View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

International Journal of Cardiology 182 (2015) 368–374

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Quantification of diastolic dysfunction via the age dependence of diastolic function — Impact of insulin resistance with and without type 2 diabetes

H. von Bibra [a,*,1], W.J. Paulus [b,2], M. St. John Sutton [c,3], C. Leclerque [d,4], T. Schuster [e,5], P.-M. Schumm-Draeger [f,6]

[a] Clinic for Endocrinology, Diabetes & Vascular Medicine, Klinikum Bogenhausen, Städt. Klinikum München GmbH, Munich, Germany
[b] Institute for Cardiovascular Research Vrije Universiteit, VU University Medical Center Amsterdam, Amsterdam, the Netherlands
[c] Department of Medicine, Cardiovascular Division, University of Pennsylvania, Philadelphia, PA, USA
[d] Clinic for Endocrinology, Diabetes & Vascular Medicine, Klinikum Bogenhausen, Städt. Klinikum München GmbH, Munich, Germany
[e] Institute for Statistics and Epidemiology in Medicine of the Technische Universität, Munich, Germany
[f] Clinic for Endocrinology, Diabetes & Vascular Medicine, Klinikum Bogenhausen, Städt. Klinikum München GmbH, Munich, Germany

ARTICLE INFO

Article history:
Received 25 September 2014
Received in revised form 18 November 2014
Accepted 1 December 2014
Available online 3 December 2014

Keywords:
Diastolic dysfunction
Tissue Doppler
Insulin resistance
Metabolic cardiomyopathy
Type 2 diabetes
Heart failure preserved ejection fraction

ABSTRACT

Background: The alarming prevalence of heart failure with preserved ejection fraction requires quantification of diastolic dysfunction (DDF). Myocardial diastolic velocity E′ implies that age is the most important determinant. We tested the hypothesis that age allows for quantification of DDF and assessment of the structural and metabolic determinants in patients with and without type 2 diabetes (D).

Methods: This prospective, cross-sectional study assessed cardiovascular, metabolic and ultrasound data in 409 consecutive patients (Diabetes Center, Bogenhausen-Munich) between 20 and 90 years without known cardiac disease and either with (n = 204) or without D but with common prevalence of cardiovascular risk factors, including a subgroup of healthy individuals (H, n = 94).

Results: In H, E′ related to age as: $E'_{norm} = -0.163 * \text{years} + 19.69$ ($R^2 = 0.77$, $p < 0.0001$). According to this 1% reduction by annual physiologic aging, DDF was quantitated as $E' - E'_{norm}$. Compared to nondiabetics, D patients were older, had greater BMI, lower E′, more cardiovascular risk and greater DDF. In nondiabetics, grading of DDF by $E - E'_{norm}$ correlated with grading by filling pressure E/E′. Determinants of DDF by multivariate analysis included pulse wave velocity, diastolic blood pressure and the triglyceride/HDL ratio (a marker of insulin resistance) in nondiabetics and in D the same risk factors in reverse sequence and heart rate. Neither left atrial size nor left ventricular mass had significant impact.

Conclusions: The physiological impact of age on myocardial function consists of a 1% annual reduction in E′ and enables precise quantification of diastolic dysfunction thereby unmasking the importance of metabolic risk for DDF.

© 2014 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

1. Introduction

Approximately half of the patients with heart failure have predominantly diastolic dysfunction and preserved left ventricular ejection fraction (HFpEF). Although prognosis is as ominous as that of systolic heart failure, there is still no effective treatment for HFpEF [1]. This is due to a number of factors that include an incomplete understanding of diastolic dysfunction and the pathophysiological mechanisms of HFpEF [2–4]. Another potential cause is the lack of consensus regarding validation and diagnosis of diastolic dysfunction [4–6] that complicates entry criteria for clinical trials. Diastolic dysfunction and the development of HFpEF increase with age but there is a lack of age-adjusted reference standards for diastolic dysfunction measurements [4]. Based on a pilot study in which we quantified normal diastolic myocardial function E'_{norm} from the close correlation between tissue Doppler derived E′ and age [7], we tested the hypothesis that the comparison of measured E′ to the calculated E'_{norm} allows quantification of diastolic dysfunction as the respective difference. Furthermore, this method provides a better understanding of diastolic dysfunction because it assesses cardiac, vascular, hemodynamic and metabolic determinants independent of normal aging in patients with and without diabetes.

* Corresponding author at: Clinic for Endocrinology, Diabetes and Vascular Medicine, Klinikum Bogenhausen, Munich, Germany.
E-mail address: vonbibra@gmx.de (H. von Bibra).

[1] This author wrote the manuscript and takes responsibility for all aspects of the reliability and the freedom from bias of the data presented and their discussed interpretation.
[2] This author supervised the design of the study and added important content to the manuscript.
[3] This author revised the manuscript.
[4] This author organized the study and obtained data.
[5] This author advised and calculated the statistics.
[6] This author arranged the research setting and its funding.

http://dx.doi.org/10.1016/j.ijcard.2014.12.005
0167-5273/© 2014 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

Table 1
Characteristics of the study population.

Characteristic	Non-diabetic control		Type 2 diabetes	p
	Healthy	With CV risk		
n	94	111	204	
Age (years)	48 ± 16	55 ± 14***	60 ± 11***##	<0.001
Men (%)	48	35**	66**###	<0.001
BMI (kg/m^2)	23 ± 3	31 ± 9***	31 ± 5***	<0.001
Blood pressure systolic (mm Hg)	119 ± 14	135 ± 17***	142 ± 21***	<0.001
Blood pressure diastolic (mm Hg)	75 ± 9	82 ± 11***	83 ± 12***	<0.001
Heart rate (bpm)	67 ± 11	68 ± 11	69 ± 11	0.227
LVED (mm)	44 ± 5	45 ± 5	43 ± 5##	0.003
LAVI (ml/m^2)	43 ± 18	47 ± 19	54 ± 22***##	<0.001
LVMI (g/m^2)	74 ± 18	85 ± 29***	85 ± 20***	<0.001
S′ (cm/s)	8.7 ± 1.3	8.3 ± 1.4*	7.7 ± 1.1***###	<0.001
E′ (cm/s)	11.8 ± 2.9	10.0 ± 2.2***	8.1 ± 1.7***###	<0.001
E′ − E_{norm} (cm/s)	0.0 ± 1.5	−0.7 ± 1.4**	−2.0 ± 1.6***###	<0.001
E/E′	6.3 ± 1.6	7.2 ± 1.8*	8.5 ± 2.5***###	<0.001
Intima-media thickness (mm)	0.56 ± 0.14	0.67 ± 0.15***	0.69 ± 0.16***	<0.001
HbA1c (%)	5.6 ± 0.3	5.6 ± 0.3	7.4 ± 1.8***###	<0.001
Insulin (μIU/ml)§	4.7 ± 2.7	15.3 ± 17.8**	14.2 ± 11.9*	0.012
HOMA-IR§	1.0 ± 0.6	3.2 ± 3.7**	4.2 ± 3.3***	0.002
Triglycerides (mg/dl)	100 ± 40	119 ± 53*	160 ± 97***##	<0.001
HDL (mg/dl)	60 ± 16	55 ± 16	49 ± 13***###	<0.001
Triglycerides/HDL	1.8 ± 1.0	2.6 ± 1.8**	3.7 ± 2.7***##	<0.001
hsCRP (mg/dl)	1.8 ± 4.8	3.5 ± 6.6	4.2 ± 9.9	0.478
Beta blocker (%)	4	26***	25***	<0.001
ACE inhibitor (%)	0	20***	39***	<0.001
AT2 receptor blocker (%)	0	15***	16***	0.020
Ca channel blocker (%)	0	8	15***	0.001
Statins (%)	0	22***	34***##	<0.001

*p < 0.05, **p < 0.01 and ***p < 0.001 vs. healthy controls; #p < 0.05, ##p < 0.01 and ###p < 0.001 vs controls with CV risk, § = in subgroup without insulin therapy.

2. Methods

2.1. Study design

This prospective observational study was designed for 1) quantification of diastolic dysfunction via the age dependence of E', 2) comparison of this quantification with traditional parameters of diastolic dysfunction and 3) evaluation of determining factors that are independent of normal aging. In order to apply the most robust, sensitive, and generally available ultrasound technique [8,9] tissue Doppler was performed in consecutive patients referred to the echocardiographic lab (Clinic for Endocrinology, Diabetes and Vascular Medicine at the Klinikum Bogenhausen in Munich). From these, 409 individuals with or without metabolic abnormalities prone to deficiency of myocardial energy availability, namely type 2 diabetes, were selected with the following inclusion (men or women between 20 and 90 years) and exclusion criteria (LVED >56 mm, LV wall thickness >14 mm, LVEF <50%, severe arterial hypertension, renal failure [creatinine > 2 mg/dl], anemia, untreated thyroid disease, type 1 diabetes mellitus and severe systemic disease). Patients were assigned to type 2 diabetes (n = 204) if on anti-diabetic medication and/or by self report. The remainder were non-diabetic controls (n = 205) representing the average population without diabetes or cardiac disease (Table 1). A healthy subgroup (H, n = 94) contained individuals without cardiovascular risk factors and obesity as defined according to the National Institutes of Health Consensus Development Panel Criteria as body mass index (BMI) >27.2 kg/m^2 in men and >27.7 kg/m^2 in women. Arterial hypertension was defined as antihypertensive treatment or systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg and hypercholesterolemia as a low-density lipoprotein cholesterol level >130 mg/dl and/or current intake of lipid lowering therapy.

The ethical committee relevant for our institution approved the study reflecting conformity of the study protocol to the ethical guidelines of the 1975 Declaration of Helsinki. Patients gave informed consent.

2.2. Echocardiography

Echocardiograms (ALOKA SSD-5500, Tokyo, Japan) were obtained in all patients by one experienced sonographer blinded to the patients' clinical data. LV and LA dimensions were measured and LA volume index and LV mass index were derived as recommended by the American and European Quantification Guidelines [10]. LAVI and LVMI were categorized into normal size, mildly-moderately abnormal size or severely abnormal size [10]. Early (E) and late diastolic (A) transmitral velocities were measured by pulsed wave Doppler. For feasibility assessment of recording LAVI, LVMI, mitral E/A and tissue Doppler (separately for each apical view), the image quality of the respective recordings was graded (1 = excellent, 2 = good, 3 = adequate, 4 = difficult, 5 = obscure, 6 = impossible) and score ≤4 was considered acceptable quality (Table 3).

2.3. Global LV function by tissue Doppler

In the 4-, 2-, and 3-chamber view, pulsed tissue Doppler was recorded at the intersection of the atrioventricular plane with each LV wall by selecting a) the lowest possible intercostal space for apical imaging, and b) a central position of the LV apex in the imaging sector. The respective 6 regional myocardial velocities were recorded during three consecutive cycles and averaged for the assessment of peak systolic (S′), early diastolic (E′) and late diastolic velocity (A′) as a measure of global LV function [8,11]. LV filling pressure was calculated as E/E′.

Based on the dominant impact of age as independent and unchangeable predictor variable for E′, the influence of all other determinants needs mathematical unmasking from this relation, so that their respective effects may be understood and potentially used for preventive strategies [4]. Accordingly, the respective regression equation of the healthy individuals was applied to calculate the age related normal value ($E'_{norm} = -0.163 * age + 19.67$) and the respective lower 95% tolerance interval ($E'_{norm} - 2.86$) for comparison with E′ in each individual. If the deficit to E'_{norm} ($E' - E'_{norm}$) was >2.86 cm/s, this individual was assigned to diastolic dysfunction, and if >50% of this cut off level to risk for dysfunction. The determinants of $E' - E'_{norm}$ were assessed regarding structural, hemodynamic and metabolic factors.

2.4. Vascular ultrasound

Intima-media thickness and vascular stiffness were evaluated in the right common carotid using a combined Doppler and echo tracking system and a 13 MHz linear array transducer as previously described [12]. This radio frequency based echo tracking method continuously detected changes in carotid diameter. Peak and minimal values were calibrated to systolic and diastolic brachial blood pressures so that intravascular pressure changes, strain pressure elasticity modulus ε and pulse wave velocity (PWV) could be calculated online. Concomitantly, blood pressure was measured three times in the right arm by an automated cuff sphygmomanometer and averaged.

2.5. Biochemistry

Fasting serum glucose, serum insulin, lipid profile and glycated hemoglobin A1c (HbA1c) were determined according to routine methods at the Department of Clinical Chemistry of the Städt. Klinikum Bogenhausen, Munich. The triglyceride/HDL ratio was used as a measure of insulin resistance for all individuals because of the large number of diabetic individuals on insulin therapy in whom the HOMA-IR cannot be applied [13]. In diabetic patients, intact proinsulin was measured by ELISA at the IKFE institute, Mainz [14].

2.6. Statistics

Sample size calculation: Multiple linear regression analysis was the primary inference approach for the assessment of the association of diastolic dysfunction and respective explanatory factors. In order to achieve accurate effect estimation and sufficient power (≥80%) in testing for associations, a sample size of 200 individuals per group was considered to be appropriate [15] taking into account the need for confounder control: with the given sample size, simultaneous inclusion of up to five covariates was feasible without loss in estimation efficiency.

Statistical analysis was performed using the SPSS version 17.0 software package (SPSS Inc., Chicago, IL). Data are expressed as mean ± standard deviation when normally distributed and otherwise as median (interquartile range). Students' t-test or nonparametric tests were used for group comparisons where appropriate. Differences between three groups were tested by analysis of variance (ANOVA) and Fisher's least significant difference (LSD) test as respective post hoc tests. Due to the lack of age-adjusted reference standards for diastolic dysfunction measurements [4], 95% tolerance limits were calculated based on a healthy control group. Accordingly, a linear regression model was employed regressing E′ on age. Assuming homoscedastic error terms, the lower 95% tolerance limit was then achieved by subtracting 1.64 times the square root of the residual variance from the respective age-specific predicted value of E′ (E'_{norm}). Subsequently, linear regression analysis was performed to explore potential predictive factors for the magnitude of dysfunction in diabetic and non-diabetic patients as defined by $E' - E'_{norm}$. Only those variables that revealed relevant bivariate correlation with the defined outcome variable (Pearson correlation coefficient > +0.2 or < −0.2) were entered into multivariate regression models and respective multivariable (covariate-adjusted) p values and standardized regression coefficients beta were calculated. All statistical tests were conducted two-sided at a local level of significance of 0.05. No correction of p-values was applied to adjust for multiple testing. However, results of all statistical tests being conducted were thoroughly reported so that an informal adjustment of p values can be performed while reviewing the data [16].

Measurements and analysis of ultrasound and of metabolic variables were performed by staff blinded for relevant patient characteristics and study protocol while the examined patients and controls were not aware about the predictive role of diastolic dysfunction. In order to reduce outlier effects and to avoid selection bias in reporting fluctuating individual data, three single measurements of blood pressure and of tissue Doppler velocities were collected independently and averaged for each individual. Potential bias in effect estimation was addressed by employing multivariable regression models for the adjustment of established confounding factors such as BMI, systolic blood pressure and LV filling pressure.

3. Results

3.1. Control and diabetes groups

The characteristics of the healthy subgroup, the non-diabetic individuals with cardiovascular risk and the diabetes group (Table 1) demonstrated the expected significant differences in BMI, cardiac data, blood pressure, metabolic variables, cardiovascular risk factors and respective therapies. Duration of diabetes was 9 ± 8 years and 74% of the diabetic patients were on insulin therapy.

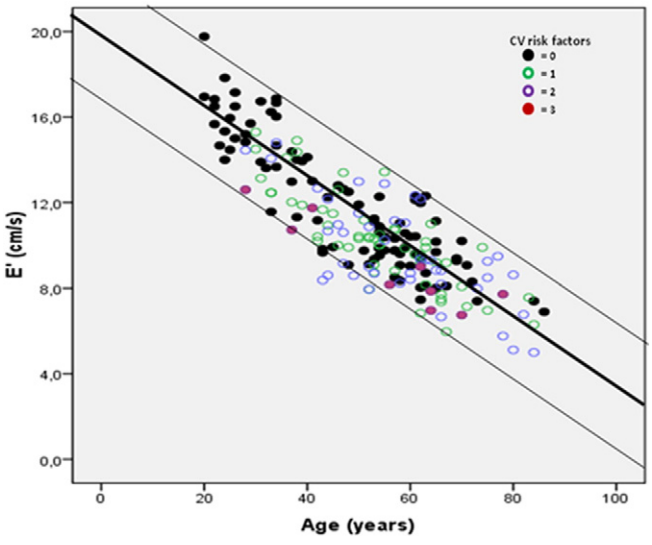

Fig. 1. E′ over age in 205 nondiabetic controls subdivided by the presence of 3 (full red dots), 2 (violet circles), 1 (green circles) or no cardiovascular risk factors (full black dots). The regression line is calculated from the latter, and denotes E_{norm} surrounded by the lines of the upper and lower 95% tolerance intervals (in ±2.86 cm/s distance).

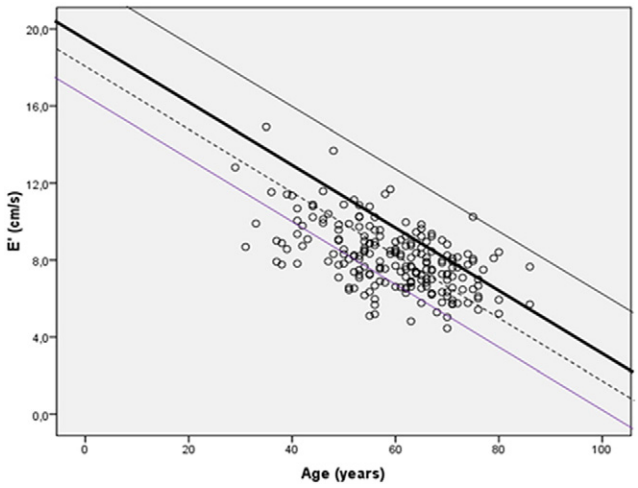

Fig. 2. The same regression lines of normal values and 95% tolerance limits. The lower one (violet) is the cut off value for diastolic dysfunction and the broken line half way between the latter and the regression line for risk of dysfunction. Patients with type 2 diabetes (n = 204) demonstrate an even distribution of normal diastolic function, risk for dysfunction and dysfunction.

Male and female non-diabetic controls had similar anthropomorphic and clinical data associated with the well known gender specific exceptions. Furthermore, they had similar cardiac data and vascular function (data not shown). The inverse linear regression equation for the relation of E′ over age for men (y = −0.167 * years + 19.97) was comparable to that of women (y = −0.161 * years + 19.48) in the healthy subgroup H and in the total 204 controls (y = −0.16 * years + 19.2 and y = −0.15 * years + 18.6, respectively) both p < 0.001. Accordingly, male and female data were pooled in subsequent analysis.

In the healthy subgroup, E′ and age showed a strong and inverse correlation; estimated regression equation: $E'_{norm} = -0.163 * \text{years} + 19.69$, $R^2 = 0.77$, $p < 0.0001$. In all non-diabetic controls (Fig. 1), the dominant influence of age on E′ is demonstrated by the standardized coefficient beta, that was −0.880 in univariate analysis and remained dominant in multivariable analysis with the incremental addition of hypertension (−0.822 and −0.072), dyslipidemia (−0.787, −0.057 and −0.133) and obesity (−0.804, −0.036, −0.123 and −0.068), respectively. Systolic function S′ and age also had an inverse correlation (estimated $S' = -0.033 * \text{years} + 10.30$, $R^2 = 0.153$, $p < 0.0001$) with a standardized coefficient beta of −0.39.

In the 204 controls, normal function, as defined by $E' - E'_{norm}$ in the methods section, was assigned to 151 (73%) individuals, risk for dysfunction to 42 (21%) and dysfunction to 12 (6%) (Fig. 1), whereas the respective prevalence in diabetes was 70 (34%), 75 (37%) and 57 (28%) (Fig. 2).

Severity grading of diastolic dysfunction by $E' - E'_{norm}$ was compared with that based on the traditional parameters E/E′, LAVI and LVMI (Table 2). In non-diabetic controls, grading by $E' - E'_{norm}$ had good agreement to that by the E/E′ ratio, but LAVI overestimated and LVMI underestimated abnormality. In the diabetes group with the evenly distributed three dysfunction classes, normal function agreed with the E/E′ derived grading but the majority of severely abnormal function was underestimated. Also in diabetes, LAVI overestimated, but LVMI underestimated abnormality.

The feasibility of measuring diastolic function criteria in all patients was best with E/A ratio (96%) and tissue Doppler in the 4-chamber view (95%), followed by that in the 2-chamber view and LVMI by the Devereux formula (each 91%) and tissue Doppler in the 3-chamber

Table 2
Distribution of dysfunction severity according to functional and structural criteria commonly associated with the assessment of diastolic function.

	Control (%)			Diabetes (%)		
	Normal	Mildly-moderately abnormal	Severely abnormal	Normal	Mildly-moderately abnormal	Severely abnormal
$E' - E'_{norm}$	73	21	6	34	37	28
E/E′	77	23	0	34	63	3
LAVI	30	32	38	17	26	57
LVMI	91	8	1	92	7	1

Severity classes were defined for E/E′ according to the European recommendations on how to diagnose diastolic heart failure [5] and for LAVI and LVMI according to the European and American recommendations of chamber quantification [9].

view (82%). Assessment of LAVI was successful only in 71% of this fairly overweight population.

3.2. Univariate linear regression analysis

Bivariate correlations were assessed for the associations of $E' - E'_{norm}$ in all controls and in diabetes patients (Table 3). Expectedly in the former, neither age nor sex was significantly associated with $E' - E'_{norm}$. LAVI and E/E′ missed significance, but dyslipidemia, pulse wave velocity, diastolic blood pressure, BMI, serum insulin, lipid levels and the triglyceride/HDL ratio had significant associations. These were also observed in the diabetes group additionally to heart rate and creatinine but not for dyslipidemia.

3.3. Multivariable linear regression analysis

For multivariable analysis in all controls, $E' - E'_{norm}$ was entered as the dependent variable into the model and significant factors from univariate analysis as components of vascular function or cardiac structure stepwise as the independent variables (Table 4, Models 1 to 4a–g). The final model 5 (R^2 0.187, $p < 0.001$) had PWV, diastolic blood pressure and triglyceride/HDL ratio as determinants with the standardized coefficients beta −0.336, −0.037 and 0.203, respectively. In type 2 diabetes, the models with the same determinants in reversed sequence (model 1 to 4a–h) improved further with the addition of heart rate, a surrogate parameter of cardiac autonomic neuropathy (Model 5, R^2 0.195, $p < 0.001$): insulin resistance, diastolic blood pressure, PWV, and heart rate had the standardized coefficients beta −0.309, −0.216, −0.143 and −0.187, respectively.

Table 3
Correlations for $E' - E'_{norm}$.

	Non-diabetic controls		Type 2 diabetes	
	r	p	r	p
Dyslipidemia	−0.380	**0.008**	−0.007	0.92
E mitral (cm/s)	0.375	<**0.001**	0.200	**0.005**
E/A	0.290	<**0.001**	0.096	0.183
E/E′	−0.155	0.080	−0.141	**0.049**
LAVI (ml/m^2)	−0.141	0.061	−0.047	0.53
LVMI (g/m^2)	−0.122	0.104	−0.102	0.157
Heart rate (bpm)	−0.055	0.45	−0.206	**0.003**
Systolic BP (mm Hg)	−0.131	0.077	−0.024	0.73
Diastolic BP (mm Hg)	−0.230	**0.002**	−0.307	<**0.001**
EPP (kPa)	−0.177	0.080	0.055	0.45
PWV (m/s)	−0.294	**0.004**	0.109	0.140
BMI (kg/m^2)	−0.187	**0.011**	−0.196	**0.006**
Glucose (mg/dl)	−0.004	0.96	−0.049	0.52
Insulin (μIU/ml)	−0.288	**0.023**		
*Intact proinsulin (pmol/l)			−0.295*	**0.027**
Triglycerides (mg/dl)	−0.225	0.023	−0.184	**0.014**
HDL (mg/dl)	−0.187	**0.020**	0.318	<**0.001**
Tri/HDL	−0.204	**0.011**	−0.285	<**0.001**
Creatinine (mg/dl)	−0.047	0.57	−0.177	**0.016**

bold letters = level of significance $p < 0.05$

3.4. Sites of E′ assessment

For evaluating the potential influence from the selection of measurement sites on the relation of E′ to age, the respective regression equations were assessed in these 76 healthy individuals who had a complete data set of tissue Doppler velocity measurements in all 6 segments from the three apical views. Accordingly, the resulting regression equation of E'_{norm} is shown as averaged from either 6 measurement sites, 4 sites (4- and 2-chamber views) or 2 sites (4-chamber view).

$$E'_6 = -0.163 * \text{years} + 19.56$$
$$E'_4 = -0.158 * \text{years} + 19.57$$
$$E'_{seplat} = -0.150 * \text{years} + 18.95.$$

4. Discussion

Early diastolic LV function quantified by tissue Doppler as myocardial velocity E′ demonstrates a 1% loss every year by physiological aging from the 20th year of age onwards. This dominant relation was used for discriminating normal function from dysfunction yielding quantitative assignment to dysfunction. This approach allowed the study of determinants of diastolic dysfunction independent of normal aging. The resulting determinants were vascular function, diastolic blood pressure, the driving force of myocardial perfusion, and the triglyceride/HDL ratio, a marker of insulin resistance. In reversed sequence, these determinants were also observed in the diabetes group, in addition to heart rate, a measure of cardiac autonomic neuropathy.

4.1. Non-diabetic population and gender

The non-diabetic subjects had been selected as representative of a population without overt cardiac disease but with the common cardiovascular risk profile including overweight, in line with the prevalence of diastolic dysfunction in epidemiological studies [4]. The representative character of our non-diabetic population has also been confirmed by comparison of echocardiographic referral individuals with a population based selection [17], and further by the almost identical relation between E′ and age in two recent studies [7,18].

Diastolic parameters from mitral inflow Doppler have been unaffected by sex similar to E′.

4.2. Age

The significant influence of the unchangeable variable age on diastolic function is well known [4,7,19].

As expressed by the coefficients beta, this influence determines >79% of diastolic function E′ but only 39% of systolic function S′ and, therefore, requires mathematical unmasking for E′. Accordingly, quantification of E'_{norm}, was derived in the healthy subgroup and applied in the whole non-diabetic group as respective estimated regression equation (Fig. 1) demonstrating a decrease of E′ from a normal value of 16 cm/s at 20 years to 7 cm/s at 80 years (1% reduction every year). If the measured E′ equals the age related E'_{norm}, the patient has normal

Table 4
Multivariable linear regression analysis.

Non-diabetic controls	$E' - E'_{norm}$ (cm/s)			
	Beta (95% CI)	*p	R^2	†p
Model 1			0.086	0.004
PWV	−0.445 (−.745 to −.145)	0.004		
Model 2 (model 1 + LAVI)			0.134	0.001
PWV	−0.446 (−.740 to −.152)	0.003		
LAVI	−0.017 (−.032 to −.002)	0.027		
Model 3 (model 1 + diastolic BP)			0.155	0.001
PWV	−0.400 (−.694 to −.107)	0.007		
Diastolic BP	−0.039 (−.067 to −.011)	0.008		
Model 4: (model 3 after correction for each of the following variables)				
a) Gender	−0.398 (−.694 to −.103)	0.009	0.156	0.002
b) BMI	−0.360 (−.658 to −.061)	0.019	0.186	<0.001
c) Systolic blood pressure	−0.405 (−.697 to −.113)	0.007	0.175	0.001
d) Heart rate	−0.403 (−.696 to −.110)	0.008	0.167	0.001
e) E/E′	−0.339 (−.636 to −.041)	0.026	0.124	0.012
f) IMT	−0.446 (−.754 to −.138)	0.005	0.164	0.001
g) hsCRP	−0.424 (−.764 to −.083)	0.015	0.172	0.002
Model 5 (model 3 + triglyceride/HDL ratio)			0.187	0.001
PWV	−0.336 (−.659 to −.013)	0.042		
Diastolic BP	−0.037 (−.066 to −.009)	0.010		
Triglyceride/HDL ratio	−0.203 (−.380 to −.046)	0.018		
T2D	$E' - E'_{norm}$ (cm/s)			
	Beta (95% CI)	*p	R^2	†p
Model 1			0.081	<0.001
Triglyceride/HDL ratio	−0.243 (−.366 to .057)	<0.001		
Model 2 (model 1 + diastolic BP)			0.137	<0.001
Triglyceride/HDL ratio	−0.206 (−.366 to −.120)	0.001		
Diastolic BP	−0.032 (−.051 to −.013)	0.001		
Model 3 (model 2 + PWV)			0.130	<0.001
Triglyceride/HDL ratio	−0.190 (−.311 to −.068)	0.002		
Diastolic BP	−0.030 (−.049 to −.011)	0.002		
PWV	−0.022 (0.042 to −.002)	0.033		
Model 4: (model 3 after correction for each of the following variables)				
a) Gender	−0.033 (−.055 to −.010)	0.006	0.141	<0.001
b) BMI	−0.031 (−.053 to .008)	0.008	0.157	<0.001
c) Systolic blood pressure	−0.028 (−.051 to −.006)	0.012	0.182	<0.001
d) E/E′	−0.033 (−.055 to −.011)	0.004	0.166	<0.001
e) IMT	−0.034 (−.057 to −.012)	0.003	0.151	<0.001
f) Glucose	−0.031 (−.057 to −.004)	0.022	0.152	<0.001
g) Creatinine	−0.030 (−.053 to −.008)	0.009	0.175	<0.001
h) hsCRP	−0.031 (−.055 to −.008)	0.010	0.143	0.001
Model 5 (model 3 + heart rate)			0.199	<0.001
Triglyceride/HDL ratio	−0.195 (−.316 to −.074)	0.002		
Diastolic BP	−0.030 (−.048 to −.012)	0.002		
PWV	0.029 (−.049 to −.009)	0.005		
Heart rate	0.137 (−.010 to .264)	0.035		

CI = tolerance interval, R^2 and †p = level of significance for the respective models for controls in top panel or diabetes in bottom panel for $E' - E'_{norm}$ as dependent variable. In models 4 (a–h), cardiovascular factors or metabolic components are separately entered as possible confounders for correction and shown not to modify the contribution of pulse wave velocity in panel a or triglyceride/HDL ratio in panel b. *p = level of significance for the association between $E' - E'_{norm}$ and the separate independent components of the models or for PWV or heart rate, respectively, after the adjustments indicated (models 4 a–h, respectively).

diastolic function. Supranormal values exceeding the upper 95% tolerance limit may be found in actively training athletes or in untreated hyperthyroidism. Values < the lower 95% tolerance limit, indicate diastolic dysfunction.

4.3. Comparison with traditional grading criteria of diastolic dysfunction

In the controls, grading of diastolic dysfunction demonstrated good agreement between the dynamic criteria $E' - E'_{norm}$ and LV filling pressure (Table 2) but in the diabetes patients only in the class of normal function. 63% of diabetes patients were assigned to mild-moderately raised E/E′ because a significantly reduced mitral E velocity in grade 2 dysfunction effectively counteracted a relevant increase of E/E′ by the decreased E′ (data not shown). As suggested also by our data in overweight and metabolic disease, elongation of the left atrium may be an early mechanism associated with volume overload from impaired LV relaxation that counteracts a clinically relevant increase of filling pressure and merits further investigation [19–21]. Accordingly, high LV filling pressures are not a pathognomonic feature of diastolic dysfunction in metabolic disease, as opposed to hypertensive heart disease and primary cardiomyopathy.

Within the structural criteria for assessing diastolic dysfunction, LAVI suggested more and LVMI less severity in both controls and diabetes. These obvious discrepancies, however, are not entirely surprising due to the heterogeneous etiology of diastolic dysfunction [20–23]. Our present data suggest that the traditional functional and structural grading criteria for diastolic dysfunction are less useful in metabolic heart disease.

4.4. Direct measurement of dynamic LV diastolic function

Structural alterations cannot be expected, if dysfunction is caused by acute ischemia/hypoxia i.e. sudden onset of energy deficiency [2]. Dynamic changes in energy delivery are the major problem in metabolic

disease [3,20]. Accordingly, this etiology of diastolic dysfunction requires dynamic indicators. However, LV filling pressure, at least as expressed by E/E′, has raised concern about the diagnosis of a mildly increased degree of myocardial dysfunction [5,19] also in metabolic disease [20].

Surprisingly, no functional criterion has yet been identified as a reliable direct measure of active myocardial relaxation, although tissue Doppler measurements have introduced E′ as a sensitive measure of diastolic myocardial function with prognostic potential [24,25]. Furthermore, the relationship between changes of E′ with those of exercise capacity has recently been reported [4,26]. Finally, the feasibility and robustness of obtaining tissue Doppler variables even in patients difficult to image supports the use of E′ to characterize diastolic function [4,6,9].

In sequential studies, E′ proved sensitive to acute alterations of oxygen supply in stress tests [11,25] or to postprandial dysmetabolism [27]. Its potential for monitoring therapeutic effectiveness has been demonstrated for improvement of metabolic control, high blood pressure, hyperlipidemia or for amelioration of insulin resistance either by diet [26], exercise [28] or pharmacological therapy [8]. In crossectional studies, however, the strong age dependence of E′ implied a broad range of values thereby limiting the evaluation of diastolic dysfunction. However, the quantitative approach with $E' - E'_{norm}$ would allow insight into the impact of noxious influences.

4.5. The dynamic metabolic nature of diastolic dysfunction

In elderly individuals, limited exercise tolerance often results from age-dependent deterioration of diastolic function. Of concern is a growing population of middle-aged subjects with impaired exercise tolerance and diastolic dysfunction due to increasing prevalence of overweight, diabetes, hypertension and atherosclerotic disease.

Diastolic dysfunction consists of 1) slow LV relaxation and LV filling in early diastole and 2) increased myocardial stiffness predominantly in late diastole, the mechanism for which is poorly understood.

Firstly, slow relaxation in early diastole results from abnormal cross-bridge detachment, calcium uptake by the sarcoplasmic reticulum or altered nitric oxide (NO) signaling [1,4]. Since cross-bridge detachment is an energy consuming process, slow relaxation may reflect a myocardial energy deficit [2,29] that may be due to microvascular dysregulation induced by insulin resistance and/or a low intra-mitochondrial creatine-phosphate/adenosine-triphosphate ratio [3,8]. Integration of these multiple covariates results in a myocardial energy supply/demand mismatch with reduced cardiac efficacy in insulin resistance or diabetes [8,30]. This untenable situation of reduced energy availability but increased myocardial oxygen requirement is exacerbated by disturbed ventricular–arterial coupling, increases in heart rate or in sympathetic tone [1,7,30].

Secondly, increased myocardial stiffness in late diastole suggests structural myocardial alterations, that may relate to the extracellular matrix in terms of collagen characteristics [24], interstitial fibrosis and inflammation [31], steatosis in insulin resistance and/or advanced glycemic end-products (AGE) in diabetes whereas the intracellular components relate to pressure induced or insulin/growth hormone induced myocellular hypertrophy and to the cytoskeletal protein titin [4,23].

4.6. Metabolic determinants of dysfunction in metabolic disease

The new approach $E' - E'_{norm}$ allows characterization of the determinants of diastolic dysfunction independent from dominant but unchangeable age and its associated risks. Our data are the first to demonstrate that these determinants in non-diabetic individuals are vascular stiffness, diastolic blood pressure and insulin resistance. This corroborates the impact of arterio-ventricular coupling [1] on cardiac function and clarifies the pivotal role of myocardial perfusion being driven by diastolic blood pressure. Of interest, the onset, severity and duration of insulin resistance influenced proinflammatory endothelial activation in a primate model of diet induced obesity [32] in line with our data that insulin resistance or serum insulin levels demonstrate utmost impact on the degree of dysfunction most likely via endothelial dysfunction. There is increasing awareness regarding the associations of insulin resistance with diastolic dysfunction, cardiomyopathy and heart failure [20,30]. Concordant with our data, hyperglycemia is not the only driver of these mechanisms [20,27]. Interestingly, no variable of cardiac structure plays a significant role in diabetic diastolic dysfunction but rather insulin resistance, diastolic blood pressure, vascular function, and autonomic neuropathy. The greatest contributor to diastolic dysfunction is the underlying insulin resistance. As a therapeutic consequence, life style modifications [26,28] and pharmaceutical strategies that improve insulin sensitivity should be vigorously applied [8,12,26] according to a paradigm shift of understanding HFpEf as an entity of comorbid lesions that are often based on metabolic dysfunction, rather than focusing on myocardial/vascular structure alone. In patients with diastolic dysfunction and metabolic disease, accordingly, metabolic therapy should be assessed in future studies and patients with relevantly elevated filling pressures should be reevaluated after treatment of volume overload.

4.7. Limitations

Tissue Doppler based E′ was sampled in 6 annular sites whereas clinical routine prefers measurements from the septal and lateral wall, leading to a slightly different regression equation and cut off level. For any selection of measurement sites and also for the use of color tissue Doppler with its intrinsically lower velocities, the respective regression equations may be implemented in the ultrasound systems to facilitate correct application.

5. Conclusion

Because the dominant impact of aging on early diastolic function E′ requires mathematical unmasking, the estimated regression equation for E'_{norm} over age was obtained in healthy individuals to quantify individual dysfunction by comparing the actual E′ to the calculated E'_{norm}. This reference data is of clinical importance especially to differentiate patients with (preclinical) diastolic dysfunction. Additionally, it improves the selection of adequate study populations for clinical trials aimed at treatment or prevention of HFpEF. Furthermore it allows for more specific research into the determinants of diastolic dysfunction with its broad range of etiologic factors including myocardial energy deficiency in overweight and diabetes. Acknowledging the epidemic increase of metabolic disease, future therapeutic interest should focus on postprandial metabolic effects and their implications for insulin signaling, NO availability, oxidative stress generation and endothelial and vascular function. This approach offers earlier implementation of therapy for preventive action and the potential for more causal therapeutic strategies for patients with HFpEF who face a dismal prognosis without effective therapy.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] B.A. Borlaug, W.J. Paulus, Heart failure with preserved ejection fraction: pathophysiology, diagnosis and treatment, Eur. Heart J. 32 (2011) 670–679.
[2] T. Serizawa, W.M. Vogel, C.S. Apstein, W. Grossman, Comparison of acute alterations in left ventricular relaxation and diastolic chamber stiffness induced by hypoxia and ischemia, J. Clin. Invest. 68 (1980) 91–102.
[3] T.T. Phan, K. Abozguia, G.N. Shivu, et al., Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction

of the left ventricle on exercise and associated with myocardial energy deficiency, J. Am. Coll. Cardiol. 54 (2009) 4002–4009.
[4] S.H. Wan, M.W. Vogel, H.H. Chen, Pre-clinical diastolic dysfunction, J. Am. Coll. Cardiol. 63 (2014) 407–416.
[5] W.J. Paulus, C. Tschöpe, J.E. Sandermann, et al., How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology, Eur. Heart J. 28 (2007) 2539–2550.
[6] W.T. Emery, I. Jadavji, J.B. Choy, R.A. Lawarance, Investigating the European Society of Cardiology Diastology Guidelines in a practical scenario, Eur. J. Echocardiogr. 9 (2008) 685–691.
[7] H. von Bibra, I.S. Thrainsdottir, A. Hansen, V. Dounis, K. Malmberg, L. Rydén, Tissue Doppler imaging for the detection and quantitation of myocardial dysfunction in patients with type 2 diabetes mellitus: a methodological study, Diabetes Vasc. Dis. Res. 2 (2005) 483–487.
[8] H. von Bibra, M. St. John, Impact of diabetes on postinfarction heart failure and left ventricular remodeling, Curr. Heart Fail. Rep. 8 (2011) 242–251.
[9] M.C. deKnegt, T. Bierung-Sorensen, P. Sogaard, J. Sivertsen, J.S. Jensen, R. Mogelvang, Concordance and reproducibility between M-mode, tissue Doppler imaging, and two dimensional strain imaging in the assessment of mitral annular displacement and velocity in patients with various heart conditions, Eur. Heart J. 15 (2014) 62–69.
[10] R.M. Lang, M. Bierig, R. Devereux, et al., American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiographic Committee, American Heart Association, European Association of Echocardiography, European Society of Cardiology recommendations for chamber quantification, Eur. J. Echocardiogr. 7 (2006) 79–108.
[11] H. von Bibra, A. Tuchnitz, A. Klein, J. Schneider-Eicke, A. Schömig, M. Schwaiger, Regional diastolic function by pulsed Doppler myocardial mapping for the detection of left ventricular ischaemia during pharmacologic stress testing — a comparison with stress echocardiography and perfusion scintigraphy, J. Am. Coll. Cardiol. 36 (2000) 444–452.
[12] H. von Bibra, T. Siegmund, A. Ceriello, M. Volozhyna, P.-M. Schumm-Draeger, Optimized postprandial glucose control is associated with improved cardiac/vascular function — comparison of three insulin regimens in well controlled type 2 diabetes, Horm. Metab. Res. 41 (2009) 109–114.
[13] T. McLaughlin, F. Abbasi, K. Cheal, J. Chu, C. Lamendola, G. Reaven, Use of metabolic markers to identify overweight individuals who are insulin resistant, Ann. Intern. Med. 139 (2003) 802–809.
[14] A. Pfützner, T. Kunt, C. Hohberg, et al., Fasting intact proinsulin is a highly specific predictor of insulin resistance in type 2 diabetes, Diabetes Care 27 (2004) 682–687.
[15] K. Kelley, S.E. Maxwell, Sample size for multiple regression: obtaining regression coefficients that are accurate, not simply significant, Psychol. Methods 8 (2003) 305–321.
[16] D.J. Saville, Multiple comparison procedures — the practical solution, Am. Stat. 44 (1990) 174–180.
[17] D. Messica-Zeitoun, M. Bellamy, J.F. Avierinos, et al., Left atrial remodeling in mitral regurgitation — methodologic approach, physiological determinants, and outcome implications: a prospective quantitative Doppler-echocardiographic and electron beam computed tomographic study, Eur. Heart J. 28 (2007) 1773–1781.
[18] P. Inelli, R. Sanchez, F. Marra, R. Esposito, M. Galderisi, The impact of aging on left ventricular longitudinal function in healthy subjects: a pulsed tissue Doppler study, Eur. J. Echocardiogr. 9 (2008) 241–249.
[19] C. Tschöpe, W.J. Paulus, Is echocardiographic evaluation of diastolic function useful in determining clinical care? — Doppler echocardiography yields dubious estimates of left ventricular diastolic pressure, Circulation 120 (2009) 810–820.
[20] Y.C. Hwang, J.H. Jee, M. Kang, E.J. Rhee, J. Sung, M.K. Lee, Metabolic syndrome and insulin resistance are associated with abnormal left ventricular diastolic function and structure independent of blood pressure and fasting plasma glucose level, Int. J. Cardiol. 179 (2012) 107–111.
[21] J. Stritzke, M.R. Markus, S. Duderstadt, MONICA/KORA investigators, et al., The aging process of the heart: obesity is the main risk factor for left atrial enlargement during aging, J. Am. Coll. Cardiol. 54 (2009) 1982–1989.
[22] L. de las Fuentes, A.L. Brown, S.J. Mathews, et al., Metabolic syndrome is associated with abnormal left ventricular diastolic function independent of left ventricular mass, Eur. Heart. J. 28 (2007) 553–559.
[23] L. van Heerebeek, N. Hamdani, L. Handoko, et al., Diastolic stiffness of the failing heart: importance of fibrosis, advanced glycation end products and myocyte resting tension, Circulation 117 (2008) 43–51.
[24] M. Kasner, D. Westermann, B. Lopez, et al., Diastolic tissue Doppler indexes correlate with the degree of collagen expression and crosslinking in heart failure and normal ejection fraction, J. Am. Coll. Cardiol. 57 (2011) 977–985.
[25] C.M. Yu, J.E. Sanderson, T.H. Marwick, J.K. Oh, Tissue Doppler imaging. A new prognosticator for cardiovascular disease, J. Am. Coll. Cardiol. 49 (2007) 1903–1914.
[26] H. von Bibra, G. Wulf, M. St John Sutton, T. Schuster, A. Pfützner, P. Heilmeyer, A low-carbohydrate/high-protein diet improves diastolic cardiac function and the metabolic syndrome in overweight–obese patients with type 2 diabetes, IJC Metab. Endocr. 2 (2014) 11–18, http://dx.doi.org/10.1016/j.ijcme.2013.12.001.
[27] H. von Bibra, M. St John Sutton, T. Schuster, A. Ceriello, T. Siegmund, P.-M. Schumm-Draeger, Oxidative stress after a carbohydrate meal contributes to the deterioration of diastolic cardiac function in non-hypertensive insulin-treated patients with moderately well controlled type 2 diabetes, Horm. Metab. Res. 45 (2013) 449–455.
[28] W. Kosmala, T. O'Moore-Sullivan, R. Plaksej, M. Przewlocka-Kosmala, T.H. Marwick, Improvement of left ventricular function by lifestyle intervention in obesity: contributions of weight loss and reduced insulin resistance, Diabetologia 52 (2009) 2306–2316.
[29] S. Neubauer, The failing heart - an engine out of fuel, NEJM 356 (2007) 1140–1151.
[30] R.M. Witteles, M.B. Fowler, Insulin-resistant cardiomyopathy — clinical evidence, mechanisms, and treatment options, J. Am. Coll. Cardiol. 51 (2008) 93–102.
[31] D. Westermann, D. Lindner, M. Kasner, et al., Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction, Circ. Heart Fail. 4 (2011) 44–52.
[32] S.M. Chadderdon, J.T. Belcik, L. Bader, et al., Proinflammatory endothelial activation detected by molecular imaging in obese nonhuman primates coincides with onset of insulin resistance and progressively increases with duration of insulin resistance, Circulation 129 (2014) 471–478.