



Prevalence of left ventricular diastolic dysfunction in the community

Results from a Doppler echocardiographic-based survey of a population sample

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KEYWORDS

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Aims The prevalence of left ventricular diastolic abnormalities in the general population is largely unclear. Thus, the aim of this study was, firstly, to identify abnormal diastolic function by echocardiography in an age-stratified population-based European sample (MONICA Augsburg, $n=1274$, 25 to 75 years, mean 51 ± 14) and, secondly, to analyse clinical and anthropometric parameters associated with diastolic abnormalities.

Methods and results The overall prevalence of diastolic abnormalities, as defined by the European Study Group on Diastolic Heart Failure (i.e. age dependent isovolumic relaxation time (92–105 ms) and early (E-wave) and late (A-wave) left ventricular filling (E/A-ratio, 1–0.5)) was 11.1%. When only subjects treated with diuretics or with left atrial enlargement were considered (suggesting diastolic dysfunction) the prevalence was 3.1%. The prevalence of diastolic abnormalities varied according to age: from 2.8% in individuals aged 25–35 years to 15.8% among those older than 65 years ($P<0.01$). Significantly higher rates of diastolic abnormalities were observed in men as compared to women (13.8% vs 8.6%, $P<0.01$). Independent predictors of diastolic abnormalities were arterial hypertension, evidence of left ventricular (LV) hypertrophy, and coronary artery disease. Interestingly, in the absence of these predisposing conditions, diastolic abnormalities (4.3%) or diastolic dysfunction (1.1%) were rare, even in subjects older than 50 years of age (4.6%) and (1.2%), respectively. In addition to these factors, diastolic dysfunction was related to high body mass index, high body fat mass, and diabetes mellitus.

Conclusion The prevalences of diastolic abnormalities and diastolic dysfunction are higher than that of systolic dysfunction and are increased (despite age-dependent diagnostic criteria) in the elderly. However, in the absence of risk factors for diastolic abnormalities or diastolic dysfunction, namely LV hypertrophy, arterial hypertension, coronary artery disease, obesity and diabetes the condition is rare even in elderly subjects. These data allow speculation on whether diastolic heart failure may be prevented by improved implementation of measures directed against predisposing conditions.

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Introduction

Thirty to fifty percent of patients hospitalized for heart failure present with diastolic dysfunction.^{1–5} Specifically, the dramatic increase in hospitalizations for heart failure among the elderly can be largely attributed to this condition.^{2,6} However, abnormalities of diastolic function may not always produce signs and symptoms of heart failure. Accordingly, diastolic heart failure has been defined as a trilogy of (a) left ventricular diastolic dysfunction, (b) normal or only mildly impaired systolic pump function and (c) typical symptoms.⁷

Thus far, the implications of diastolic dysfunction have been predominantly studied in patients with symptomatic heart failure.^{3–5,8} By contrast, the prevalence of diastolic abnormalities in the community with or without clinical symptoms is largely unclear.⁹ Moreover, little information is available on characteristics that predispose individuals to present with an abnormal diastolic function. Such information may be valuable since treatment at an early asymptomatic stage may delay or prevent progression to symptomatic heart failure and its consequences. We thus report on a large-scale epidemiological study that used two-dimensional and Doppler echocardiography to investigate the prevalence and predictors of diastolic abnormalities and diastolic dysfunction in the community setting.

Subjects and methods

Study population

As a component of the international collaborative WHO MONICA project, the MONICA Augsburg study investigated the cardiovascular risk factor profile of randomly selected subjects of the Augsburg population in cross-sectional surveys. Echocardiographic examinations were performed in a total of 827 males and 851 females, aged 25 to 75 years.¹⁰ All patients gave written informed consent and completed a questionnaire on demography, current medication, history of myocardial infarction or diabetes mellitus, and answered questions on lifestyle and nutrition, health behaviour, and psychosocial factors. Blood pressure was taken as a mean of two readings on the right arm with the random zero method, measured under standardized conditions with the participant seated (after 5 min rest). Body mass index was calculated as kg m^{-2} , the percentage of body fat was obtained by bioelectric impedance measurements, and an electrocardiogram was

recorded in a standardized fashion as previously reported.^{11–13}

Echocardiographic measurements

Two-dimensional echocardiograms from standard left parasternal and apical windows, derived M-mode echocardiograms, and Doppler recordings were performed by two expert sonographers on a commercially available echocardiograph (Hewlett Packard, Sonos 1500, Andover, MA, USA) with a 2.5 or 3.5 MHz transducer. M-mode tracings were recorded on stripchart paper at a speed of 50 mm s^{-1} . To reduce interobserver variability, all M-mode tracings were analysed by a single experienced observer. Measurements for M-mode guided calculation of left ventricular mass were taken just below the tip of the mitral valve. Left ventricular internal end-diastolic (LVEDD) and end-systolic diameters (LVESD) and septal (Swth) and posterior wall thickness (Pwth) were performed according to the guidelines of the American Society of Echocardiography. Left ventricular mass (LVM) was calculated according to the formula $\text{LVM (g)} = 1.04((\text{LVEDD} + \text{Swth} + \text{Pwth})^3 - \text{LVEDD}^3) - 13.6$.¹⁴ The rank correlation for 144 duplicate measurements by the two sonographers was 0.91 for the determination of LVM. Left ventricular mass was indexed to body surface area as left ventricular mass index (LVMI) in g m^{-2} body surface area.¹² Left ventricular end-systolic and end-diastolic volumes (LVESV, LVEDV) were determined with the Teichholz equations.¹⁵ The ejection fraction was calculated as $\text{EF} = (\text{LVEDV} - \text{LVESV}) / \text{LVEDV}$. Doppler echocardiographic recordings were performed by pulsed wave Doppler with the sample volume at the tips of the mitral valve in the apical four chamber view and registered at a paper speed of 100 mm s^{-1} . Early (E) and late (A) diastolic velocities, velocity time integrals and ratios of early and late velocities as well as velocity time integrals (E/A) were determined as previously described.¹³ Isovolumetric relaxation time (IVRT) was determined as the interval between the end of the aortic outflow and the start of the mitral inflow signal.

The definitions used in this study were as follows: a preserved left ventricular systolic function was a calculated ejection fraction of ≥ 45 .⁷ This also represents the mean minus 2 SD as obtained in 897 healthy subjects. Diastolic abnormalities were defined as proposed by the European Study Group on Diastolic Heart Failure.⁷ Specifically, an abnormal E/A-ratio was considered when $\text{E/A}_{<50 \text{ years}}$ was < 1 , or $\text{E/A}_{>50 \text{ years}}$ was < 0.5 , or $\text{IVRT}_{<30 \text{ years}}$ was $> 92 \text{ ms}$, or $\text{IVRT}_{30-50 \text{ years}}$ was $> 100 \text{ ms}$, or $\text{IVRT}_{>50 \text{ years}}$ was

>105 ms in the presence of a preserved ejection fraction. The term diastolic dysfunction refers to echocardiographically derived diastolic abnormalities in the presence of current diuretic therapy and/or left atrial enlargement. Left atrial enlargement was a left atrial diameter of more than 45 mm or a left atrial maximal area of more than 20 cm². Of the 40 individuals with evidence of diastolic dysfunction, 16 presented with diuretic therapy and 29 with left atrial enlargement. Unfortunately, in the MONICA project as well as other epidemiological surveys a validated symptom score for heart failure was not available. Hypertension was considered at a blood pressure of $\geq 140/90$ mmHg, current intake of antihypertensive medication, or both. Diabetes mellitus was defined as a history of diabetes. LV hypertrophy was defined as LV mass indexed to a body surface area of >131 g m⁻² in men and 100 g m⁻² in women.¹¹ Body mass index (BMI) was computed as weight divided by height squared (kg m⁻²). Obesity was defined according to the National Institute of Health Consensus Development Panel criteria as a BMI ≥ 27.3 kg m⁻² in men and ≥ 27.8 kg m⁻² in women.¹⁶ The body fat mass was considered to be high if greater than 70% of lean body mass (>90% quantile). Myocardial infarction was a history of myocardial infarction or on ECG evidence.

Statistical methods

Participants with or without evidence of diastolic abnormalities or diastolic dysfunction were characterized, regarding means and proportions of risk factors according to the definitions explained above. Initial comparisons between groups were performed with the use of either the Dunnett's test for parametric continuous variables or the Kruskal–Wallis test for non-parametric variables. Categorical variables were analysed using a likelihood ratio test. We also developed a multivariate logistic regression model using a significance level of $P < 0.10$ for entry and $P > 0.20$ for removal. The reduced models were compared in order to avoid losing predictive capability by the reduction of the model. We estimated odds ratios using the Mantel–Haenszel method. To estimate the relative impact of predictors on diastolic abnormalities and diastolic dysfunction, we calculated the population-attributable risk percent.¹⁷ Population-attributable risk percent expresses the proportion of diastolic abnormalities or diastolic dysfunction in the study population that is attributable to the exposure of predisposing factors and, theoretically, could be eliminated if the exposure was eliminated. It was calculated using the formula $PAR\% =$

$(P_e(OR - 1) / (P_e(OR - 1) + 1)) * 100$, where PAR% indicated population-attributable risk percent, P_e represents the proportion of the population exposed to the risk factor and OR indicates odds ratio (multivariately adjusted). All P -values were two-tailed, and values less than 0.05 were considered to indicate statistical significance. All confidence intervals were calculated at the 95% level.

Results

Optimal quality of two-dimensional echocardiographic examinations was obtained in 1418 of the 1678 participants for determination of the left ventricular ejection fraction. Nineteen participants (2.3%) were not considered to have isolated diastolic abnormalities because their ejection fraction was less than 45%. Doppler mitral profiles of sufficient quality were obtained in 1274 participants for the determination of diastolic filling velocities and in 988 for analysis of IVRT. No systematic differences in terms of age, gender, body mass index and systolic blood pressure were detected between subjects with complete and incomplete echocardiographic data.

Fig. 1 indicates the threshold levels for measurements of IVRT and the E/A-ratio that define diastolic abnormalities as indicated by the European Study Group on Diastolic Heart Failure. The scattergram indicates that IVRT increased and the E/A ratio decreased appreciably with age in the study participants. Based on the cutpoints, 141 individuals were diagnosed as having diastolic abnormalities. Of these, 81 displayed a prolonged IVRT and 68 had a decreased E/A-ratio. Both criteria were met by eight individuals. In this overlap group, 75% had arterial hypertension, 62.5% obesity, 25% LV hypertrophy; 37.5% were older than 65 years. Despite the use of age-adjusted cutpoints, the probability of having diastolic abnormalities by echocardiographic criteria increased from 9 to 21% in men ($P < 0.03$) and from 5 to 14% in women ($P < 0.04$) with the age ranges from 25 to 75 years, based on logistic regression analysis. The overall prevalence of diastolic abnormalities in our population-based study was 11.1% (13.8% in men and 8.6% in women). When only participants with diuretic treatment and/or left atrial enlargement were considered, i.e. those with evidence of diastolic dysfunction, the prevalence was 3.1% (3.9% in men and 2.3% in women, $P = \text{ns}$).

The anthropometric features of individuals with normal diastolic function, diastolic abnormalities and diastolic dysfunction (Table 1) demonstrate several differences with respect to the age- and

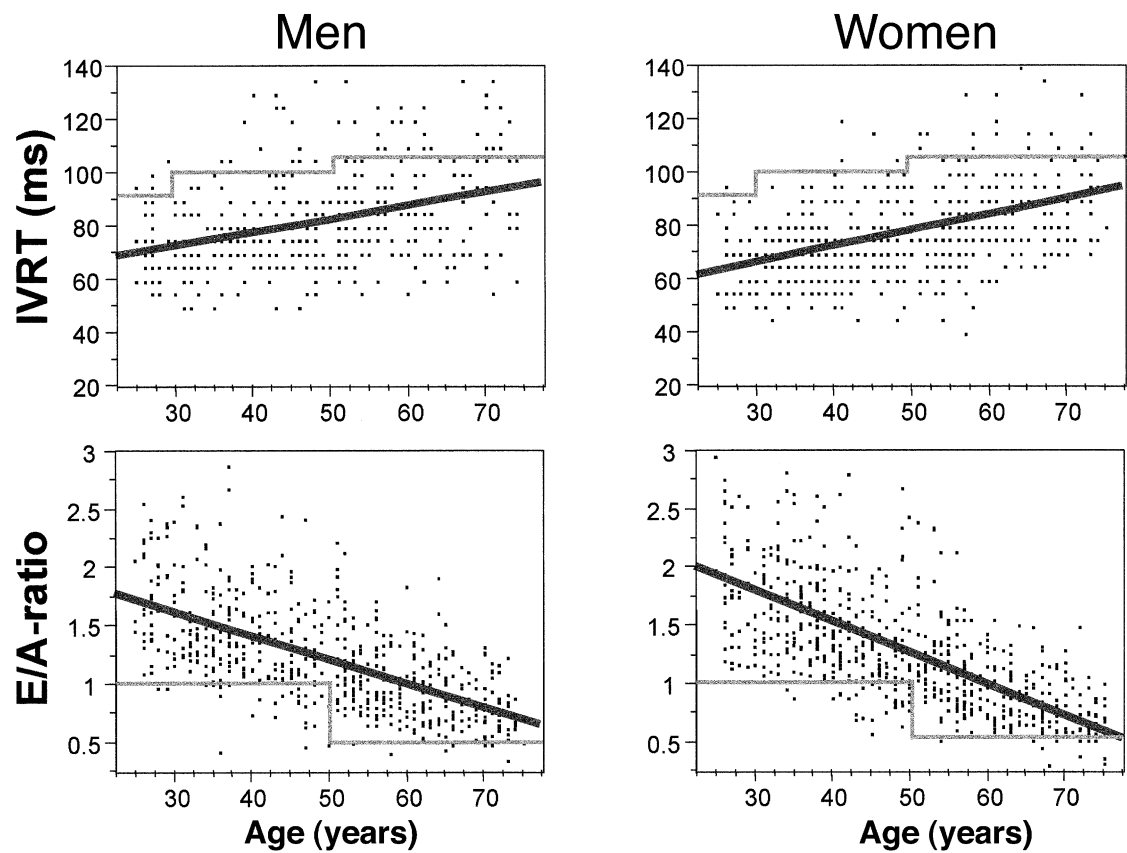


Fig. 1 Gender-specific relation between isovolumic relaxation time and E/A-ratio with age in male and female study participants. The steplike pattern represents the threshold levels (—) that define diastolic abnormalities as indicated by the European Study Group on Diastolic Heart Failure. The solid line deliniates the regression of measures for diastolic filling and age.

Table 1 Clinical and anthropometrical characteristics (mean±SD) in study participants with and without diastolic abnormalities or diastolic dysfunction			
	Normal diastolic function (n=1145)	Diastolic abnormalities (n=141)	Diastolic dysfunction (n=40)
Age (years)	48.9±13.7	52.4±12.1**	56.9±11.2*
Women (%)	54.1	41.1*	40.0*
BP≥140/90 mmHg (%)	32.0	47.5**	57.5**
Diabetes (%)	3.2	4.3	7.5*
Myocardial infarction (%)	0.5	1.4*	2.5*
LV hypertrophy (%)	6.2	14.7**	28.6**
Smoker (%)	28.0	29.8	15.0
BMI (kg m ⁻²)	26.1±4.0	27.4±3.9*	28.5±3.8**
FAT/FFM (%)	44.8±16.9	48.8±18.5*	52.7±20.5**
LDL-cholesterol (mg dl ⁻¹)	141±42	150±48	154±42
Systolic BP (mmHg)	131±19	140±21**	154±42**
Diastolic BP (mmHg)	80±11	84±12**	86±15**

BMI, body mass index; FFM, fat-free mass; FAT, fat mass; BP, blood pressure; LV, left ventricular; LDL, low density lipoprotein.
*/**, P<0.05/P<0.01 vs normal diastolic function.

sex-adjusted data. There were no significant differences in anthropometric criteria between individuals who displayed either pathological IVRT or E/A-ratio or both (data not shown). The independent predictors of diastolic abnormalities and diastolic

dysfunction are shown in Table 2 in a more detailed multivariate stepwise logistic regression analysis. Independently associated with diastolic abnormalities were arterial hypertension, LV hypertrophy, evidence of myocardial infarction, and male

Table 2 Factors that independently predict diastolic abnormalities and diastolic dysfunction with their increase of risk of having those diastolic abnormalities from multivariate logistic regression model and the population attributable risk percent (PAR%)

Risk factor	Diastolic abnormalities			Diastolic dysfunction		
	Odds ratio (95% CI)	P-value	PAR%	Odds ratio (95% CI)	P-value	PAR%
Arterial hypertension	1.9 (1.3–2.9)	<0.01	26.7	2.8 (1.5–5.5)	<0.01	42.1
LV hypertrophy	2.2 (1.4–3.7)	<0.01	8.5	7.6 (3.3–16.7)	<0.01	33.7
Myocardial infarction	2.0 (0.9–4.2)	<0.10	0.8	4.3 (1.1–26.5)	<0.05	2.6
Obesity*	1.1 (0.7–1.6)	ns	3.5	1.6 (1.0–3.0)	<0.05	18.0
FAT/FFM >70%	1.4 (0.7–2.6)	ns	4.4	2.9 (1.0–8.2)	<0.05	17.9
Diabetes	1.1 (0.4–2.6)	ns	0.4	2.3 (1.0–6.9)	<0.05	4.2
Male gender	1.5 (1.0–2.2)	<0.01	19.1	1.7 (0.9–3.2)	ns	24.8
Age ≥65 years	1.4 (0.9–4.2)	ns	6.4	1.7 (0.8–3.4)	ns	10.6

Because of colinearity, different models were analysed for anthropometric and echocardiographic indices.

*BMI ≥27.3 kg m⁻² in men and ≥27.8 kg m⁻² in women; CI, 95% confidence interval.

Abbreviations, see Table 1.

Table 3 Echocardiographic characteristics (mean±SD) in study participants with and without diastolic abnormalities or diastolic dysfunction

	Normal diastolic function (n=1145)	Diastolic abnormalities (n=141)	Diastolic dysfunction (n=40)
Septal wall (mm)	10.3±1.9	11.5±2.4**	12.6±0.3**
Posterior wall (mm)	8.5±1.4	9.3±1.6**	10.0±1.4**
LVEDD (mm)	47.8±4.6	48.8±5.1	50.4±4.6**
LVESD (mm)	30.8±4.0	31.5±4.5	32.4±5.2*
LV mass (g)	152.1±42.4	184.5±56.1**	216.9±70.9**
LV mass/BSA (g m ⁻²)	82.4±18.7	96.4±25.2**	109.4±31.8**
LA diameter (mm)	37.8±4.8	39.4±4.7**	42.1±5.6**
Ejection fraction (%)	64.5±7.2	64.2±8.0	64.6±7.2
E-wave (m s ⁻¹)	64.8±14.4	54.4±13.9**	55.2±14.6**
A-wave (m s ⁻¹)	54.2±16.4	63.8±18.5**	69.7±20.4**
E/A ratio	1.3±0.5	0.92±0.35**	0.85±0.31**
IVRT (ms)	75.4±13.1	105.9±24.5**	116.0±20.8**

*/**, P<0.05/P<0.01 vs normal diastolic function; BSA, body surface area; LVEDD/ESD, left ventricular end-diastolic/end-systolic diameters; E-/A-wave, early and late left ventricular filling; LA, left atrial; IVRT, isovolumetric relaxation time.

gender. In addition, diastolic dysfunction was independently associated with a high body mass index, high percent body fat mass, and diabetes mellitus (Table 2). More than 50% of the predictive capability of the final multivariate models were attributable to the presence of these risk factors. The population attributable risk was highest in individuals with arterial hypertension.

Table 3 shows the associations between diastolic abnormalities as well as diastolic dysfunction and cardiac geometric and functional parameters as assessed by echocardiography. Other than ejection fraction, all echocardiographic variables were significantly associated with diastolic abnormalities or diastolic dysfunction. As with anthropometric data, these associations were similar in those with pathological E/A and/or prolonged IVRT (data not shown).

Fig. 2 displays the prevalence of diastolic abnormalities and diastolic dysfunction in various clini-

cally defined subgroups. Specifically, the crude frequency of diastolic abnormalities was highest in individuals with LV hypertrophy, in subjects with evidence of myocardial infarction and in individuals with arterial hypertension. Fig. 3 also shows that as the number of predisposing risk factors increased, so did the prevalences of diastolic abnormalities and diastolic dysfunction.

In the absence of predisposing risk factors, i.e. in 'healthy' individuals, the frequency of diastolic abnormalities (4.3%) and diastolic dysfunction (1.1%) were markedly lower. The same low frequency was found in 'healthy' subjects older than 50 years of age (4.6 and 1.2%, respectively).

Discussion

In this population-based community setting we observed that the prevalence of LV diastolic abnormalities, as defined by the European Study Group

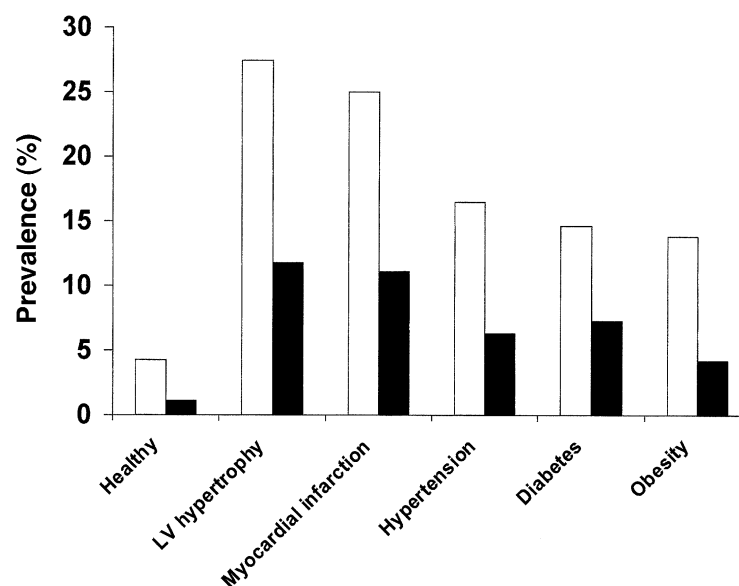


Fig. 2 Prevalences of diastolic abnormalities and diastolic dysfunction in different clinical subgroups. The crude frequency of an abnormal diastolic function was highest in individuals with LV hypertrophy, former myocardial infarction and hypertension. Diastolic abnormalities (□) were diagnosed as proposed by the European Study Group on Diastolic Heart Failure. Diastolic dysfunction (■) was considered in subjects with diastolic abnormalities plus diuretic therapy and/or left atrial enlargement.

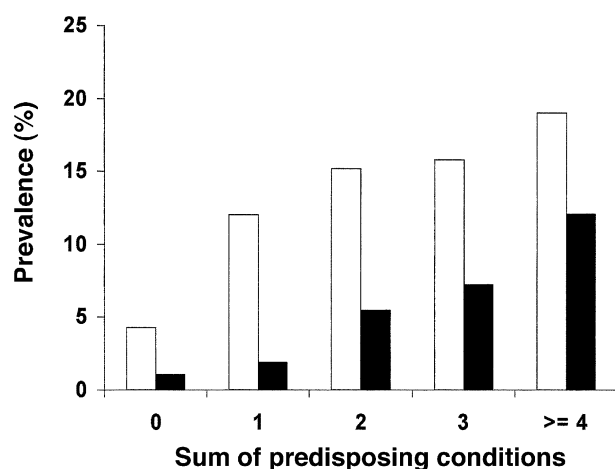


Fig. 3 Prevalence of diastolic abnormalities (□) and diastolic dysfunction (■) in the total study sample by the sum of individual predisposing risk factors, LV hypertrophy, myocardial infarction, hypertension, diabetes, obesity and age ≥ 65 years. (Sum of predisposing conditions/ n : 0/ n =488, 1/ n =371, 2/ n =270, 3/ n =132, ≥ 4 / n =58.)

on Diastolic Heart Failure, is substantially higher than that of its systolic counterpart. In fact, echocardiographically derived diastolic abnormalities were identified in one out of ten subjects and evidence for diastolic dysfunction (when only subjects treated with diuretics or with left atrial enlargement were considered) was found in 3% of the overall 'normal' population.

Interestingly, the present study also demonstrates that diastolic abnormalities are frequently associated with other pathologic conditions such as arterial hypertension, LV hypertrophy, and coronary artery disease. In addition to these factors, diastolic dysfunction was related to obesity and diabetes mellitus. Therefore, diastolic abnormalities may represent an early cardiac abnormality in subjects with such risk factors who may develop, as a consequence, functional abnormalities of the heart including diastolic dysfunction.

The predominant role of arterial hypertension for the development of diastolic heart failure was initially established by the Framingham Heart Study^{18–20} and was corroborated by experimental findings demonstrating the detrimental structural and functional effects of pressure overload on the myocardium and coronary vasculature.^{21–24} In our subgroup taken from a representative sample of the European MONICA–Augsburg population, hypertension was extremely common, affecting 40% of the participants. As in other countries²⁵ hypertension was not adequately controlled in the majority of patients. Indeed, we observed that of the hypertensive individuals 16.5% displayed signs of diastolic abnormalities and 6.3% signs of diastolic dysfunction, generating a population attributable risk of 27 and 42%, respectively.

LV hypertrophy undoubtedly reflects the progressive sequelae of hypertension on the heart and,

thus, may constitute an intermediate step towards the precipitation of diastolic dysfunction. Here we demonstrate that one fourth of subjects with LV hypertrophy have Doppler-derived evidence of diastolic abnormalities. Interestingly, hypertension and LV hypertrophy appeared to be partially independent predictors for the prevalence of diastolic abnormalities or diastolic dysfunction in our multivariate model. Thus, other factors that lead to LV hypertrophy may contribute to these associations as well.³⁶ Alternatively, hypertension, albeit being prevalent previously, may no longer be detectable in some individuals with LV hypertrophy and subsequent diastolic abnormalities.

Signs of diastolic dysfunction have also been reported in many patient groups with coronary artery disease.^{26–33} The overall prevalence of diastolic abnormalities in presently studied patients with a history of myocardial infarction or ECG evidence of coronary artery disease was 25%. That is somewhat lower than reported previously. Of note, however, we excluded individuals with impaired systolic function and thus only patients with relatively small myocardial infarctions entered the analysis. Moreover, we did not study the effects of exercise that may precipitate diastolic dysfunction specifically in individuals with significant coronary stenosis. Finally, the epidemiological setting precluded precise diagnostic testing for coronary artery disease.

Consistent with some but not all other reports, diastolic abnormalities were noted to be more common in males than in females.⁹ Higher prevalence rates of hypertension, LV hypertrophy and coronary artery disease in men may partly account for this difference. Nevertheless, in the multivariate analysis, a gender-related association with diastolic abnormalities was confirmed with significantly higher rates in men than in women. Therefore, gender may be an independent factor in the pathogenesis of diastolic dysfunction, as previously suggested for systolic heart failure and LV hypertrophy.³⁴

Obesity and especially a high body fat mass predicted diastolic dysfunction in this population. Many studies have demonstrated a strong correlation between BMI and, in particular, an elevated body fat mass with arterial hypertension and LV hypertrophy.^{9,11,35–38} Depending on fat distribution and the relation between the increase of body fat mass and fat-free mass, different effects on the heart were reported.¹² Interestingly, a significant correlation was found between blood pressure, peripheral resistance and body fat mass.¹² By contrast, fat-free mass was rather correlated with LV volumes but not with arterial blood pressure.¹²

Thus, the presently observed correlation between an elevated fat mass and diastolic dysfunction may result from pressure overload and a disproportional increase of septal and posterior wall thickness in obese individuals.

The criteria used in the present investigation allow, with increasing age, adaptation of the upper limit for the isovolumic relaxation time and the lower limit for the E/A-ratio.⁷ Nevertheless, previous as well as the present investigators, based on these criteria, demonstrated a pronounced increase in diastolic abnormalities in the elderly.^{2,5,8,9} However, hypertension, LV hypertrophy, coronary artery disease and obesity, i.e. conditions associated with diastolic abnormalities, also display an increasing prevalence with increasing age. In fact, structural or functional adaptations of the heart that impair LV filling appear to integrate the consequences of such risk factors over time.^{21,39,40} Interestingly, in the absence of these predisposing conditions, the prevalence of diastolic abnormalities in the elderly was remarkably low. Nevertheless, the nature of the decrease in the E/A-ratio or the prolongation of IVRT with aging is partially unclear and a precise discrimination between pathologic or physiologic changes remains difficult.

The present study is limited by its exclusive utilization of echocardiographic techniques for the diagnosis of diastolic abnormalities. In fact, most of the non-invasive parameters for assessment of LV diastolic function by Doppler echocardiography are heart rate-, preload- and afterload-dependent, and may vary over time in a given patient. However, alternative techniques are either invasive or require exposure to radioisotopes, such that population screening using more precise methods is not currently feasible. Another limitation may be that we used an ejection fraction $\geq 45\%$ as the sole index of normal systolic function. We may have thus overlooked regional or mildly impaired systolic dysfunction. However, the present as well as other population surveys are consistent with respect to a relatively low prevalence of systolic dysfunction such that a relevant misclassification is highly unlikely. A further potential source of error is the large variability of the echocardiographic parameters. However, this is in part due to the wide variation of flow patterns, and the rather U-shaped than linear relationship between the E/A-ratio and severity of diastolic function. Ultimately, more invasive techniques may be required in order to directly measure diastolic filling pressures, chamber and muscle stiffness constants as well as systolic function for optimal estimation of diastolic dysfunction in the population.

In conclusion, the prevalences of diastolic abnormalities and diastolic dysfunction are higher than that of systolic dysfunction and are increased in the elderly. LV hypertrophy, hypertension, coronary artery disease, diabetes and obesity show strong and independent associations with diastolic abnormalities. In the absence of these risk factors, the condition is rare even in those of 50–75 years of age. Our estimates of the population-attributable risks suggest that a large proportion of diastolic heart failure may be effectively prevented by improved implementation of measures directed against these predisposing conditions.

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