Clinical research

Left ventricular concentric geometry is associated with impaired relaxation in hypertension: the HyperGEN study

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Aims We tested the hypothesis that abnormal left ventricular (LV) relaxation is associated with concentric LV geometry.

Methods and results Doppler LV filling properties were studied in 1384 hypertensive participants without cardiovascular disease, from the HyperGEN population (731 women, 784 obese, 236 diabetic) and compared in four LV geometry groups; normal, concentric remodelling (3.5%), eccentric (23%), and concentric LV hypertrophy (4%), based on echocardiographic LV mass index (in g/m2.7). Abnormal LV relaxation was identified by European Society of Cardiology criteria in 275 subjects (20%). After accounting for significant confounders, E/A ratio and isovolumic relaxation time were not related to the presence of LV hypertrophy, but indicated abnormal relaxation when LV geometry was concentric (both P, 0.0001). Deceleration time of E velocity was prolonged with LV hypertrophy (P < 0.03), but the behaviour in relation to concentric LV geometry differed in the presence (prolonged) or absence (reduced) of LV hypertrophy (P = 0.05), a difference independently related to the magnitude of both transmitral gradients and stroke volume (all P < 0.05). Logistic regression showed that, compared with normal LV geometry, the odds of abnormal LV relaxation was 2.3-fold greater when LV geometry was concentric and that LV hypertrophy conferred a borderline higher risk than normal LV mass.

Conclusions In hypertensive individuals without prevalent cardiovascular disease from a multi-ethnic population-based sample, delayed LV relaxation is independently associated with concentric LV geometry.

KEYWORDS
Cardiac function; Hypertrophy; Arterial hypertension; Diastolic function; Cardiovascular risk

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Introduction

Abnormalities of left ventricular (LV) filling are frequently reported in arterial hypertension, especially characterized by impaired relaxation. There is sufficient information to attribute part of these abnormalities to the increased LV mass consequent to arterial hypertension, but loading conditions influencing the pattern of LV geometry also have major impact on early LV filling. Whether the pattern of LV geometry (i.e. concentric or eccentric) is associated with specific abnormalities of LV filling is still uncertain. However, the correlation reported between abnormal relaxation and abnormal midwall shortening suggests that concentric geometry might be especially important for determination of characteristics of early diastolic filling. Accordingly, this study has been designed to evaluate whether LV concentric geometry matches prolonged LV relaxation in the hypertensive population of the HyperGEN study, in the presence of normal LV systolic function.

Methods

Study population

The HyperGEN study is a component of the NHLBI Family Blood Pressure Program, designed to assess the genetic basis of hypertension in population-based samples. The HyperGEN study is a cross-sectional survey based on a sibling-pair design that recruited persons with onset of hypertension before age 60, and at least one additional hypertensive sibling who could be enrolled in the study. The population is comprised of 2466 participants (2103 hypertensive and 363 normotensive), including obese individuals and type 2 diabetics, while excluding type 1 diabetes. Further details about recruitment and characteristics have previously been reported.

Hypertensive participants were initially considered for the present analysis. For our purpose, we excluded all individuals with prevalent cardiovascular disease [myocardial infarction, angina, coronary artery bypass grafting (CABG), percutaneous transluminal coronary angiography (PTCA), transient ischaemic attack (TIA) and/or stroke, and congestive heart failure], atrial fibrillation, significant aortic and/or mitral valve disease (by colour Doppler), or an ejection fraction <50%. Thus, 1384 subjects were analysed, with normal LV systolic function, including obese individuals and participant with type 2 diabetes.

Metabolic profile

Type 2 diabetes mellitus was diagnosed if fasting blood glucose was >126 mg/dL or when hypertensive participants were taking hypoglycaemic medications. Obesity was identified as body mass index (BMI) >30 kg/m² in both genders.

Anti-hypertensive therapy with one or more medications was used in 75% of hypertensive individuals selected for the present analysis. Therefore, anti-hypertensive medication classes were considered in analyses as covariates.

Echocardiographic methods

Imaging and Doppler echocardiograms were performed using standardized acquisition methods employed in multiple studies from the Echocardiography Reading Centre. Measurements were made as previously reported, from M-mode or 2D-images according to the recommendations of the American Society of Echocardiography. LV mass was calculated and normalized by height². Relative wall thickness was calculated as posterior wall thickness/LV internal radius. LV concentric geometry was identified when relative wall thickness was >0.42 and LV hypertrophy when LV mass index was >49.2 g/m² for men and 46.7 g/m² for women. The combinations of LV mass index and relative wall thickness defined four LV geometric patterns: normal geometry, concentric remodelling, eccentric LV hypertrophy, and concentric LV hypertrophy.

Stroke volume was generated from Doppler interrogation of transaortic flow at aortic annular level and aortic cross-sectional area and normalized by z-derived LV end-diastolic volume to generate ejection fraction. LV systolic function was also estimated by midwall shortening.

Pulsed Doppler interrogation of mitral inflow was performed as previously reported. Isovolumic relaxation time (IVRT), peak E and A velocities, and deceleration time of E-velocity were measured as described. Definition of abnormal LV relaxation was made according to the European Society of Cardiology guidelines, using IVRT (>92 ms up to 30 years, >100 ms between 31 and 50 years, and >105 ms over 50) or the combination of E/A ratio (<1 up to 50 years, <0.5 over 50) and deceleration time of E velocity (>220 ms up to 50, >280 over 50). The other participants were classified as ‘normal relaxation’. Reliability of Doppler-echocardiographic measures from our laboratories have been previously reported.

Statistical analysis

Data were analysed using SPSS 9.0 software (SPSS, Chicago, IL, USA). Mean ± 1 SD are shown for continuous variables and χ² distribution (with Monte Carlo method for computation of exact two-tailed P-value, when appropriate) was used for categories. Continuous variables were tested to detect substantial deviations from normality by computing the Kolmogorov-Smirnov Z. As the assumption of satisfactory normal distribution was met for all variables, there was no need to manipulate the data.

LV hypertrophy and LV geometry effects were evaluated by two-factor analysis of covariance in a full-factorial design, using Type III sums of squares. With this procedure, interaction between the two factors was also studied. Comparison was adjusted for relevant confounders, including age, sex, race, presence of diabetes, BMI and type of anti-hypertensive therapy (using indicator variables for diuretics, β-blockers, ACE-inhibitors, Ca ++ channel-blockers, and AT1-receptor inhibitors or other vasodilators). Estimated marginal means are given and displayed in figures, after adjustment for the mean of covariates.

Logistic regression analysis was used for classification based on diastolic patterns (i.e. normal vs. abnormal relaxation), by an enter procedure. Simple contrast (with normal LV geometry as the reference) was used for categorical variables. The null hypothesis was rejected at two-tailed P ≤ 0.05.

Results

Characteristics of the study population

Among the 1384 hypertensive participants, 1109 (or 80%), 731 women, 408 Caucasian) had normal relaxation and 275 (or 20%, 155 women, 105 Caucasian) had abnormal
LV relaxation. Obesity was present in 57% of participants with normal relaxation and 54% of those with abnormal relaxation; prevalence of diabetes was 17 and 19%, respectively (both \( P > 0.2 \)).

In this population of hypertensive adults, 317 (23%) had eccentric LV hypertrophy (74% women; 73% obese), 55 (4%) had concentric LV hypertrophy (71% women; 58% obese), and 49 (3.5%) had concentric LV remodelling (71% women; 59% obese). The other subjects (958 or 70%) exhibited normal LV geometry (60% women; 51% obese; both \( P < 0.0001 \)). Diabetes was present in 15% of participants with normal LV geometry, 18% with concentric remodelling, 20% with eccentric LV hypertrophy, and 36% with concentric LV hypertrophy (\( P < 0.001 \)).

Hypertensive participants with abnormal LV relaxation had similar age, BMI, heart rate, plasma glucose and cholesterol, and ejection fraction, but higher blood pressure and lower midwall shortening than subjects with normal relaxation, even after adjusting for covariates (Table 1).

### LV geometry and diastolic filling pattern

Diastolic characteristics were compared among the different LV geometric patterns. Abnormal LV relaxation was present in 18% (173 of 963) of hypertensive subjects with normal LV geometry, in 31% (15 of 49) of those with concentric LV remodelling, in 20% (64 of 317) of those with eccentric LV hypertrophy, and in 42% (23 of 55) of those with concentric LV hypertrophy (\( P < 0.0001 \)).

Figure 1 displays that, after accounting for covariates, peak E velocity was higher in the presence, than in the absence, of LV hypertrophy (\( P < 0.03 \)), but was not significantly different between patients with normal or concentric LV geometry. Peak A velocity was higher with, than without, LV hypertrophy (\( P < 0.002 \)), but also when LV geometry was concentric (\( P < 0.02 \), with

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**Table 1** General characteristics of hypertensive individuals in relation to LV diastolic properties; estimated marginal means adjusted for age, sex, race, presence of diabetes, BMI, and type of anti-hypertensive therapy ± 1 SD are displayed.

<table>
<thead>
<tr>
<th></th>
<th>Normal relaxation ((n = 1109))</th>
<th>Abnormal relaxation ((n = 275))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)(^a)</td>
<td>53.33 ± 10.89</td>
<td>54.37 ± 11.09</td>
<td>0.158</td>
</tr>
<tr>
<td>BMI ((\text{kg/m}^2))(^a)</td>
<td>31.99 ± 6.93</td>
<td>31.77 ± 6.74</td>
<td>0.637</td>
</tr>
<tr>
<td>Plasma glucose ((\text{mg/dL}))(^a)</td>
<td>108.42 ± 41.43</td>
<td>111.65 ± 44.61</td>
<td>0.254</td>
</tr>
<tr>
<td>Plasma cholesterol ((\text{mg/dL}))(^a)</td>
<td>201.00 ± 37.91</td>
<td>200.99 ± 38.60</td>
<td>0.994</td>
</tr>
<tr>
<td>Systolic BP ((\text{mmHg}))</td>
<td>131.87 ± 20.16</td>
<td>136.84 ± 24.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP ((\text{mmHg}))</td>
<td>74.39 ± 11.07</td>
<td>76.81 ± 13.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure ((\text{mmHg}))</td>
<td>57.48 ± 15.76</td>
<td>60.03 ± 17.76</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Heart rate ((\text{beats/min}))</td>
<td>68.97 ± 10.85</td>
<td>68.09 ± 12.37</td>
<td>0.224</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>66.45 ± 5.65</td>
<td>66.37 ± 6.01</td>
<td>0.835</td>
</tr>
<tr>
<td>Midwall shortening (%)</td>
<td>17.38 ± 1.77</td>
<td>16.90 ± 1.95</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^a\)Unadjusted value by one-factor ANOVA. BP, blood pressure.
the highest value when LV hypertrophy and concentric geometry coexisted. The E/A ratio was not influenced by the presence of LV hypertrophy, but it was lower with concentric than with normal LV geometry \((P < 0.0001, \text{Figure 1})\). IVRT was prolonged with concentric LV geometry, and was only slightly influenced by the presence of LV hypertrophy \((P = 0.05, \text{Figure 1A})\). Deceleration time of E velocity was prolonged with LV hypertrophy \((P = 0.05, \text{Figure 1B})\), and was unaffected by LV geometry, as it was prolonged with concentric LV hypertrophy, while being reduced with concentric LV remodelling, a difference that was statistically significant \((P = 0.05, \text{two-factor interaction})\).

**Figure 2** shows that stroke volume was higher in the presence than in the absence of LV hypertrophy \((C)\) and lower when LV geometry was concentric \((P < 0.0001)\). Stroke volume positively correlated with ANCOVA residuals (i.e. adjusting for LV hypertrophy, LV geometry, age, sex, race of diabetes, BMI, and type of anti-hypertensive therapy) of peak E \((r = 0.13, P < 0.0001)\), peak A velocity \((r = 0.11, P < 0.0001)\), and deceleration time of E-velocity \((r = 0.07, P < 0.008)\). No relations were found with residuals of IVRT or E/A ratio.

Logistic regression, controlling for the effects of sex, obesity, and diabetes showed that the probability of abnormal LV relaxation was 2.3-fold higher when LV geometry was concentric and that LV hypertrophy conferred a borderline higher probability of prolonged relaxation than normal LV mass (Table 2).

### Discussion

In the present analysis, we tested the hypothesis that concentric LV geometry is a major correlate of abnormal LV relaxation, in participants from a bi-ethnic survey, free of prevalent cardiovascular diseases other than arterial hypertension and with normal systolic LV chamber function. The selection of subjects with normal ejection fraction allowed minimization of the chance of underlying restrictive physiology, though it could not control for the possible increased myocardial stiffness possibly co-existing with prolonged relaxation. We found that impaired LV relaxation is independently associated with concentric LV geometry and, as expected, is also characterized by mild midwall dysfunction.\(^2,3,15,26,27\) Association with increased LV mass is substantially weaker.

Previous observations reported relations between impaired LV filling and LV hypertrophy,\(^1,4,6,30,31\) which already raised the possibility, though did not prove, that LV geometric pattern could influence LV filling characteristics also independently of the amount of LV mass. In a group of 94 hypertensive patients, indices of abnormal relaxation were more impaired in the presence of concentric LV geometry.\(^32\) In the LIFE study, Watchell et al.\(^33\) found that, in the context of a markedly prolonged average IVRT, the degree of impaired LV relaxation differed significantly among patients with different LV geometric patterns, primarily because of association with increased
LV mass. This observation was influenced by the very high prevalence of LV hypertrophy and very low proportion of concentric LV remodelling (mostly by study selection) among the LIFE patients. With this selection, based on excluding subjects with normal LV mass, concentric LV hypertrophy could be expected to be characterized by greater LV mass than eccentric LV hypertrophy.34

In a large sample of hypertensive patients studied in a clinical setting in Italy, with high prevalence of concentric LV geometry, we have recently shown that the E/A ratio is lower when LV geometry is concentric, remarkably because a higher late transmitral gradient, as the hallmark of greater left atrial ejection force.35 Findings from the present study, in a population with mild LV geometric abnormalities (and low prevalence of concentric LV geometry), indicate that abnormal LV relaxation is in fact most related to concentric LV geometry and to an increase in late transmitral gradient.

The association between concentric LV geometry and abnormal relaxation can be explained by a number of mechanisms. Loading conditions (volume-pressure) differ between the two LV geometric patterns14 and relaxation is markedly influenced by pressure overload.3,13,36,37 which is greater in the presence of concentric LV geometry.14 Concentric LV geometry is also associated with unfavourable metabolic abnormalities,38,39 which are thought to influence cellular mechanisms of active relaxation.40,41 Pressure overload-dependent abnormalities of coronary microcirculation and fibrosis-related extracellular matrix disarray might also interfere with normal LV relaxation.42–44 The different magnitude of absolute early and late transmitral gradients and the time of deceleration of early filling (seen in Figure 2) also suggest that mean atrial pressure is higher when LV hypertrophy is present (likely due at least in part to greater circulating volume, as suggested by analysis of ANCOVA residuals) but these different gradients do not affect LV relaxation measures, consistent with the demonstration that preload does not influence relaxation.12,45

Although attention has been paid to minimize the interference of increased myocardial stiffness (by excluding subjects with even mildly reduced ejection fraction), the simple Doppler method used in this epidemiological survey cannot account for some late diastolic effect of increased myocardial stiffness. However, the possibility that some subjects with pseudonormal LV filling pattern were classified as normal could marginally influence diastole-based classification (and logistic analysis), while the strength of associations found among continuous variables would only be reduced by this potential misclassification. The association found in concentric LV remodelling among small stroke volume, reduced transmitral gradients, and faster deceleration of E velocity (as seen in Figure 2) suggests that circulating volume can, at least in part, explain the inconsistent diastolic filling characteristics of this LV geometric pattern. Other more recent techniques could better discriminate early LV relaxation from late myocardial compliance effects,46,47 but would not have been feasible on an epidemiological scale, especially at the time when the HyperGEN was projected.

Conclusion

In hypertensive individuals without prevalent cardiovascular disease from a bi-ethnic population-based study, delayed LV relaxation is independently associated with LV concentric geometry.

Acknowledgements

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Appendix: list of HyperGEN participating institutions and principal staff

<table>
<thead>
<tr>
<th>Network Center/Field Center</th>
<th>Principal Investigators</th>
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<tbody>
<tr>
<td>University of Utah</td>
<td>Steven C. Hunt, Roger R. Williams (deceased), HIlary Coon, Paul N. Hopkins, Janet Hood, Lily Wu, Jan Skuppin</td>
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<tr>
<td>University of Alabama at Birmingham Field Center</td>
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<tr>
<td>University of Minnesota Field Center</td>
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<tr>
<td>University of North Carolina Field Center</td>
<td>Gerardo Heiss, Barry I. Freedman, Kari North, Kathryn Rose, Amy Haire</td>
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<tr>
<td>Data Coordinating Center, Washington University</td>
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</tr>
<tr>
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<td>Mark Leppert, Steven C. Hunt, Jean-Marc Lalouel, Robert Weiss</td>
</tr>
<tr>
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<td>Susan E. Old, Millicent Higgins (retired), Cashell Jaquish, Martha Lundberg, Mariana Gerschenson</td>
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</tbody>
</table>
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