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Prevalence of Left Ventricular Diastolic Dysfunction in a General Population

Tatiana Kuznetsova, MD, PhD; Lieven Herbots, MD, PhD; Begoña López, PhD; Yu Jin, MD; Tom Richart, MD, MBE; Lutgarde Thijs, MSc; Arantxa González, PhD; Marie-Christine Herregods, MD, PhD; Robert H. Fagard, MD, PhD; Javier Díez, MD, PhD; Jan A. Staessen, MD, PhD

Background—Because the process of myocardial remodelling starts before the onset of symptoms, recent heart failure (HF) guidelines place special emphasis on the detection of subclinical left ventricular (LV) systolic and diastolic dysfunction and the timely identification of risk factors for HF. Our goal was to describe the prevalence and determinants (risk factors) of LV diastolic dysfunction in a general population and to compare the amino terminal probrain natriuretic peptide level across groups with and without diastolic dysfunction.

Methods and Results—In a randomly recruited population sample (n=539; 50.5% women; mean age, 52.5 years), we measured early and late diastolic peak velocities of mitral inflow (E and A), pulmonary vein flow by pulsed-wave Doppler, and the mitral annular velocities (Ea and Aa) at 4 sites by tissue Doppler imaging. A healthy subsample of 239 subjects (mean age, 43.7 years) provided age-specific cutoff limits for normal E/A and E/Ea ratios and the differences in duration between the mitral A and the reverse pulmonary vein flows during atrial systole (ΔAd−ARd). The number of subjects in diastolic dysfunction groups 1 (impaired relaxation), 2 (elevated LV end-diastolic filling pressure), and 3 (elevated E/Ea and abnormally low E/A) were 53 (9.8%), 76 (14.1%), and 18 (3.4%), respectively. We used Δ(Ad<ARd+10) to confirm possible elevation of LV filling pressures in group 2. Compared with subjects with normal diastolic function (n=392, 72.7%), group 1 (209 versus 251 pmol/L; $P=0.015$) and group 2 (209 versus 275 pmol/L; $P=0.0003$) but not group 3 (209 versus 224 pmol/L; $P=0.65$) had a significantly higher adjusted NT-probrain natriuretic peptide. Higher age, body mass index, heart rate, systolic blood pressure, serum insulin, and creatinine were significantly associated with a higher risk of LV diastolic dysfunction.

Conclusions—The overall prevalence of LV diastolic dysfunction in a random sample of a general population, as estimated from echocardiographic measurements, was as high as 27.3%. **(*Circ Heart Fail*. 2009;2:105-112.)**

Key Words: epidemiology ■ echocardiography ■ tissue Doppler imaging ■ diastole

Diastolic heart failure (HF) is a progressive disorder characterized by impaired left ventricular (LV) relaxation, increased LV stiffness, increased interstitial deposition of collagen, and modified extracellular matrix proteins. Diastolic HF, also referred to as HF with normal ejection fraction, currently accounts for 40% to 50% of all HF cases and has a prognosis, which is as ominous as that of systolic HF.[1] With life expectancy increasing, HF is growing into a major health problem. Because the process of myocardial remodelling starts before the onset of symptoms, recent HF guidelines[2] place special emphasis on the detection of subclinical LV systolic and diastolic dysfunction and the timely identification of risk factors for HF.

Clinical Perspective see p 112

The echocardiographic techniques to assess early subclinical changes in systolic and diastolic LV function evolved rapidly over the past 10 years. New techniques of tissue Doppler imaging (TDI) enable the measurement of myocardial velocities and provide valuable information about LV diastolic function in addition to classical M-mode and 2D echocardiography and pulsed-wave Doppler. Presently, only few population-based studies[3,4] described the prevalence of preclinical LV diastolic dysfunction, using the new TDI indexes along with classical pulsed-wave Doppler velocities. These studies applied a comprehensive Doppler analysis to

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grade LV diastolic dysfunction in older adults (aged 60 to 86 years)[4] or in subjects aged 45 years or older.[3] Age is an important determinant of transmitral and myocardial Doppler velocities. The prevalence of LV diastolic dysfunction increased with age,[5] but depended on applied arbitrary cutoff levels. Taking into account the growing prevalence of HF, our study aimed to describe the prevalence and determinants (risk factors) of LV diastolic dysfunction in an unselected general population. In addition, we compared the circulating amino terminal probrain natriuretic peptide (NT-proBNP) level across groups with and without diastolic dysfunction.

Methods

Study Participants

The Ethics Committee of the University of Leuven approved the Flemish Study on Environment, Genes, and Health Outcomes (FLEMENGHO).[6] From August 1985 to December 2005, we identified a random population sample stratified by sex and age from a geographically defined area in northern Belgium.[6] 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 older than 18 years were eligible. We reinvited 690 former participants for a follow-up examination at our field center, including echocardiography. After excluding 20 patients who were bed-ridden or institutionalized, we obtained informed written consent from 551 subjects (participation rate, 82%). We excluded a further 12 subjects, because of atrial fibrillation (n=6) or the presence of an artificial pacemaker (n=2), or because of diastolic function could not be reliably determined (n=4). Thus, the number of participants statistically analyzed totaled 539 subjects.

Echocardiography

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

Data Acquisition

One experienced physician (T.K.) did the ultrasound examination,[7] using a Vivid7 Pro (GE Vingmed, Horten, Norway) interfaced with a 2.5- to 3.5-MHz phased-array probe, according to the recommendations of the American Society of Echocardiography.[8] 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 2-dimensional image. The ultrasound beam was positioned just below the mitral valve at the level of the posterior chordae tendineae. To record mitral and pulmonary vein (PV) flow velocities from the apical window and the isovolumetric relaxation time (IVRT), the observer positioned the Doppler sample volume at the mitral valve tips, in the right superior PV, and between the LV outflow and mitral inflow, respectively.

Using TDI, the observer recorded low-velocity, high-intensity myocardial signals at a high frame rate (>190 FPS), whereas adjusting the imaging angle to ensure a parallel alignment of the ultrasound beam with the myocardial segment of interest. 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

Two sonographers analyzed digitally stored images, averaging 3 heart cycles for statistical analysis, using a workstation running the EchoPac version 4.0.4 software package (GE Vingmed). The LV internal diameter and interventricular septal and posterior wall thickness were measured at end-diastole from the 2-dimensionally guided M-mode tracing as described in the guidelines of the American Society of Echocardiography.[8] End-diastolic LV dimensions were used to calculate LV mass by an anatomically validated formula.[8] Relative wall thickness was calculated as the ratio at end-diastole of the thickness of interventricular septum plus posterior wall to the LV internal diameter. LV end-systolic and end-diastolic volumes and ejection fraction (EF) were calculated with the use of Teicholtz's method.

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 (AR). From the TDI recordings, we measured peak early (Ea) and peak late (Aa) diastolic mitral annular velocities, and the Ea/Aa ratio at the 4 acquisition sites (septal, lateral, inferior, and posterior).

To determine reproducibility, 2 experienced echocardiographists (T.K. and L.H.) analyzed the recordings of 17 subjects. We determined the absolute and relative biases between the 2 readers as well as 95% limits of agreement between readers (Supplemental Figure A).

Other Measurements

At the examination center, trained study nurses administered a questionnaire to collect detailed information on each subject's medical history, smoking and drinking habits, and intake of medications. NT-proBNP was measured in plasma samples by a competitive enzyme immunoassay (EIA) for research use (Biomedica Gruppe, Vienna, Austria).[9] The standard range provided by the manufacturer of the EIA is from 0 to 1000 pmol/L (median, 208 pmol/L; 95th, percentile 300 pmol/L). Hypertension was defined as a blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic (average of 5 consecutive auscultatory readings at the examination center) or as the use of antihypertensive drugs. Body mass index was weight in kilograms divided by the square of height in meters. Obesity was body mass index of 30 kg/m^2 or higher. Central obesity was waist circumference of at least 102 or 88 cm in men and women, respectively. Diabetes was fasting blood glucose of at least 6.7 mmol/L or use of insulin or oral antidiabetic agents. LV hypertrophy was LV mass index of exceeding 125 g/m^2 in men and 110 g/m^2 in women. To generate a healthy reference sample, we excluded participants if one or more of the following conditions were present: hypertension (n=182), diabetes (n=11), obesity (n=79), central obesity (n=108), LV hypertrophy (n=43), or cardiac diseases (valvular abnormalities, n=25; myocardial infarction and/or coronary revascularization, n=15). The number of subjects in the healthy reference group consisted of 239.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Statistical Methods

For database management and statistical analysis, we used SAS software version 9.1 (SAS Institute, Cary, NC). We compared means and proportions by means of a large sample z-test and the χ^2 test, respectively. We performed single and stepwise linear regression to identify correlates of the Doppler indices as measured on a continuous scale. We searched for variables associated with LV diastolic dysfunction using stepwise logistic regression. We set the probability values for variables to enter and to stay in the regression models at 0.05. We ran regression diagnostics to exclude the possibility that collinearity might have inappropriately influenced our multivariate models. We computed the variance inflation factor (VIF), Mallow Cp, and the adjusted R^2. The variance inflation factor measures to what extent variance, standard error, parameter estimates are inflated by introducing redundant highly intercorrelated explanatory variables in multiple regression models. Mallow Cp is a function of the residual sum of squares of regression models with more or less explanatory variables. The adjusted R^2 expresses the goodness of fit of the models. Higher adjusted R^2 and lower Mallow Cp indicate a

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Table 1. Characteristics of Participants

Clinical Measurements			Echocardiographic Measurements		
Characteristic	Entire Population (n=539)	Healthy Reference Group (n=239)	Characteristic	Entire Population (n=539)	Healthy Reference Group (n=239)
Anthropometrics			Conventional echocardiography		
Women	272 (50.5)	114 (47.7)	Left atrium, cm	3.96±0.54	3.73±0.45
Age, years	52.4±15.3	43.7±12.9	LV internal diameter, cm	5.04±0.50	5.03±0.44
Height, cm	168.5±9.4	170.9±9.1	Interventricular septum, cm	0.99±0.18	0.91±0.14
Weight, kg	74.8±13.5	70.4±11.7	Posterior wall, cm	0.88±0.15	0.81±0.12
Body mass index, kg/m^2	26.3±4.0	24.0±2.9	Relative wall thickness	0.37±0.074	0.34±0.055
Waist circumference, cm	88.6±11.5	82.4±9.4	LV mass index, g/m^2	92.7±21.7	83.8±15.7
Systolic pressure, mm Hg	130.2±18.3	118.3±9.6	Ejection fraction, %	68.8±7.8	67.1±6.4
Diastolic pressure, mm Hg	79.2±9.2	75.1±6.9	Doppler data		
Heart rate, beats/min	60.6±9.7	59.7±8.6	E peak, cm/s	75.8±16.3	79.9±15.5
Questionnaire data			A peak, cm/s	66.6±17.7	56.8±12.7
Current smoking	116 (21.5)	71 (29.7)	E/A ratio	1.23±0.46	1.48±0.46
Drinking alcohol	228 (42.3)	123 (51.5)	Ea peak*, cm/s	11.4±3.67	13.8±3.13
Hypertensive	221 (41.0)	. . .	Aa peak*, cm/s	10.5±2.03	9.84±2.06
Treated for hypertension	121 (23.6)	. . .	Ea/Aa ratio*	1.18±0.59	1.53±0.62
Biochemical data			E/Ea ratio	7.14±2.18	5.96±1.25
Serum creatinine, μmol/l	85.8±15.7	83.6±11.8	IVRT, ms	101.5±15.6	97.7±13.0
NT-proBNP, pmol/L	229 (129–436)	214 (129–398)	Δ(Adur–ARdur), ms	0.44±13.0	1.58±3.96
Insulin, μU/mL	4.57 (1.99–11.0)	3.71 (1.99–7.94)			

Data are presented as mean±SD, n (%), or geometric mean (10% to 90% interval).
IVRT indicates isovolumetric relaxation time; Adur, mitral inflow A-wave duration; ARdur, pulmonary vein atrial reversal flow duration.
*Averaged of septum, lateral, inferior and posterior mitral annulus sites.

better model. In logistic regression, we used the option "RIDGING" as implemented in the SAS package. We included in the logistic model important anthropometric and hemodynamic characteristics defined by stepwise selection (age, sex, body mass index, heart rate, blood pressure, and antihypertensive treatment), physiologically relevant biochemical parameters, such as serum insulin, serum creatinine, NT-proBNP, and total cholesterol, and variables reflecting cardiac structure that might influence LV diastolic function.

Results

Characteristics of Participants

The 539 participants included 272 (50.5%) women, and 221 (41.0%) hypertensive patients of whom 121 (23.6%) were on antihypertensive drug treatment. Only 8 subjects (1.5%) had EF equal or less than 50%. Ea, Ea/Aa, and E/Ea were higher ($P<0.0001$) at the lateral than at the other acquisition sites (data not shown). Table 1 shows the clinical and echocardiographic characteristics of the study participants in an entire population and in a healthy reference group.

Determinants of Transmitral and TDI Doppler Velocities in a General Population

In all subjects, the transmitral E/A ratio and the averaged mitral annular Ea/Aa ratio both significantly and independently decreased with age, body mass index, heart rate and diastolic blood pressure (Table 2). Both ratios increased with the pulse pressure. The transmitral E/A ratio, but not the averaged Ea/Aa ratio increased with the EF. Furthermore, the averaged E/Ea ratio significantly and independently increased with female sex, age, body mass index, systolic blood pressure, and LV mass index (Table 2). The explained variance totaled 69.0% for the transmitral E/A ratio, 74.4% for the averaged mitral annular Ea/Aa ratio and 51.0% for the E/Ea ratio. Age accounted for most of the explained variance (53.9%, 62.4%, and 34.2%, respectively).

Transmitral and TDI Doppler Indexes in 239 Healthy Subjects

Figure 1 shows age-specific percentiles of the E/A and E/Ea ratios in the healthy subsample of 239 subjects (Supplemental Table A). There was a significant decline in the E/A ratio with age ($P<0.0001$; Figure 1, left) because of a significant decrease in E velocity as well as an increase in A velocity (data not shown). The E/Ea ratio significantly increased with age ($P<0.0001$) in the reference group (Figure 1, right). However, the 97.5% percentile of the E/Ea ratio in all ages combined did not exceed the proposed cutoff limit of 8.5 for the normal filling pressure. In the reference group, the Δ(Ad–ARd) was not dependent on age. The 2.5% to 97.5% percentiles interval ranged from –5.71 to 8.57, respectively (Supplemental Table A).

Prevalence of LV Diastolic Dysfunction in the Population Based on Age-Specific Doppler Criteria

We combined the Doppler measurements of the mitral inflow, the reverse flow in the PV, and averaged TDI mitral annulus velocities to determine stages of LV diastolic dysfunction. The first group included subjects with an abnormally low age-specific transmitral E/A ratio indicative of impaired

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Table 2. Correlates of the Transmitral E/A, Averaged Mitral Annular Ea/Aa, and E/Ea Ratios in Stepwise Regression in All Subjects

Parameter	Transmitral E/A	VIF	Averaged TDI Ea/Aa	VIF	E/Ea	VIF
R^2	0.684		0.736		0.504	
Adjusted R^2	0.680		0.733		0.497	
Root MSE	0.257		0.304		1.52	
Mallow Cp	4.83		6.61		8.00	
Partial regression coefficients						
Age (+10 years)	−0.230±0.010*	1.57	−0.292±0.011*	1.54	0.387±0.064*	1.70
Female (0, 1)	. . .		0.057±0.027†	1.07	0.714±0.189*	1.24
Body mass index (+1 kg/m^2)	−0.015±0.003*	1.26	−0.029±0.004*	1.23	0.071±0.019*	1.20
Heart rate (+10 beats/minute)	−0.12±0.013*	1.08	−0.088±0.014*	1.14	. . .	
Systolic BP (+10 mm Hg)	. . .		. . .		0.324±0.047*	1.60
Diastolic BP (+10 mm Hg)	−0.069±0.015*	1.32	−0.104±0.017*	1.32	. . .	
Pulse Pressure (+10 mm Hg)	0.031±0.010‡	1.45	0.046±0.011*	1.45	. . .	
LV mass index (+10 g/m^2)	. . .		. . .		0.172±0.041*	1.65
Ejection fraction (+10%)	0.047±0.016‡	1.10	. . .		. . .	
Use of RAAS inhibitors (0, 1)	. . .		. . .		−0.844±0.285‡	1.09
Use of β-blockers (0, 1)	. . .		. . .		0.487±0.212†	1.15

Values are mutually adjusted partial regression coefficients±SE.
MSE indicates mean squared error; BP, blood pressure; RAAS, renin-angiotensin-aldosterone system.
*P≤0.001; †P≤0.05; ‡P≤0.01.

relaxation (<2.5th percentile of the reference subgroup; Supplemental Table A), but without evidence of increased LV filling pressures (E/Ea, ≤8.5). The second group had mildly-to-moderately elevated end-diastolic filling pressure with E/Ea >8.5, and E/A ratio within the normal age-specific range (from 2.5th to 97.5th percentiles of the reference subgroup; Supplemental Table A). We used the differences in durations between the mitral A flow and the reverse PV flow during atrial systole (Ad<ARd+10) to confirm possible elevation of filling pressures in group 2. Group 3 had both an elevated E/Ea ratio and an abnormally low age-specific E/A (combined dysfunction). The number of subjects in groups 1, 2, and 3 were 53 (9.8%), 76 (14.1%), and 18 (3.4%), respectively. Table 3 presents the prevalence of diastolic dysfunction by age group. The clinical and echocardiographic characteristics of subjects by group of diastolic function appear in Tables 4 and 5, respectively. Compared with subjects with normal diastolic function (n=392, 72.7%), those with elevated end-diastolic filling pressure had a significantly higher sex-, age-, body mass index–, and serum creatinine–adjusted NT-proBNP (209 versus 275 pmol/L; P=0.0003), with a similar trend (209 versus 251 pmol/L; P=0.015) for those with impaired relaxation (group 1). However, there was no statistical difference in NT-proBNP level

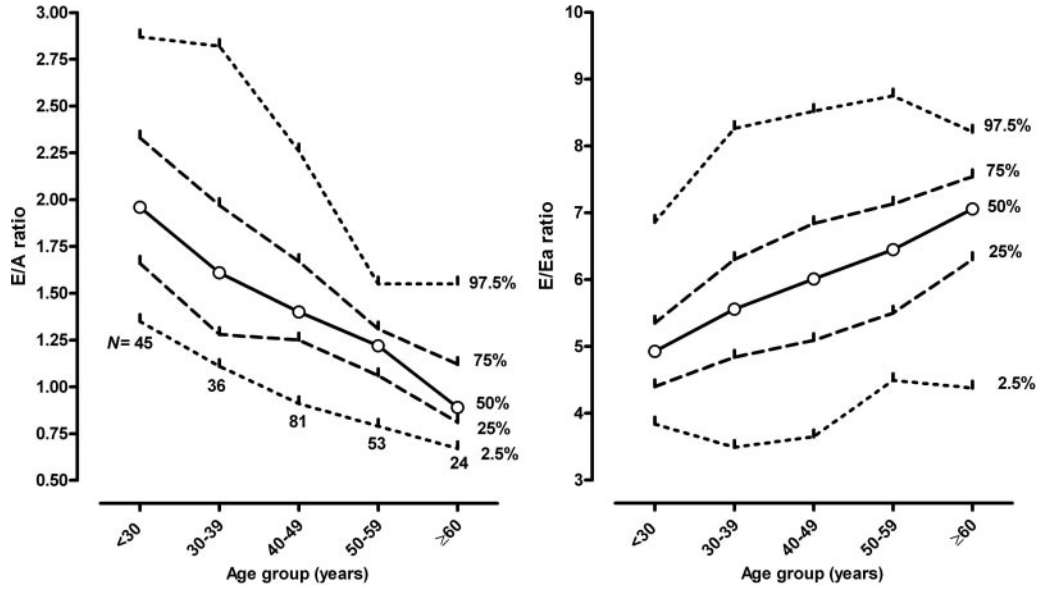

Figure 1. Age-specific percentiles of the E/A (left) and E/Ea (right) ratios for the healthy reference sample (n=239).

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Table 3. Age Distribution of the Total and Reference Samples and by Diastolic Function Group

	Age Group (years)					
	<30	30–39	40–49	50–59	60–69	≥70
Group						
Total	55 (10.2)	49 (9.1)	131 (24.3)	131 (24.3)	99 (18.4)	74 (13.7)
Reference	45 (18.8)	36 (15.1)	81 (33.9)	53 (22.2)	19 (7.9)	5 (2.1)
Diastolic function						
Normal function	52 (13.3)	47 (12.0)	120 (30.6)	104 (26.5)	52 (13.3)	17 (4.3)
Group 1: impaired relaxation	3 (5.7)	1 (1.9)	7 (13.2)	17 (32.1)	13 (24.5)	12 (22.6)
Group 2: elevated end-diastolic pressure	. . .	1 (1.3)	3 (3.9)	8 (10.5)	27 (35.5)	37 (48.7)
Group 3: combined dysfunction	. . .	. . .	1 (3.6)	2 (11.1)	7 (38.9)	8 (44.4)

Data are presented as n (%). Impaired relaxation (group 1) indicates low E/A and normal E/Ea; elevated end-diastolic pressure (group 2), normal E/A and high E/Ea; combined dysfunction (group 3), low E/A and high E/Ea.

between the group with normal diastolic function and group with combined dysfunction (209 versus 224 pmol/L; $P=0.66$).

Figure 2 shows the adjusted odds of having LV diastolic dysfunction. Higher age, body mass index, heart rate, and systolic blood pressure were significantly associated with a higher risk of LV diastolic dysfunction. Use of β-blockers was weakly but positively associated with a higher risk of LV diastolic dysfunction (95% CI, 0.98 to 3.84; $P=0.056$). The prevalence of diastolic dysfunction also increased with serum insulin, serum creatinine and NT-proBNP.

Discussion

In this random sample of a general population, the overall prevalence of LV diastolic dysfunction, as estimated from echocardiographic measurements was as high as 27.3% and increased in frequency with age. The reported prevalence of

Table 4. Clinical Characteristics of Participants by Diastolic Function Group

Characteristic	Normal Function (n=392)	Impaired Relaxation (n=53)	Elevated End-Diastolic Pressure (n=76)	Combined Dysfunction (n=18)
Transmitral E/A ratio	Normal	↓	Normal	↓
E/Ea ratio	Normal	Normal	↑	↑
Age, years	47.6±13.6	60.2±14.0*	67.9±9.0*†	69.1±9.2*†
Women	187 (47.2)	23 (43.4)	48 (63.2)*†	14 (77.8)*†
Body mass index, kg/m^2	25.5±3.6	28.0±3.8*	28.5±4.9*	29.5±2.6*
Systolic pressure, mm Hg	125.5±15.9	136.3±15.3*	146.6±18.9*†	147.1±19.2*†
Diastolic pressure, mm Hg	78.6±8.9	83.7±9.6*	77.8±9.7	83.8±7.9*‡
Heart rate, beats/minute	60.1±8.9	67.5±11.8*	57.5±9.2*†	64.9±10.1‡
Questionnaire data				
Current smoking	91 (23.2)	14 (26.4)	10 (13.2)	1 (5.6)
Drinking alcohol	187 (47.7)	19 (35.8)	20 (26.3)*	2 (11.1)*†
Hypertensive	112 (28.6)	36 (67.9)*	59 (77.6)*	14 (77.8)*
Treated for hypertension	53 (13.5)	25 (47.2)*	41 (53.9)*	8 (44.4)*
β-blockers	33 (8.4)	12 (22.6)*	29 (38.2)*	4 (22.2)*
ACE or ARB	15 (3.8)	12 (22.6)*	9 (11.8)*	2 (11.1)
Diuretics or CCB	26 (6.6)	10 (18.9)*	25 (32.9)*	5 (27.8)*
Cardiac valve disorder	7 (1.8)	3 (5.7)	13 (17.1)*	2 (11.1)
History of CHD	1 (0.26)	2 (3.8)	9 (11.8)*	1 (5.6)
Diabetes	5 (1.3)	1 (1.9)	3 (3.95)	2 (11.1)*
Biochemical data				
NT-proBNP, pmol/L	214 (123 to 398)	269* (132 to 524)	302* (148 to 602)	245 (117 to 512)
Serum creatinine, μmol/L	84.0±12.0	95.0±31.2*	88.2±14.7*	87.9±13.9
Insulin, μU/mL	4.27 (2.0 to 8.91)	5.75* (3.02 to 12.9)	5.24* (3.02 to 10.0)	8.13*‡ (2.95 to 20.0)

Data are presented as mean±SD, n (%), or geometric mean (10% to 90% interval).

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CCB, calcium channel blocker; CHD, coronary heart disease.

*$P\leq0.05$ versus normal; †$P\leq0.05$ versus impaired relaxation group; ‡$P\leq0.05$ versus elevated end-diastolic pressure group.

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Table 5. Echocardiographic Characteristics of Participants by Diastolic Function Group

Characteristic	Normal Function (n=392)	Impaired Relaxation (n=53)	Elevated End-Diastolic Pressure (n=76)	Combined Dysfunction (n=18)
Transmitral E/A ratio	Normal	↓	Normal	↓
E/Ea ratio	Normal	Normal	↑	↑
Conventional echocardiography				
Left atrium diameter, cm	3.88±0.52	4.06±0.66	4.25±0.49*	4.14±0.47*
LV internal diameter, cm	5.03±0.45	5.07±0.65	5.05±0.62	4.85±0.42
Interventricular septum, cm	0.96±0.17	1.04±0.18*	1.08±0.17*	1.22±0.20*†‡
Posterior wall, cm	0.85±0.14	0.92±0.15*	0.96±0.14*	1.04±0.15*†
Relative wall thickness	0.36±0.07	0.39±0.08*	0.41±0.08*	0.45±0.07*†‡
LV mass index, g/m^2	88.4±18.5	99.5±24.5*	107.0±25.5*	115.9±24.3*†
Ejection fraction, %	68.4±7.0	66.0±10.2	71.8±8.7*†	71.6±9.5
Transmitral doppler data				
E peak, cm/s	78.3±14.9	53.8±18.9*	81.3±13.6†	63.0±16.4*†‡
A peak, cm/s	60.6±14.2	78.9±12.5*	82.2±16.1*	96.2±18.2*†‡
E/A ratio	1.37±0.44	0.70±0.15*	1.02±0.23*†	0.65±0.09*‡
IVRT, ms	98.3±13.2	114.9±16.4*	108.5±16.7*†	107.1±24.3
Adur-ARdur, ms	1.42 (2.9 to 7.1)	18.5* (1.42 to 32.1)	−20.0*† (−37.1 to −6.8)	19.2*‡ (−12.8 to 31.4)
Tissue doppler velocities§				
Ea peak, cm/s	12.7±3.27	8.28±1.93*	7.80±1.23*	5.94±1.02*†‡
Aa peak, cm/s	10.2±2.01	12.1±1.77*	10.5±1.88†	11.6±1.20*‡
Ea/Aa ratio	1.35±0.60	0.71±0.22*	0.77±0.19*	0.52±0.10*†‡
E/Ea ratio	6.37±1.34	6.66±1.11	10.6±2.09*†	10.7±2.30*†

Data are presented as mean±SD or geometric mean (10% to 90% interval).

IVRT indicates isovolumetric relaxation time; Adur, mitral inflow A-wave duration; ARdur, pulmonary vein atrial reversal flow duration.

*P≤0.05 versus normal; †P≤0.05 versus impaired relaxation group; ‡P≤0.05 versus elevated end-diastolic pressure group.

§Averaged of septum, lateral, inferior and posterior mitral annulus sites.

diastolic dysfunction in the general population[3,4,10,11] varies from 11.1% to 34.7%, and is influenced by a number of factors, including the characteristics of the population studied, the choice of the imaging modalities, and the criteria applied to diagnosed LV diastolic dysfunction.

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.[12] Even these techniques are complex because no single measurement reflects diastolic function. Thus, a comprehensive assessment of a number of variables is required to evaluate diastolic function as correctly as possible.[13] We assessed LV diastolic function, using the transmitral and pulmonary blood flows, and the TDI mitral annular velocities. Lower transmitral E/A ratio and lower mitral annular Ea/Aa ratio both reflect impaired myocardial relaxation, characterized by decreased early, but enhanced atrial filling of the LV. In keeping with previous studies in the general population,[4,14] we also demonstrated that LV relaxation as reflected by both indexes substantially decreased with age in all study participants and in the healthy reference group. Current guidelines propose criteria to diagnose diastolic dysfunction which are not standardized for age.[1,12] It is likely that by ignoring age and by applying

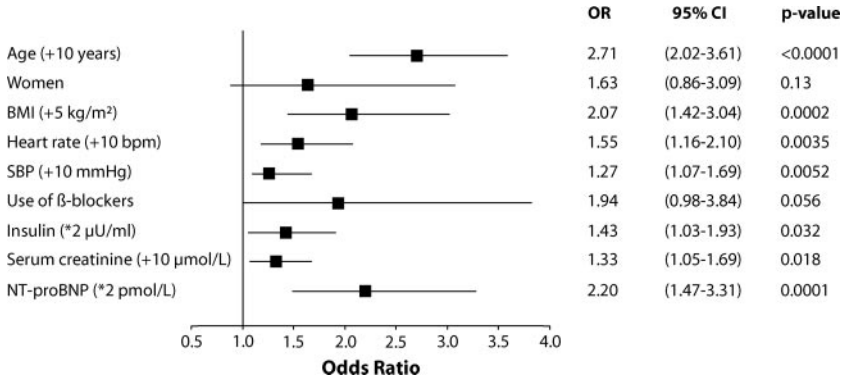

Figure 2. Association between diastolic dysfunction and clinical and biochemical characteristics. Black squares and horizontal lines represent the odds ratios and 95% CIs for the mutually adjusted covariates, identified by stepwise regression.

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the same threshold values for the Doppler indexes throughout the age range, one may underestimate the prevalence of subclinical diastolic dysfunction (impaired relaxation), especially in young subjects.

The Doppler blood flow measurements and the TDI mitral annulus velocities can reflect abnormal LV relaxation as well as elevated LV filling pressure. Combining transmitral flow velocity with annular velocity (E/Ea ratio) might be a tool for assessing the LV filling pressure, which combines the influence of the transmitral driving pressure and myocardial relaxation.[15,16] In our general population, only 6 subjects (1.1%) had an E/Ea ratio in excess of the proposed threshold of 15 as the diagnostic criteria for an elevated end-diastolic pressure. The majority of patients with elevated LV end-diastolic filling pressure in the presence of normal EF (>50%), as determined in several previous studies by invasive pressure-volume loops, had an E/Ea ratio between 8 and 15.[15,17] Ommen et al[15] suggested that the accurate prediction of LV filling pressures for an individual patient requires a further characterization of the intermediate E/Ea group, for instance with PV flow information. In our study, we used the difference in duration between the mitral A flow and the reverse PV flow during atrial systole (Ad<ARd+10) to confirm a possible elevation of filling pressures. Moreover, we described one of the categories of diastolic dysfunction (group 3) as having a low E/A ratio but an elevated E/Ea ratio. To our knowledge, this is heretofore undescribed group of patients. This implies that there is a significant relaxation abnormality in the LV, such that both left atrial pressure and LV diastolic pressure are elevated in parallel, and the peak transmitral flow velocity may therefore be low.

There is no universally accepted method for dichotomizing continuous variables. The cut-off points of continuous echocardiographic measurements should be based on the distribution of these measurements in a randomly selected noninstitutionalized sample of the general population.[18,19] In the present study, we selected a healthy subgroup from a general population to propose cut-off limits for LV diastolic dysfunction. Our age-specific percentiles of mitral E/A ratio are in close agreement with previously reported age-specific thresholds from the Tromsø population study (Supplemental Table B).[14] In our study, the 97.5th percentile of E/Ea ratio in the healthy subgroup was 8.4. In previous invasive studies, an E/Ea ratio <8 accurately indicated normal LV end-diastolic filling pressure.[15] The reference limit derived from our healthy reference subgroup for the difference in duration between the mitral A flow and the reverse PV flow (Ad<ARd+10) was less than in previous studies of patients with coronary heart disease or cardiomyopathy (Ad<ARd+30).[20] However, the invasive study by Yamamoto et al[21] demonstrated that a difference between A-wave and AR durations of less than 0 ms predicted a LV end-diastolic pressure of 20 mm Hg or greater with high sensitivity (82%) and specificity (92%).[20]

Cardiomyocytes produce BNP in response to an increase of atrial or ventricular diastolic stretch to stimulate natriuresis and vasodilatation and to facilitate LV relaxation.[22] Secreted proBNP is subsequently cleaved in the blood into NT-proBNP and BNP. In patients with HF and normal EF, early diastolic LV relaxation indexes correlate with NT-proBNP values.[22] NT-proBNP values also vary with the degree of LV diastolic dysfunction. We observed progressively higher values in subjects with an impaired relaxation pattern (group 1), and in subjects with elevated end-diastolic pressure (group 2). However, in subjects with a combined dysfunction who had an elevated E/Ea ratio and an abnormally low age-specific E/A (group 3), NT-proBNP level was not different from subjects with normal diastolic function. This finding highlights the necessity to identify a panel of circulatory biomarkers which might more accurately reflect diastolic dysfunction. We cannot exclude the possibility that hitherto unidentified mechanisms, such as a genetic variation in the generation or breakdown of BNP might explain the findings in group 3.

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 quantitative traits, which arise through a complex interaction between multiple genes, hemodynamic and environmental factors and are prone to measurement error, especially the Doppler measurement of pulmonary flow. In the present study, only one experienced observer recorded all Doppler images for offline postprocessing. Second, our sample size was smaller than in the Canberra[4] and Olmsted[3] studies. On the other hand, we covered an age-range from 17.6 to 89.5 years (mean age, 52.4 years). The age span in the Canberra and Olmsted studies ranged from 60 to 86 years (mean age, 69.4 years) and from 45 to 75 years and older (mean age, 62.8 years), respectively. Third, we did not specifically score the symptoms and signs of HF. However, in a population based research of 6 HF scores, Mosterd et al[23] demonstrated that the objective measurements of cardiac function are necessary to reduce the false-positive rate and to detect in an accurate manner the early stages of HF. We used the same detailed and validated questionnaire[6] at enrolment and at the echocardiographic examination and checked for changes in the health status of our subjects. All our participants were ambulatory and physically apt to come to the examination center. Moreover, in continuous and categorical analyses, the correlates of LV diastolic function were as expected and constitute an internal validation of our study.

In conclusion, the overall prevalence of LV diastolic dysfunction in a random sample of a general population, as estimated from echocardiographic measurements and as confirmed by NT-proBNP level, was as high as 27.3%. Higher age, body mass index, heart rate, systolic blood pressure, serum insulin, and creatinine were significantly associated with a higher risk of LV diastolic dysfunction in population. Our findings have clinical relevance in view of the high risk of overt HF in patients with impaired LV diastolic function.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Because the process of myocardial remodeling starts before the onset of symptoms, recent heart failure guidelines place special emphasis on the detection of subclinical left ventricular (LV) systolic and diastolic dysfunction and the timely identification of risk factors for heart failure. Our goal was to describe the prevalence and risk factors of LV diastolic dysfunction in a general population. In a randomly recruited population sample (n=539; mean age, 52.5 years), we measured early and late diastolic peak velocities of mitral inflow (E and A), pulmonary vein flow by pulsed-wave Doppler, and mitral annular velocities (Ea and Aa) at 4 sites by tissue Doppler imaging. A healthy subsample of 239 subjects (mean age, 43.7 years) provided age-specific cutoff limits for normal E/A and E/Ea ratios and the differences in duration between the mitral A and the reverse pulmonary vein flows during atrial systole. The number of subjects in diastolic dysfunction groups 1 (impaired relaxation), 2 (elevated LV end-diastolic filling pressure), and 3 (elevated E/Ea and abnormally low E/A) were 53 (9.8%), 76 (14.1%), and 18 (3.4%), respectively. The overall prevalence of LV diastolic dysfunction in a general population, as estimated from echocardiographic measurements and as confirmed by amino terminal probrain natriuretic peptide level was 27.3%. Higher age, body mass index, heart rate, systolic blood pressure, serum insulin, and creatinine were significantly associated with a higher risk of LV diastolic dysfunction in population. Our findings have clinical relevance in view of the high risk of overt HF in patients with impaired LV diastolic function.

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SUPPLEMENTAL MATERIAL

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Supplemental Table A. Transmitral E/A, averaged E/Ea and Δ(Adur–ARdur) in the Healthy Reference Group

Age	<30	30-39	40-49	50-59	≥60	All	<30	30-39	40-49	50-59	≥60	All
E/A Ratio							**Δ(Adur–ARdur) (ms)**					
N	45	36	81	53	24	**239**	45	35	80	51	23	**234**
X	1.98	1.67	1.47	1.18	0.97	**1.48**	1.01	1.96	1.36	1.54	1.54	**1.44**
SD	0.42	0.41	0.34	0.21	0.23	**0.46**	3.15	3.02	4.26	4.64	4.09	**3.95**
$P_{2.5}$	1.35	1.11	0.91	0.79	0.67	**0.79**	-5.71	-5.70	-5.71	-8.56	-7.13	**-5.71**
P_5	1.36	1.15	0.93	0.79	0.74	**0.86**	-2.85	-2.86	-4.99	-5.71	-5.71	**-5.70**
P_{10}	1.37	1.24	1.06	0.87	0.75	**0.92**	-2.85	-1.42	-2.86	-2.86	-4.22	**-2.85**
P_{25}	1.66	1.28	1.25	1.06	0.81	**1.19**	-1.42	0.00	-2.85	0.00	0.00	**-1.42**
P_{50}	1.96	1.61	1.40	1.22	0.89	**1.39**	1.42	1.43	1.42	1.42	1.43	**1.42**
P_{75}	2.33	1.97	1.67	1.31	1.12	**1.70**	2.85	4.29	4.28	4.27	5.70	**4.27**
P_{90}	2.45	2.14	1.93	1.47	1.28	**2.08**	4.28	5.71	7.85	7.13	5.71	**5.71**
P_{95}	2.53	2.50	2.03	1.51	1.41	**2.43**	5.71	7.13	9.27	8.55	6.90	**8.56**
$P_{97.5}$	2.87	2.82	2.26	1.55	1.55	**2.51**	5.71	8.56	9.98	8.56	8.56	**8.57**
E/Ea Ratio												
N	45	36	81	53	24	**239**						
X	5.07	5.63	6.02	6.47	6.89	**5.97**						
SD	0.91	1.06	1.25	1.19	0.94	**1.25**						
$P_{2.5}$	3.84	3.49	3.65	4.49	4.38	**3.84**						
P_5	3.93	3.64	4.32	4.62	5.11	**4.01**						
P_{10}	4.04	4.55	4.54	4.92	5.82	**4.47**						
P_{25}	4.40	4.84	5.09	5.50	6.30	**5.01**						
P_{50}	4.93	5.56	6.01	6.45	7.06	**5.96**						
P_{75}	5.35	6.30	6.84	7.13	7.54	**6.81**						
P_{90}	6.25	7.17	7.56	8.09	7.93	**7.64**						
P_{95}	6.78	7.47	8.29	8.61	8.05	**8.09**						
$P_{97.5}$	6.86	8.26	8.52	8.75	8.21	**8.39**						

N, X, SD, $P_{2.5}$, P_5, P_{10}, P_{25}, P_{50}, P_{75}, P_{90}, P_{95}, $P_{97.5}$ indicate number of subjects, mean, standard deviation and percentiles.

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Supplemental Table B. Age-specific Percentiles for the E/A Ratio in the Tromsø [15] and FLEMENGHO Studies.

	2.5 percentile		97.5 percentile	
Age group (years)	**Tromsø**	**FLEMENGHO**	**Tromsø**	**FLEMENGHO**
40-49	0.92	0.91	2.25	2.26
50-59	0.78	0.79	1.61	1.55
>60	0.63	0.67	1.53	1.55

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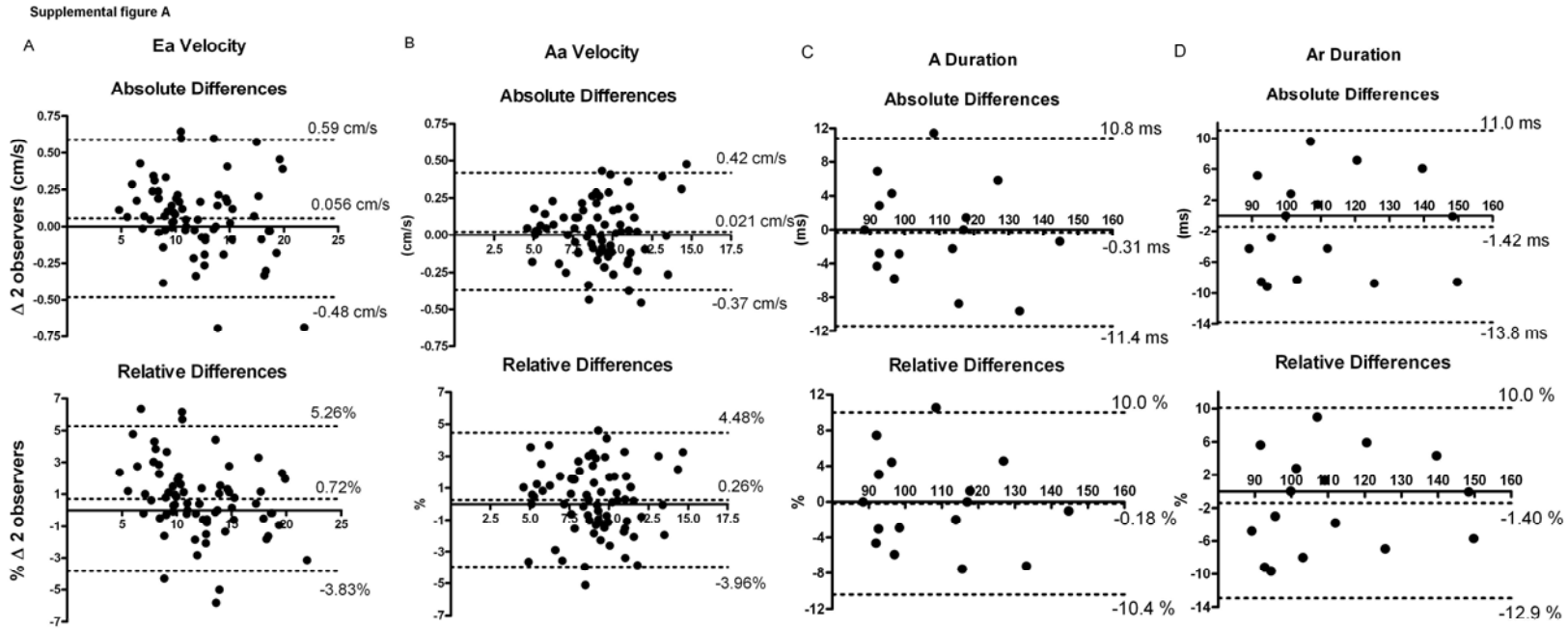
Supplemental Figure A



Bland-Altman plots with the 95% limits of agreement for Ea and Aa velocities at 4 acquisition sites (septal, lateral, inferior, and posterior) (panels A and B) and for A-wave and pulmonary vein reversal A duration (panels C and D). Two observers analyzed the recordings of 17 subjects. Absolute and relative biases between the 2 readers were calculated as (x1 – x2) vs averaged and (100*(x1 – x2)/averaged) vs averaged, respectively.