<table>
<thead>
<tr>
<th>LV geometric pattern</th>
<th>Normal</th>
<th>Concentric remodelling</th>
<th>Eccentric hypertrophy</th>
<th>Concentric hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N) (%)</td>
<td>651 (61)</td>
<td>137 (13)</td>
<td>213 (20)</td>
<td>73 (6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 ± 9</td>
<td>63 ± 9(^a)</td>
<td>62 ± 8(^b)</td>
<td>62 ± 8(^b)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>143 ± 17</td>
<td>147 ± 21</td>
<td>148 ± 18(^d)</td>
<td>148 ± 20</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>86 ± 10</td>
<td>86 ± 12</td>
<td>86 ± 10</td>
<td>87 ± 12</td>
</tr>
<tr>
<td>EDVI (mL/m²)</td>
<td>37.6 ± 9.3</td>
<td>35.5 ± 9.9</td>
<td>43.1 ± 11.5(^d)</td>
<td>37.4 ± 10.1</td>
</tr>
<tr>
<td>ESVI (mL/m²)</td>
<td>14.4 ± 4.5</td>
<td>12.9 ± 3.9(^e)</td>
<td>17.4 ± 7.1(^d)</td>
<td>14.5 ± 4.9</td>
</tr>
<tr>
<td>LVMI (g/m)</td>
<td>94.0 ± 19.1</td>
<td>95.0 ± 17.7</td>
<td>145.3 ± 24.1(^f)</td>
<td>149.9 ± 29.3(^f)</td>
</tr>
<tr>
<td>RWT</td>
<td>0.38 ± 0.06</td>
<td>0.55 ± 0.06(^f)</td>
<td>0.40 ± 0.05(^f)</td>
<td>0.57 ± 0.08(^f)</td>
</tr>
</tbody>
</table>

ANOVA used to test differences between geometrical patterns with post hoc pairwise comparisons (Bonferroni’s correction). \(^aP < 0.05\); \(^bP < 0.01\); \(^dP < 0.001\) vs. normal geometry. Abbreviations as in Table 1 with EDVI, end-diastolic volume index; ESVI, end-systolic volume index.
Adjusted analysis

Myocardial longitudinal function

Figure 1 illustrates the distribution of longitudinal peak systolic and early diastolic myocardial velocities by quintiles of RWT and by pattern of LV geometry. Compared with the first quintile, peak Sa velocity was significantly higher in each of the three uppermost quintiles of RWT (adjusted peak Sa velocity in first and fifth quintiles 8.4 cm/s and 9.0 cm/s respectively, \( P < 0.001 \)). Compared with normal LV geometry, both concentric and eccentric hypertrophy were associated with lower adjusted mean Sa velocity (8.5 cm/s, \( P = 0.02 \) and 8.4 cm/s, \( P = 0.004 \), respectively, vs. 8.9 cm/s), but only eccentric hypertrophy reached the corrected level of significance. Although peak Sa velocity was lower among subjects with eccentric hypertrophy compared with those with concentric hypertrophy, this difference was not statistically significant.

After adjustment for covariates, RWT in the fifth quintile was associated with impaired early diastolic myocardial velocity when compared with the first quintile (8.1 vs. 8.7 cm/s, \( P < 0.001 \)). Subjects with abnormal LV geometry, with or without increased LV mass, had significantly impaired Ea velocity compared with those with normal geometry. Concentric hypertrophy was associated with a significantly lower Ea velocity when compared with eccentric hypertrophy (7.6 vs. 8.3 cm/s, \( P = 0.003 \)) and concentric remodelling (7.6 vs. 8.2 cm/s, \( P = 0.01 \)).

Left ventricular filling pressure (E/Ea ratio)

Left ventricular filling pressure, as estimated by the E/Ea ratio, did not vary significantly with increasing quintile of RWT (Figure 2). However, the adjusted E/Ea ratio in subjects with normal geometry was significantly lower compared to those with concentric hypertrophy (E/Ea = 9.7 vs. 10.8, \( P = 0.003 \)), but not with eccentric hypertrophy (E/Ea = 10.3, \( P = 0.03 \)). Concentric hypertrophy was associated with higher E/Ea when compared with concentric remodelling, but this also failed to reach corrected statistical significance (10.8 vs. 10, \( P = 0.02 \)).

Ejection fraction

Figure 3 shows that adjusted EF increased with each quintile of RWT and was significantly higher in the fifth quintile when compared with the first quintile (64.8 vs. 62.4%, \( P < 0.001 \)). Compared to normal LV geometry, EF was significantly higher with concentric remodelling (65.6 vs. 64%, \( P = 0.005 \)) and significantly lower with eccentric hypertrophy (62.5 vs. 64%, \( P = 0.005 \)). Subjects with concentric hypertrophy had significantly lower EF compared to those with concentric remodelling (63.6 vs. 65.6%, \( P = 0.003 \)). Although EF was lower with eccentric hypertrophy when compared to concentric hypertrophy, the difference was not statistically significant.

E/A ratio

The E/A ratio decreased with increasing RWT (Figure 4) and was significantly lower in the fifth quintile when compared with the first quintile (0.92 vs. 0.98, \( P = 0.01 \)).

Discussion

In this study of hypertensive subjects, hypertrophic remodelling was independently associated with subclinical impairment of systolic and diastolic LV function as well as increased LV filling pressure, when compared with subjects with normal geometry.
or non-hypertrophic concentric remodelling. After adjustment for LV mass, increasing degrees of concentric remodelling, expressed as the RWT, were paradoxically associated with enhanced longitudinal and radial LV systolic function. Although impaired diastolic function was observed with concentric remodelling, this did not result in a rise of LV filling pressure.

Concentric hypertrophy is associated with the greatest risk of future cardiovascular events and this pattern of remodelling is believed to ultimately progresses to LV dilatation and failure in hypertensives. An increase in LV mass can also occur in situations where wall thickness remains normal, but the LV cavity dilates through myocyte elongation resulting in eccentric hypertrophy. Eccentric hypertrophy is typically associated with states of volume overload, such as mitral regurgitation, but in hypertension it may represent the early manifestation of a cardiomyopathic process without an intervening phase of concentric hypertrophy. This alternative pathway for the development of heart failure in hypertension is supported by studies that have demonstrated eccentric hypertrophy to be associated with more severe systolic dysfunction compared with concentric hypertrophy. In this present population, longitudinal systolic function was significantly impaired in both concentric and eccentric hypertrophy compared with normal LV geometry. Subjects with eccentric hypertrophy had worse longitudinal systolic function and lower EF compared with those with concentric hypertrophy, however, the differences were not statistically significant after adjustment for covariates.

Although increased LV mass is also strongly associated with the development of diastolic heart dysfunction, the influence of concentric remodelling in the absence of LVH upon diastolic function had not been adequately defined. Previous studies have relied on transmitral Doppler assessment, a less reproducible and less capable method than TD imaging of identifying elevations in LV filling pressure—the hallmark of symptomatic diastolic dysfunction. Elevated LV filling pressure carries strong prognostic value in patients with heart failure, and its estimation using the E/Ea ratio is a similarly powerful prognosticator in various cardiac grades.
diseases. In this study, increasing degrees of concentric remodelling were associated with impaired relaxation and reduced early diastolic myocardial velocity, but not with significantly increased E/Ea ratio. Concentric hypertrophy, however, impacted adversely upon both the isotropic properties of the LV and its filling pressure.

We observed the phenomenon of enhanced longitudinal function and augmented EF with increasing degrees of concentric remodelling, but when remodelling was associated with increased LV mass, deteriorating LV function was accompanied by increased LV filling pressure. The classical views of Grossman and Meerson concerning the hypertrophic growth response of the LV to pressure overload asserts that myocyte thickening is a compensatory response to normalize wall-stress. Adaptive remodelling with augmented systolic function has been demonstrated in transgenic hypertrophic rat heart models with selective activation of extracellular signal-regulated kinase, an important member of the mitogen-activated protein kinase pathway. However, experimental studies have also questioned the wall-stress hypothesis with evidence that increased wall thickness can be maladaptive and attenuate systolic function. Evidence of LV hyperfunction associated with changes in LV geometry has not been demonstrated in a clinical study of hypertensive subjects before. The MESA study, which also employed quantitative parameters of regional myocardial function, assessed the effects of LV geometry upon systolic function in a cohort with normotensive and hypertensive individuals. Cardiac MRI derived peak systolic circumferential strain and LVEF decreased with increasing degrees of concentric remodelling in men. However, in women, a gradual increase in function was initially observed with evidence of dysfunction occurring in the highest quintile of mass to volume ratio, with the authors concluding that a degree of concentric remodelling enhances myocardial function up to a threshold that differs in men and women.

Limitations

As the design of this present study is cross-sectional, it is difficult to establish causality. Pre-existing impairments in myocardial function may have itself led to LVH/increased RWT through the activation of neurohumoral pathways. Long-term follow-up of this cohort will be able to clarify the progression of the early manifestations of hypertensive heart disease described here and whether subjects with LVH are more likely to develop heart failure compared with individuals with non-hypertrophic concentric remodelling. Another limitation of the study is the use of an office-based sphygmomanometer technique for measuring BP rather than measuring ambulatory 24 h BP. However, we used standard criteria to define the presence of hypertension which included ascertainment of a previous history of hypertension and/or the use of antihypertensive medications, both of which were likely to have been determined by office-based BP measurements in the majority of the subjects.

Conclusion

In this bi-ethnic cohort, subclinical impairment of cardiac function was evident in hypertensive subjects with LVH. However, non-hypertrophic concentric remodelling appears to provoke a compensatory systolic response of the LV to pressure load physiology.

Funding

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Conflicts of interest: none.

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