Right Ventricular Involvement in Diabetic Cardiomyopathy

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OBJECTIVE—To compare magnetic resonance imaging-derived right ventricular (RV) dimensions and function between men with type 2 diabetes and healthy subjects, and to relate these parameters to left ventricular (LV) dimensions and function.

RESEARCH DESIGN AND METHODS—RV and LV volumes and functions were assessed in 78 men with uncomplicated type 2 diabetes and 28 healthy men within the same range of age using magnetic resonance imaging. Steady-state free precession sequences were used to assess ventricular dimensions. Flow velocity mapping across the pulmonary valve and tricuspid valve was used to assess RV outflow and diastolic filling patterns, respectively. Univariate general linear models were used for statistical analyses.

RESULTS—RV end-diastolic volume was significantly decreased in patients compared with healthy subjects after adjustment for BMI and pulse pressure (177 ± 28 mL vs. 197 ± 47 mL, $P < 0.01$). RV systolic function was impaired: peak ejection rate across the pulmonary valve was decreased (433 ± 54 mL/s vs. 463 ± 71 mL/s, $P < 0.01$) and pulmonary flow acceleration time was longer (124 ± 17 ms vs. 115 ± 25 ms, $P < 0.05$). Indexes of RV diastolic function were impaired: peak filling rate and peak deceleration gradient of the early filling phase were 315 ± 63 mL/s vs. 356 ± 90 mL/s ($P < 0.01$) and 2.3 ± 0.8 mL/s$^2 \times 10^{-3}$ vs. 2.8 ± 0.8 mL/s$^2 \times 10^{-3}$ ($P < 0.01$), respectively. All RV parameters were strongly associated with its corresponding LV parameter ($P < 0.001$).

CONCLUSIONS—Diabetic cardiomyopathy affects the right ventricle, as demonstrated by RV remodeling and impaired systolic and diastolic functions in men with type 2 diabetes, in a similar manner as changes in LV dimensions and functions. These observations suggest that RV impairment might be a component of the diabetic cardiomyopathy phenotype.

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Cardiovascular disease is one of the major adverse consequences of type 2 diabetes. Patients with type 2 diabetes have an increased cardiovascular mortality rate (1). Even in the absence of significant coronary artery disease and hypertension, subclinical left ventricular (LV) dysfunction presents in type 2 diabetes (2). This so-called diabetic cardiomyopathy has a complex and multifactorial pathogenesis. Atherosclerosis, subclinical microinfarctions, mitochondrial dysfunction, and lipotoxicity all have been proposed as contributors to diabetic cardiomyopathy. Furthermore, it has been recognized that deposition of advanced glycation end products, caused by long-standing hyperglycemia, affects ventricular stiffness (3). The formation of advanced glycation end products yields fibrosis by cross-linking collagen (4), thus increasing myocardial stiffness. This may lead to a decreased LV end-diastolic volume and impaired subclinical LV function (5–7).

All proposed mechanisms leading to LV impairment in type 2 diabetes are systemic changes and therefore also might hamper right ventricular (RV) function. RV involvement in diabetic cardiomyopathy might be of importance because the right ventricle has a substantial contribution to overall myocardial contractility. RV function has proven to be of importance for patient risk stratification in heart failure (8) and for prediction of development of atrial fibrillation (9). In general, RV dysfunction and fibrosis are associated with lethal ventricular arrhythmias, sudden death, exercise limitation, and impaired RV cardiac output (10). In addition, the prevalence of cardiac conduction abnormalities is increased in diabetic patients (11).

However, only limited data exist on RV involvement in type 2 diabetes. Whereas animal studies have shown that dysfunction of the right ventricle might play a role in diabetic cardiomyopathy (12), the right ventricle is largely overlooked in human studies. Only a few echocardiographic studies discuss the right ventricle in diabetes (13–17). These studies were limited by inclusion of patients with cardiovascular diabetes-related complications (13–15,17), and study populations consisted partially (13,14) or entirely of type 1 diabetic patients (16). Moreover, none of these studies reported RV volumes.

The right ventricle is a difficult structure from which to obtain reproducible echocardiographic signals because of the irregular geometrical shape and the anterior position within the thorax. Without mathematical modeling, conventional two-dimensional echo techniques commonly underestimate or overestimate the true size of the adult right ventricle (18). Cardiovascular magnetic resonance imaging (MRI) has become the reference standard for the assessment of RV function and volumes because good reproducibility has been shown (19,20).

To our knowledge, no studies to date have evaluated volumetric as well as systolic and diastolic functional involvement of the right ventricle in uncomplicated type 2 diabetes compared with healthy subjects assessed by MRI. Accordingly, the purpose of the current study was to compare MRI-derived RV dimensions and systolic and diastolic function between

well-controlled uncomplicated type 2 diabetic patients and healthy subjects, in relation to LV dimensions and function.

RESEARCH DESIGN AND METHODS

Subjects

Data were derived from the PIRAMID trial (Pioglitazone Influence on tRiglyceride Accumulation in the Myocardium In Diabetes), in which participants were randomized to pioglitazone or metformin after baseline measurements to study the effects of these agents on cardiac function and metabolism (21). This prospective trial included a total of 78 men with uncomplicated, well-controlled type 2 diabetes of short duration and with verified absence of cardiac ischemia. In the PIRAMID trial, only men were included because in women hormonal status and use of contraceptives have been shown to influence metabolism. Inclusion and exclusion criteria have been reported previously (21). In summary, the inclusion criteria were age 45–65 years; type 2 diabetes diagnosed according to the World Health Organization criteria (22) and treated with sulfonylurea derivates and/or metformin in stable doses; glycated hemoglobin 6.5–8.5%; and sitting blood pressure <150/85 mmHg, with or without use of antihypertensive medication. Exclusion criteria included known cardiovascular disease or diabetes-related complications, and contraindications for MRI. In addition, to exclude inducible myocardial ischemia or silent infarction caused by coronary artery disease, high-dose dobutamine stress echocardiography was performed.

When patients were eligible for inclusion in the PIRAMID trial, they entered a 10-week run-in period during which their previous blood glucose-lowering agents (metformin monotherapy, 39.8%; sulfonylurea monotherapy, 25.6%; and metformin and sulfonylurea combination therapy, 34.6%) were washed out. They were transferred to glimepiride monotherapy, which was titrated until a stable dose was reached. MRI assessments were made after this run-in period.

Thirty healthy male control subjects were recruited. Control subjects were included if they met the following criteria: age 45–65 years and no known acute or chronic disease based on medical history, physical examination, and standard laboratory tests (blood counts, fasting blood glucose, lipids, serum creatinine, liver enzymes, and electrocardiogram). Exclusion

criteria included hypertension, chronic use of any drug, substance abuse, and impaired glucose tolerance, as excluded by a 75-g oral glucose test (23). Written informed consent was obtained from all participants. This study was conducted in accordance with the ethics principles of the Declaration of Helsinki and was consistent with Good Clinical Practice guidelines and applicable local regulatory requirements.

Cardiovascular MRI protocol

All participants underwent blood sampling and MRI scanning for assessment of heart function after an overnight fast. All MRI studies were performed with a 1.5-T whole-body MRI scanner (Gyroscan ACS/NT15; Philips, Best, the Netherlands), with subjects in the supine position at rest. Image postprocessing was performed with software packages developed in-house (MASS and FLOW; Medis, Leiden, the Netherlands).

To assess dimensions and systolic function of the right ventricle and left ventricle, the entire heart was imaged in short-axis orientation using electrocardiographically gated breath-hold balanced steady-state free precession imaging. Endocardial contours of the right ventricle and left ventricle were manually drawn in end-diastolic phase and end-systolic phase. The papillary muscles, trabeculae carnae, trabecula septomarginalis (moderator band), and RV outflow tract were included in the RV volume (Fig. 1*A* and *B*). Imaging parameters were as follows: repetition time = 3.4 ms; echo time =1.7 ms; flip-angle = 35°; slice thickness = 10 mm; slice gap = 0 mm; field of view = 400 × 400 mm; and reconstructed matrix size = 256 × 256. Dimensions were end-diastolic volume (EDV) and end-systolic volume (ESV) for the right ventricle and left ventricle. Functional parameters were derived as follows for each ventricle: stroke volume (SV) was calculated by subtracting the ESV from the EDV, cardiac output was calculated by multiplying the SV by the heart rate, and ejection fraction was calculated by dividing the SV by the EDV and multiplying by 100. Because RV afterload may affect RV function, we assessed the peak ejection rate and pulmonary flow acceleration time. We therefore performed an electrocardiographically gated gradient echo sequence with velocity encoding to measure blood flow across the pulmonary valve for determination of RV outflow. The peak ejection rate was defined as the highest velocity. The pulmonary flow acceleration time was

defined as the time from the onset of flow to the peak ejection rate (Fig. 1*C*). The following imaging parameters were used: repetition time = 6.5 ms; echo time = 1 ms; flip-angle = 20°; slice thickness = 8 mm; field of view = 350 × 350 mm; matrix size = 256 × 256; echo planar imaging-factor = 3; velocity encoding gradient = 150 cm/s; and scan percentage = 80%.

To determine RV and LV diastolic functions, an electrocardiographically gated gradient echo sequence with velocity encoding was performed to measure blood flow across the tricuspid valve and mitral valve, respectively. Similar imaging parameters as described for the pulmonary valve were used, with the exception of the velocity encoding gradient (100 cm/s). For the left ventricle, no echo planar imaging-factor was used. Diastolic parameters included peak filling rates of the early filling phase (E) and atrial contraction (A), and their ratio (E/A). Also, the peak deceleration gradient of the E (hereafter referred to as E deceleration peak) was calculated (Fig. 1*D*).

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 17.0 (SPSS, Chicago, IL). Data are expressed as mean ± SD when normally distributed; data not normally distributed are expressed as median (interquartile range). Non-normally distributed data were log-transformed, and unpaired *t* tests (or, when appropriate, nonparametric tests) were used for comparisons. A univariate general linear model was used to compare RV dimensions and function. The RV parameters were adjusted for BMI and pulse pressure. Diabetic state was entered as fixed factor and BMI and pulse pressure were entered as covariates. Associations between RV parameters and the corresponding LV parameters were tested using univariate general linear models, adjusted for diabetic state. $P < 0.05$ was considered statistically significant.

RESULTS—Parts of these data were previously used for publication in subgroups (6,7,24). One healthy subject was excluded for the current study because of poor scan quality. Another healthy subject was excluded because of a coincidental finding, namely an aneurysmatic focal abnormality of the left ventricle. Patient characteristics are shown in Table 1.

Mean BMI was higher in patients compared with controls (28.7 ± 3.5 kg/m² vs. 26.8 ± 2.6 kg/m², $P < 0.01$). Mean systolic blood pressure was within normal
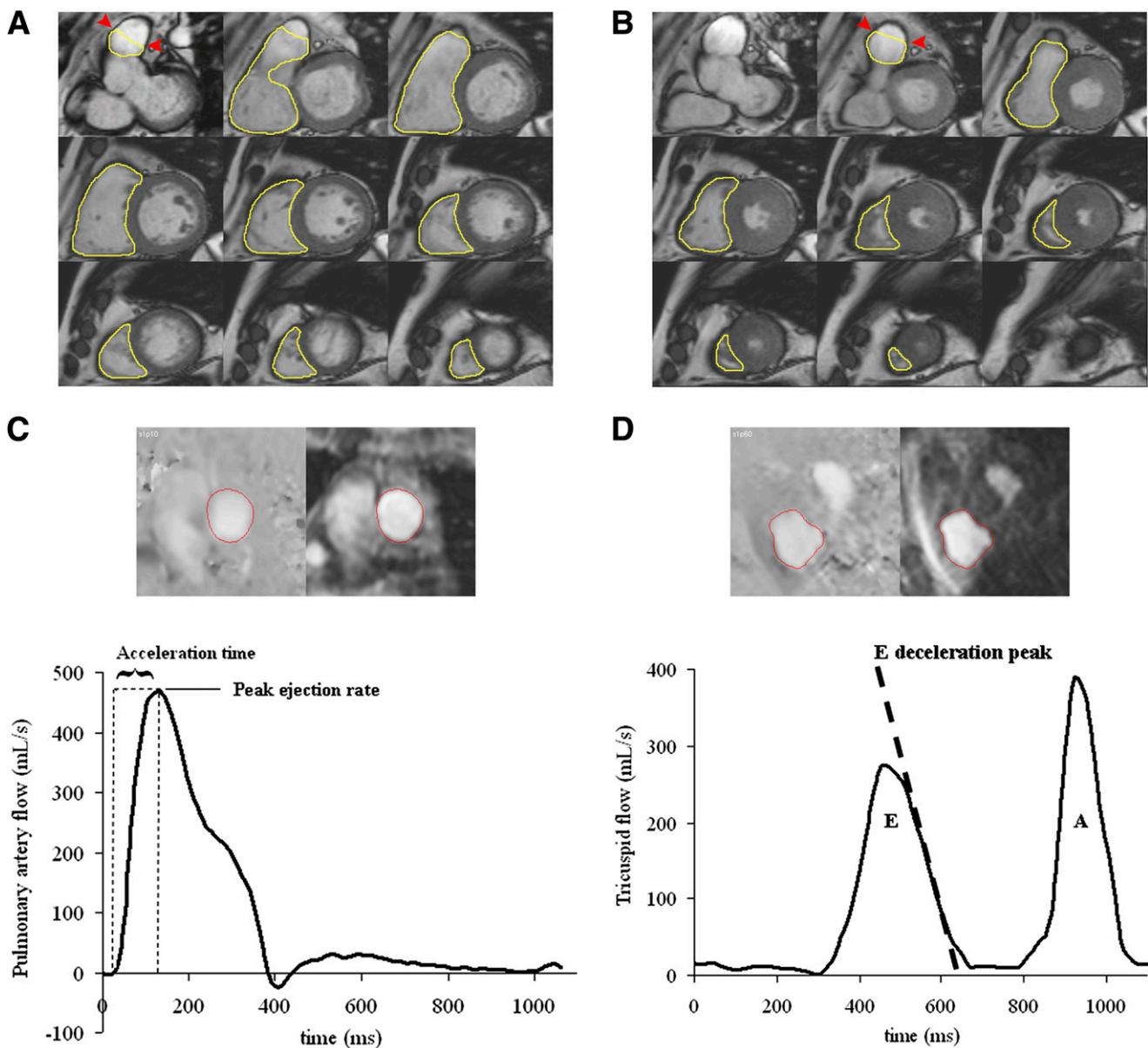
Figure 1—*Example of MRI analyses of the right ventricle. Endocardial contour drawing of the right ventricle in end-diastolic (A) and end-systolic phases (B). The RV outflow tract ends at the pulmonary valves (arrowheads). C: Phase contrast velocity map (left) and modulus image (right) across the pulmonary valve in one cardiac phase to assess pulmonary flow pattern. D: Phase contrast velocity map (left) and modulus image (right) across the tricuspid valve in one cardiac phase to assess diastolic filling pattern. (A high-quality color representation of this figure is available in the online issue.)*

range, although it was higher in patients compared with controls (128 ± 12 mmHg vs. 116 ± 10 mmHg, $P < 0.001$). Pulse pressure (systolic blood pressure–diastolic blood pressure) was higher in patients (52 ± 10 mmHg vs. 46 ± 9 mmHg, $P < 0.01$). Smoking habits and alcohol use did not differ between the two groups. Alcohol abuse was an exclusion criterion. Healthy subjects performed physical exercise more regularly. In 73 patients, microalbuminuria was assessed at screening (before the glimepiride run-in period) either by 24-h urine collection or by assessing the albumin/creatinine ratio in a spot sample. Thirteen of these patients had microalbuminuria (>30 mg in 24-h urine collection or albumin/creatinine ratio > 2.5 in a spot sample).

RV MRI parameters
RV dimensions and function data are shown in Table 2. Because BMI differed between the groups, parameters were adjusted for BMI. In addition, adjustments were made for pulse pressure. RV EDV was decreased in patients compared with controls (177 ± 28 mL vs. 197 ± 47 mL,

$P < 0.01$) (Fig. 2A). A similar difference was observed for the RV ESV (83 ± 18 mL vs. 93 ± 28 mL, $P < 0.05$). All differences remained significant after adjustment for BMI and pulse pressure.

Several parameters of systolic function were impaired in patients. Although RV ejection fraction was preserved, RV SV (95 ± 15 vs. 104 ± 21, $P < 0.05$) and peak ejection rate across the pulmonary valve (433 ± 54 vs. 463 ± 71 mL/s, $P < 0.05$) were decreased, and pulmonary flow acceleration time was longer (124 ± 17 vs. 115 ± 25 ms, $P < 0.05$) in patients as

Table 1—Clinical and biochemical characteristics

Characteristics	Healthy subjects $n = 28$	Type 2 diabetic patients $n = 78$
Clinical		
Age (years)	54.5 ± 7.7	56.5 ± 5.6
BMI (kg/m^2)	26.8 ± 2.6	28.7 ± 3.5*
Waist circumference (cm)	100 ± 9	104 ± 10*
Systolic blood pressure (mmHg)	116 ± 10	128 ± 12*
Diastolic blood pressure (mmHg)	73 ± 8	76 ± 7
Pulse pressure (mmHg)	46 ± 9	52 ± 10*
Heart rate (bpm)	59 (53–63)	64 (60–70)*
Time since diagnosis diabetes (years)	NA	4 (2–6)
Alcoholic consumers (*n*)†	20 (80)	58 (74)
Smokers (*n*)†	4 (16)	17 (22)
Physically active (*n*)†	24 (96)	50 (64)*
Biochemical		
Glycated hemoglobin (%)	5.4 ± 0.2	7.1 ± 1.0*
Plasma glucose (mmol/L)	5.3 (5.0–5.5)	8.3 (7.4–9.8)*
Plasma insulin (pmol/L)	36 (24–51)	66 (37–100)*
Total cholesterol (mmol/L)	5.3 ± 0.7	4.7 ± 1.0*
HDL cholesterol (mmol/L)	1.4 (1.2–1.6)	1.1 (0.9–1.3)*
LDL cholesterol (mmol/L)	3.4 ± 0.64	2.7 ± 0.78*
Plasma triglycerides (mmol/L)	0.9 (0.7–1.2)	1.5 (1.0–2.2)*
Nonesterified fatty acids (mmol/L)	0.4 ± 0.2	0.5 ± 0.2

Data are mean ± SD, median (interquartile range), or *n* (%). NA, not applicable. *$P < 0.05$. †Data are missing for three healthy subjects.

compared with healthy subjects after adjustment for BMI and pulse pressure.

Moreover, RV diastolic function was impaired in patients as compared with healthy subjects. RV E peak filling rate, RV E deceleration peak, and RV E/A were 315 ± 63 mL/s vs. 356 ± 90 mL/s ($P < 0.05$), 2.3 ± 0.8 mL/s^2 × 10^{-3} vs. 2.8 ± 0.8 mL/s^2 x 10^{-3} ($P < 0.05$), and 0.85 (0.73–1.06) vs. 0.95 (0.82–1.28) ($P < 0.05$), respectively (Fig. 2*B*). The RV E peak filling rate and RV E deceleration peak remained significantly lower in patients after adjustment for BMI and pulse pressure. The E/A peak remained lower in patients after adjustment for pulse pressure ($P = 0.041$) but tended to be significant after adjusting for BMI ($P = 0.073$).

Table 2—MRI study parameters

Parameters	Healthy subjects $n = 28$	Type 2 diabetic patients $n = 78$
RV dimensions		
End-diastolic volume (mL)	197 ± 47	177 ± 28*†
End-systolic volume (mL)	93 ± 28	83 ± 18*†
RV systolic function		
Stroke volume (mL)	104 ± 21	95 ± 15*†
Cardiac output (mL/min)	6,060 (5,432–6,661)	6,227 (5,524–7,091)
Ejection fraction (%)	53 ± 4	54 ± 5
Peak ejection rate (mL/s)	463 ± 71	433 ± 54*†
Pulmonary flow acceleration time (ms)	115 ± 25	124 ± 17†
RV diastolic function		
E peak filling rate (mL/s)	356 ± 90	315 ± 63*†
E deceleration peak (mL/s^2 × 10^{-3})	2.8 ± 0.8	2.3 ± 0.8*†
A peak filling rate (mL/s)	349 ± 60	353 ± 68
E/A	0.95 (0.82–1.28)	0.85 (0.73–1.06)*

Data are mean ± SD or median (interquartile range). *$P < 0.05$ unadjusted for pulse pressure and BMI. †$P < 0.05$ after adjustment for pulse pressure and BMI.

Comparison of RV parameters between patients and healthy subjects could not be adjusted reliably for physical exercise because only one healthy subject did not exercise. When RV parameters were compared between physically active and inactive patients, no statistically significant differences were encountered. In addition, when RV parameters were compared between patients with and without micro-albuminuria, no statistically significant differences were encountered. Therefore, we think that physical exercise and micro-albuminuria cannot explain the RV impairment in our diabetic population.

LV MRI parameters
LV EDV and LV ESV were lower in patients compared with controls (respectively, 156 ± 25 mL vs. 176 ± 36 mL, $P < 0.01$; and 59 [52–71] mL vs. 72 [61–81] mL, $P < 0.01$) (Fig. 2*A*). LV diastolic function was impaired in a similar manner as for the right ventricle. LV E peak filling rate, LV E deceleration peak, and LV E/A were lower compared with healthy subjects (respectively, 417 ± 84 mL/s vs. 484 ± 112 mL/s, $P < 0.01$; 3.4 [2.9–4.0] mL/s^2 × 10^{-3} vs. 4.6 (2.8–5.2) mL/s^2 × 10^{-3}, $P < 0.01$; and 1.04 ± 0.25 vs. 1.23 ± 0.35; $P < 0.01$) (Fig. 2*B*). All differences remained statistically significant after adjustment for BMI and pulse pressure.

All RV parameters were strongly associated with their corresponding LV parameters, unconfounded by diabetic state. Corresponding unstandardized β values were: EDV = 0.753; ESV = 0.508; SV = 1.034; cardiac output = 0.994; ejection fraction = 0.618; E peak filling rate = 0.847; E deceleration peak = 0.602; A peak filling rate = 0.353; and E/A peak = 0.497 (all $P < 0.001$). Moreover, there were no significant interactions with diabetic state.

CONCLUSIONS—The main finding in the current study is that RV dimensions and function are impaired in men with uncomplicated type 2 diabetes, similar to the left ventricle. This suggests that both ventricles are influenced by the metabolic abnormalities characterizing diabetes. Although RV function has been evaluated in several diseases, including sepsis (25), pulmonary embolism (26), rheumatoid arthritis (27), and idiopathic dilated cardiomyopathy (28), most studies discussing diabetic cardiomyopathy have focused on the left ventricle only.

Impairment of RV systolic function, measured by tricuspid annular plane
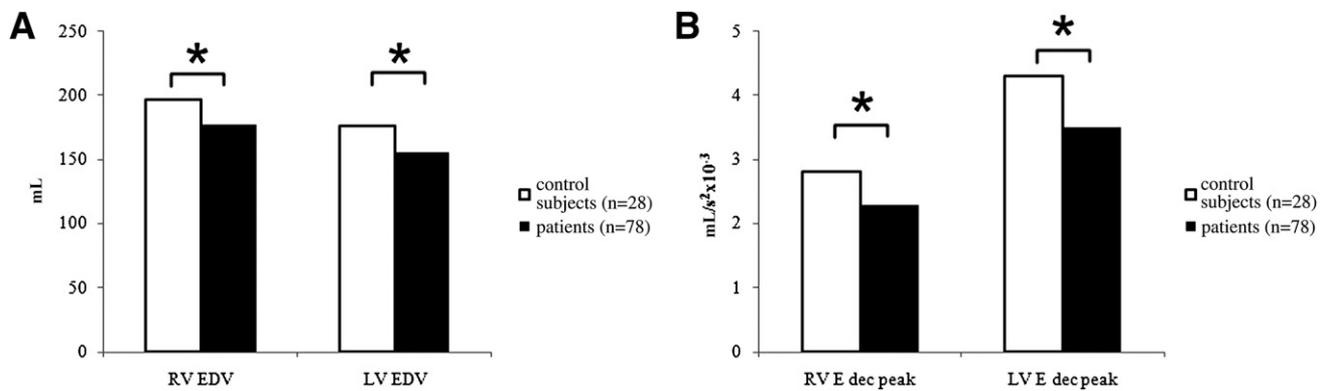
Figure 2—*End-diastolic volume and E deceleration peak of the right ventricle and left ventricle. RV end-diastolic volume was decreased in type 2 diabetic patients compared with healthy controls, similar to the left ventricle* (A). *Likewise, the E deceleration peak was impaired in both ventricles* (B). *P < 0.05. E dec peak, E deceleration peak.

systolic excursion, has been reported in Zucker diabetic fatty rats (12). In our diabetic population, RV systolic function as measured by the peak ejection rate and the acceleration time of the pulmonary artery flow was impaired, whereas RV ejection fraction was preserved and did not differ between groups. This pattern of pulmonary artery flow is characteristic for pulmonary hypertension (29) and may reflect an increase in RV afterload. In diabetes, microangiopathy of the alveolar–capillary network in the lung (30) may cause increased RV afterload and, consequently, RV systolic dysfunction may occur.

In the current study, parameters of RV diastolic function were impaired in patients compared with healthy subjects. RV E deceleration peak and RV E peak filling rate were lower in patients, indicating impaired myocardial relaxation and/or increased myocardial stiffness, which are the hallmarks of diastolic dysfunction (31). Furthermore, RV EDV was decreased in patients.

In the left ventricle, diffuse interstitial fibrosis and collagen deposition within the myocardium are the primary structural changes observed in diabetic cardiomyopathy and eventually lead to impaired ventricular relaxation (32,33). In addition, deposition of advanced glycation end products and increased cardiomyocyte resting tension are important mechanisms in diabetic cardiomyopathy causing diastolic stiffness (33). Because we observed reduced parameters of diastolic function and reduced EDV of the right ventricle in addition to the left ventricle, it may be hypothesized that the mechanisms responsible for LV stiffness also affect the right ventricle. Alternatively, the present changes could be the consequence of left ventricle changes.

A possible explanation for the coexistence of RV and LV abnormalities in diabetic patients may be that subendocardial fibers are interwoven between the right ventricle and the left ventricle in the interventricular septum (34). Therefore, it may be suggested that the diffuse fibrotic processes that take place in diabetes could affect the function of both ventricles. Dibble et al. (35) reported an independent association between septal function and RV systolic function. However, they did not investigate the association between septal function and RV diastolic function.

Effects on the right ventricle in diabetic cardiomyopathy have not been investigated extensively, and the few human studies focusing explicitly on this subject have used various techniques. Previous studies reporting on impaired RV diastolic function in diabetic patients (13–17) were limited by the inclusion of patients with diabetes-related cardiovascular complications and/or inclusion of type 1 diabetic patients. None of these studies has evaluated RV volumes to study geometrical changes of the right ventricle in diabetes. Therefore, besides inclusion of well-controlled uncomplicated type 2 diabetic patients, a strength of this study is the combination of RV volumetric and functional assessment by MRI to investigate RV involvement in diabetic cardiomyopathy.

Some limitations of this study need to be addressed. First, only men were included. Exclusion of women limits the generalizability of the current study and, therefore, further studies are needed to extend our findings to the female population. Second, the rather small number of patients and healthy subjects might cause underpowering of the study. Our findings possibly are hampered by the relatively

small study population and therefore need to be interpreted with caution.

In conclusion, diabetic cardiomyopathy affects the right ventricle, as demonstrated by RV remodeling and impaired systolic and diastolic function in men with type 2 diabetes, similar to changes in LV dimensions and function. These observations suggest that RV impairment might be a component of the diabetic cardiomyopathy phenotype.

wrote the manuscript. R.L.W., R.W.v.d.M., and L.J.R. collected data. R.L.W., R.W.v.d.M., and H.J.L. analyzed and interpreted data. H.J.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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