Independent Associations of Glucose Status and Arterial Stiffness With Left Ventricular Diastolic Dysfunction

An 8-year follow-up of the Hoorn Study

Katja van den Hurk, phd[1]
Marjan Alssema, phd[1]
Otto Kamp, md, phd[2]
Ronald M. Henry, md, phd[3]
Coen D. Stehouwer, md, phd[3]

Yvo M. Smulders, md, phd[4]
Giel Nijpels, md, phd[5]
Walter J. Paulus, md, phd[6]
Jacqueline M. Dekker, phd[1]

OBJECTIVE—To investigate relative contributions of glucose status and arterial stiffness to markers of left ventricular (LV) systolic and diastolic dysfunction after 8 years of follow-up.

RESEARCH DESIGN AND METHODS—In the population-based prospective Hoorn Study, 394 individuals with preserved LV systolic and diastolic function participated, of whom 87 had impaired glucose metabolism and 128 had type 2 diabetes. Measurements including arterial ultrasound and echocardiography were performed according to standardized protocols.

RESULTS—The presence of type 2 diabetes was associated with more severe LV systolic and diastolic dysfunction 8 years later: LV ejection fraction was 2.98% (95% CI 0.46–5.51) lower, and left atrial (LA) volume index, LV mass index, and tissue Doppler-derived E/e′ were 3.71 mL/m^2 (1.20–6.22), 5.86 g/m$^{2.7}$ (2.94–8.78), and 1.64 units (0.95–2.33) higher, respectively. Furthermore, presence of impaired glucose metabolism or type 2 diabetes was associated with 8-year increases in LV mass index. More arterial stiffness (measured as a lower distensibility) was associated with LV diastolic dysfunction 8 years later: LA volume index, LV mass index, and E/e′ at follow-up were higher. Subsequent adjustments for baseline mean arterial pressure and/or LV diastolic dysfunction did not eliminate these associations. Associations of type 2 diabetes and arterial stiffness with markers of LV diastolic dysfunction were largely independent of each other.

CONCLUSIONS—Both glucose status and arterial distensibility are independently associated with more severe LV diastolic dysfunction 8 years later and with deterioration of LV diastolic dysfunction. Therefore, type 2 diabetes and arterial stiffness may relate to LV diastolic dysfunction through different pathways.

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Metabolic disturbances and arterial stiffness are both recognized contributors to left ventricular (LV) stiffness and LV systolic and diastolic dysfunction. The most frequent comorbid conditions of heart failure with normal LV ejection fraction (HFNEF) (mainly characterized by LV diastolic dysfunction) are hypertension, type 2 diabetes, and obesity (1). Moreover, a recent review of medical records revealed that even after exclusion of heart failure patients, 23% of individuals with type 2 diabetes had LV diastolic dysfunction (2). Data from the MONICA (Monitoring of Trends and Determinations in Cardiovascular Disease) registry have shown that hypertension and obesity—both associated with type 2 diabetes and arterial stiffness—independently predicted left atrial (LA) enlargement, a sensitive indicator of an elevated LV preload (3).

HFNEF patients were shown to display combined stiffening of arteries and the LV, which was not ascribable to age, body weight, or arterial pressure (4). Data from Olmsted County confirm that arterial stiffness is increased in HFNEF patients and in hypertensive patients without heart failure (5). Arterial stiffness is hypothesized to lead to increased arterial wave reflections, which in turn lead to an increased cardiac afterload and myocardial oxygen demand and simultaneously to a decreasing diastolic coronary perfusion pressure (6). These direct effects of arterial stiffening are thought to contribute to both systolic and diastolic LV dysfunction but predominantly to the former (7,8). Besides these mechanisms, there may also be indirect effects due to shared underlying pathways that lead to stiffening of both arterial and LV walls (9). As previously shown in our cohort, individuals with type 2 diabetes commonly have stiffer arteries (10). Both arterial and LV stiffness in type 2 diabetes have been related to deposition of advanced glycation end products, fibrosis, and an elevated myocyte resting tension (11,12). These effects might predominantly contribute to LV diastolic dysfunction and might underlie both type 2 diabetes– and arterial stiffness–related LV diastolic dysfunction. In the current study, we investigated whether glucose status and arterial stiffness were prospectively associated with (changes in) LV systolic and diastolic dysfunction. Secondly, we assessed whether these associations were independent of each other.

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RESEARCH DESIGN AND METHODS

—Echocardiographic measurements were performed in 1999–2001 (baseline) and 2007–2009 (follow-up) examinations of the Hoorn Study. The Hoorn Study is a population-based cohort study on glucose metabolism and cardiovascular diseases, previously described in detail (10). At baseline, 290 individuals with normal glucose metabolism (NGM), 187 with impaired glucose metabolism (IGM), and 345 with type 2 diabetes participated. At follow-up, 167 (20%) individuals were excluded a priori because of incomplete baseline data (n = 26), mental incompetence to participate (n = 12), or death (n = 129). Of the remaining 655 individuals, 441 (67%) participated. Thirteen (3%) of those were excluded in the present analyses because of missing echocardiography data at follow-up. To restrict the study population to individuals at risk of developing LV systolic and/or diastolic dysfunction, we also excluded 34 individuals (8%) with an LV ejection fraction <50% or an LA volume index >40 mL/m^2 at baseline. The local ethics committee approved the study, and written informed consent was obtained from all participants.

Echocardiography

Echocardiography was performed at baseline and follow-up with the use of an HP SONOS 5500 echocardiography system (2–4 MHz transducer) according to a standardized protocol consisting of two-dimensional, M-mode, and pulsed wave Doppler assessments as previously described (13). At follow-up, this protocol was expanded with tissue Doppler assessments of mitral annular velocities.

LV systolic dysfunction was determined by measuring LV ejection fraction (14). A set of three markers of LV diastolic dysfunction was determined: LA volume index, LV mass indexed to height to the power of 2.7 (14), and the ratio of early (E) mitral valve flow to early (e′) diastolic lengthening velocity (E/e′) using tissue and pulsed wave Doppler assessments. Incident heart failure was considered present if signs and symptoms were accompanied by LV systolic (LV ejection fraction <35%) and/or diastolic dysfunction (15). Presence of incident LV diastolic dysfunction (grade 2 or 3) was assessed according to international recommendations (16).

Arterial stiffness

In the present analyses, we primarily focused on previously described ultrasound-derived distensibility coefficients of carotid, brachial, and femoral arteries to assess stiffness of the arterial wall (10). Additionally, systemic arterial compliance was determined according to the time-decay method and by calculating the ratio of stroke volume to aortic pulse pressure (17). Compliance coefficients and Young elastic modulus were assessed with ultrasound. Augmentation index was determined using applanation tonometry. In a subset of the study population, carotid-femoral pulse wave velocity was approached by measuring carotid-femoral transit time, adjusted for height in the statistical analyses.

Reproducibility

Reproducibility of arterial ultrasound measurements at baseline was assessed by calculating intraobserver intersession coefficients of variation as previously described (10). At follow-up, intraobserver intersession coefficients of variation in 10 individuals (aged 70.3 ± 3.6 years) were comparable: 4.2, 13.1, 4.1, and 6.1% for LV ejection fraction, LA volume, LV mass, and E/e′, respectively.

Other baseline measurements

For assessment of glucose status, all participants except those with previously diagnosed diabetes underwent a standard 75-g oral glucose tolerance test and were classified into NGM, IGM (impaired fasting glucose and/or impaired glucose tolerance), and type 2 diabetes groups according to the 1999 World Health Organization criteria (18). Health status, medical history, medication use, and smoking habits were assessed by questionnaires (10). Waist circumference, blood pressures (systolic, mean arterial, and pulse pressures), and levels of cholesterol, insulin, HbA$_{1c}$, and C-reactive protein were determined as previously described (10).

Statistical analysis

Descriptive statistics are presented as means ± SD or, in the case of a skewed distribution, as median (interquartile range). The F test for ANOVA in the case of continuous variables or χ^2 tests in the case of proportions were performed to test for differences between groups of glucose status. In the case of skewed distributions, the above tests were done on log-transformed data. For every variable that had >10% missing data, the number missing is presented in the legends of Tables 1–3. Reasons for missing data have previously been described (10,17).

Linear regression analyses, adjusted for age and sex, were performed to assess associations of glucose status and arterial stiffness with markers of LV systolic and diastolic dysfunction at follow-up. Regression models with arterial stiffness as an independent variable were subsequently adjusted for mean arterial pressure to investigate to what extent these associations were explained by elevated blood pressure. For investigation of changes in markers, LV systolic and diastolic dysfunction according to glucose status or arterial stiffness, we adjusted all models for baseline values of these markers (models assessing E/e′ adjusted for baseline LA volume index). LV systolic and diastolic dysfunction in type 2 diabetes and arterial stiffness might partially be due to underlying factors, like overweight, hypertension, insulin resistance, or previous cardiovascular events (19). Therefore, we additionally analyzed which potentially underlying or mediating factors contribute to these associations and to what extent by adding these factors one by one or simultaneously to the models (Supplementary Data). A secondary purpose of these analyses was to investigate potential residual confounding by these factors. Product terms were entered to test for effect modification by sex or medication use at follow-up and for interactions of glucose status with arterial stiffness or prior cardiovascular disease. Associations of arterial distensibility coefficients, systemic arterial compliance, and arterial compliance coefficients were shown per lower unit to reflect associations with greater arterial stiffness. Additional analyses, adjusted for age and sex, were performed to investigate whether diabetes duration had an effect on markers of LV systolic and diastolic function. P values <0.05, or <0.10 in case of interaction analyses, were considered statistically significant. Statistical analyses were performed with SPSS for Windows (version 15.0; SPSS, Chicago, IL).

RESULTS

—A total of 394 individuals in the age range of 50–87 years were included in the present analyses, 87 (22%) of whom had IGM and 128 (32%) of whom had type 2 diabetes. Compared with individuals who were not included, these individuals were younger and less likely to have type 2 diabetes and had more favorable levels of arterial stiffness and LV systolic and diastolic dysfunction at baseline (data not shown). Individuals with type 2 diabetes were younger, had higher BMI and blood pressure, and had

Table 1—Characteristics according to glucose status

	NGM	IGM	Type 2 diabetes	P
n	179	87	128	
Age (years)	66 (63–69)	68 (64–73)	65 (58–71)	0.000
Male	82 (46)	47 (54)	67 (52)	0.351
Smoker	23 (13)	12 (14)	10 (8)	0.283
Waist circumference (cm)	91 ± 11	97 ± 10	100 ± 11	0.000
Systolic blood pressure (mmHg)	136 ± 21	140 ± 16	143 ± 17	0.002
Mean arterial pressure (mmHg)	95 ± 11	98 ± 10	100 ± 10	0.000
Blood pressure–lowering medication	39 (22)	24 (28)	46 (36)	0.026
Total cholesterol (mmol/L)	5.8 ± 1.0	5.8 ± 0.9	5.6 ± 1.1	0.161
HDL cholesterol (mmol/L)	1.5 ± 0.4	1.4 ± 0.4	1.3 ± 0.3	0.000
Lipid-lowering medication	20 (11)	18 (21)	22 (17)	0.101
HbA_{1c} (%)	5.7 ± 0.4	5.9 ± 0.4	6.6 ± 0.9	0.000
HOMA of insulin resistance[a]	1.9 (1.4–2.5)	3.0 (2.3–4.2)	4.1 (2.8–6.0)	0.000
HOMA of β-cell function[a]	78 (64–103)	90 (72–126)	70 (49–97)	0.000
C-reactive protein (mg/L)	1.4 (0.7–2.9)	2.2 (1.0–4.4)	2.4 (1.0–4.6)	0.000
Microalbuminuria	11 (6)	14 (16)	21 (17)	0.007
Coronary artery disease	10 (6)	4 (5)	12 (10)	0.214
Prior cardiovascular disease	70 (39)	36 (42)	57 (48)	0.372
B-type natriuretic peptide (pmol/L)[b]	4.1 (2.0–7.8)	3.1 (1.7–6.7)	2.9 (1.2–5.8)	0.002
Arterial stiffness (baseline)				
Systemic arterial compliance: time decay method (mL/mmHg)[c]	0.81 ± 0.31	0.79 ± 0.30	0.76 ± 0.32	0.507
Systemic arterial compliance: stroke volume/aortic pulse pressure (mL/mmHg)[d]	1.17 ± 0.34	1.13 ± 0.31	1.00 ± 0.35	0.000
Carotid artery compliance coefficient ($10^{-3} \cdot kPa^{-1}$)[e]	0.60 ± 0.21	0.59 ± 0.29	0.56 ± 0.25	0.420
Central pulse pressure (mmHg)[f]	60 ± 15	62 ± 11	66 ± 12	0.016
Brachial pulse pressure (mmHg)	50 ± 13	51 ± 11	55 ± 14	0.003
Carotid-femoral transit time (ms)[g]	57 ± 18	56 ± 16	56 ± 16	0.887
Brachial artery compliance coefficient ($10^{-3} \cdot kPa^{-1}$)	0.15 ± 0.07	0.12 ± 0.06	0.12 ± 0.07	0.000
Femoral artery compliance coefficient ($10^{-3} \cdot kPa^{-1}$)[f]	0.49 ± 0.21	0.35 ± 0.15	0.31 ± 0.14	0.000
Carotid artery Young elastic modulus (kPa)[i]	0.81 ± 0.35	0.90 ± 0.50	0.96 ± 0.52	0.014
Aortic augmentation index (% point)[f]	31 ± 8	32 ± 8	32 ± 9	0.936
Carotid artery distensibility coefficient ($10^{-3} \cdot kPa^{-1}$)[e]	13.1 (10.4–16.0)	8.6 (6.2–11.6)	5.8 (4.5–7.6)	0.001
Brachial artery distensibility coefficient ($10^{-3} \cdot kPa^{-1}$)	12.0 (8.9–15.5)	6.2 (4.8–8.4)	3.7 (3.2–5.3)	0.000
Femoral artery distensibility coefficient ($10^{-3} \cdot kPa^{-1}$)[h]	11.6 (8.2–14.7)	5.7 (4.3–7.7)	3.9 (2.9–4.8)	0.000
Echocardiography (baseline)				
LV ejection fraction (%)	64 ± 6	64 ± 6	61 ± 7	0.004
LA volume index (mL/m²)	21 (19–24)	20 (18–24)	24 (20–28)	0.000
LV mass index (g/m^2.7)	38 (33–43)	37 (31–45)	40 (33–47)	0.032
Echocardiography (follow-up)				
LV ejection fraction (%)[j]	54 ± 9	53 ± 9	51 ± 10	0.033
LA volume index (mL/m²)[k]	22 (17–27)	23 (18–29)	24 (20–32)	0.007
LV mass index (g/m^2.7)[l]	38 (32–45)	42 (33–53)	44 (37–52)	0.001
E/e′	8.3 (7.1–10.2)	8.7 (7.4–10.0)	9.2 (8.1–11.5)	0.001
Heart failure[m]	24 (15)	15 (19)	23 (21)	0.410
LV diastolic dysfunction grade 2 or 3	55 (31)	52 (61)	88 (72)	0.003

Data are means ± SD, median (interquartile range) in the case of a skewed distribution, or n (%) in the case of proportions. HOMA, homeostasis model assessment. Missing data are as follows: [a]n = 23, [b]n = 74, [c]n = 91, [d]n = 60, [e]n = 39, [f]n = 60, [g]n = 216, [h]n = 52, [i]n = 42, [j]n = 109, [k]n = 75, [l]n = 91, [m]n = 41.

greater arterial stiffness and more severe LV systolic and diastolic dysfunction at baseline compared with individuals without type 2 diabetes (Table 1). Group differences in LV systolic and diastolic dysfunction remained present at follow-up. Heart failure incidence was not significantly different: 23 (21%) in type 2 diabetes versus 15 (19%) in IGM and 24 (15%) in NGM. Incidence of LV diastolic dysfunction grade 2 or 3 was higher with deteriorating glucose status: 88 (72%) in type 2 diabetes versus 52 (61%) in IGM and 55 (31%) in NGM.

Glucose status

The presence of type 2 diabetes was associated with more severe levels of all markers of LV systolic and diastolic dysfunction: LV ejection fraction, LA volume index, LV mass index, and E/e′ (Table 2). After adjustment for age and sex, LV ejection fraction at follow-up was 2.98% lower in individuals with type 2 diabetes at baseline compared with that in subjects with NGM. Individuals with type 2 diabetes had a 3.71 mL/m² higher LA volume

Table 2—*Markers of LV systolic and diastolic dysfunction at follow-up according to baseline glucose status (NGM = reference)*

Outcome at follow-up	IGM	Type 2 diabetes
n	87	128
LV ejection fraction (%)[a]		
Adjusted for age and sex	−0.75 (−3.61 to 2.11)	−2.98 (−5.51 to −0.46)*
Adjusted for age, sex, and baseline LV ejection fraction	−0.74 (−3.59 to 2.11)	−1.76 (−4.27 to 0.75)
LA volume index (mL/m^2)[b]		
Adjusted for age and sex	0.59 (−2.15 to 3.33)	3.71 (1.20–6.22)*
Adjusted for age, sex, and baseline LA volume index	1.33 (−1.28 to 3.95)	1.92 (−0.52 to 4.37)
LV mass index (g/m$^{2.7}$)[c]		
Adjusted for age and sex	3.11 (−0.23 to 6.45)	5.86 (2.94–8.78)*
Adjusted for age, sex, and baseline LV mass index	2.93 (0.00–5.85)*	3.41 (0.81–6.01)*
E/e′		
Adjusted for age and sex	0.47 (−0.30 to 1.24)	1.64 (0.95–2.33)*
Adjusted for age, sex, and baseline LA volume index	0.54 (−0.24 to 1.33)	1.43 (0.71–2.15)*

Data are regression coefficients (95% CI). Missing data are as follows: [a]$n = 109$, [b]$n = 75$, [c]$n = 91$. *$P < 0.05$.

index, 5.86 g/m$^{2.7}$ higher LV mass index, and 1.64 higher E/e′. These associations were attenuated after adjustment for baseline markers of LV systolic and diastolic dysfunction, but type 2 diabetes was still significantly associated with a higher LV mass index (3.41 g/m$^{2.7}$) and E/e′ (1.43). Individuals with IGM compared with those with NGM had a 2.93 g/m$^{2.7}$ higher LV mass index, independent of baseline LV mass index.

Associations of type 2 diabetes with markers of LV systolic and diastolic dysfunction were largely independent of blood pressure, lipid levels, renal function, C-reactive protein, and coronary artery disease (Supplementary Data Table A). Adjustment for HbA$_{1c}$ levels or insulin resistance diminished the associations of type 2 diabetes with LV ejection fraction and LA volume index. Associations between type 2 diabetes and LV mass index

were attenuated after adjustment for waist circumference. Interaction analyses showed that type 2 diabetes was particularly associated with a lower LV ejection fraction in individuals with prior CVD. A longer diabetes duration (per year) was associated with a 0.59 mL/m^2 higher LA volume index at follow-up but not with other markers of LV systolic and diastolic function.

Arterial stiffness

Greater stiffness of carotid, brachial, and femoral arteries, measured as lower distensibility coefficients, was associated with higher levels of LA volume index, LV mass index, and E/e′ (Table 3). After adjustment for age and sex, every $10^{-3} \cdot$ kPa^{-1} lower carotid artery distensibility coefficient was associated with a 0.31 mL/m^2 higher LA volume index and a 0.58 g/m$^{2.7}$ higher LV mass index. Every $10^{-3} \cdot$ kPa^{-1} lower brachial artery distensibility coefficient was associated with a 0.43 mL/m^2 higher LA volume index and a 0.09 higher E/e′. Every $10^{-3} \cdot$ kPa^{-1} lower femoral artery distensibility coefficient was associated with a 0.80 mL/m^2 higher LA volume index, a 0.91 g/m$^{2.7}$ higher LV mass index, and a 0.09 higher E/e′. These associations were independent of mean arterial pressure, except for associations with E/e′. After adjustment for baseline markers of LV diastolic dysfunction, $10^{-3} \cdot$ kPa^{-1} lower distensibility coefficients of carotid, brachial, and femoral arteries remained significantly associated

Table 3—*Markers of LV systolic and diastolic dysfunction at follow-up according to baseline arterial distensibility coefficients*

Outcome at follow-up according to variables in the model	Stiffness of carotid artery[a]	Stiffness of brachial artery	Stiffness of femoral artery[b]
LV ejection fraction (%)[c]			
Age and sex (model 1)	−0.11 (−0.40 to 0.18)	0.07 (−0.19 to 0.33)	−0.28 (−0.83 to 0.27)
Model 1 plus mean arterial pressure	−0.03 (−0.34 to 0.28)	0.13 (−0.13 to 0.39)	−0.16 (−0.73 to 0.42)
Model 1 plus baseline LV ejection fraction	−0.06 (−0.34 to 0.22)	0.02 (−0.23 to 0.27)	−0.21 (−0.74 to 0.33)
LA volume index (mL/m^2)[d]			
Age and sex (model 1)	0.31 (0.04–0.58)*	0.43 (0.17–0.68)*	0.80 (0.26–1.34)*
Model 1 plus mean arterial pressure	0.22 (−0.07 to 0.51)	0.36 (0.09–0.62)*	0.62 (0.06–1.18)*
Model 1 plus baseline LA volume index	0.29 (0.04–0.54)*	0.38 (0.14–0.62)*	0.73 (0.23–1.24)*
LV mass index (g/m$^{2.7}$)[e]			
Age and sex (model 1)	0.58 (0.27–0.89)*	0.24 (−0.07 to 0.55)	0.91 (0.31–1.52)*
Model 1 plus mean arterial pressure	0.54 (0.20–0.88)*	0.15 (−0.17 to 0.47)	0.71 (0.08–1.34)*
Model 1 plus baseline LV mass index	0.25 (−0.03 to 0.54)	0.10 (−0.17 to 0.37)	0.40 (−0.14 to 0.95)
E/e′			
Age and sex (model 1)	0.06 (−0.01 to 0.13)	0.09 (0.01–0.16)*	0.19 (0.04–0.35)*
Model 1 plus mean arterial pressure	0.03 (−0.05 to 0.11)	0.05 (−0.02 to 0.13)	0.12 (−0.04 to 0.28)
Model 1 plus baseline LA volume index	0.06 (−0.01 to 0.13)	0.08 (0.00–0.15)*	0.18 (0.03–0.34)*

Data are regression coefficients (95% CI). Missing data are as follows: [a]$n = 39$, [b]$n = 52$, [c]$n = 109$, [d]$n = 75$, [e]$n = 91$. *$P < 0.05$. All associations are shown per $10^{-3} \cdot$ kPa^{-1} lower distensibility coefficient.

with a 0.29, 0.38, and 0.73 mL/m^2 higher LA volume index, respectively.

Associations of femoral distensibility coefficients with markers of LV systolic and diastolic dysfunction were partly dependent on body weight and systolic blood pressure (Supplementary Data Table A). Lower compliance coefficients of brachial and femoral arteries, as well as a higher Young elastic modulus or pulse pressure, were similarly associated with more severe LV diastolic dysfunction (Supplementary Data Table B). A higher aortic augmentation index was the only marker of arterial stiffness that was significantly associated with LV systolic dysfunction: LV ejection fraction was 0.21% lower with every percentage point higher aortic augmentation index. Carotid-femoral

transit time was measured in a subset of 178 individuals, and LV ejection fraction was 0.14% lower with every second shorter carotid-femoral transit time, though not significantly (P = 0.13).

Combined influence of glucose status and arterial stiffness
There was no interaction between glucose status and arterial distensibility coefficients in their associations with LV systolic and diastolic dysfunction (P values for interaction >0.10). Figure 1 shows the associations of glucose status and SD scores of arterial stiffness (measured as femoral artery distensibility coefficients) with SD scores for all four markers of LV systolic and diastolic dysfunction, adjusted for age and sex. The right half of

each histogram shows that β values hardly changed if glucose status and arterial stiffness were combined in one model. For instance, the presence of type 2 diabetes was associated with a 0.26 SD lower LV ejection fraction after adjustment for age and sex. After subsequent adjustment for arterial stiffness, this β value remained similar, despite a loss of statistical significance: 0.25 (P = 0.08). Associations of glucose status with LA volume index, LV mass index, and E/e′ hardly changed either after adjustment for arterial stiffness. Furthermore, each SD higher arterial stiffness score was associated with a 0.14 SD higher LA volume index after adjustment for age and sex. After subsequent adjustment for glucose status, this β value was 0.12 (P = 0.02). Associations of arterial
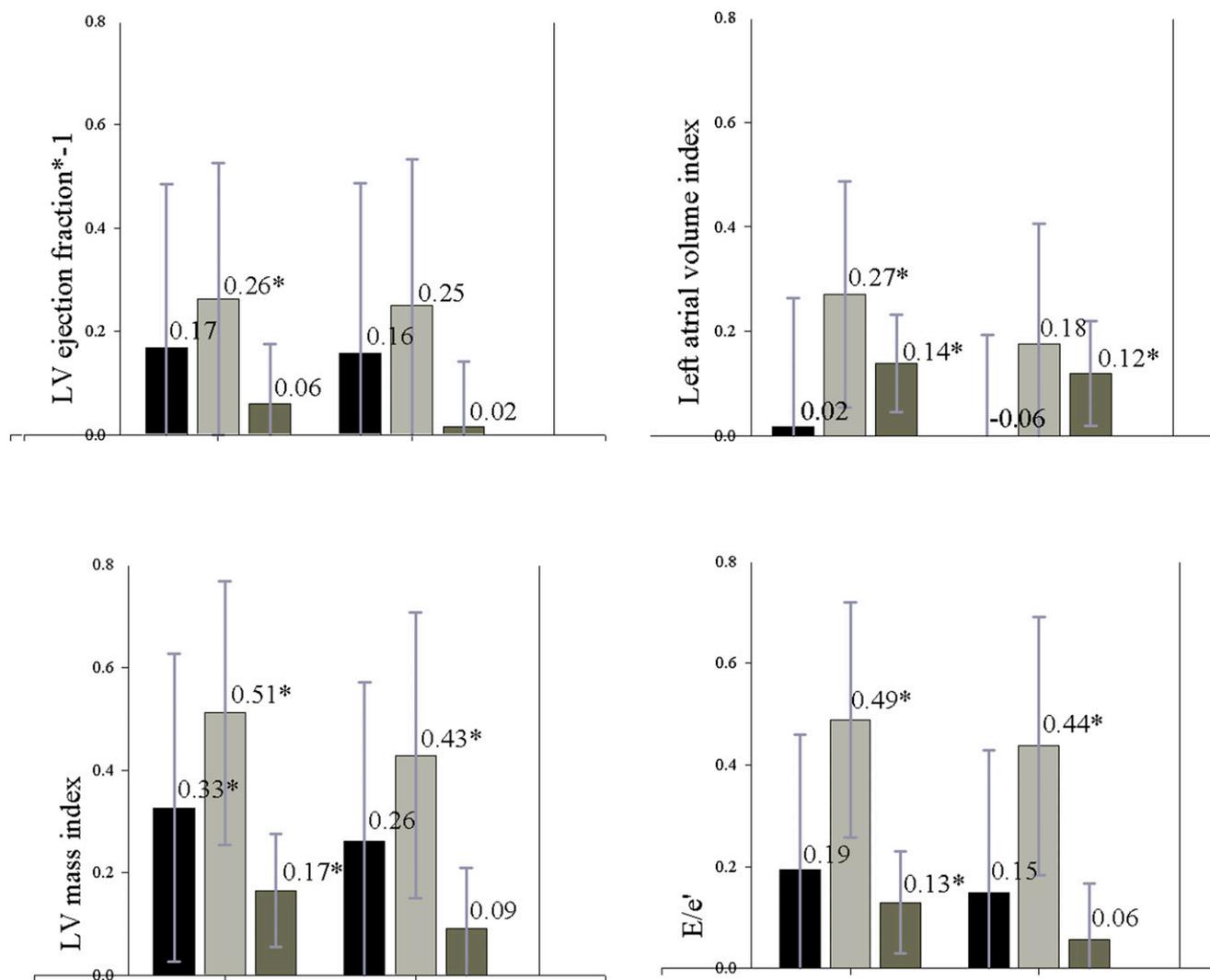
Figure 1—*Standardized associations of impaired glucose metabolism (black bars), type 2 diabetes (light gray bars), and lower femoral artery distensibility coefficients (dark gray bars) with markers of LV systolic and diastolic dysfunction, adjusted for age and sex (left half of each histogram) and, additionally, for each other (right half of each histogram). *P < 0.05.*

stiffness with LV mass index and E/e′ did not change significantly either after adjustment for glucose status, despite a loss of statistical significance.

There was no significant effect modification by sex, use of ACE inhibitors, or lipid-lowering, glucose-lowering, or blood pressure–lowering medication at follow-up on the associations of glucose status or arterial stiffness with markers of LV systolic and diastolic dysfunction ($P > 0.10$, data not shown). Therefore, analyses were not stratified.

CONCLUSIONS—This study shows that both glucose status and arterial distensibility coefficients were prospectively associated with more severe LV diastolic dysfunction. Furthermore, associations of glucose status and arterial stiffness with LV diastolic dysfunction were largely independent of each other and indicated a deterioration of LV diastolic dysfunction compared with baseline.

Strengths include the population-based design and comprehensive assessment of glucose status, arterial stiffness, and LV systolic and diastolic dysfunction. These data provide a unique insight into many different aspects of arterial stiffness and their influence on LV systolic and diastolic dysfunction. A limitation is the absence of a tissue Doppler assessment at baseline. LV diastolic dysfunction at baseline was therefore based on LA volume index only, and this might have been subject to some misclassification. Furthermore, differences between attendees and nonattendees suggest that a "healthy cohort bias" may have occurred in this study. We also had missing data for some echocardiographic markers, predominantly in individuals with high BMI. This most likely led to an underestimation of actual associations.

Glucose status
Our findings that LV systolic and diastolic dysfunction was more severe in type 2 diabetic patients than in individuals with NGM are in line with previous data reporting associations between glucose metabolism and LV systolic and diastolic dysfunction (20,21). The type 2 diabetes–associated LV diastolic dysfunction at follow-up could not completely be explained by an already more severe LV diastolic dysfunction at baseline. These results imply that LV diastolic dysfunction deteriorates more in individuals with than in those without type 2 diabetes. There was a trend toward more severe LV systolic and diastolic dysfunction in

individuals with IGM as well, but this was not statistically significant. Individuals with a longer duration of type 2 diabetes appeared to have a higher LA volume index at follow-up.

Arterial stiffness
LV diastolic dysfunction was more severe with greater arterial stiffness. Peripheral markers of arterial stiffness, like arterial distensibility and compliance coefficients, and brachial pulse pressure were most consistently associated with markers of LV diastolic dysfunction. Associations of arterial distensibility coefficients with LV diastolic dysfunction were not due to elevated blood pressure, since adjustment for mean arterial pressure only resulted in a small reduction of the associations. Associations of arterial distensibility coefficients with LA volume index and E/e′ at follow-up were largely independent of baseline LA volume index. This might imply that *1*) arterial stiffness precedes deterioration of LV diastolic dysfunction or *2*) stiffening of arteries and LV walls occurs simultaneously. The first might be due to arterial wave reflections that lead to an increased LV load and decreased coronary perfusion (6). The second might be due to coinciding structural changes in arterial and LV walls (9). In the current study, wave reflections seemed especially harmful to LV systolic function, since augmentation index was the only marker of arterial stiffness that was significantly associated with LV ejection fraction, followed by carotid-femoral transit time. LV diastolic dysfunction seemed to be more coherent to peripheral artery stiffening than to central artery stiffening. This might support the second theory: that stiffening of arteries and LV walls occurs simultaneously. Nonetheless, our findings need to be confirmed in other longitudinal studies.

Combined influence of glucose status and arterial stiffness
Type 2 diabetes and arterial stiffness were largely independently associated with LV systolic and diastolic dysfunction in the current study. More severe LV systolic and diastolic dysfunction in type 2 diabetes therefore cannot be explained or can or just partly be explained by increased arterial stiffness. Other mechanisms that might play a role in the development of LV systolic and diastolic dysfunction in type 2 diabetes include an altered cardiac metabolism or increased stiffening of the LV due to myocardial fibrosis or an elevated cardiomyocyte resting tension (11,22–24).

This might be reflected by the lowered associations between type 2 diabetes and markers of LV systolic and diastolic dysfunction after adjustment for HbA$_{1c}$. Overweight and obesity are known to be associated with a higher LV mass index, and indeed, waist circumference seemed to play a role in type 2 diabetes–related higher LV mass index (25). LV systolic function was particularly worsened in type 2 diabetic patients with prior cardiovascular disease. Since individuals with type 2 diabetes already had a worse cardiovascular profile at baseline, the influence of changes in cardiovascular risk factors earlier in life on LV systolic and diastolic dysfunction may also be worth examining.

To conclude, the presence of type 2 diabetes and the presence of arterial stiffness are both associated with deterioration of LV diastolic dysfunction. It is likely that type 2 diabetes and arterial stiffness relate to LV diastolic dysfunction through different pathways, since these associations were independent of each other. A better understanding of the mechanisms behind those different pathways in changes in LV diastolic dysfunction could help identify targets for prevention of heart failure.

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