Tissue Doppler imaging describes diastolic function in men prone to develop hypertension over twenty years

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Introduction

Left ventricular hypertrophy (LVH) in hypertension determined by Cornell voltage product in ECG or by echocardiography is an independent risk factor of cardiovascular morbidity and mortality.1–3 LVH is rather strongly associated with heart failure and cardiac arrhythmias.4 The association between the degree of LVH in hypertension is related to both BP level and a pathophysiologic role of neurohormonal factors.5–7 We have previously demonstrated that arterial plasma vasopressin and aldosterone, predicts LV mass in middle-aged men who developed hypertension over a period of 20 years.8,9 In this cohort we did not find differences in diastolic function between the groups. However, the presence of LV diastolic dysfunction using conventional echo-Doppler parameters is often underestimated in hypertensive patients.10 Tissue velocities imaging (TVI) can be used to assess LV systolic and diastolic function in the myocardium and is promising as a more sensitive parameter regarding myocardial dysfunction.11

The aims of the present study were to assess whether myocardial velocities can differentiate diastolic LV function, and explore the relationship between myocardial velocities and LV parameters, in previously prospectively studied normotensives (NT), subjects who developed hypertension during follow-up (new HT) and sustained hypertensives (HT).

Methods

This present cohort cross-sectional study was done in 2004. Subjects of 60 years of age were divided into three prespecified groups, NT, new HT and HT (Figure 1), i.e. groups of subjects with clear differences in BP level, development and duration of the hypertensive disease.8 At baseline in 1984, they were all untreated and had normal ECG, ocular fundi, urinalysis and kidney function estimated by creatinine clearance.

All subjects were studied at the same time of the day in the same quiet room and at constant room temperature. The subjects fasted.
and abstained from smoking for the preceding 8 h and abstained from alcohol for the preceding 24 h before the studies. The Regional Committee for Medical Research Ethics approved the protocol. All the participants gave written consent.

**Subjects**

Fifty-six subjects (22 hypertensives and 34 normotensives) were available for examination. At the time of follow-up the NT (n = 17) had office BP 140/90 mmHg and 24 h BP ≥125/80 mmHg or were taking antihypertensive medication (n = 5). The same criteria were used for the HT (n = 22) and n = 16 were taking antihypertensive medication. They were all hypertensive at follow-up. Characteristics of the three present groups stratified according to BP registrations in 2004 are given in Table 1.

Five subjects were excluded because of coronary heart disease before analysis of systolic and diastolic parameters were performed. Examined subjects were all asymptomatic. They had no sign of coronary artery disease, cardiac arrhythmias, hypertrophic cardiomyopathy, valvular heart disease or reduced EF (EF > 50%).

**Echocardiography in 2004**

Echocardiography was done by one experienced investigator using a GE-Vingmed Vivid 7 echocardiograph (Horten, Norway) with a 1.7 MHz probe in second harmonic mode. The echo investigator had no knowledge about participants’ BP status. EF was calculated by the biplane method, and LV systolic dysfunction was defined as EF < 50%. Lateral and medial mitral annulus excursion (MAEMed and MAEMed) were measured. LV internal dimension and interventricular septal and posterior wall thickness were measured in end-diastole and end-systole according to the recommendations of the American Society of Echocardiography. LVH was defined as LV mass index > 116 g/m². Relative wall thickness (RWT) was calculated as 2 x posterior wall thickness in diastole (PWTd)/LV internal diameter in diastole (LVIdd). Increased RWT was present when this ratio was >0.43. Pulsed-wave (PW) recordings of the early diastolic (E) and atrial (A) wave, the E/A-ratio, E-wave deceleration time (DT), isovolumic relaxation time (IVRT) and pulmonary vein (PV) signal have been described previously. All participants were in sinus rhythm, and measurements up to three cycles were averaged.

Tissue velocities imaging (TVI) data were recorded digitally in the apical four-chamber view at a mean frame rate of 181 Hz. The post-processing procedure included measurement of tissue velocity profiles. The sample volumes were placed at the junction of the LV wall with the mitral annulus of the septal and lateral myocardial segments and two mid-ventricular sites in the same walls. The apical four chamber view was chosen to assess the longitudinal systolic and diastolic function. The cycles were transferred to a computer with a software package, which provided off-line data processing and analysis (Echopac, GE-VingMed). The positive peak tissue isovolumic velocity (IVC), positive systolic velocity (S'), early diastolic (E') and late diastolic (A') velocities and peak velocity of the isovolumic relaxation (IVR) were measured both at the lateral (lat) and medial (med) parts of the mitral annulus.

**Blood pressure measurements**

Office BP was measured using a manual mercury sphygmomanometer. Mean values for SBP and DBP were calculated on the basis of two BP measurements. Ambulatory BP was recorded with a validated oscillometric device (model 90207; Spacelab; Redmond, WA, USA). BP’s were measured every 20 min during daytime, from

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**Table 1** Characteristics of groups in 2004 (n = 51 male participants 62 years of age)

<table>
<thead>
<tr>
<th>Variable (years)</th>
<th>Normotensives n = 17</th>
<th>New HT n = 15</th>
<th>Hypertensives n = 19</th>
<th>ANOVA P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.1 ± 0.4</td>
<td>62.1 ± 0.4</td>
<td>62.5 ± 0.7</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 ± 2.9</td>
<td>26.6 ± 4.2</td>
<td>28.3 ± 3.8</td>
<td>0.100</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>134 ± 12</td>
<td>151 ± 11a</td>
<td>165 ± 25p,c</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>85 ± 6</td>
<td>96 ± 8t</td>
<td>102 ± 8s,c</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>102 ± 7</td>
<td>114 ± 8s</td>
<td>123 ± 13p,c</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>64 ± 7</td>
<td>64 ± 10</td>
<td>73 ± 14s</td>
<td>0.012</td>
</tr>
<tr>
<td>24 h SBP</td>
<td>118 ± 5</td>
<td>130 ± 13d</td>
<td>135 ± 13d</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24 h DBP</td>
<td>72 ± 4</td>
<td>79 ± 8s</td>
<td>85 ± 9t,c</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate.

ap < 0.005 new hypertensives vs. normotensives.
bp < 0.001 hypertensives vs. normotensives.
s < 0.01 hypertensives vs. new HT.
ap < 0.01 new hypertensives vs. normotensives.
s < 0.05 new hypertensives vs. normotensives.
Table 2  Left ventricular geometric and functional parameters of groups in 2004 (n = 51 male participants 62 years of age)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensives n = 17</th>
<th>New HT n = 15</th>
<th>Hypertensives n = 19</th>
<th>ANOVA P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass index (g/m²)</td>
<td>101 ± 17</td>
<td>111 ± 27</td>
<td>116 ± 21</td>
<td>0.051</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>199 ± 30</td>
<td>226 ± 66</td>
<td>235 ± 38</td>
<td>0.029</td>
</tr>
<tr>
<td>RWT (ms)</td>
<td>0.32 ± 0.05</td>
<td>0.36 ± 0.07b</td>
<td>0.36 ± 0.05c</td>
<td>0.025</td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>5.4 ± 0.4</td>
<td>5.4 ± 0.6</td>
<td>5.5 ± 0.4</td>
<td>0.485</td>
</tr>
<tr>
<td>LA area (cm²)</td>
<td>24 ± 4</td>
<td>24 ± 7</td>
<td>25 ± 4</td>
<td>0.508</td>
</tr>
<tr>
<td>E/A</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.3</td>
<td>1.2 ± 0.3</td>
<td>0.810</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>243 ± 53</td>
<td>207 ± 24</td>
<td>225 ± 54</td>
<td>0.268</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>85 ± 16</td>
<td>89 ± 12</td>
<td>88 ± 14</td>
<td>0.552</td>
</tr>
<tr>
<td>Ratio PVs/PVd</td>
<td>1.37 ± 0.22</td>
<td>1.36 ± 0.28</td>
<td>1.38 ± 0.28</td>
<td>0.907</td>
</tr>
<tr>
<td>Ratio PVs/PVd VTI</td>
<td>1.51 ± 0.29</td>
<td>1.40 ± 0.27</td>
<td>1.58 ± 0.36</td>
<td>0.530</td>
</tr>
<tr>
<td>EF (%)</td>
<td>57 ± 5</td>
<td>56 ± 5</td>
<td>57 ± 5</td>
<td>0.636</td>
</tr>
<tr>
<td>MAELat</td>
<td>17 ± 3</td>
<td>17 ± 2</td>
<td>16 ± 2</td>
<td>0.504</td>
</tr>
<tr>
<td>MAEMed</td>
<td>14 ± 2</td>
<td>14 ± 2</td>
<td>13 ± 2</td>
<td>0.311</td>
</tr>
<tr>
<td>CO (/l/min)</td>
<td>5.3 ± 0.8</td>
<td>5.0 ± 0.6</td>
<td>5.5 ± 0.9</td>
<td>0.476</td>
</tr>
</tbody>
</table>

LV, left ventricular; RWT, relative wall thickness; LVIDd, left ventricular internal diameter in diastole; LA, left atrium; E/A, early diastolic and atrial wave of mitral flow; DT, deceleration time; IVRT, isovolumetric relaxation time; Ratio PVs/PVd, ratio of the pulmonal vein velocity in systole and diastole; Ratio PVs/PVd VTI, ratio of the velocity time integral of the pulmonary vein in systole and diastole; EF, ejection fraction; MAELat, mitral annulus excursion (lateral) and MAEMed, mitral annulus excursion (medial); CO, cardiac output.

*P < 0.01 hypertensives vs. normotensives.
**P < 0.05 new hypertensives vs. normotensives.
***P < 0.05 hypertensives vs. normotensives.

LV systolic and diastolic function

There were no significant differences (ANOVA) between the groups regarding systolic function estimated by EF, MAELat, and MAEMed and diastolic function estimated by E/A ratio, DT of mitral flow, IVRT or PV signal. LV parameters by echocardiography in the groups are given in Table 2.

7 a.m. to 10 p.m. and every 30 min during the night. The average of all measurements is given as 24-h SBP and DBP. Cuffs with bladders of appropriate size were used. The same device was used in all subjects.

Statistics

SPSS 12.1 (SPSS Inc., Chicago, IL, USA) was used for data management and statistical analysis. Results are presented as mean ± SD. Parametric tests were used for normally distributed data. Non-normally distributed data were natural log (ln) transformed. After subdivision into 3 groups, sustained normotensives, new hypertensives and sustained hypertensives, comparisons were performed by ANOVA with linear trend analysis. Univariate relations between variables were assessed also by Spearman (r) correlation coefficient and further examined with multiple linear regression analysis using a stepwise procedure with assessment of co-linear diagnostics. Regression analysis was used to assess the relationship between E and S’, and the relationship between myocardial velocities and LV mass index. A 2-tailed P value < 0.05 was considered statistically significant.

Results

The cohort consisted of homogenous middle-aged Caucasian men, i.e. same gender, age and race. There were no significant differences in body build between the three groups. Significant BP differences between the groups regardless of antihypertensive treatment were demonstrated. Only small differences in LV geometric parameters were demonstrated. Heart rate (HR) differed between sustained HT versus sustained NT and new HT (Table 1).

LV systolic and diastolic function

There were no significant differences (ANOVA) between the groups regarding systolic function estimated by EF, MAELat and MAEMed and diastolic function estimated by E/A ratio, DT of mitral flow, IVRT or PV signal. LV parameters by echocardiography in the groups are given in Table 2. The conventional echocardiographic parameters did not correlate to EF in multivariate regression analysis.

There were no significant differences between the groups regarding systolic myocardial velocities. However, sustained HT, i.e. subjects with long-standing hypertensive disease and more pronounced BP elevation, had a lower numerical average S’ at the mitral annulus compared to NT and new HT, i.e. subjects who developed hypertension through follow-up. There were no significant findings between the groups regarding IVC. Regarding the diastolic TVI parameters, E are indicative of abnormal relaxation and recoil.18 ELat (P = 0.006) and EMed (i.e. myocardial E-velocity at the lateral and medial mitral annulus) (P = 0.041) demonstrated significant differences between NT and HT subjects. IVR gave no additive information about the diastolic function. There were no significant findings regarding E/LALat and E/EMed and gave no additive findings compared to the traditional diastolic parameters. E/E’, as a parameter for left ventricular filling pressure,19 both E/ELat (P = 0.002) and E/EMed (P = 0.003) gave significant differences between normotensives and hypertensives. (Table 3 and Figure 2a and b) Examination of mid segments of septum and lateral wall gave no additive information.

Significant bivariate correlations were found between SLat and ELat (r = 0.34, P = 0.020) and E/ELat (r = −0.29, P = 0.047). ELat was independently explained by SLat (R² = 0.24, P = 0.028) in regression analysis. E/ELat was also independently explained by SLat (R² = 0.14, P = 0.005). In both regression models LV mass index and BPs were entered as covariates.

Systolic and diastolic parameters vs. LV parameters

In univariate analysis of the study population LA dimension was positively correlated to LV mass index (r = 0.34, P = 0.018) and LV mass (r = 0.43, P = 0.003). RWT correlated...
Table 3  Left ventricular parameters of groups in 2004 (n = 56 male participants 62 years of age)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensives n = 17</th>
<th>New HT n = 15</th>
<th>Hypertensives n = 19</th>
<th>ANOVA P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVC_Lat (ms)</td>
<td>2.0 ± 1.4</td>
<td>2.0 ± 1.3</td>
<td>2.1 ± 1.4</td>
<td>0.812</td>
</tr>
<tr>
<td>IVC_Med (ms)</td>
<td>2.3 ± 1.6</td>
<td>2.1 ± 1.3</td>
<td>2.7 ± 1.4</td>
<td>0.458</td>
</tr>
<tr>
<td>S_Lat (cm/s)</td>
<td>7.0 ± 1.5</td>
<td>7.0 ± 1.3</td>
<td>6.0 ± 1.3</td>
<td>0.053</td>
</tr>
<tr>
<td>S_Med (cm/s)</td>
<td>6.4 ± 1.0</td>
<td>6.0 ± 0.9</td>
<td>6.0 ± 1.0</td>
<td>0.258</td>
</tr>
<tr>
<td>IVR_Lat (ms)</td>
<td>1.3 ± 1.2</td>
<td>1.2 ± 1.2</td>
<td>1.0 ± 1.0</td>
<td>0.539</td>
</tr>
<tr>
<td>IVR_Med (ms)</td>
<td>1.9 ± 1.6</td>
<td>1.2 ± 0.7</td>
<td>1.8 ± 1.5</td>
<td>0.857</td>
</tr>
<tr>
<td>E_Lat (cm/s)</td>
<td>8.7 ± 2.1</td>
<td>7.2 ± 2.2†</td>
<td>6.8 ± 1.3‡</td>
<td>0.006</td>
</tr>
<tr>
<td>E_Med (cm/s)</td>
<td>6.5 ± 1.3</td>
<td>6.5 ± 1.9</td>
<td>5.5 ± 1.0</td>
<td>0.041</td>
</tr>
<tr>
<td>A_Lat (cm/s)</td>
<td>7.3 ± 1.5</td>
<td>7.9 ± 1.9</td>
<td>7.2 ± 2.4</td>
<td>0.885</td>
</tr>
<tr>
<td>A_Med (cm/s)</td>
<td>8.2 ± 0.8</td>
<td>7.3 ± 0.9</td>
<td>7.7 ± 1.2</td>
<td>0.641</td>
</tr>
<tr>
<td>E/E_Lat</td>
<td>8.1 ± 2.3</td>
<td>10.9 ± 3.7‡</td>
<td>11.6 ± 2.6‡</td>
<td>0.002</td>
</tr>
<tr>
<td>E/E_Med</td>
<td>10.8 ± 2.8</td>
<td>11.6 ± 2.5</td>
<td>14.5 ± 4.2</td>
<td>0.003</td>
</tr>
</tbody>
</table>

IVC, isovolumic contraction; sys, systolic; IVR, isovolumic relaxation; E, early diastolic velocity; A, late diastolic velocity; lat, lateral basal part of left ventricle; med, medial basal part of left ventricle.

*P < 0.05 new hypertensives versus normotensives.

†P < 0.01 hypertensives versus normotensives.

‡P < 0.05 hypertensives versus new hypertensives.

§P < 0.05 hypertensives versus normotensives.

Figure 2 (A) Diastolic function. Comparison of E_Lat between the groups. NT, normotensives; new HT, new hypertensives; HT, hypertensives. ††P < 0.01 normotensives versus hypertensives; †P < 0.05 normotensives versus new hypertensives. (B) Diastolic function. Comparison of E/E_Lat between the groups. NT, normotensives; new HT, new hypertensives; HT, hypertensives. †† P < 0.01 normotensives versus hypertensives; †P < 0.05 normotensives versus new hypertensives.

positively with IVRT (r = 0.46, P = 0.001) and demonstrated a negative relation with E/A ratio (r = -0.34, P = 0.016). MAE_Lat showed a positive correlation to EF (r = 0.36, P = 0.013). There was no relationship between PV-signal and ventricular parameters. None of the conventional echocardiographic parameters correlated significantly to LV mass index in multivariate regression analysis.

S_Lat correlated negatively to LV mass index (r = -0.31, P = 0.026) and LV mass (r = -0.31, P = 0.026). E_Lat showed a negative correlation to both LV mass index (r = -0.32, P = 0.031) and LV mass (r = -0.39, P = 0.007) and E/E_Lat demonstrated a positive association both to LV mass index (r = 0.31, P = 0.035) and LV mass (r = 0.43, P = 0.003). Further details are given in Table 4. In the most significant multivariate regression models LV mass index as independent variable correlated to E_Lat (R² = 0.12, P = 0.032) and E/E_Lat (R² = 0.11, P = 0.036). S_Lat and BPs were entered as covariates.

Discussion

In the present cohort cross-sectional study we assessed conventional echocardiographic and TVI parameters regarding diastolic function and explored the relationship to LV
parameters in groups of sustained hypertensives, subjects who developed hypertension during follow-up and sustained normotensives previously prospectively studied. A method for reliably detecting the onset of LV systolic and diastolic dysfunction in subjects with essential hypertension before transition to irreversible damage of the myocardium would be of crucial importance. Significant differences between groups in $E_{\text{Lat}}$ and $E/E_{\text{Lat}}$ were demonstrated. Associations between $E_{\text{Lat}}$ and $E/E_{\text{Lat}}$ versus $S_{\text{Lat}}$ and LV mass index were also found.

Peak early diastolic mitral annulus velocity ($E$) is associated with mortality in patients with cardiac disease.22–24 $E$ is relatively load-independent and correlates to isovolumic relaxation and is indicative of abnormal relaxation. However, $E$ of the mitral annulus occurs after the pressure decline and LA-LV pressure cross-over and is probably more a measure of recoil and also related to the previous systole.18 In the present study both $E_{\text{Lat}}$ and $E_{\text{Med}}$ describe significant differences between the groups in LV diastolic function and might reflect a reduction in systolic function as well. Also in subjects who developed hypertension through follow-up there are decreased early diastolic myocardial velocities at the plane of mitral annulus compared to normotensive controls. Furthermore, LV pressure overload predispenses to neurohormonal activation and ventricular remodeling, but conventional parameters are of limited value estimating LV filling pressures when EF is within normal ranges.25–27 However, $E/E'$ has demonstrated satisfying correlates to pulmonary capillary wedge pressure and LV filling pressures, and this ratio is a reliable variable for diastolic dysfunction and future cardiac morbidity and mortality.19 Both $E/E_{\text{Lat}}$ and $E/E_{\text{Med}}$ showed significant differences within the cohort with controls and hypertensives with no known cardiac diseases and normal EF. Increased fibrosis in the LV is known to be a part of the pathological process in hypertensive subjects.28 It could possibly explain both the lower myocardial diastolic velocities of the mitral annulus and reduced mitral flow to annulus ratio of hypertensives. $E/E'$ may reflect changes in the myocardium before significant changes in filling pressures. In clinical practice it is necessary to have parameters easy to obtain together with appropriate reproducibility. We found the lateral part of the mitral annulus to better discriminate diastolic function between normotensive and hypertensive subjects with normal EF and no known cardiac diseases. Lateral myocardial tissue parameters might be the most sufficient to obtain in daily clinical practice.

Previous studies have demonstrated significant differences in $S'$ between normotensive and hypertensive subjects,29 but the latter subjects had higher BPs than subjects in the present study. Differences in systolic and diastolic velocities have been observed between healthy controls and subjects with pronounced LVH.20 Yet another study has described differences in diastolic TVI parameters between hypertensive and normotensive subjects.21 However, there is a numerical difference between the groups in our cohort regarding $S'$, and a light depression of systolic function in both groups with hypertensive disease cannot be ruled out. The significant bivariate correlations between $S'$ versus $E'$, and $S'$ as an explanatory variable of $E'$ in multivariate regression analysis might explain a relationship between systolic and diastolic function. Reducitions in $S'$ and $E'$ have also been demonstrated in a larger study.30 These subjects had a variety of cardiac diseases and make the result somewhat more difficult to interpret regarding isolated hypertensive disease. Relationships between brain natriuretic peptide (BNP) compared to $S'$ and $E'$ have also been shown in patients with a spectrum of cardiac diseases other than hypertension, indicating a coherence between development of heart failure and reduced $S'$ and $E'$.31 In other conditions, e.g. hypertrophic cardiomyopathy, mitral valve disease and diabetes, early impairment of systolic and diastolic velocities derived by TDI is demonstrated and probably supports the present findings among subjects with hypertension.32–35

There were relationships between diastolic myocardial tissue parameters and LV mass index, both in bivariate correlations and regression analysis. Subjects who developed hypertension through 20 years and sustained hypertensives probably have a higher LV mass index than normotensives, although not significant. However, they have a significantly lower $E_{\text{Lat}}$ and higher $E/E_{\text{Lat}}$ compared to normotensive controls. In these subjects with normal or mild increased LV mass index, even small increases might be associated with reduced diastolic function. Changes in relaxation, recoil and increased fibrosis and pressure overload could explain the abnormalities in the mitral annulus motion and the relation to LV mass index in hypertensive subjects.

As previously discussed,8 the prospective study was invasive, i.e. arterial hormones, and this limited the sample size. Many of the patients with hypertension used antihypertensive medication, which may have interfered with the systolic and diastolic myocardial function. Caution should be exerted in interpreting the results as there are not yet defined reference values for myocardial velocities.

Conclusion

Myocardial diastolic velocities and mitral flow to annulus ratio differentiated LV function between the hypertensive and normotensive groups. The parameters probably parallel changes in LV mass index, reflecting pathophysiologic mechanisms regarding relaxation, recoil and contraction. Lateral myocardial tissue parameters might be the most sufficient to obtain in daily clinical practice.

Acknowledgments

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References


