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

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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.

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.

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[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.

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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].