Longitudinal Changes in Left Ventricular Diastolic Function in a General Population

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Background—Data on changes in left ventricular diastolic function (LVDF) over time in the general population are sparse. We, therefore, investigated in the population cohort clinical correlates of longitudinal changes in Doppler diastolic indexes analyzed as continuous measures and assessed factors predictive of the changes in LVDF grades over time.

Methods and Results—We measured early and late diastolic peak velocities of mitral inflow (E and A) by conventional Doppler, and the mitral annular velocities (e' and a') by tissue Doppler imaging in 650 participants (mean age, 50.7 years) at baseline and after 4.7 years (5th to 95th percentile, 3.7–5.4). In stepwise regression, the multivariable-adjusted correlates of the change in the transmitral and tissue Doppler imaging diastolic indexes included sex, age, baseline serum insulin, blood pressure, and heart rate. During follow-up, LVDF grades remained unchanged in 87.2% (95% confidence interval, 84.6%–89.8%), improved in 3.7% (95% confidence interval, 2.25%–5.15%), and worsened in 9.1% (95% confidence interval, 6.9%–11.3%). Baseline age was a strong predictor of worsening of LVDF from normal/mild grade to more advanced grade (odds ratio, 3.22; P<0.0001). A doubling of baseline insulin was associated with a 184% increase in the odds of worsening of LVDF (P<0.0001). Moreover, baseline diastolic blood pressure and the change in systolic blood pressure over time predicted worsening of LVDF (P<0.014).

Conclusions—The key findings of this study are that LVDF tended to worsen over time and was associated with advanced age, higher baseline insulin level, and hemodynamic parameters, such as heart rate and blood pressure. (Circ Cardiovasc Imaging. 2015;8:e002882. DOI: 10.1161/CIRCIMAGING.114.002882.)

Key Words: Doppler echocardiography • epidemiology • left ventricular function • longitudinal survey

Because life expectancy and the prevalence of risk factors, such as hypertension, obesity, insulin resistance and diabetes mellitus are rising globally, heart failure is growing into a major health problem. Impairment of left ventricular diastolic function (LVDF) appears early in the course of heart disease. Recent heart failure guidelines, therefore, place special emphasis on the detection of subclinical LV dysfunction and the timely identification of risk factors for progression to symptomatic heart failure. Conventional echocardiography combined with new imaging techniques such as tissue Doppler imaging (TDI) is a sensitive tool to detect early subclinical deterioration of LV function. Recent community-based studies revealed a higher than hitherto expected prevalence of LV diastolic dysfunction, using comprehensive conventional and TDI echocardiographic imaging. For instance, in the Flemish Study on Environment, Genes, and Health Outcomes (FLEMENGHO), the frequency was 27.3%. LV diastolic dysfunction is also associated with increased risk for various cardiovascular diseases. However, data on the longitudinal tracking of LVDF over time are sparse. To our knowledge, community-based studies explored the factors predictive of the development of subclinical LV diastolic dysfunction. In the clinical setting, Aljaroudi et al reported that in patients with normal baseline LV ejection fraction, worsening of diastolic function grade was an independent predictor of mortality. However, serial imaging studies are also needed to clarify the clinical correlates of change in LVDF indexes. These data are currently lacking. We, therefore, investigated...
in the FLEMENGHO cohort clinical correlates of longitudinal changes in Doppler diastolic indexes analyzed as continuous measures. We also assessed factors predictive of the changes in LVDF grades over time.

Methods

Study Participants

The Ethics Committee of the University of Leuven approved the FLEMENGHO study. From August 1985 until December 2005, we identified a random population sample stratified by sex and age from a geographically defined area in northern Belgium.12 Households, defined as those who lived at the same address, were the sampling unit. We numbered households consecutively, and generated a random number list by use of SAS random function. Households with a number matching the list were invited; household members aged >18 years were eligible. From 2005 to 2009, we invited 1031 former participants for a re-examination at our field center, including echocardiography (Figure 1). All our participants at baseline were ambulatory and physically apt to come to the examination center. We have to exclude 27 patients who were bed-ridden or institutionalized. We obtained informed written consent from 828 subjects (participation rate, 80%). To study the changes of LVDF, we invited these participants for a follow-up examination on average 5 years after their first echocardiographic examination. We excluded 147 participants because they died (n=25), were lost to follow-up (n=19) or declined invitation to participate in the echocardiographic examination (n=103) (Figure 1). For this analysis, we additionally excluded 16 subjects because of atrial fibrillation at baseline (n=8) or at follow-up (n=6) or the presence of an artificial pacemaker (n=4), or because of diastolic function could not be reliably determined (n=13). Thus, the number of subjects statistically analyzed totaled 650.

Echocardiography

The participants refrained from smoking, heavy exercise, and drinking alcohol or caffeine-containing beverages for at least 3 hours before echocardiography. The BP during echocardiography was the average of 2 readings, obtained with a validated OMRON 705IT device (Omron Corp, Tokyo, Japan) at the end of the echocardiographic examination.

Data Acquisition

One experienced physician (T.K.) did both ultrasound examinations,5 using a Vivid7 Pro and Vivid E9 (GE Vingmed, Horten, Norway), respectively, interfaced with a 2.5- to 3.5-MHz phased-array probe, according to the recommendations of the American Society of Echocardiography.13 With the subjects in partial left decubitus and breathing normally, the observer obtained images, together with a simultaneous ECG signal, along the parasternal long and short axes and from the apical 4- and 2-chamber long-axis views. All recordings included at least 5 cardiac cycles and were digitally stored for off-line analysis. M-mode echocardiograms of the LV were recorded from the parasternal long-axis view under control of the two-dimensional (2D) image. The ultrasound beam was positioned just below the mitral valve at the level of the posterior chordae tendineae. To record pulsed wave Doppler transmitial and pulmonary vein (PV) flow velocities from the apical window, the observer positioned a 1- to 3-mm Doppler sample volume at the mitral valve tips and in the right superior PV, respectively.

Using TDI, the observer recorded low-velocity, high-intensity myocardial signals at a high frame rate (>190 frames per second), while adjusting the imaging angle to ensure a parallel alignment of the ultrasound beam with the myocardial segment of interest. To record mitral annulus velocities, from the apical window, the sonographer placed a 5-mm Doppler sample at the septal, lateral, inferior, and posterior sites of the mitral annulus.

Off-Line Analysis

The postprocessing of echocardiograms was performed by an observer (T.K.) blinded to the participants’ characteristics in a few weeks after the initial and follow-up examinations. Digitally stored images were analyzed using a workstation running the EchoPac software (GE Vingmed). All measurements were averaged ≥3 heart cycles for statistical analysis. The LV internal diameter and interventricular septal and posterior wall thickness were measured at end-diastole from the 2D-guided M-mode tracing. When optimal orientation of M-mode ultrasound beam could not be obtained, the reader performed linear measurements on correctly oriented 2D images. End-diastolic LV dimensions were used to calculate LV mass by an anatomically validated formula according to the recommendations of the American Society of Echocardiography.14 We calculated LV ejection fraction from LV end-systolic and end-diastolic volumes measured from the apical 4 and 2 chambers views, using the standard Simpson method. We measured left atrial (LA) diameters in 3 orthogonal planes, such as the parasternal long, lateral, and supero-inferior axes. LA volume index was calculated using the prolate-ellipsoid method and was indexed to body surface area.

From the transmitral flow signal, we measured peak early diastolic velocity (E), peak late diastolic velocity (A), the E/A ratio, and A flow duration. From the PV flow signal, we measured the duration of PV reversal time during atrial systole. From the TDI recordings, we measured peaks systolic (s’) and early (e’) and late (a’) diastolic mitral annular velocities, and the e’/a’ ratio at the 4 acquisition sites (septal, lateral, inferior, and posterior). We calculated the E/e’ ratio by dividing transmitral E peak by e’ averaged from the 4 acquisition sites.

We combined the mitral inflow and TDI velocities to classify the stages of LV diastolic dysfunction at baseline and follow-up as previously described.5,6 The first group included subjects with an abnormally low age-specific transmitral E/A ratio indicative of impaired relaxation, but without evidence of increased LV filling pressures (E/e’≤8.5). The second group had mild-to-moderate elevated LV filling pressure (E/e’>8.5), and E/A ratio within the normal age-specific range. We also used the differences in durations between the mitral A flow and the reverse PV flow during atrial systole (Ad-CARD+10) or LA volume index (≥29 ml/m2) to confirm possible elevation of the LV filling pressures in group 2. We reclassified ≥5% of subjects as having normal diastolic function, because, although their E/e’ was between 8.5 and 10, other echocardiographic parameters, including PV flow and LA volume index were normal. Group 3 had an elevated E/e’ ratio and an abnormally low age-specific E/A ratio (combined dysfunction).

Intraobserver (T.K.) reproducibility coefficient of a measurement was the 2SD interval about the mean of the relative differences across pairwise readings. As reported previously,14 for conventional Doppler parameters, the reproducibility was 5.0% for transmitral E peak and

Figure 1. Flowchart for participants in the study. FLEMENGHO indicates Flemish Study on Environment, Genes, and Health Outcomes; and LV, left ventricular.
6.6% for transmitral A peak. For tissue Doppler velocities, the reproducibility across the 4 sampling sites ranged from 4.5% to 5.3% for e′ velocities and from 4.0% to 4.5% for a′ velocities.

### Other Measurements

The conventional BP was the average of 5 consecutive auscultatory readings obtained with the subject in the seated position. Hypertension was defined as a BP of at least 140 mm Hg systolic or 90 mm Hg diastolic or as the use of antihypertensive drugs. Body mass index was weight in kilograms divided by the square of height in meters. Venous blood samples were drawn for measurement of blood glucose, serum insulin, and total cholesterol. Diabetes mellitus was determined by self-reported diagnosis, fasting glucose level of at least 126 mg/dL, or use of antidiabetic agents.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Participants</th>
<th>Echocardiographic Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Measurements</strong></td>
<td><strong>Conventional echocardiography</strong></td>
</tr>
<tr>
<td><strong>Examination 1</strong> (2005–2009)</td>
<td><strong>Examination 2</strong> (2009–2013)</td>
</tr>
<tr>
<td><strong>Anthropometrics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>50.7±14.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.5±4.28</td>
</tr>
<tr>
<td>Systolic pressure, mmHg</td>
<td>128.8±16.8</td>
</tr>
<tr>
<td>Diastolic pressure, mmHg</td>
<td>79.8±9.3</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>96.1±10.3</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>49.0±14.3</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>60.3±9.4</td>
</tr>
<tr>
<td><strong>Questionnaire data</strong></td>
<td></td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>123 (18.9)</td>
</tr>
<tr>
<td>Drinking alcohol, n (%)</td>
<td>267 (41.0)</td>
</tr>
<tr>
<td>Hypertensive, n (%)</td>
<td>268 (41.2)</td>
</tr>
<tr>
<td>Treated for hypertension, n (%)</td>
<td>160 (24.6)</td>
</tr>
<tr>
<td>( \beta )-blockers, n (%)</td>
<td>98 (15.0)</td>
</tr>
<tr>
<td>ACE or ARB, n (%)</td>
<td>52 (8.0)</td>
</tr>
<tr>
<td>CCB or ( \alpha )-blockers, n (%)</td>
<td>27 (4.1)</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>58 (8.9)</td>
</tr>
<tr>
<td>History of CHD, n (%)</td>
<td>18 (2.8)</td>
</tr>
<tr>
<td>History of diabetes mellitus, n (%)</td>
<td>26 (4.0)</td>
</tr>
<tr>
<td><strong>Biochemical data</strong></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, ( \mu )mol/L</td>
<td>84.2±16.1</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.26±0.96</td>
</tr>
<tr>
<td>Insulin, ( \mu )mol/L</td>
<td>4.79 (2.00–10.0)</td>
</tr>
</tbody>
</table>

Values are mean (±SD), number of subjects (%) or geometric mean (10%–90% percentile interval). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; CHD, coronary heart disease; LA, left atrium; LV, left ventricle; and TDI, tissue Doppler imaging.

* Averaged of septum, lateral, inferior, and posterior mitral annulus sites.
Changes in LV Diastolic Function

Statistical Methods
For database management and statistical analysis, we used SAS software, version 9.3 (SAS Institute, Cary, NC). We compared changes in means and proportions by means of a paired t test and the McNemar tests, respectively. Statistical significance was a 2-sided significance level of 0.05.

We performed forward stepwise linear regression to determine clinical correlates of change in the Doppler diastolic indexes as measured on a continuous scale during a mean follow-up period of 4.7 years. The baseline characteristics considered as covariables in linear regression were sex, age, body mass index, HR, systolic BP (SBP) and DBP, serum insulin, creatinine, and diabetes mellitus. These variables were chosen on the basis of their cross-sectional association with LV Doppler diastolic indexes in the previously published reports and in this study (Tables I and II in the Data Supplement). We also included in models the changes in body mass index, HR, SBP, and DBP, and coding for antihypertensive drug intake (starting treatment between baseline and follow-up or remaining on treatment). We set the P values for variables to enter and to stay in the regression models at 0.05.

We searched for variables associated with change in LV diastolic (dys-)function grading using stepwise logistic regression including the covariables mentioned above. In a sensitivity analysis, we used inverse probability weighting to adjust for possible selection bias caused by dropouts.

Results
Characteristics of Participants
Follow-up echocardiographic data were available in 650 participants of whom 330 (50.8%) were women. At baseline, the mean age was 50.7 (SD, 14.6) years. The median follow-up was 4.7 years (5th to 95th percentile, 3.7–5.4 years). Table 1 shows the clinical and echocardiographic characteristics of the study participants by the examination phase. At the follow-up examination, the prevalence of hypertension increased from 41.2% (n=268) to 51.2% (n=333; P<0.0001). From examination 1 to 2, SBP, DBP, and mean BP increased by 3.60±13.6, 2.55±8.66, and 2.90±9.18 mm Hg, respectively (P<0.0001 for all; Table 1). In contrast, pulse pressure (P=0.07) and HR (P=0.19) did not significantly change over time (Table 1). Body mass index increased slightly at examination 2 (+0.72±1.87 kg/m²; P<0.0001). We also observed significant changes in LA volume index and LV mass index, averaging 2.82 mL/m² and 3.61 g/m², respectively (Table 1).

Correlates of Changes in Diastolic Function Indexes
During follow-up, transmitral and TDI early and late diastolic velocity significantly decreased (P<0.0001 for all; Table 1) although the magnitude of decrease was greater for early than late diastolic velocities (Figure 2). Subsequently, we observed that the E/A and e′/a′ ratios changed by −5.3% (−33.7% to 29.7%) and −8.0% (−38.2% to 28.7%), respectively (P<0.0001 for all; Table 1; Figure 2), whereas E/e′ ratio increased by 6.1% (−20.0% to 38.1%; P<0.0001; Table 1; Figure 2). Figure 3 shows histograms of change over time in the diastolic Doppler velocities and their ratios.

Table 2 lists the correlates of the 4.7 years change in LVDF Doppler velocities and ratios. As expected, the significant correlate of change in any of LV diastolic index was baseline LV diastolic index, being inversely associated with Δ LV diastolic index (Table 2). We also observed that the magnitude of decrease in most of diastolic indexes was greater in men than in women (Table 2). Advanced age and higher baseline HR as well as an increased HR during follow-up were related to larger decreases in the transmitral E velocity, E/A and e′/a′ ratios during the follow-up period (Table 2). The decreases in the E/A and e′/a′ ratios during follow-up were also more pronounced in subjects with higher DBP at baseline and more increase in DBP during follow-up. Baseline HR and Δ HR were associated with significant increase in the transmitral A and TDI a′ velocities (P<0.0001; Table 2). Longitudinal decrease in TDI e′ velocity was significantly correlated with baseline age, DBP, and serum insulin, and with Δ body mass index and Δ DBP over time (Table 2). An increase in E/e′ ratio over time was significantly correlated with higher baseline age, SBP, and serum insulin as well as with greater increases in body mass index and SBP during follow-up (Table 2). For the change in Doppler diastolic velocities and ratios, the range of the explained total variance by the covariables (Table 2) varied between 11.2% and 36.5%.

Changes in LV Diastolic Dysfunction Grade and Factors Predictive of Worsening Diastolic Function Grade
During follow-up, the prevalence of LV diastolic dysfunction of any degree slightly increased from 23.5% (95% confidence interval [CI], 20.2%–26.8%) to 27.5% (95% CI, 24.1%–30.9%; P<0.001). Within-subject changes in LVDF grade during 4.7 years were presented in Table 3. LVDF grades remained unchanged in 567 participants (87.2%; 95% CI, 84.6%–89.8%), improved in 24 participants (3.7%; 95% CI, 2.25%–5.15%), and worsened in 59 participants (9.1%; 95% CI, 6.9%–11.3%).

In multivariable stepwise logistic regression (Table 4), the risk of progressing from normal LVDF to impaired relaxation was directly associated with age at baseline (P<0.0001), HR at baseline (P=0.0008), and increase in HR during follow-up (P<0.0001). Moreover, we observed that subjects who started or remained on antihypertensive treatment more often progressed to impaired relaxation (P=0.005). Advanced age was a strong predictor of worsening of LVDF from ≤1 grade to ≥2 (odds ratio, 3.22; P<0.0001). We also found that a doubling of baseline insulin was associated with an 18.4% increase in risk of worsening of LVDF (P<0.0001). Moreover,
baseline DBP and an increase in SBP over time predicted progression from grades $\leq 1$ to grade $\geq 2$. Risk estimates for a 10 mm Hg increment in baseline DBP and in $\Delta$ SBP were 102% and 47%, respectively ($P \leq 0.014$).

Table III in the Data Supplement lists characteristics of subjects who did not return for examination 2. Non-participants had significantly higher baseline HR, serum insulin and prevalence of smokers than participants (Table III in the Data Supplement). The use of inverse probability weighting to adjust for possible bias caused by dropouts did not materially affect the factors predicting progression of LVDF (Table IV in the Data Supplement). Figure I in the Data Supplement showed examples of different patterns of LVDF changes as assessed by transmitral Doppler and mitral annular TDI velocities.

**Discussion**

Because of aging population and the increasing burden of diastolic heart failure, it is important to understand determinants of LV diastolic dysfunction during the adult life course. Serial imaging studies should clarify the progression of LV function changes. In this context, we evaluated in the general
Table 2. Correlates of 4.7 Years Change in LVDF

<table>
<thead>
<tr>
<th>Variables</th>
<th>∆ E (cm/s)</th>
<th>∆ A (cm/s)</th>
<th>∆ E/A</th>
<th>∆ e’ (cm/s)</th>
<th>∆ a’ (cm/s)</th>
<th>∆ e’/a’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LVDF index, +1 SD</td>
<td>2.06±0.27‡</td>
<td>−1.11±0.009‡</td>
<td>−0.61±0.066‡</td>
<td>−2.04±0.62†</td>
<td>−0.036±0.018*</td>
<td>−0.24±0.11†</td>
</tr>
<tr>
<td>Heart rate, +10 bpm</td>
<td>1.25±0.37‡</td>
<td>−0.557±0.012‡</td>
<td>...</td>
<td>0.38±0.006‡</td>
<td>−0.055±0.012‡</td>
<td>...</td>
</tr>
<tr>
<td>Body mass index, +1 kg/m²</td>
<td>0.31±0.08†</td>
<td>0.0065±0.0022†</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>SBP, +10 mmHg</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.25±0.051†</td>
</tr>
<tr>
<td>DBP, +10 mmHg</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>−0.18±0.070*</td>
</tr>
<tr>
<td>Serum insulin, per doubling</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.94±0.071†</td>
</tr>
</tbody>
</table>

We performed stepwise multiple regression to assess the independent correlations of changes in LVDF indexes with baseline risk factors, such as sex, age, body mass index, heart rate, systolic and diastolic blood pressure, serum creatinine, insulin, and coding for antihypertensive drug intake (starting treatment between baseline and follow-up or remaining on treatment). We also included in stepwise models the changes in these risk factors. Values are mutually adjusted partial regression coefficients (% of explained variances).

<table>
<thead>
<tr>
<th>Significant correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P</strong>&lt;0.05, significance of the partial regression coefficient.</td>
</tr>
<tr>
<td><strong>P</strong>&lt;0.01, significance of the partial regression coefficient.</td>
</tr>
<tr>
<td><strong>P</strong>&lt;0.001, significance of the partial regression coefficient.</td>
</tr>
</tbody>
</table>

population clinical correlates of longitudinal changes in Doppler diastolic indexes analyzed as continuous measures and assessed factors predictive of the worsening of LVDF grade over time. The key findings of this study are that LV diastolic dysfunction tended to worsen over time and was associated with advanced age, higher baseline insulin level, and hemodynamic parameters, such as HR and BP.

The gold standard for assessing diastolic function remains the pressure-volume relationship, but this requires an invasive approach. Doppler measurements of mitral inflow and the TDI technique open up the possibility of evaluating noninvasively diastolic function. In our study, we assessed LVDF noninvasively using the transmural flow and the TDI mitral annular velocities. Previous studies validated these indexes versus invasive measures of diastolic function. LV diastolic dysfunction is defined as functional abnormalities that exist during LV relaxation and filling. Impaired myocardial relaxation is characterized by decreased early (E peak), but enhanced atrial LV filling (A peak) as well as less vigorous mitral annulus motion during early diastole (TDI e’ peak). Moreover, e’ peak velocity along the LV longitudinal axis is less susceptible to the effects of an increased preload and, therefore, provides a more direct measure of myocardial relaxation than, for instance, the transmural E peak velocity. In addition, combining transmural flow velocity with annular velocity (E/e’ ratio) might be a tool for assessing the LV filling pressure, which combines the influence of the transmural driving pressure and myocardial relaxation.
Diastolic Function Classes, Examination 2

<table>
<thead>
<tr>
<th>Diastolic Function Groups, Examination 1</th>
<th>Normal Function, Group 0</th>
<th>Impaired Relaxation, Group 1</th>
<th>Elevated LV Filling Pressure, Group 2</th>
<th>Combined Dysfunction, Group 3</th>
<th>Total (Examination 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal function, group 0</td>
<td>454*</td>
<td>33†</td>
<td>6†</td>
<td>11*</td>
<td>497 (76.5%)</td>
</tr>
<tr>
<td>Impaired relaxation, group 1</td>
<td>16‡</td>
<td>30*</td>
<td>8†</td>
<td>10*</td>
<td>62 (9.5%)</td>
</tr>
<tr>
<td>Elevated LV filling pressure, group 2</td>
<td>1‡</td>
<td>6‡</td>
<td>55†</td>
<td>13†</td>
<td>75 (11.5%)</td>
</tr>
<tr>
<td>Combined dysfunction, group 3</td>
<td>0‡</td>
<td>1‡</td>
<td>5‡</td>
<td>10*</td>
<td>16 (2.5%)</td>
</tr>
<tr>
<td>Total (examination 2)</td>
<td>471 (72.5%)</td>
<td>70 (10.8%)</td>
<td>74 (11.4%)</td>
<td>35 (5.4%)</td>
<td>650 (100%)</td>
</tr>
</tbody>
</table>

*No. of subjects with no change in LV diastolic function grade between 2 examinations.
†Participants with worsening LV diastolic function.
‡Participants with improved grade.

LV indicates left ventricle.

In our previous reports, which focused on the prevalence and comparison of echocardiographic criteria for LV diastolic dysfunction between European populations, we found that the age-standardized prevalence of LV diastolic dysfunction varied between 22.4% and 25.1%. Age-specific cut-off limits for the transmural E/A ratio and the threshold for the E/e' ratio, which we used for the classification of LV diastolic dysfunction, were consistent and reproducible across independently recruited population cohorts. The same also applied to the cross-sectional correlates of the conventional Doppler and TDI indexes. These observations lend support to our longitudinal epidemiological approach, which allowed us to understand the correlates of LVDF indexes as well as trace the natural history of LVDF in the participants with and without LV diastolic dysfunction at baseline.

Age, body mass index, and hemodynamic factors, such as HR and DBP, were major determinants of LV Doppler diastolic indexes in our previous cross-sectional study based on single-occasion measurements. In this analysis, we demonstrated that these covariates were also significant correlates of tracking of LVDF indexes during a 4.7-year period. In addition, baseline LV Doppler diastolic indexes were significant predictors of change in diastolic indexes. To our knowledge, our study was the first to describe the correlates of longitudinal changes in LV Doppler diastolic function indexes.

During follow-up, we observed a progression of LV diastolic dysfunction: 9.1% of participants showed worse diastolic function and 87.2% of participants had LVDF unchanged. Presently, only 1 population-based study described the progression of LV diastolic dysfunction in the general population. Similar to our study, this study applied a comprehensive Doppler analysis to grade LV diastolic dysfunction in subjects aged ≥45 years. The authors reported more marked progression of diastolic dysfunction than in our study. Indeed, in the Kane et al’s study, 23.4% of participants showed worse LVDF grade. The difference between studies has to be interpreted, keeping in mind that in our study the mean age was 50.7 years, whereas in the Olmsted cohort the mean age was 61.0 years. In both the studies, the worsening of diastolic dysfunction increased with advanced age at baseline. Moreover,

### Table 4. Factors Predictive of the Development or Worsening of Diastolic Dysfunction From Examination 1 to 2

<table>
<thead>
<tr>
<th>Factor</th>
<th>Remains in the Same LVDF Grade</th>
<th>Change of LVDF Grade</th>
<th>Mutually Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of LV diastolic dysfunction (normal LVDF→1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>454</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>46.1±13.0</td>
<td>57.7±12.5</td>
<td>2.43 (1.61–3.71)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline heart rate, bpm</td>
<td>59.6±8.8</td>
<td>61.0±9.9</td>
<td>2.46 (1.49–4.05)*</td>
<td>0.0008</td>
</tr>
<tr>
<td>Δ heart rate, bpm</td>
<td>−0.40±7.49</td>
<td>4.76±7.24</td>
<td>4.81 (2.59–8.95)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Start of AHT or remain on AHT, (1 vs 0)</td>
<td>65 (14.3%)</td>
<td>13 (39.4%)</td>
<td>3.32 (1.43–7.68)</td>
<td>0.005</td>
</tr>
<tr>
<td>Worsening of LV diastolic dysfunction (LVDF grade ≤1→≥2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>533</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>47.4±13.4</td>
<td>61.2±10.8</td>
<td>3.22 (1.97–5.23)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline Insulin, μU/mL</td>
<td>3.98 (2.00–8.91)</td>
<td>7.41 (3.02–22.9)</td>
<td>2.84 (1.84–4.38)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline DBP, mmHg</td>
<td>79.4±9.13</td>
<td>83.7±10.1</td>
<td>2.02 (1.20–3.39)*</td>
<td>0.008</td>
</tr>
<tr>
<td>Δ SBP, mmHg</td>
<td>3.41±12.3</td>
<td>7.92±20.1</td>
<td>1.47 (1.08–1.99)*</td>
<td>0.014</td>
</tr>
</tbody>
</table>

*OR are expressed per 10 units increase.
†Odds ratios is expressed for a doubling baseline insulin.

We performed stepwise logistic regression to assess the independent correlations of changes in LVDF grade with baseline risk factors and their changes as described in Table 2. AHT indicates antihypertensive therapy; CI, confidence interval; DBP, diastolic blood pressure; LVDF, left ventricular diastolic function; OR, odds ratio; and SBP, systolic blood pressure.
the difference could also be explained by the fact that we used age-specific criteria for LVDF grading. It is probable that by applying the same threshold values for the Doppler indexes throughout the age range, we may overestimate the prevalence of mild subclinical diastolic dysfunction in older participants.

The HR determines the time that is available for ventricular relaxation, diastolic filling, and coronary perfusion. An increase in HR might affect the diastolic function by several mechanisms: it decreases time of LV filling, and causes incomplete or impaired relaxation. Indeed, in our study we observed that higher baseline HR and Δ HR during the follow-up period was associated with the development of impaired relaxation. In line with our findings, Burns et al17 have shown that increased HR produced by atrial pacing results in significant changes in conventional and tissue Doppler parameters of LVDF. The authors demonstrated that an increase in HR led to a significant reduction in the early mitral inflow velocity, an increase in A and a’ velocities.

In our previous cross-sectional study,3 we found that the prevalence of diastolic dysfunction increased with serum insulin level. In this longitudinal analysis, we found that baseline insulin level was associated with the worsening of LV diastolic dysfunction grade. Our findings are in line with previous data reporting association between glucose metabolism and LVDF.14,15 Moreover, recent longitudinal study in type 2 diabetic patients implied that LV diastolic dysfunction deteriorates more in subjects with than in those without type 2 diabetes mellitus.16 The biological pathways leading to the alterations of myocardial composition and, thus, of LV diastolic properties in subjects with impaired insulin resistance and glucose metabolism might be mediated by changes in the coronary microcirculation.20 Microvascular damage may lead to myocardial cell injury and reactive fibrosis/hypertrophy.21

Our study has to be interpreted within the context of its potential limitations and strengths. First, the Doppler blood flow measurements and the TDI velocities are prone to measurement error. In this study, 1 experienced observer recorded all Doppler images using a highly standardized imaging protocol. All digitally stored images were centrally postprocessed using a highly standardized imaging protocol. All digitally stored images were centrally postprocessed to a significant reduction in the early mitral inflow velocity, an increase in A and a’ velocities.

In our previous cross-sectional study,3 we found that the prevalence of diastolic dysfunction increased with serum insulin level. In this longitudinal analysis, we found that baseline insulin level was associated with the worsening of LV diastolic dysfunction grade. Our findings are in line with previous data reporting association between glucose metabolism and LVDF.14,15 Moreover, recent longitudinal study in type 2 diabetic patients implied that LV diastolic dysfunction deteriorates more in subjects with than in those without type 2 diabetes mellitus.16 The biological pathways leading to the alterations of myocardial composition and, thus, of LV diastolic properties in subjects with impaired insulin resistance and glucose metabolism might be mediated by changes in the coronary microcirculation.20 Microvascular damage may lead to myocardial cell injury and reactive fibrosis/hypertrophy.21

Our study has to be interpreted within the context of its potential limitations and strengths. First, the Doppler blood flow measurements and the TDI velocities are prone to measurement error. In this study, 1 experienced observer recorded all Doppler images using a highly standardized imaging protocol. All digitally stored images were centrally postprocessed by a single observer at baseline and follow-up with a good reproducibility. Moreover, previous work of Hare et al22 suggested that transmitral and tissue Doppler velocities were reasonably reproducible in 346 consecutive patients undergoing sequential echocardiography. Second, patterns of transmitral flow and mitral annulus velocities also depend on the compliance and contractile function of the LA. Thus, we did not evaluate LVDF in participants with sustained atrial fibrillation. Third, as in our study we included only white European populations, the generalizability of the findings to other ethnicities is currently limited and should also be further explored by additional research.

In conclusion, LV diastolic dysfunction tended to worsen over time and was associated with advanced age, higher baseline insulin level and hemodynamic parameters, such as HR and BP.

Acknowledgments
We acknowledge the expert assistance of Linda Custers, Marie-Jeanne Jehoul, Daisy Thijs, Hanne Tuyens, and Annick De Soete (Leuven, Belgium).

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Because life expectancy and the prevalence of risk factors, such as hypertension, obesity, insulin resistance, and diabetes mellitus are rising globally, heart failure is growing into a major health problem. Impairment of left ventricular diastolic function seems early in the course of heart disease. Therefore, it is important to understand determinants of LV diastolic dysfunction during the adult life course. Serial imaging studies should clarify the progression of LV function changes. In this context, we evaluated in the general population clinical correlates of longitudinal changes in Doppler diastolic indexes analyzed as continuous measures and assessed factors predictive of the worsening of left ventricular diastolic function grade over time. In our previous cross-sectional study based on single-occasion measurements, age, body mass index, and hemodynamic factors such as heart rate and diastolic blood pressure were major determinants of LV Doppler diastolic indexes. In this analysis, we demonstrated that these covariates were also significant correlates of tracking of left ventricular diastolic function indexes during a 4.7-year period. In addition, baseline LV Doppler diastolic indexes were significant predictors of change in diastolic indexes. Another key finding of this study was that LV diastolic dysfunction tended to worsen over time and was associated with advanced age, higher baseline insulin level, and hemodynamic parameters, such as heart rate and blood pressure.
Longitudinal Changes in Left Ventricular Diastolic Function in a General Population
Tatiana Kuznetsova, Lutgarde Thijs, Judita Knez, Nicholas Cauwenberghs, Thibault Petit, Yu-Mei Gu, Zhenyu Zhang and Jan A. Staessen

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SUPPLEMENTAL MATERIAL

Longitudinal Changes in Left Ventricular Diastolic Function
in a General Population

Short title: Changes in LV Diastolic Function
**SUPPLEMENTAL Table S1.** Correlates of the E/A, e’/a’ and E/e’ ratios in stepwise regression by examination

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Transmitral E peak (cm/s)</th>
<th>Transmitral A peak (cm/s)</th>
<th>Transmitral E/A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Examination 1</td>
<td>Examination 2</td>
<td>Examination 1</td>
</tr>
<tr>
<td>Adjusted R² (%)</td>
<td>30.9</td>
<td>38.0</td>
<td>55.5</td>
</tr>
<tr>
<td>Partial regression coefficients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (0,1)</td>
<td>9.09±1.10‡</td>
<td>9.48±1.00‡</td>
<td>6.46±0.92‡</td>
</tr>
<tr>
<td>β±SE</td>
<td>7.1</td>
<td>7.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>55.5</td>
<td>55.3</td>
<td>64.1</td>
</tr>
<tr>
<td>Age (+10 years)</td>
<td>–4.97±0.42‡</td>
<td>–5.73±0.40‡</td>
<td>6.03±0.35‡</td>
</tr>
<tr>
<td>β±SE</td>
<td>13.8</td>
<td>19.5</td>
<td>38.9</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>7.1</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td>BMI (+1 kg/m²)</td>
<td>...</td>
<td>...</td>
<td>0.74±0.11‡</td>
</tr>
<tr>
<td>β±SE</td>
<td>...</td>
<td>...</td>
<td>3.6</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>...</td>
<td>...</td>
<td>3.6</td>
</tr>
<tr>
<td>HR (+10 beats/minute)</td>
<td>–3.63±0.59‡</td>
<td>–4.44±0.52‡</td>
<td>3.71±0.49‡</td>
</tr>
<tr>
<td>β±SE</td>
<td>5.2</td>
<td>8.2</td>
<td>8.4</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>1.4</td>
<td>0.76</td>
<td>2.1</td>
</tr>
<tr>
<td>SBP (+10 mm Hg)</td>
<td>2.55±0.42‡</td>
<td>1.80±0.37‡</td>
<td>1.73±0.31‡</td>
</tr>
<tr>
<td>β±SE</td>
<td>0.74</td>
<td>1.84</td>
<td>...</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>DBP (+10 mm Hg)</td>
<td>–3.53±0.69‡</td>
<td>–2.54±0.58‡</td>
<td>...</td>
</tr>
<tr>
<td>β±SE</td>
<td>2.88</td>
<td>1.84</td>
<td>...</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Use of RAAS blockers</td>
<td>–5.05±1.98*</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>β±SE</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Use of β-blockers</td>
<td>–3.44±1.55*</td>
<td>–3.76±1.37†</td>
<td>...</td>
</tr>
<tr>
<td>β±SE</td>
<td>0.52</td>
<td>0.71</td>
<td>...</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are mutually adjusted partial regression coefficients ±SE. BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure. Significance of the partial regression coefficient: * P<0.05, †P<0.01, and ‡P<0.001. There were no differences between the partial regression coefficients in two studies.
**SUPPLEMENTAL Table S2.** Correlates of TDI e', e'/a', and E/e' in stepwise regression by examination

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TDI e' peak (cm/s)</th>
<th>TDI e'/a' peak</th>
<th>E/e'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Examination 1</td>
<td>Examination 2</td>
<td>Examination 1</td>
</tr>
<tr>
<td>Adjusted R² (%)</td>
<td>73.7</td>
<td>71.8</td>
<td>72.7</td>
</tr>
<tr>
<td>Partial regression coefficients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (0,1)</td>
<td>...</td>
<td>...</td>
<td>0.056±0.028*</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>63.5</td>
<td>62.5</td>
<td>58.9</td>
</tr>
<tr>
<td>Age (+10 years)</td>
<td>-1.81±0.058‡</td>
<td>-1.75±0.052‡</td>
<td>-0.34±0.011‡</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>0.17</td>
<td>0.63</td>
<td>0.17</td>
</tr>
<tr>
<td>BMI (+1 kg/m²)</td>
<td>-0.17±0.018‡</td>
<td>-0.13±0.018‡</td>
<td>-0.032±0.003‡</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>7.0</td>
<td>5.7</td>
<td>7.7</td>
</tr>
<tr>
<td>HR (+10 beats/minute)</td>
<td>-0.27±0.080‡</td>
<td>-0.30±0.075‡</td>
<td>-0.11±0.015‡</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>0.44</td>
<td>0.54</td>
<td>3.3</td>
</tr>
<tr>
<td>SBP (+10 mm Hg)</td>
<td>0.13±0.058*</td>
<td>...</td>
<td>0.050±0.010‡</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>0.20</td>
<td>0.96</td>
<td>0.20</td>
</tr>
<tr>
<td>DBP (+10 mm Hg)</td>
<td>-0.69±0.095‡</td>
<td>-0.57±0.076‡</td>
<td>-0.14±0.018‡</td>
</tr>
<tr>
<td>Partial r² (%)</td>
<td>2.5</td>
<td>2.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Use of RAAS blockers</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Use of β-blockers</td>
<td>-0.82±0.22‡</td>
<td>-0.55±0.20†</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are mutually adjusted partial regression coefficients ±SE. BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure. Significance of the partial regression coefficient: * P<0.05, †P<0.01, and ‡P<0.001. There were no differences between the partial regression coefficients in two studies.
### SUPPLEMENTAL Table S3. Characteristics of Participants and Non-participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants (n=650)</th>
<th>Non-participants (n=137)</th>
<th>P</th>
<th>Characteristic</th>
<th>Participants (n=650)</th>
<th>Non-participants (n=137)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>Echocardiographic Measurements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anthropometrics</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>Conventional echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>50.7±14.6</td>
<td>48.4±18.1</td>
<td>0.16</td>
<td>LA volume index, ml/m²</td>
<td>23.0±6.13</td>
<td>21.9±6.55</td>
<td>0.07</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.5±4.28</td>
<td>26.3±4.40</td>
<td>0.60</td>
<td>LV internal diameter, cm</td>
<td>5.05±0.45</td>
<td>5.01±0.53</td>
<td>0.39</td>
</tr>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>128.8±16.8</td>
<td>129.5±18.5</td>
<td>0.65</td>
<td>Interventricular septum, cm</td>
<td>0.98±0.16</td>
<td>0.97±0.17</td>
<td>0.46</td>
</tr>
<tr>
<td>Diastolic pressure, mm Hg</td>
<td>79.8±9.3</td>
<td>79.3±10.1</td>
<td>0.62</td>
<td>Posterior wall, cm</td>
<td>0.89±0.14</td>
<td>0.90±0.15</td>
<td>0.49</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>96.1±10.3</td>
<td>96.1±11.5</td>
<td>0.96</td>
<td>Relative wall thickness</td>
<td>0.37±0.06</td>
<td>0.38±0.07</td>
<td>0.57</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>49.0±14.3</td>
<td>50.1±14.9</td>
<td>0.39</td>
<td>LV mass index, g/m²</td>
<td>92.2±21.0</td>
<td>92.3±24.8</td>
<td>0.95</td>
</tr>
<tr>
<td>Heart rate, beats/minute</td>
<td>60.3±9.4</td>
<td>63.4±10.5</td>
<td>0.002</td>
<td>Ejection fraction, %</td>
<td>63.4±6.60</td>
<td>63.5±6.76</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Questionnaire data</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>Doppler data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>123 (18.9)</td>
<td>38 (27.1)</td>
<td>0.03</td>
<td>TDI s' peak#, cm/s</td>
<td>9.07±1.42</td>
<td>9.11±1.59</td>
<td>0.78</td>
</tr>
<tr>
<td>Drinking alcohol, n (%)</td>
<td>267 (41.0)</td>
<td>54 (38.6)</td>
<td>0.61</td>
<td>Transmitral E peak, cm/s</td>
<td>75.8±15.9</td>
<td>74.9±15.8</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypertensive, n (%)</td>
<td>268 (41.2)</td>
<td>53 (37.9)</td>
<td>0.48</td>
<td>Transmitral A peak, cm/s</td>
<td>64.8±17.0</td>
<td>63.5±19.1</td>
<td>0.43</td>
</tr>
<tr>
<td>Treated for hypertension, n (%)</td>
<td>160 (24.6)</td>
<td>32 (22.9)</td>
<td>0.69</td>
<td>E/A ratio</td>
<td>1.26±0.47</td>
<td>1.31±0.54</td>
<td>0.27</td>
</tr>
<tr>
<td>History of CHD, n (%)</td>
<td>18 (2.76)</td>
<td>3 (2.14)</td>
<td>0.68</td>
<td>TDI e' peak#, cm/s</td>
<td>11.5±3.57</td>
<td>11.7±4.00</td>
<td>0.55</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>26 (3.99)</td>
<td>7 (5.00)</td>
<td>0.26</td>
<td>TDI a’ peak#, cm/s</td>
<td>10.2±2.07</td>
<td>9.69±2.19</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Biochemical data</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>TDI e’/a’ ratio#</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, µmol/l</td>
<td>84.2±16.1</td>
<td>81.0±13.9</td>
<td>0.02</td>
<td>TDI e’/a’ ratio#</td>
<td>1.24±0.64</td>
<td>1.35±0.73</td>
<td>0.10</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.26±0.96</td>
<td>5.15±1.03</td>
<td>0.20</td>
<td>E/e’ ratio</td>
<td>7.07±2.14</td>
<td>7.02±2.28</td>
<td>0.84</td>
</tr>
<tr>
<td>Insulin, µmol/l</td>
<td>4.79</td>
<td>5.01</td>
<td>0.02</td>
<td>(2.00 to 10.0)</td>
<td>(2.00 to 14.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (±SD), number of subjects (%) or geometric mean (10%–90% percentile interval). CHD, coronary heart disease; LV, left ventricle; LA, left atrium. #Averaged of septum, lateral, inferior and posterior mitral annulus sites.
### SUPPLEMENTAL Table S4. Factors Predictive of the Development or Worsening of Diastolic Dysfunction From Examination 1 to Examination 2 with Correction for Drop-out Bias

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mutually adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Development of LV diastolic dysfunction</strong> (Normal LVDF $\rightarrow$ 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>2.37 (1.48-3.71)$^a$</td>
<td>0.0004</td>
</tr>
<tr>
<td>Baseline heart rate, beats/min</td>
<td>2.59 (1.48-4.81)$^a$</td>
<td>0.0007</td>
</tr>
<tr>
<td>Δ heart rate, beats/min</td>
<td>4.05 (2.16-7.93)$^a$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Start or remain on AHT, (1 vs 0)</td>
<td>3.00 (1.22-7.37)</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>Worsening of LV diastolic dysfunction</strong> (LVDF grade ≤ 1 $\rightarrow$ ≥ 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>3.11 (1.97-5.23)$^a$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline Insulin, μU/ml</td>
<td>2.88 (2.01-4.13)$^b$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline DBP, mmHg</td>
<td>2.16 (1.34-3.39)$^a$</td>
<td>0.001</td>
</tr>
<tr>
<td>Δ SBP, mmHg</td>
<td>1.34 (1.00-1.97)$^a$</td>
<td>0.050</td>
</tr>
<tr>
<td>Δ heart rate, beats/min</td>
<td>0.60 (0.39-0.90)$^a$</td>
<td>0.038</td>
</tr>
</tbody>
</table>

$^a$Odds ratios (OR) are expressed per 10 unit increase. $^b$Odds ratios is expressed for a doubling baseline insulin. LVDF, left ventricular diastolic dysfunction; AHT, antihypertensive therapy, DBP, diastolic blood pressure; SBP, systolic blood pressure.
Legend to Supplemental Figure S1

Examples of different patterns of diastolic function as assessed by transmitral Doppler and mitral annular TDI velocities at baseline and follow-up. E - early mitral inflow; A - atrial mitral inflow; e' - early diastolic annular velocity; a' - late diastolic annular velocity. A. Unchanged pattern of LV diastolic function in 48-year old woman who had normal age-specific transmitral E/A ratio (from 2.5th to 97.5th percentiles of the reference subgroup) and no evidence of increased LV filling pressures (E/e’ < 8.5) at baseline and follow-up. B. Development of LV diastolic dysfunction in 53-year old man with E/A ratio within the normal age-specific range at baseline and follow-up (from 2.5th to 97.5th percentiles of the reference subgroup), but with an elevated E/e’ ratio (13.0) at follow-up because of a significant decrease of TDI e’. C. Development of LV diastolic dysfunction in 63-year old woman who demonstrated at follow-up an abnormally low age-specific transmitral E/A ratio (0.57) indicative of impaired relaxation (less than 2.5th percentile of the reference subgroup) together with moderately elevated end-diastolic filling pressure with E/e’ =13.1.