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Magnetic Resonance Assessment of Aortic Pulse Wave Velocity, Aortic Distensibility, and Cardiac Function in Uncomplicated Type 2 Diabetes Mellitus

Rutger W. van der Meer, MD,[1] Michaela Diamant, MD, PhD,[2] Jos J. M. Westenberg, PhD,[1] Joost Doornbos, PhD,[1] Jeroen J. Bax, MD, PhD,[3] Albert de Roos, MD, PhD,[1] and **Hildo J. Lamb, MD, PhD[1]**

Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands[1]
Department of Endocrinology/Diabetes Center, VU University Medical Center, Amsterdam, The Netherlands[2]
Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands[3]

ABSTRACT

Background: **Type 2 diabetes mellitus (DM2) may augment arterial stiffening and thereby modulates left ventricular (LV) function. Cardiovascular magnetic resonance (CMR) is well suited to assess aortic pulse wave velocity (PWV) and aortic distensibility, both markers of arterial stiffness, without the use of geometric assumptions. Furthermore, CMR is a reliable method for assessing left ventricular (LV) function. The purpose of this study was to assess LV function, PWV, and aortic distensibility in patients with DM2 using MR.** ***Methods:*** **Fourteen patients with well controlled, uncomplicated DM2, and 16 age and gender matched healthy subjects were included. PWV was calculated based on MR velocity mapping at two predefined aortic locations. Aortic distensibility was measured in the mid ascending aorta. LV volumes were measured by fast gradient-echo imaging to assess systolic function. Furthermore, mitral inflow was measured by MR velocity mapping to assess diastolic LV function.** ***Results:*** **Mean PWV was higher in patients as compared to healthy subjects (6.83 ± 1.60 m/s vs. 5.65 ± 0.75 m/s, $p < 0.05$). This difference was independent of blood pressure. PWV correlated significantly ($p < 0.05$) with fasting plasma glucose and insulin levels. Aortic distensibility was lower in patients as compared to healthy subjects ($4.50 \times 10^{-3} \pm 2.24 \times 10^{-3}$ mmHg^{-1} vs. $7.42 \times 10^{-3} \pm 3.34 \times 10^{-3}$ mmHg^{-1}, $p < 0.05$). Distensibility correlated negatively with PWV and positively with LV diastolic function ($p < 0.05$).** ***Conclusion:*** **A combined CMR assessment of aortic PWV, aortic distensibility, and heart function reveals abnormal PWV and distensibility in patients with DM2, independent of blood pressure. Furthermore, aortic distensibility correlates with diastolic left ventricular function.**

INTRODUCTION

Type 2 diabetes mellitus (DM2) is rapidly becoming a worldwide epidemic (1) and is associated with high morbidity and mortality due to cardiovascular complications (2). Many mechanisms have been proposed to be the underlying cause of the deleterious effects of diabetes on the cardiovascular system. It has been shown that DM2 may augment arterial stiffening and thereby modulates left ventricular (LV) function, coronary blood flow and arterial function throughout the cardiovascular system (3–5). A strong and independent association between increased arterial stiffness and the presence of coronary artery disease has been demonstrated (6).

As arterial stiffness has become established as a cardiovascular risk factor in its own right (3, 7–9), there is a need for a simple, reliable, noninvasive method of detecting early disturbances in arterial stiffness at a time when therapeutic intervention can be most beneficial (10). Arterial stiffness can be estimated from area or diameter changes of the artery related to the distending pressure (distensibility) or by measuring the pulse wave velocity (PWV).

Currently, ultrasound and tonometry are the most often used methods to assess pulse wave velocity by measuring the pulse wave at 2 points in the vasculature and by estimating the path

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Correspondence to:
RW van der Meer
Department of Radiology (C2-S)
Leiden University Medical Center
Albinusdreef 2, 2300 RC Leiden
The Netherlands
tel: 0031 71 5261322; fax: 0031 71 5248256
email: r.w.van_der_meer@lumc.nl

length of the pulse wave (PWV = distance/time in m/s). However, body habitus and age-related vessel tortuosity may affect estimation of the path length when the distance of the pulse wave is estimated over the body surface (11).

Cardiovascular magnetic resonance (CMR) is well suited to assess aortic PWV (12, 13). CMR is a noninvasive technique that allows direct imaging of the thoracic and abdominal aorta without the use of geometric assumptions. In contrast to ultrasound and tonometry, CMR allows the accurate and direct measurement of the path length of pulse waves in the proximal and distal aorta, even in the presence of a tortuous vessel, which is a major advantage over other techniques (14). Furthermore, CMR has proven to be a reliable and accurate method for assessing LV function (15, 16). Although previous studies with nonCMR techniques have demonstrated the pathophysiological changes in aortic distensibility, PWV, and cardiac function in patients with DM2, there are no previous reports on the combined evaluation of aortic and cardiac function using a comprehensive CMR protocol.

Accordingly, the purpose of the present study was to combine the assessment of aortic PWV, aortic distensibility, and LV function using CMR in patients with DM2 in one comprehensive evaluation.

MATERIALS AND METHODS

Study subjects

Fourteen patients (11 male and 3 female) with well controlled, uncomplicated DM2 and 16 age and gender matched healthy subjects were studied (Table 1). Consecutive patients were selected from general practices after approval of their physicians. Selection criteria were DM2 of short duration (<5 years, diagnosed according to WHO criteria) (17), no signs or symptoms or history of cardiovascular disease, a normal electrocardiogram (ECG), blood pressure (BP) <150/90 mm Hg, good metabolic control (glycated hemoglobin [HbA1c] <7.0%), no use of drugs other than sulfonylureas and/or metformin and no diabetic complications including albuminuria, retinopathy, and neuropathy. Healthy subjects had no history or clinical evidence of cardiovascular disease and diabetes (screening visits consisted of a medical history, physical examination, an ECG and screening laboratory tests such as fasting plasma glucose, lipids and HbA1c). HbA1c was determined by HPLC after hemolysis (reference range 4.3–6.3% in nondiabetic subjects; Bio Rad, Richmond, California, USA). C-reactive protein (CRP) levels were measured using an enzyme linked immunosorbent assay (CRP EIA HS assay, [Kordia, Leiden, The Netherlands]; normal range 0.2–6.0 mg/L).

Table 1. Patient characteristics

	Patients (n = 14)	Healthy Subjects (n = 16)
Male/Female (n)	11/3	12/4
Age (y)	55 (8)	55 (7)
Duration of diabetes mellitus 2 (months)	26 (22)	NA
Body Mass Index (kg/m^2)	26.0 (1.8)*	24.6 (1.3)
Systolic blood pressure (mm Hg)	133 (15)	127 (12)
Diastolic blood pressure (mm Hg)	79 (8)	75 (8)
Pulse Pressure (mm Hg)	54 (10)	52 (8)
Mean arterial pressure (mm Hg)	97 (10)	92 (9)
Heart rate (bpm)	70 (10)	63 (11)
Fasting plasma glucose (mmol/L)	7.5 (1.9)*	5.3 (0.4)
Fasting plasma insulin (pmol/L)	18.9 (10)*	9.1 (3)
HbA1c (%)	5.8 (1.2)*	4.9 (0.6)
C-reactive protein (mg/L)†	0.93 (2.62)	0.72 (1.21)

Values are means (SD).
*$p < 0.05$.
†Values are medians (interquartile range).
NA = not applicable.

The local ethics committee approved the protocol and all subjects gave informed consent.

CMR acquisition technique and image analysis

CMR studies were performed with the use of a 1.5-T whole-body MR scanner (Gyroscan ACS/NT15, Philips, Best, the Netherlands) in the supine position at rest. Images were analyzed quantitatively using dedicated software (FLOW or MASS, Medis, Leiden, The Netherlands).

Aortic pulse wave velocity

A retrospectively ECG-gated gradient-echo pulse sequence with velocity encoding was applied to measure through-plane flow at 2 predefined positions in the ascending and abdominal aorta. Imaging parameters included the following: echo-time = 4.83 ms, repetition time = 14 ms, flip-angle = 20 degrees, slice thickness = 8 mm, field of view = 350 mm, matrix size = 256 × 256, Venc = 150 cm/s, scan percentage = 80%. The predefined imaging planes were perpendicular to the aorta at 2 levels: 1) at the mid ascending aorta and 2) just above the bifurcation of the abdominal aorta (Fig. 1). The temporal resolution was approximately 25 ms depending on the heart rate. The in-plane spatial resolution was 1.37 × 1.76 mm after reconstruction.

A single observer, blinded to the clinical status of the subjects, analyzed these flow measurements to calculate aortic PWV. Aortic PWV was calculated as $\Delta x/\Delta t$ (expressed in m/s), where Δx is the aortic path length between the 2 imaging levels and Δt is the time delay between the arrival of the foot of the pulse wave (13, 18) at these levels (Fig. 1). Aortic PWV was calculated twice within a month to examine intra-observer variability.

Aortic distensibility

Distensibility of the aorta derived from flow measurements at the mid ascending aorta was calculated using the following formula:

$$D = (A_{max} - A_{min})/(A_{min} \times \text{pulse pressure}) \text{ (19)},$$

where D = distensibility ($mmHg^{-1}$), A_{max} = maximal aortic area (mm^2), A_{min} = minimal aortic area (mm^2), pulse pressure = systolic BP – diastolic BP (mmHg). The blood pressure

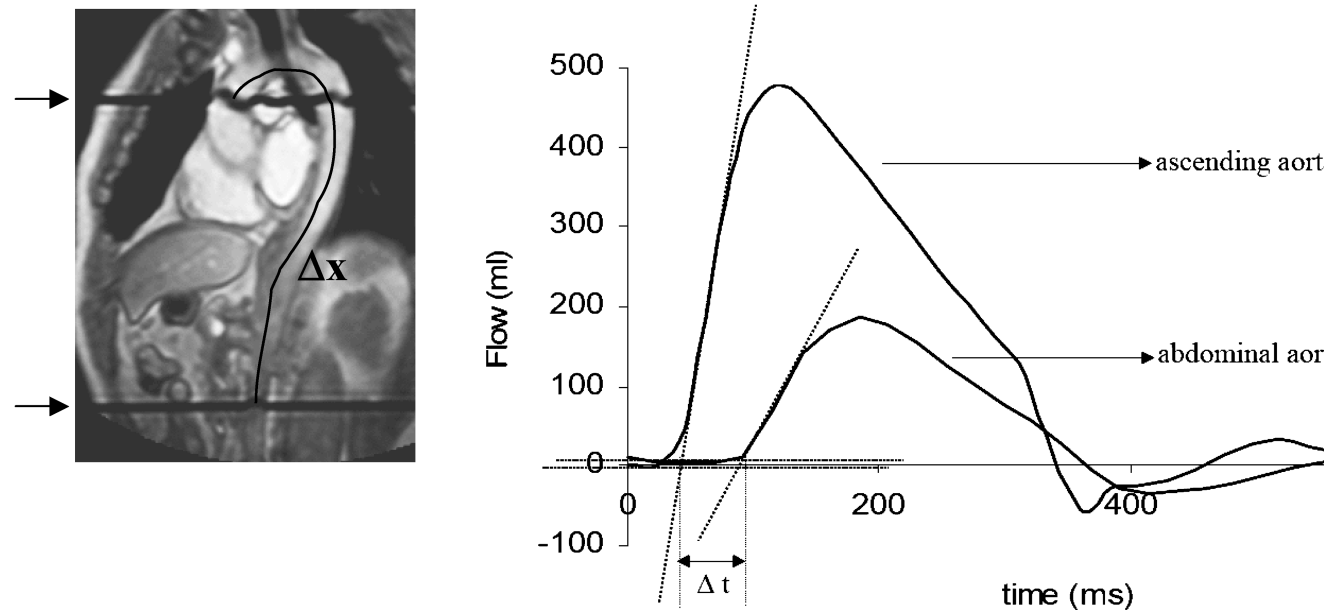

Figure 1. PWV determination. In Panel I, a gradient echo image in plane with the long axis of the aorta is shown. A presaturation slab is noted proximal in the ascending aorta and at the abdominal level (arrows). Velocity maps were obtained at both levels. A standardized approach was used to provide consistent data to measure the path length between the middle of both levels (Δx) indicated by the curved line following the midline course of the aorta. In panel II the flow curves in the ascending and abdominal aorta are shown. The intersection of the tangent line to the upstroke and the baseline was considered as the arrival time of the pulse wave. Δt denotes the time delay of the arrival of the proximal and abdominal flow curve. Aortic pulse wave velocity is defined by $\Delta x/\Delta t$ (m/s).

was recorded using a semi-automated sphygmomanometer (Dinamap, Critikon, Tampa, Florida, USA) during the CMR examination. Mean arterial pressure (MAP) was calculated as (systolic BP – [2 × diastolic BP])/3.

Aortic contours were drawn twice within a month interval to assess intra-observer variability in distensibility.

Left ventricular function

Systolic and diastolic LV functions were measured. The entire heart was imaged in the short-axis orientation using ECG-gated breath-hold multishot echo-planar imaging as described before (20). Imaging parameters included the following: echo-time = 6 ms, repetition time = 11 ms, temporal resolution = 35–39 ms per cardiac phase, depending on the heart rate, flip-angle = 30 degrees, slice thickness = 10 mm, field of view = 400 mm, reconstructed matrix size = 256 × 256. End-diastolic chamber volume (EDV), end-systolic chamber volume (ESV), stroke volume (SV), ejection fraction (EF), and left ventricular mass (LVM) were assessed. Furthermore, an ECG-gated gradient-echo sequence with velocity encoding was performed to measure blood flow across the mitral valve for the determination of LV diastolic function. Imaging parameters included the following: echo-time = 4.83 ms, repetition time = 14 ms, flip-angle = 20 degrees, slice thickness = 8 mm, field of view = 350 mm, matrix size = 256 × 256, Venc = 100 cm/s, scan percentage = 80%. In each cardiac phase, the area of the mitral valve was manually traced, and the corresponding flow-versus-time curve was derived automatically. Flow velocities in early diastole (E) and at atrial contraction (A) were assessed and the early peak filling rate, which is the maximal flow rate of E, the atrial peak filling rate, which is the maximal flow rate of A, and the ratio of E and A peak filling rates(E/A) were used for analysis. Furthermore, the peak acceleration and peak deceleration gradients of E were calculated automatically (Fig. 2) (21, 22).

Statistical analysis

Statistical analysis was performed with SPSS for windows version 11.5. Data are expressed as mean (SD). Only CRP, due to abnormal distribution, was expressed as median (interquartile range) and logarithmically transformed when used in the analyses. Between group differences were calculated using a two-tailed independent sample T-test. Multivariate testing was performed by using the general linear model. Data of patients and healthy subjects were pooled to calculate Pearson r-values for correlations. Significance was assumed when $p < 0.05$ (two tailed).

RESULTS

Patient characteristics

Table 1 lists the characteristics of the participants. Patients, as compared to healthy subjects, showed a higher body mass index (BMI) as well as higher fasting plasma glucose and insulin levels.

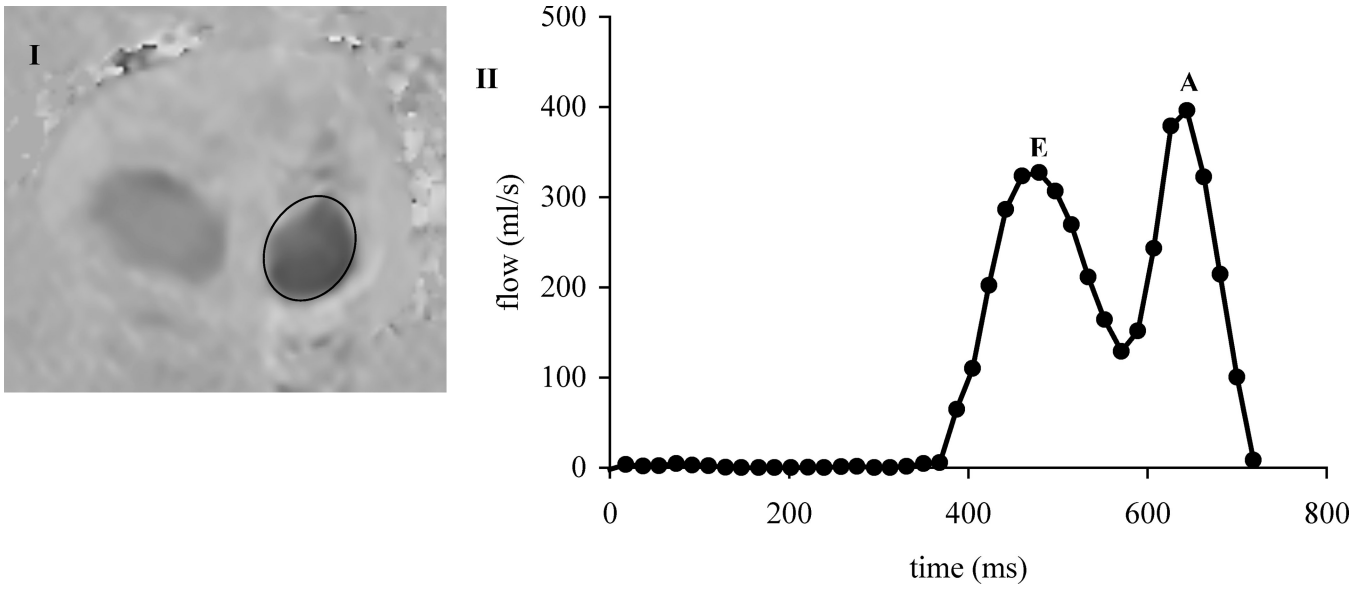

Figure 2. Left Ventricular Diastolic Function. Panel I shows a phase contrast velocity map across the mitral valve in one cardiac phase. The mitral valve contour is traced. Panel II shows a flow-versus-time curve of a patient with DM2 across the mitral valve. The biphasic inflow pattern consists of two peaks, representing the early filling phase (E) and the atrial contraction (A). Analysis of E and A was performed by calculation of the early peak filling rate, which is the maximal flow rate of E, the atrial peak filling rate, which is the maximal flow rate of A, and the ratio of E and A peak filling rates. Furthermore, the peak acceleration and peak deceleration gradients of E were automatically calculated by assessing the steepest tangent to the upstroke and downstroke of E.

There were no differences in age, blood pressure, and heart rate between patients and healthy subjects.

Pulse wave velocity

Aortic PWV was significantly higher in patients than in healthy subjects (Table 2). CMR measured aortic PWV showed an inverse correlation with aortic distensibility (Table 2) whereas positive correlations were found with systolic and diastolic blood pressure, MAP, and fasting plasma glucose and insulin levels (Table 3). Multivariate analysis showed that the difference in PWV between patients and controls was statistically significant after correction for SBP and PP separately ($p < 0.05$). The difference in PWV between patients and controls was borderline significant after correction for DBP and MAP separately ($p = 0.06$). In healthy subjects, but not in DM2 patients, aortic PWV correlated with age ($r = 0.53$, $p < 0.05$ and 0.12, $p > 0.05$, respectively).

Table 2. Aortic vascular and left ventricular dynamics

Parameter	Healthy Subjects (N = 16)	Patients (N = 14)	Correlation with aortic distensibility (N = 28)
Aortic pulse wave velocity (m/s)	5.65 (0.75)	6.83 (1.60)*	−0.517*
Distensibility ($\times 10^{-3}$mm Hg^{-1})	7.42 (3.34)	4.50 (2.24)*	NA
Left ventricular end diastolic volume (mL)	141 (26)	146 (35)	0.288
Left ventricular end systolic volume (mL)	54 (9)	59 (18)	0.201
Left ventricular stroke volume (mL)	87 (20)	87 (22)	0.278
Left ventricular ejection fraction (%)	60.9 (6.6)	59.9 (7.0)	0.079
Left ventricular end systolic mass (g)	113.9 (30.6)	119.5 (33.5)	0.088
E peak filling rate (mL/s)	454.8 (108.6)	379.5 (70.1)*	0.517*
E acceleration peak (mL/s^2 $\times$ 10^{-3})	7.66 (1.85)	6.38 (1.42)*	0.285
E deceleration peak (mL/s^2 $\times$ 10^{-3})†	3.72 (1.32)	2.73 (0.74)*	0.542*
E/A peak flow ratio	1.32 (0.36)	1.08 (0.28)	0.413*

*Mean values (SD) are significantly different (independent samples t-test) or correlation is significant (Pearson correlation, $p < 0.05$).
†One patient was considered as an outlier and censored for this parameter.
A = atrial contraction, E = early diastole, NA = not applicable.

Intra-observer reproducibility for CMR measured aortic PWV was excellent. The average difference was -0.08 ± 0.25 ($p > 0.05$). Limits of agreement were -0.59 to 0.42, and no trend was observed. The two calculations were significantly correlated ($r = 0.98$, $p < 0.001$).

Distensibility

Distensibility could not be calculated in 1 out of 14 patients and 1 out of 16 healthy subjects due to technical problems with BP measurements during MR data acquisition. Distensibility of the aorta was significantly lower in patients as compared to healthy subjects (Table 2).

Furthermore, fasting plasma insulin, glucose, CRP levels and heart rate showed statistically significant correlations with aortic distensibility (Table 3).

Intra-observer reproducibility for CMR measured aortic distensibility was excellent. The average difference was 0.02 ± 0.9 ($p > 0.05$). Limits of agreement were –1.79 to 1.82. There was no trend observed. The two calculations were significantly correlated ($r = 0.96$, $p < 0.001$).

Left ventricular function

Parameters of systolic function were similar in patients as compared to controls (Table 2). There was no correlation between aortic stiffness and left ventricular systolic function. Patients and healthy subjects showed similar LV masses ($p > 0.05$), and there was no correlation between PWV or distensibility of the aorta and LV mass (Table 2). A positive correlation was observed between aortic distensibility and diastolic functional parameters (Table 2). Furthermore, E peak filling rate, E acceleration peak of mitral flow velocity, and E deceleration peak of mitral flow velocity were significantly lower in patients as compared to healthy subjects. In addition, the E/A peak flow ratio showed a borderline significant difference ($p = 0.055$) between patients and healthy subjects.

Table 3. Diabetic and anthropometric parameters correlated with aortic pulse wave velocity and distensibility

	Correlation with pulse wave velocity (N = 30)	Correlation with aortic distensibility (N = 28)
Systolic blood pressure (mm Hg)	0.387*	−0.490*
Diastolic blood pressure (mm Hg)	0.423*	−0.467*
Mean arterial pressure (mm Hg)	0.431*	−0.517*
Fasting plasma insulin (mU/L)	0.523*	−0.422*
Fasting plasma glucose (mmol/L)	0.599*	−0.388*
log C-reactive protein (mg/L)	0.358	−0.429*
Heart rate (bpm)	0.245	−0.441*
Patient Length (cm)	0.084	−0.071

*$p < 0.05$ (Pearson correlation).

DISCUSSION

This study demonstrates the potential value of an integrated CMR protocol for comprehensive evaluation of aortic and cardiac function in patients with type 2 diabetes mellitus. Although the pathophysiology of aortic and cardiac function in diabetic patients has been extensively studied with other techniques than CMR, there are only a few studies that have studied the possible relationship between aortic and cardiac function using CMR as a noninvasive tool. The main findings in our study are that aortic stiffening as characterized by pulse wave velocity and aortic distensibility was significantly increased in patients as compared to healthy subjects. In addition, aortic distensibility correlated with left ventricular diastolic function. The sample size was adequate to identify significant differences in aortic pulse wave velocity and aortic distensibility between patients and healthy controls. The observations are similar to that found using less-precise modalities in previous studies that required larger sample sizes, owing to the high reproducibility of MR measurements.

Aortic stiffness

The present magnetic resonance findings of an increased pulse wave velocity and a decreased aortic distensibility in diabetic subjects are in agreement with previous studies that used techniques other than MRI (3, 4, 5, 23, 24). Cruickshank et al. used ultrasound to demonstrate that pulse wave velocity is an independent predictor of mortality in the diabetic population (3). Whereas previous studies mainly used ultrasound or applanation tonometry to assess pulse wave velocity or vascular distensibility, our study showed the usefulness of CMR in assessing both parameters of aortic stiffness in one session. Another important advantage of CMR is that aortic path length can be measured directly, thereby providing a potentially more accurate pulse wave velocity than ultrasound or applanation tonometry, where path length has to be estimated. Furthermore, CMR is capable of assessing the pulse waves locally in the aorta, thus minimizing influences of peripheral arteries on aortic pulse wave velocity determination as may be the case with peripheral applanation tonometry (25). This is of importance since it is known that diabetes has greater impact on pulse wave velocity of the elastic central arteries as compared to the muscular peripheral arteries (26).

We were able to show correlations between both parameters of aortic stiffness and fasting plasma glucose and insulin levels. Raised blood glucose and insulin levels in diabetic subjects can partially explain the stiffening of the aorta. Hyperglycemia causes vascular damage through various mechanisms, including the formation of advanced glycation end products (AGEs), oxidative stress and vascular inflammation. Collectively, all these mechanisms can contribute to aortic stiffening. We observed that CMR measured aortic pulse wave velocity and distensibility correlate to systolic and diastolic blood pressure as well as to mean arterial pressure. The difference in pulse wave velocity between patients and controls was still statistically significant after correction for systolic blood pressure and pulse pressure. The

difference in pulse wave velocity between patients and controls was borderline significant after correction for diastolic blood pressure and mean arterial pressure separately ($p = 0.06$). Therefore, we conclude that diabetes mellitus type 2 may induce an aortopathy independent of blood pressure. Furthermore, aortic distensibility correlated to heart rate. There was no correlation between pulse wave velocity and heart rate as suggested previously (27). The younger age group and smaller range of heart rate in the present study might explain this observation. The correlation of aortic pulse wave velocity with age is already well known (28). We found a correlation of pulse wave velocity with age in the healthy population only. No such correlation was found in diabetic subjects, probably because pulse wave velocity in these patients is affected by multiple factors.

Cardiac function

In the current study, no difference in left ventricular systolic function between patients and healthy controls was observed. However, markers of left ventricular diastolic function (early peak filling rate, early acceleration peak, and early deceleration peak, calculated from the transmitral filling patterns) were decreased in diabetic subjects. Furthermore, the difference in the E/A peak flow ratio showed borderline significance between patients and healthy subjects. These findings are in accordance with previous ultrasound studies that indicate that diastolic dysfunction may occur in approximately 40% of diabetic patients (24, 29, 30). Interestingly, the present CMR data show that when aortic distensibility decreased, the early filling rate, the early deceleration peak, and the E/A peak flow ratio decreased as well. This observation suggests that aortic distensibility is related to changes in left ventricular diastolic function. This pattern of changes in early diastolic flow velocities corresponds to an increase in myocardial compliance and a decrease in active relaxation of the left ventricle (31). Although our study does not allow establishing a causal relation between aortic distensibility and left ventricular diastolic function, it is known that left ventricular diastolic function may become impaired by aortic stiffness through various mechanisms. Stiffening of the aorta increases end systolic wall stress and reduces aortic pressure throughout diastole (32). This leads to an increased myocardial oxygen demand, hypertrophy and compromised coronary perfusion. An increased systolic left ventricular pressure, left ventricular hypertrophy, and compromised coronary perfusion can delay myocardial relaxation and cause diastolic heart failure. There is some evidence in patients with syndrome X, indicating a link between increased arterial stiffening and myocardial perfusion impairment (33). Panting et al. were able to show subendocardial hypoperfusion during the intravenous administration of adenosine in patients with syndrome X but did not report any relation with subendocardial hypoperfusion and LV systolic function, diastolic function, or aortic physiology (34). Nevertheless, adenosine stress myocardial perfusion might be a useful tool to test the relationship between aortic pulse wave velocity, aortic distensibility, myocardial function and myocardial perfusion impairment, especially in patients with type 2 diabetes mellitus of whom a considerable part is suffering from silent myocardial ischemia (35, 36). Furthermore, stiffening of the aorta may cause myocardial hypertrophy (37), which may lead to an increase in systolic and diastolic myocardial stiffness (38). In our study, no significant left ventricular hypertrophy was noted in diabetic patients. However, LV diastolic dysfunction may occur even in the absence of left ventricular hypertrophy (21, 39).

Limitations

A limitation of this study is that local assessment of aortic pulse pressure was not performed, which would have defined aortic distensibility more accurately than the use of brachial pulse pressure (40).

CONCLUSIONS

A comprehensive CMR protocol is well suited to assess aortic and cardiac function in diabetic patients. A combined CMR assessment of aortic PWV, aortic distensibility, and heart function reveals abnormal PWV and distensibility in patients with DM2, independent of blood pressure. Furthermore, aortic distensibility correlates with diastolic left ventricular function.

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