



Tissue advanced glycation end products are associated with diastolic function and aerobic exercise capacity in diabetic heart failure patients

Suzan Willemsen, Jasper W.L. Hartog, Yoran M. Hummel, Marieke H.I. van Ruijven, Iwan C.C. van der Horst, Dirk J. van Veldhuisen, and Adriaan A. Voors*

Department of Cardiology, University Medical Center Groningen, University of Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands

Received 16 May 2010; revised 16 July 2010; accepted 19 July 2010

Aims

Advanced glycation end products (AGEs) are increased in patients with diabetes and are associated with diastolic dysfunction through the formation of collagen crosslinks in the heart. The association among AGEs, diastolic function, and aerobic capacity in heart failure (HF) patients with and without diabetes is, however, unknown. We therefore studied the association among tissue AGEs, diastolic function, and aerobic capacity in patients with HF with or without diabetes.

Methods and results

In chronic HF patients (with and without left ventricular systolic dysfunction), tissue AGEs [skin autofluorescence (AF)], diastolic function (echocardiographic mean E' and E/E'), and aerobic capacity [peak oxygen uptake (VO_2) on cardiopulmonary exercise testing] were obtained. A total of 49 diabetics and 156 non-diabetics were included. Diabetics were older and had more cardiovascular risk factors, but left ventricular ejection fractions (LVEF) were similar. Tissue AGEs were higher in diabetics compared with non-diabetics (2.8 ± 0.8 vs. 2.3 ± 0.7 a.u.; $P < 0.001$). Furthermore, there was a correlation between tissue AGEs and mean E' ($r = -0.30$; $P < 0.001$, after adjustment for age, $r = -0.21$; $P = 0.004$). Aerobic capacity was significantly lower in diabetic patients with HF (peak VO_2 : 17.4 ± 5.1 vs. 21.7 ± 6.1 mL/min/kg; $P = 0.001$), even after adjustment for age and LVEF. Peak VO_2 was related to skin AF ($P = 0.03$), independent of age, diabetes, LVEF, and New York Heart Association functional class.

Conclusion

Patients with diabetes and HF have similar LVEF but poorer exercise capacity compared with non-diabetic HF patients. Our data suggest that these findings might be explained by the observed association among tissue AGE levels, diastolic function, and exercise capacity.

Keywords

Heart failure • Diastolic function • Diabetes • Advanced glycation end products

Introduction

The prevalence of heart failure (HF) is increasing, partly due to an ageing population, but also due to an increasing prevalence of diabetes.^{1,2} Patients with diabetes have an increased risk of developing HF, independent of their higher age.³ This could be explained by a higher risk of myocardial infarction, vascular dysfunction, and diastolic dysfunction in diabetes.⁴ However, several other metabolic factors have been postulated to explain the increased risk of HF in patients with diabetes.

Advanced glycation end products (AGEs) are formed during a non-enzymatic reaction between proteins and sugar residues, called the Maillard reaction.^{5,6} Advanced glycation end products accumulation occurs during life and enhanced AGE accumulation plays a role in the pathophysiology of chronic HF, renal dysfunction, and diabetic complications.⁵ Accumulation of AGEs affects the physiological properties of proteins and multiple vascular and tissue changes via the interaction of AGEs.⁵

Increased AGEs have been found in diabetic patients and in patients with HF.⁷ Wu *et al.* and Loimaala *et al.*^{8,9} showed that

* Corresponding author. Tel: +31 50 3612355, Fax: +31 50 3614391, Email: a.a.voors@thorax.umcg.nl

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2010. For permissions please email: journals.permissions@oxfordjournals.org.

diabetics have a more impaired diastolic function and poorer exercise capacity compared with non-diabetics. Furthermore, Parthenakis et al.¹⁰ showed that, in HF patients, diastolic function is the most important predictor of exercise intolerance measured with cardiopulmonary exercise testing. We hypothesized that elevated AGEs are related to diastolic function and exercise capacity, and therefore studied the association among tissue AGEs, diastolic function, and aerobic exercise capacity in HF patients with and without diabetes.

Methods

Patients and study design

The present study analysed the data of all patients who were screened at the outpatient clinic for a double-blind, placebo-controlled, randomized trial in patients with chronic HF (BENEFICIAL). The study design, baseline characteristics, and inclusion and exclusion criteria have been published elsewhere.¹¹ Briefly, patients with New York Heart Association (NYHA) II–IV stable HF for at least 3 months and left ventricular ejection fraction (LVEF) of ≤ 0.45 were eligible for the study. Main exclusion criteria were the inability of patients to undergo exercise testing, cardiac resynchronization therapy, pacemaker therapy, active, and/or treated malignancies within 12 months prior to inclusion, and clinically significant renal disturbance. Patients receiving treatment directed towards glucose regulation were considered as diabetics. A total of 205 patients were screened at the outpatient department. In each patient, echocardiography and skin autofluorescence (AF; skin AF is a validated non-invasive method to study tissue AGEs)^{12,13} were planned, and blood was drawn for laboratory analysis. These measurements were performed on the same day. Before randomization, a first rehearse cardiopulmonary aerobic capacity test was performed during a preceding visit to familiarize the patient with the procedures ($n = 133$). The BENEFICIAL study was approved by the local medical Ethics Committee and was conducted in accordance with the guidelines of the Declaration of Helsinki. All subjects gave written informed consent.

Skin autofluorescence

Tissue AGE accumulation was assessed using a validated skin AF reader (AGE reader; patent PCT/NL99/00607; DiagnOptics BV, Groningen, The Netherlands) as described previously.^{12,13} In short, the AGE reader illuminates a skin surface of $\sim 2 \text{ cm}^2$, guarded against surrounding light, with an excitation light source between 300 and 420 nm (peak excitation of $\sim 370 \text{ nm}$). Light from the skin is measured with a spectrometer in the 420–600 nm range, using 200 μm glass fibres. The value of skin AF is calculated as the ratio of the light intensity in the 420–600 nm wavelength range and the light intensity in the 300–420 nm wavelength range. Meerwaldt et al.¹³ have shown that repeated skin AF measurements on one day show an overall Altman error rate of 5.03%. Intra-individual seasonal variance shows an Altman error rate of 5.87%. The differences between repeated measurements do not alter depending on the skin AF level. Skin AF was measured at the volar side of the lower arm at ~ 10 – 15 cm below the elbow fold. The measurement was performed three times at a healthy skin site (i.e. without visible vessels, scars, or other skin abnormalities) and an average was calculated.

Echocardiography

Patients underwent two-dimensional echocardiography.¹⁴ Echocardiography was performed by experienced technicians using a VIVID 7

system (General Electric, Horten, Norway) with a 2.5–3.5 MHz probe. Measurements included left ventricular and atrial dimensions. Diastolic function was evaluated with peak early (E) and late (A) diastolic filling velocities, isovolumetric relaxation time (IVRT), left atrial end-diastolic volume (LAEDV), left atrial end-systolic volume (LAESV), and deceleration time (Dct) of the early peak filling. Early diastolic tissue velocity (E') was measured in colour-coded tissue Doppler imaging (CC-TDI) and calculated in pulse-wave tissue Doppler imaging with the formula described by Hummel et al.¹⁵ Furthermore, left ventricular mass (LVmass) and left atrial volume index (LAVI) were calculated.¹⁴ E' values were measured on the lateral and septal wall areas using CC-TDI. E/E' was calculated by dividing the E by the average E' . Systolic dysfunction was determined by Simpson's LVEF and defined as LVEF $\leq 45\%$. When Simpson's LVEF could not reliably be determined, LVEF was estimated visually.¹⁴ Diastolic function was categorized as no, mild, moderate, or severe diastolic dysfunction according to the Recommendations for the Evaluation of Left Ventricular Diastolic Function by the American Society of Echocardiography.¹⁴

Cardiopulmonary aerobic capacity testing

Cardiopulmonary aerobic capacity testing was performed according to the modified Bruce protocol, which increases the workload more gradually than the Bruce protocol. The first stage is performed at 1.7 m.p.h. and 0% grade, the second stage at 1.7 m.p.h. and 5% grade, and the third stage corresponds to the first stage of the Bruce protocol.¹⁶ Each exercise test started with an acclimatization period of standing on the treadmill. A standard 12-lead electrocardiogram was recorded continuously during exercise testing. Blood pressure was registered on a regulatory basis using a manual cuff sphygmomanometer. Patients were encouraged to continue the exercise until their peak oxygen uptake (VO_2) was reached, they became uncomfortably symptomatic, or discontinuation was indicated for safety reasons. Oxygen uptake, carbon dioxide production, and minute ventilation were measured using breath-by-breath gas analysis. Peak VO_2 is determined as an average value of the two highest VO_2 values at peak performance, expressed as mL/min/kg and as mL/min/fat free mass as well as a percentage of predicted peak oxygen consumption.

Statistical analysis

Variables that were normally distributed were expressed as mean \pm SD, whereas non-normally distributed variables were expressed as median (25–75% inter-quartile range). Nominal parameters were expressed as n (%). Differences in characteristics between patient groups were analysed using a t-test, when the parameter was normally distributed or a Mann–Whitney U-test when normality was not met. Correlation coefficients were calculated using Pearson's correlation coefficients. Based on earlier studies on predictors of exercise capacity in diabetic patients, we predefined variables that were entered in the multivariate model. Variables were considered in the multivariate models when a P -value < 0.1 was obtained in univariate regression. Variables that did not retain significance in the multivariable regression analysis were subsequently removed from the model (backward selection). To test whether the model was appropriate and whether assumptions for linear regression were met, the model was tested for colinearity, interaction terms, and lack-of-fit analysis with variance. Residuals were tested for normality of distribution. Analyses were performed with SPSS 16.0.2 (SPSS Inc., Chicago, IL, USA). All statistical tests were two sided and a P -value < 0.05 was considered statistically significant.

Results

Patient characteristics

Baseline characteristics of the study population are summarized in Table 1. Mean age was 63 ± 12 years, 168 (82%) were male, and diabetic patients were older ($P = 0.001$). Skin AF was higher in patients with diabetes (2.8 ± 0.8 vs. 2.3 ± 0.7 a.u., $P < 0.001$).

There was no difference in LVEF (0.35 ± 0.11 vs. $0.37 \pm 0.12\%$, $P = 0.26$) or LVmass (219 ± 65 vs. 234 ± 81 g, $P = 0.26$) between patients with and without diabetes. Diastolic function was classified as mild in 88 (44%) patients, moderate in 38 (19%) patients, and severe in 5 (3%) patients, which was not statistically significant between diabetic and non-diabetic patients. However, mean E' was lower (4.8 ± 1.9 vs. 5.6 ± 2.0 cm/s, $P = 0.02$) and

Table 1 Baseline characteristics

Variables	Total population (n = 205)	No diabetes (n = 156)	Diabetes (n = 49)	P-value
Age, years (mean \pm SD)	63 ± 12	61 ± 12	68 ± 10	0.001
Sex (male), n (%)	168 (82)	129 (83)	39 (80)	0.62
Race (Caucasian), n (%)	202 (99)	155 (99)	47 (96)	0.08
Cardiovascular risk factors, history of				
Hypercholesterolaemia, n (%)	151 (74)	106 (68)	45 (92)	0.001
Hypertension, n (%)	76 (37)	51 (33)	25 (51)	0.02
Duration of hypertension, years [median (range)]	15 ± 12	14 ± 11	16 ± 13	0.52
Smoking, n (%)	169 (83)	131 (84)	38 (78)	0.31
Body mass index, kg/m ² (mean \pm SD)	28 ± 5	28 ± 4	30 ± 6	0.01
Rhythm, n (%)				0.26
Sinus rhythm	179 (87)	138 (88)	41 (84)	
Atrial flutter/fibrillation	22 (11)	14 (9)	8 (16)	
Other	4 (3)	4 (3)	0 (0)	
Systolic blood pressure, mmHg (mean \pm SD)	121 ± 19	119 ± 19	126 ± 19	0.05
Diastolic blood pressure, mmHg (mean \pm SD)	73 ± 10	74 ± 11	72 ± 8	0.12
Heart rate, b.p.m. (mean \pm SD)	70 ± 14	67 ± 12	79 ± 16	<0.001
Aetiology of HF, n (%)				0.46
Ischaemic	131 (64)	95 (61)	36 (74)	
Idiopathic	47 (23)	39 (25)	8 (16)	
Rhythm disturbances	12 (6)	10 (6)	2 (4)	
Other	15 (7)	12 (8)	3 (6)	
NYHA functional class, n (%)				0.03
II	121 (59)	97 (62)	24 (49)	
III	73 (36)	54 (35)	19 (39)	
IV	11 (5)	5 (3)	6 (12)	
Skin AF, a.u. (mean \pm SD)	2.4 ± 0.8	2.3 ± 0.7	2.8 ± 0.8	<0.001
Laboratory assessments				
Hb, mmol/L (mean \pm SD)	8.8 ± 0.9	8.9 ± 0.8	8.5 ± 0.9	0.03
eGFR, mL/min/1.73 m ² (mean \pm SD)	75 ± 23	77 ± 21	69 ± 26	0.05
HbA1c, % [median (range)]	5.8 (5.6–6.6)	5.7 (5.5–6.0)	7.1 (6.6–7.9)	<0.001
Echocardiography				
LVEDD, ms (mean \pm SD)	57 ± 9	57 ± 9	56 ± 9	0.76
LVESD, ms (mean \pm SD)	45 ± 11	45 ± 11	44 ± 11	0.95
E/A ratio [median (range)]	0.87 (0.67–1.16)	0.88 (0.72–1.17)	0.74 (0.61–1.08)	0.11
IVRT, ms (mean \pm SD)	100 ± 22	98 ± 22	105 ± 24	0.09
Dct, ms (mean \pm SD)	219 ± 63	222 ± 62	207 ± 66	0.16
Mean E' , cm/s (mean \pm SD)	5.4 ± 2.0	5.6 ± 2.0	4.8 ± 1.9	0.02
E/E' [median (range)]	13 (10–18)	12 (9–17)	14 (11–20)	0.02
LAEDV (mm)	38 (27–64)	36 (27–59)	49 (30–74)	0.05
LAESV (mm)	69 (51–94)	68 (50–90)	76 (53–98)	0.23
LAVI (mL/m ²)	34 (26–46)	32 (25–45)	37 (27–49)	0.26
LVmass (g)	223 ± 69	219 ± 65	234 ± 81	0.26

Continued

Table 1 Continued

Variables	Total population (n = 205)	No diabetes (n = 156)	Diabetes (n = 49)	P-value
LVEF (mean ± SD)	0.37 ± 0.12	0.37 ± 0.12	0.35 ± 0.11	0.26
Peak VO ₂ , mL/min/kg (n = 133) (mean ± SD)	20.8 ± 6.1	21.7 ± 6.1	17.4 ± 5.1	0.001
Medication use, n (%)				
ACE inhibitor/ARB	190 (93)	144 (92)	46 (94)	0.71
Beta-blocker	182 (89)	138 (89)	44 (90)	0.80
Diuretics	116 (57)	80 (51)	36 (74)	0.01
Aldosterone antagonists	56 (27)	39 (25)	17 (35)	0.18

HF, heart failure; NYHA, New York Heart Association; skin AF, skin autofluorescence; Hb, haemoglobin; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin type A1c; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVRT, isovolumetric relaxation time; Dct, deceleration time; LAEDV, left atrial end-diastolic volume; LAESV, left atrial end-systolic volume; LAVI, left atrial volume index; LVmass, left ventricular mass; LVEF, left ventricular ejection fraction; Peak VO₂, peak oxygen uptake; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Table 2 Determinants of skin autofluorescence

Variables	Skin AF					
	Univariate			Multivariate (r = 0.51, r ² = 0.26, P < 0.001)		
	β	B (95% CI)	P	β	B (95% CI)	P
Age	0.38	0.03 (0.02;0.03)	<0.001	0.26	0.02 (0.01;0.03)	<0.001
Diabetes	0.31	0.55 (0.31;0.79)	<0.001	0.21	0.38 (0.16;0.61)	0.001
BMI	−0.07	−0.01 (−0.03;0.01)	0.31			
Smoking	0.18	0.23 (0.05;0.40)	0.01	0.20	0.25 (0.10;0.41)	0.002
eGFR	0.32	0.71 (0.41;1.02)	<0.001	−0.18	−0.01 (−0.01;−0.00)	0.01

Skin AF, skin autofluorescence; BMI, body mass index; eGFR, estimated glomerular filtration rate.

LAEDV was larger [36 (27–59) vs. 49 (30–74) mm, *P* = 0.05] in patients with diabetes.

Multivariable linear regression showed that skin AF was determined by age, diabetes, smoking, and estimated glomerular filtration rate (Table 2).

Association between tissue advanced glycation end products and diastolic function

Table 3 shows baseline characteristics of patients with low or high tissue AGEs. Skin AF was measured in 197 (96%) of 205 patients. Patients with skin AF above the mean were older (*P* < 0.001), more often had diabetes (*P* < 0.001), a more impaired diastolic function measured with mean *E'* (*P* < 0.001), and aerobic exercise capacity (*P* < 0.001). Figure 1 demonstrates the relation between higher tissue AGEs and mean *E'*. Skin AF was significantly correlated with diastolic function measured with mean *E'* (*r* = −0.310; *P* < 0.001, after adjustment for age, *r* = −0.212; *P* = 0.004). Multivariable linear regression analysis showed that skin AF remained independently associated with diastolic function (*P* < 0.001, Table 4), after adjustment for potential confounders,

such as age, LVEF, hypercholesterolaemia, hypertension, duration of hypertension, and body mass index.

Association between tissue advanced glycation end products and exercise capacity

Exercise capacity was measured in 133 (65%) of 205 patients and was lower in diabetics compared with non-diabetics (17.6 ± 5.1 vs. 22.4 ± 6.0 mL/min/kg, *P* < 0.001). Table 5 shows that peak VO₂ was related to skin AF (*P* = 0.03), independent of age, diabetes, LVEF, and NYHA functional class.

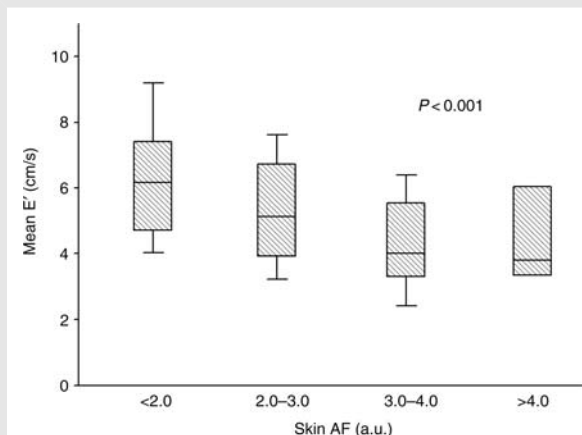
Discussion

The present study shows that tissue AGEs are higher in diabetic HF patients compared with patients with HF without diabetes and are independently associated with diastolic function and cardiopulmonary aerobic exercise testing. This is the first study that describes the association among tissue AGEs, diastolic function, and aerobic exercise capacity in patients with HF with and without diabetes.

Table 3 Baseline characteristics divided by mean skin autofluorescence

Variables	Total population (n = 197)	Skin AF <mean (n = 110)	Skin AF >mean (n = 87)	P-value
Age, years (mean \pm SD)	63 \pm 12	59 \pm 11	68 \pm 11	<0.001
History of diabetes, n (%)	46 (23)	14 (13)	32 (37)	<0.001
Smoking, n (%)	165 (84)	90 (82)	75 (86)	0.43
Systolic blood pressure, mmHg (mean \pm SD)	121 \pm 19	120 \pm 19	122 \pm 20	0.58
Diastolic blood pressure, mmHg (mean \pm SD)	73 \pm 10	75 \pm 11	71 \pm 10	0.01
Aetiology, ischaemic, n (%) of HF	126 (64)	63 (57)	63 (72)	0.03
NYHA functional class, n (%)				0.003
II	114 (58)	74 (67)	40 (46)	
III/IV	83 (42)	36 (33)	47 (54)	
Laboratory assessments				
Hb, mmol/L (mean \pm SD)	8.8 \pm 0.9	9.0 \pm 0.7	8.4 \pm 0.9	<0.001
eGFR, mL/min/1.73 m ² (mean \pm SD)	74 \pm 22	79 \pm 19	68 \pm 24	0.001
HbA1c, % [median (range)]	5.8 (5.6–6.6)	5.7 (5.5–6.2)	6.0 (5.6–6.9)	0.003
Echocardiography				
E/E' [median (range)]	12 (10–18)	11 (9–14)	14 (10–21)	<0.001
Mean E', cm/s (mean \pm SD)	5.5 \pm 2.0	6.0 \pm 1.8	4.8 \pm 1.9	<0.001
LAEDV (mm)	39 (28–65)	37 (27–62)	41 (28–68)	0.65
LAVI (mL/m ²)	34 (25–46)	32 (25–44)	36 (27–48)	0.19
LVEF, % (mean \pm SD)	0.37 \pm 0.11	0.37 \pm 0.11	0.36 \pm 0.12	0.40
Peak VO ₂ , mL/min/kg (mean \pm SD) (n = 131)	20.5 \pm 6.1	22.4 \pm 6.0	17.6 \pm 5.1	<0.001

HF, heart failure; NYHA, New York Heart Association; Hb, haemoglobin; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin type A1c; LAEDV, left atrial end-diastolic volume; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; Peak VO₂, peak oxygen uptake.

**Figure 1** Relation between mean E' and skin autofluorescence (Skin AF).

Patients with diabetes have an increased risk of developing HF, and multiple factors might explain this relation.^{17,18} Recently, it was suggested that AGEs might be an important contributor to the development of HF among patients with diabetes.⁵ The association between AGEs and HF can be explained by two main mechanisms. First, AGEs affect the physiological properties of proteins in tissues by creating crosslinks. Second, AGEs cause multiple vascular and tissue changes via the interaction with AGE receptors.

Exposure to AGEs can cause a significant delay in calcium re-uptake causing diastolic dysfunction.

Others have shown that exercise capacity in diabetic patients is more impaired compared with non-diabetics.^{8,9} In the present study, we extended these findings to patients with HF. Several studies have shown the importance of diastolic dysfunction as an independent predictor of reduced exercise capacity, even after adjusting for age.^{8-10,19} In the present study, we found similar systolic function and LVmass, but lower early diastolic velocities, suggestive of poorer diastolic function, although other diastolic parameters of diastolic dysfunction did not show significant differences between patients with and without diabetes. Interestingly, we found diastolic function to be a predictor of exercise capacity. After adjustment for tissue AGEs, the predictive value of diastolic function became non-significant. The most important novel finding of the present study is, however, that we provided evidence for an association between tissue AGEs and both mean E' and exercise capacity, suggesting that AGEs might explain the impaired diastolic function (measured with mean E'), and therefore, the poorer exercise capacity in diabetic HF patients.

Two limitations should be noted. First, tissue AGEs were measured non-invasively at the volar side of the right arm. Although this measurement has been validated against AGEs that are present in the skin, the skin-AF reader has not been validated directly against AGEs present in the heart. Second, we studied diastolic function in patients with systolic HF. However, diastolic function is frequently present in patients with systolic HF, and Bursi *et al.*²⁰ showed that diastolic function was even more impaired in patients with systolic

Table 4 Determinants of mean early diastolic tissue velocity

Variable	Mean E'					
	Univariate			Multivariate ($r = 0.46$, $r^2 = 0.22$, $P < 0.001$)		
	β	B (95% CI)	P	β	B (95% CI)	P
Skin AF	-0.31	-0.79 (-1.15;-0.43)	<0.001	-0.26	0.70 (-1.06;-0.34)	<0.001
Age	-0.32	-0.05 (-0.07;-0.03)	<0.001			
History of ischaemia	0.18	0.74 (0.15;1.33)	0.01			
LVEF	0.38	0.06 (0.04;0.09)	<0.001	0.36	0.06 (0.04;0.09)	<0.001
Hypercholesterolaemia	-0.12	-0.55 (-1.21;-0.11)	0.10			
Body mass index	0.11	0.04 (-0.02;0.10)	0.14			
Hypertension	-0.12	-0.48 (-1.08;0.11)	0.11			
Duration of hypertension, per 5 years	-0.24	-0.21 (-0.41;-0.04)	0.05			
History of diabetes	-0.20	-0.95 (-1.65;-0.25)	0.01			

Peak VO₂, peak oxygen uptake; Skin AF, skin auto fluorescence; LVEF, left ventricular ejection fraction.

Table 5 Determinants of peak oxygen uptake

Variables	Peak VO ₂					
	Univariate			Multivariate ($r = 0.58$, $r^2 = 0.34$, $P < 0.001$)		
	β	B (95% CI)	P	β	B (95% CI)	P
Skin AF	-0.38	-3.04 (-4.34;-1.74)	<0.001	-0.18	-1.47 (-2.79;-0.14)	0.03
Age	-0.32	-0.17 (-0.26;-0.08)	<0.001	-0.20	-0.11 (-0.19;-0.03)	0.01
Diabetes	-0.29	-4.3 (-6.8;-1.9)	0.001	-0.18	-2.70 (-5.00;-0.42)	0.02
LVEF	0.34	0.22 (0.12;0.33)	<0.001	0.29	0.19 (0.09;0.28)	<0.001
NYHA	-0.29	-3.62 (-5.72;-1.52)	0.001	-0.17	-2.18 (-4.07;-0.29)	0.02
Mean E'	0.17	0.54 (0.00;1.07)	0.05			

Peak VO₂, peak oxygen uptake; Skin AF, skin autofluorescence; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

HF compared with patients with diastolic HF. If AGEs provide a pathophysiological explanation for impaired diastolic function and poorer exercise capacity in diabetic HF patients, this might provide a novel treatment option. Although diastolic dysfunction is common and strongly related to symptoms, there is no standardized treatment to improve diastolic function.^{21–25} The stiffness due to accumulation of AGEs could also be a target for intervention with AGE breakers by reversing structural changes that are related to diastolic function. The largest effect of AGE breakers can be expected in older patients with diabetes or renal failure, who will have a high amount of AGEs and may, therefore, benefit the most from AGE intervention. Several AGE cross-link breakers, such as alagebrium and TRC4186, are currently under investigation for use in diabetic and non-diabetic HF patients.

Conclusion

Patients with diabetes and HF have similar LVEF but poorer exercise capacity compared with non-diabetic HF patients. Our data suggest that these findings might be explained by the observed association among tissue AGE levels, diastolic function, and exercise capacity.

Funding

D.J.V. and A.A.V. are clinical established investigators of the Netherlands Heart Foundation (D97-017 and 2006T37). J.W.L.H. is supported by a grant from the Netherlands Heart Foundation (2006T012).

Conflict of interest: none declared.

References

1. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Tendera M, Auricchio A, Bax J, Bohm M, Corra U, della Bella P, Elliott PM, Follath F, Gheorghiadu M, Hasin Y, Hernborg A, Jaarsma T, Komajda M, Kornowski R, Piepoli M, Prendergast B, Tavazzi L, Vachiery JL, Verheugt FW, Zamorano JL, Zannad F. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008;**10**:933–989.

2. Fox CS, Pencina MJ, Meigs JB, Vasan RS, Levitzky YS, D'Agostino RB Sr. Trends in the incidence of type 2 diabetes mellitus from the 1970s to the 1990s: the Framingham Heart Study. *Circulation* 2006;**113**:2914–2918.
3. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004;**27**:1879–1884.
4. Preis SR, Pencina MJ, Hwang SJ, D'Agostino RB Sr, Savage PJ, Levy D, Fox CS. Trends in cardiovascular disease risk factors in individuals with and without diabetes mellitus in the Framingham Heart Study. *Circulation* 2009;**120**:212–220.
5. Hartog JW, Voors AA, Bakker SJ, Smit AJ, van Veldhuisen DJ. Advanced glycation end-products (AGEs) and heart failure: pathophysiology and clinical implications. *Eur J Heart Fail* 2007;**9**:1146–1155.
6. Miyata T, Sugiyama S, Saito A, Kurokawa K. Reactive carbonyl compounds related uremic toxicity ('carbonyl stress'). *Kidney Int Suppl* 2001;**78**:S25–S31.
7. Smit AJ, Hartog JW, Voors AA, van Veldhuisen DJ. Advanced glycation endproducts in chronic heart failure. *Ann N Y Acad Sci* 2008;**1126**:225–230.
8. Wu YW, Hsu CL, Wang SS, Tsai MW, Chu SH, Chen YS, Yang WS, Wu YT. Impaired exercise capacity in diabetic patients after coronary bypass surgery: effects of diastolic and endothelial function. *Cardiology* 2008;**110**:191–198.
9. Loimaala A, Groundstroem K, Rinne M, Nenonen A, Huhtala H, Vuori I. Exercise training does not improve myocardial diastolic tissue velocities in Type 2 diabetes. *Cardiovasc Ultrasound* 2007;**5**:32.
10. Parthenakis FI, Kanoupakis EM, Kochiadakis GE, Skolidis EI, Mezilis NE, Simantirakis EN, Kanakarakis MK, Vardas PE. Left ventricular diastolic filling pattern predicts cardiopulmonary determinants of functional capacity in patients with congestive heart failure. *Am Heart J* 2000;**140**:338–344.
11. Willemsen S, Hartog JW, Hummel YM, Posma JL, van Wijk LM, van Veldhuisen DJ, Voors AA. Effects of alagebrium, an advanced glycation end-product breaker, in patients with chronic heart failure: study design and baseline characteristics of the BENEFICIAL trial. *Eur J Heart Fail* 2010;**12**:294–300.
12. Meerwaldt R, Hartog JW, Graaff R, Huisman RJ, Links TP, den Hollander NC, Thorpe SR, Baynes JW, Navis G, Gans RO, Smit AJ. Skin autofluorescence, a measure of cumulative metabolic stress and advanced glycation end products, predicts mortality in hemodialysis patients. *J Am Soc Nephrol* 2005;**16**:3687–3693.
13. Meerwaldt R, Links T, Graaff R, Thorpe SR, Baynes JW, Hartog J, Gans R, Smit A. Simple noninvasive measurement of skin autofluorescence. *Ann N Y Acad Sci* 2005;**1043**:290–298.
14. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;**22**:107–133.
15. Hummel YM, Klip IJ, de Jong RM, Pieper PG, van Veldhuisen DJ, Voors AA. Diastolic function measurements and diagnostic consequences: a comparison of pulsed wave- and color-coded tissue Doppler imaging. *Clin Res Cardiol* 2010;**99**:453–458.
16. Sheffield LT, Roitman D. Stress testing methodology. *Prog Cardiovasc Dis* 1976;**19**:33–49.
17. Solang L, Malmberg K, Ryden L. Diabetes mellitus and congestive heart failure. Further knowledge needed. *Eur Heart J* 1999;**20**:789–795.
18. van der Horst IC, de Boer RA, Hillege HL, Boomsma F, Voors AA, van Veldhuisen DJ. Neurohormonal profile of patients with heart failure and diabetes. *Neth Heart J* 2010;**18**:190–196.
19. Lapu-Bula R, Robert A, De Kock M, D'Hondt AM, Detry JM, Melin JA, Vanoverschelde JL. Relation of exercise capacity to left ventricular systolic function and diastolic filling in idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol* 1999;**83**:728–734.
20. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA, Roger VL. Systolic and diastolic heart failure in the community. *JAMA* 2006;**296**:2209–2216.
21. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;**27**:2338–2345.
22. Stewart KJ. Exercise training and the cardiovascular consequences of type 2 diabetes and hypertension: plausible mechanisms for improving cardiovascular health. *JAMA* 2002;**288**:1622–1631.
23. van Veldhuisen DJ, Cohen-Solal A, Bohm M, Anker SD, Babalis D, Roughton M, Coats AJ, Poole-Wilson PA, Flather MD. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol* 2009;**53**:2150–2158.
24. Yip GW, Wang M, Wang T, Chan S, Fung JW, Yeung L, Yip T, Lau ST, Lau CP, Tang MO, Yu CM, Sanderson JE. The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction. *Heart* 2008;**94**:573–580.
25. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;**362**:777–781.