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Original Article

Simultaneous assessment of vascular distensibility and vessel wall area at coronary, carotid, and aortic level in diabetic patients using CMR: detection of vascular remodeling

David Jean Winkel[1*], Lukas Stoiber[2*], Tingting Xiong[3], Matthias Stuber[4,5], Allison G Hays[6], Ursula Plöckinger[7], Patrick Doeblin[2], Christian Stehning[8], Sebastian Kelle[2,9,10]

[1]Department of Radiology, University Hospital of Basel, Basel, Switzerland; [2]Department of Cardiology, Angiology and Intensive Care Medicine, Deutsches Herzzentrum der Charité, Berlin, Germany; [3]Third Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [4]Department of Diagnostic and Interventional Radiology, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland; [5]Center for Biomedical Imaging (CIBM), Lausanne, Switzerland; [6]Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland; [7]Interdisciplinary Center of Metabolism: Endocrinology, Diabetes and Metabolism, Charité University Medicine Berlin, Berlin, Germany; [8]Philips Clinical Science, Hamburg, Germany; [9]Department of Internal Medicine and Cardiology, Charité University Medicine Berlin, Berlin, Germany; [10]DHZK (German Center for Cardiovascular Research), Partner Site Berlin, Berlin, Germany. [*]Equal contributors.

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Abstract: Aims: No data is available about the significance of cardiovascular magnetic resonance (CMR) derived vascular distensibility (VD) and vessel wall ratio (VWR) for risk stratification in patients with type 2 diabetes mellitus (T2DM). Therefore, this study aimed to investigate the effects of T2DM on VD and VWR using CMR in both central and peripheral territories. Methods: Thirty-one T2DM-patients and nine controls underwent CMR. Angulation of the aorta, the common carotid, and the coronary arteries was performed to obtain cross-sectional vessel areas. Results: In T2DM the Carotid-VWR and the Aortic-VWR correlated significantly. Mean values of Carotid-VWR and Aortic-VWR were significantly higher in T2DM than in controls. Coronary-VD was significantly lower in T2DM than in controls. No significant difference in Carotid-VD or Aortic-VD in T2DM vs. controls, respectively, could be observed. In a subgroup of thirteen T2DM patients with coronary artery disease (CAD), Coronary-VD was significantly lower and Aortic-VWR was significantly higher compared to T2DM patients without CAD. Conclusion: CMR allows a simultaneous evaluation of the structure and function of three important vascular territories to detect vascular remodeling in T2DM.

Keywords: Coronary artery disease, diabetes mellitus, type 2, cross-sectional studies, vascular remodeling, CMR, cardiac MRI, magnetic resonance imaging, caritid, aorta distensibility

Introduction

The prevalence of T2DM is increasing worldwide [1]. T2DM comprises a broad spectrum of long-term cardiovascular complications and places a burden on both patients and society. T2DM is associated with an up to 8-fold increased mortality from cardiovascular disease [2]. Patients with T2DM have reduced vascular elasticity and thickened vessels in carotids, coronaries, and the aorta, and these vascular abnormalities are associated with an increased risk of cardiovascular events [3, 4]. The capacity of a vessel to distend to a given pressure provides valuable information about vascular age [3, 5-7]. Ultrasound-based methods like Carotid-Intima-Media-Thickness (CIMT) provide information on vascular anatomy and their application is standard of care for the peripheral vasculature. However, the elastic properties of the coronaries and thoracic aorta cannot be obtained with this technique. Cardiovascular magnetic resonance (CMR) has been shown to detect morphologic and functional changes in central and peripheral vascular territories with good reproducibility and no

exposure to radiation [8]. CMR allows for a simultaneous assessment of the elastic response of a vessel to the blood flow, reflected by vascular distensibility (VD), and the morphology of the vascular wall itself. Measurements of VD provide information on alteration of the vasculature due to systolic pressure or aging, even before the onset of atherosclerosis [9-11]. Furthermore, CMR is less observer-dependent than other imaging modalities and well suited to examine vascular pathologies in multiple territories and serial studies [12]. Successful application of CMR for coronary, aortic, and carotid distensibility and quantification of atherosclerosis has been described [4, 11-15].

The relationship between VD and vessel wall morphology is still unclear. Moreover, no information is available on the elastic properties among different vessels in patients with long-term T2DM. This study aimed to investigate the effects of T2DM on vascular distensibility and morphology using CMR in both central and peripheral territories.

Materials and methods

Patient study

Thirty-one (n = 31) patients with T2DM were prospectively included in this study. Inclusion criteria were a) known T2DM and b) referral for a risk stratification using CMR in the setting of the prospective trial. Exclusion criteria were a) age < 18 years and b) incomplete or missing CMR dataset. All patients were referred to our cardiological outpatient department. Nine (n = 9) healthy subjects served as controls. All healthy controls were referred to our cardiology outpatient clinic for routine check-up examinations. Exclusion criteria for healthy subjects were the same as for the patient cohort. All participants underwent CMR, using a 3.0 Tesla scanner (Ingenia 3.0T, Philips, Best, The Netherlands). The study was approved by the local institutional review board (Charité-Universitätsmedizin Berlin; DMAINS-BER-01-2005). Written informed consent was provided by all patients before inclusion. All datasets were anonymized.

CMR protocol

CMR was performed according to a standard protocol and following the recommendations of the Society for Cardiovascular Magnetic Resonance (SCMR) Board of Trustees Task Force on Standardized Protocols [16-18]. Cine images were registered during 10-15 s breath-holds using standard vector ECG gating and steady-state free precession (SSFP) imaging. Cross-sectional scans of the common carotid arteries, the ascending aorta, and the proximal segment of one coronary artery were performed to obtain area measurements. **Figure 1** illustrates the corresponding points of measurement.

The peripheral blood pressure (BP) was recorded directly before, during, and directly after the examination, and the average of these three values was used in the calculation of VD.

Common carotid artery imaging

The acquisition protocol for carotid artery vessel wall area (VWA) measurements has been described previously [19]. Briefly, a standardized series of oblique axial slices were planned perpendicular to the course of the common carotid artery. The carotid bifurcation on the oblique sagittal images was used as a landmark to ensure that the acquisition was planned at the same location for all participants. All measurements of the carotid artery were performed exactly 10 mm below the bifurcation of both the left and right carotid artery. A two-dimensional turbo-spin echo, black-blood pre-pulsed acquisition protocol using a 15-channel head coil was performed. The MRI parameters were as follows: repetition time (TR) 2 heartbeats; echo time (TE) 30 ms; inter-echo spacing turbo-spin-echo (TSE) es 11.3 ms; spatial resolution 0.5 × 0.5 × 4 mm^3. Images were acquired in diastole only. The acquisition protocol for carotid artery distensibility measurements was as follows: Scout images were planned perpendicular at the level of the carotid bifurcation. We then acquired a two-dimensional, segmented gradient-echo, ECG-triggered scan with the following MRI parameters: TR 6.1 ms; TE 4 ms; field of view (FOV) 250 × 210 mm^2; flip angle (FA) 10 degrees; spatial resolution 0.98 × 0.98 × 10 mm^3, 35 phases per heartbeat.

Ascending aorta imaging

The aortic vessel wall area acquisitions were done as previously described [20]. Briefly, scout scans were planned perpendicular to the aorta at the level of the ascending aorta. We used a

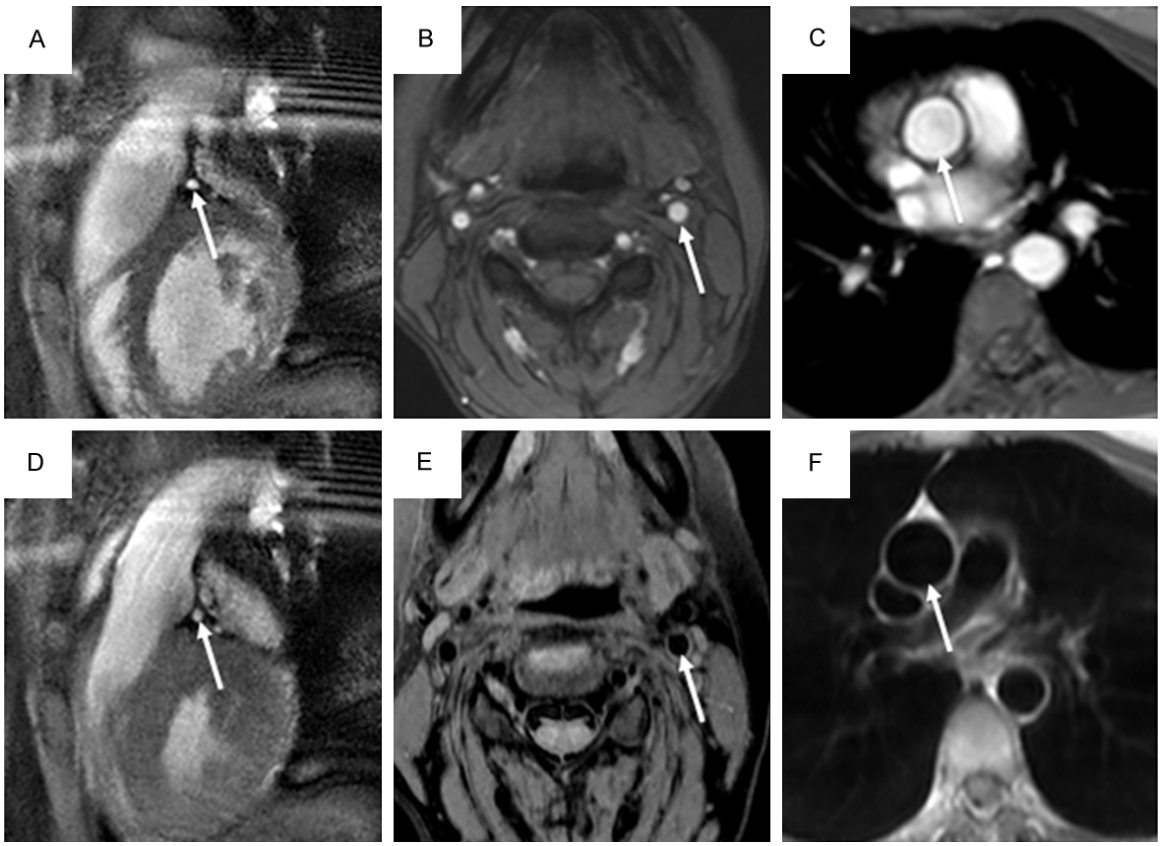

Figure 1. CMR images with cross-sectional measurements displaying three different parts of the vasculature. (A, D) Cross-sectional view of the left coronary artery in end-diastolic (A) and end-systolic phases (D) of the cardiac cycle. (B, E) Cross-sectional view indicating Left Common Carotid Artery (B) and corresponding black blood sequence (E). (C, F) Cross sectional view indicating Ascending Aorta (C) and corresponding black blood sequence (F).

two-dimensional turbo-spin echo, black-blood pre-pulsed acquisition protocol with a 28-channel coil-combination (16-channel anterior coil and a 12-channel posterior coil under the table) with the following scan parameters: TR 2 beats; TE 10 ms; FOV 340 × 310 mm^2; spatial resolution 1.5 × 2 × 8 mm^3. The acquisition protocol for ascending aorta distensibility measurements was as follows: After positioning the slice perpendicular to the ascending aorta, we acquired a 2-dimensional, segmented gradient-echo, electrocardiogram (ECG)-triggered scan with the following MRI parameters: TR 3.7 ms; TE 2.2 ms; FOV 350 × 270 mm^2, FA 10 degrees; spatial resolution 2.2 × 2.2 × 10 mm^3; 30 phases per heartbeat.

Coronary artery imaging

Coronary artery distensibility measurements were performed as previously described [13]. Scout scans were performed to determine the 3-dimensional course of the proximal coronary arteries. Magnetic resonance angiography of the right coronary artery (RCA) or left anterior descending artery (LAD) and/or left circumflex artery (RCX) was performed using a 2-dimensional, gradient-echo technique with a spiral acquisition window of 15 ms, 21 spiral interleaves, and fat suppression using a 28-channel coil-combination (16-channel anterior coil and a 12-channel posterior coil under the table). The MRI parameters were as follows: TR 18 ms; TE 0.85 ms; FOV 220 × 220 mm^2; FA 20 degrees; spatial resolution 0.9 × 0.9 × 8 mm^3; 30 phases per heartbeat.

Image analysis

The carotid, aortic and coronary images were analyzed for the absolute cross-sectional luminal area using full-width half-maximum criteria (cine version 3.15.17, GE, Milwaukee, Wisconsin) [21, 22]. The images were magnified, and a circular region of interest was manually traced around the artery lumen. The computer

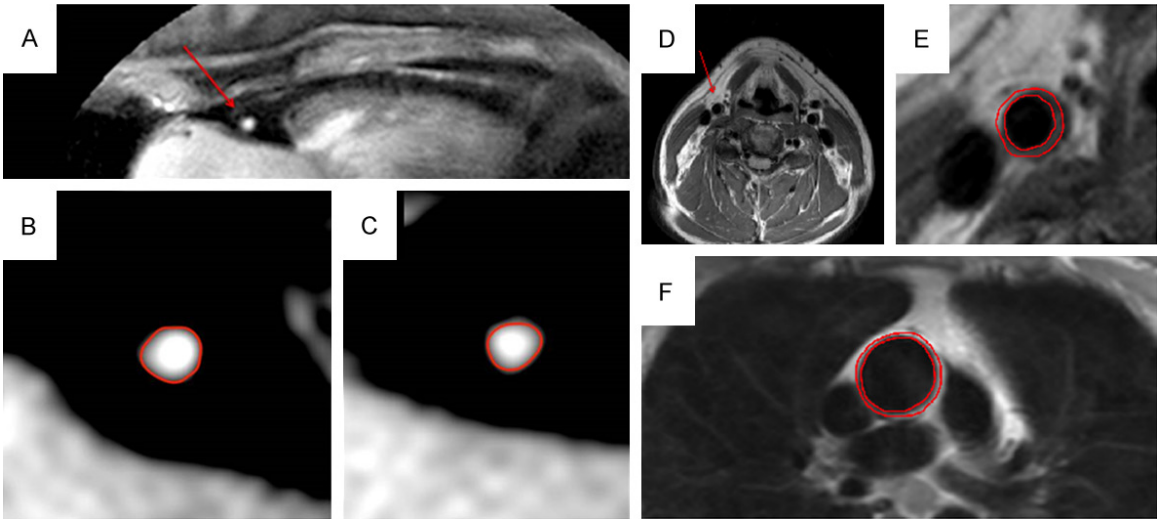

Figure 2. CMR images demonstrating the measurement methods. (A) Arrow indicating the right coronary artery. (B, C) Measurements of the coronary distensibility: The image from (A) was magnified, and a circular region of interest was manually traced around the artery lumen. The computer algorithm then automatically measured the cross-sectional luminal area. The distensibility ($mmHg^{-1} \times 10^3$) was determined as follows: (lumenmax - lumenmin)/(pulse pressure × lumenmin). Measurements of the aortic and carotid distensibility were performed analogously. (D, E) Measurements of the vessel wall area (VWA): Arrow in (D) indicating the right common carotid artery with image (E) demonstrating a magnification of the vessel with depiction of the inner and outer border of the vessel wall, allowing to calculate the VWA. Image in (F) analogously demonstrating the inner and outer border of the ascending aorta. Ultimately, the vessel wall ratio (VWR = 106 * VWA/body surface area) was calculated.

algorithm then automatically measured the cross-sectional luminal area. The VD ($mmHg^{-1} \times 10^3$) was determined as follows: (lumenmax - lumenmin)/(pulse pressure × lumenmin). The VWA was assessed by View Forum R5 (Philips Healthcare, Best, The Netherlands) by manually tracing the inner and outer border of the vessel wall and by then subtracting the calculated areas. The pulse pressure was calculated as the difference between the systolic and diastolic brachial blood pressure. lumenmax and lumenmin were defined as the maximal and minimal cross-sectional areas measured throughout the cardiac cycle, respectively. For all vascular territories, cross-sectional luminal area and VWA were assessed, and the vessel wall ratio (VWR = 106 * VWA/body surface area) was calculated. **Figure 2** illustrates the specific measurement methods.

Cross-sectional areas in 10 subjects were measured two times by the same observer and once by an additional observer to obtain inter- and intra-observer variability.

Statistical analysis

The Statistical Package for Social Sciences, version 20.0 for Windows (SPSS, Chicago, Illinois) was used for all statistical analyses. The data are presented as mean ± standard deviation (SD) unless stated otherwise. The study characteristics were compared using the χ^2- and Student's *t*-test. The Student's *t*-test was used to compare the distensibility and VWR measurements between and within the study groups. Bivariate analysis was used to test for the correlation of VWR and VD measurements within the two study groups. To test for inter- and intra-observer variability, the data were analyzed using reliability analysis based on a two-way mixed model of absolute agreement type and a confidence interval of 95%. The data acquired was used to create Bland-Altman-Plots. A *P*-value of < 0.05 was considered statistically significant.

Results

Study population

Forty (n = 40) participants were included in this study. The patients and healthy subjects' characteristics are shown in **Table 1**.

The mean age in T2DM patients was 62 years, 20/31 (64%) were male, and mean BP was 137/78 mmHg. In the control group, the mean

Table 1. Patient's characteristics

Characteristics	Healthy subjects (n = 9)	Diabetic patients (n = 31)	*P*-value
Age (years)	53 ± 2	62 ± 10	P < 0.001
Male	2 (22%)	20 (64%)	P = 0.025
Body-Mass Index (BMI)	25 ± 5.03 (26.23)	31.28 ± 4.3 (31.35)	P = 0.003
SBP (mmHg)	122 ± 14 (123)	137 ± 18 (133)	P = 0.017
DBP (mmHg)	77 ± 11 (75)	78 ± 11 (75)	P = 0.741
Pulse Pressure (mmHg)	50 ± 14 (48)	59 ± 15 (55)	P = 0.001
Heart Rate (beats/min)	67 ± 9 (62)	75 ± 15 (72)	P = 0.064
Hypertension	0 (0%)	31 (100%)	P < 0.001
Smoking	0 (0%)	6 (13%)	P < 0.001
Dyslipidemia	0 (0%)	30 (97%)	P < 0.001
Diabetes	0 (0%)	31 (100%)	P < 0.001
HbA1c (%)	n/a	6.96 ± 0.65	n/a
CAD	0 (0%)	13 (42%)	P < 0.001
Previous CABG	0 (0%)	0 (0%)	NS
Previous PCI	0 (0%)	13 (42%)	P < 0.001
Previous MI	0 (0%)	5 (16%)	P < 0.001

Data expressed as mean value ± standard deviation (SD). Values in brackets represent median values. CABG: Coronary artery bypass graft; CAD: Coronary artery disease; DBP: Diastolic blood pressure; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; SBP: Systolic blood pressure.

age was 53 years, 2/9 (22%) were male, and the mean BP was 122/77 mmHg.

MRI findings

VD and VWR in carotid arteries, aorta, and coronary arteries: **Table 2** and **Figure 3** provide an overview of the VD and VWR of the corresponding vessels in healthy subjects and T2DM patients.

In T2DM the Carotid-VWR and the Aortic-VWR (r = 0.492, P = 0.011) correlated significantly. Mean values of Carotid-VWR and Aortic-VWR were significantly higher in T2DM than in controls: 20.75 ± 6.02 vs. 13.18 ± 1.90 × 10^{-6}, P < 0.001 and 147 ± 31.63 vs. 85.38 ± 8.54 × 10^{-6}, P < 0.001. Also, the Carotid-VWA and Aorta-VWA showed to be significantly increased in the diabetic group vs. controls: 42.33 ± 11.55 vs. 24.41 ± 3.88 mm^2, P < 0.001 and 300.68 ± 66.40 vs. 158.30 ± 23.40 mm^2, P < 0.001.

Differences in absolute cross-sectional luminal areas were not statistically significant. There was a significant difference in coronary artery VD between the groups: 6.35 ± 2.87 $mmHg^{-1}$ × 10^3 in controls vs. 2.41 ± 1.66 $mmHg^{-1}$ × 10^3 in patients, P < 0.001. The carotid VD (3.91 ± 1.78 vs. 2.97 ± 1.28 $mmHg^{-1}$ × 10^3, P = 0.192) or aortic VD (3.18 ± 1.40 vs. 3.61 ± 2.39 $mmHg^{-1}$ × 10^3, P = 0.549) were comparable between the groups.

Correlation between central and peripheral vascular distensibility: There was no significant correlation between aortic and carotid VD (r = 0.430; P = 0.215) in T2DM patients, whereas we found a significant correlation in healthy controls (r = 0.855; P = 0.007).

No significant correlation of carotid and coronary VD or aortic and coronary VD was found in both T2DM and healthy controls (carotid and coronary artery VD (r = -0.074; P = 0.840), (r = 0.236; P = 0.573); aortic and coronary VD (r = 0.446; P = 0.196), (r = 0.380; P = 0.356) for T2DM and controls respectively). Correlation curves are illustrated in **Figure 4**.

T2DM patients with coronary artery disease (CAD): For the subgroups of thirteen T2DM patients with and eighteen T2DM patients without CAD (confirmed by coronary angiography) **Table 3** and **Figures 5**, **6** provide an overview of the aortic areas, vascular distensibility (VD), and VWAs of the corresponding vessels.

The absolute cross-sectional inner and outer area measurements were similar in both groups. However, coronary artery VD significantly

Table 2. CMR findings of cross-sectional luminal areas, vascular distensibility, and vessel wall areas

Characteristics	Healthy subjects (n = 9)	Diabetic patients (n = 31)	*P*-value
Cross-sectional luminal area measurements (mm^2)			
Common Carotid Artery			
Lumen max	38.78 ± 11.04 (38.17)	45.23 ± 10.64 (45.52)	0.145
Lumen min	33.62 ± 10.65 (32.09)	38.12 ± 9.61 (37.26)	P = 0.304
Ascending Aorta			
Lumen max	823.38 ± 215.32 (877.86)	905.76 ± 176.22 (894.15)	P = 0.278
Lumen min	737.00 ± 210.79 (774.10)	759.65 ± 153.95 (715.46)	P = 0.739
Coronary Artery			
Lumen max	18.06 ± 5.95 (15.64)	16.89 ± 4.42 (16.14)	P = 0.529
Lumen min	14.23 ± 5.19 (13.07)	14.93 ± 3.74 (14.59)	P = 0.660
Vascular distensibility ($mmHg^{-1} \times 10^{-3}$)			
Common Carotid Artery	3.91 ± 1.78 (3.71)	2.97 ± 1.28 (2.76)	P = 0.192
Ascending Aorta	3.01 ± 1.38 (2.64)	3.61 ± 2.39 (3.00)	P = 0.549
Coronary Artery	6.35 ± 2.87 (6.20)	2.41 ± 1.66 (1.81)	P < 0.001
Vessel Wall Area (mm^2)			
Common Carotid Artery			
Outer Area	55.63 ± 12.31 (54.35)	79.57 ± 19.26 (78.58)	P = 0.002
Inner Area	31.23 ± 9.07 (29.75)	37.24 ± 9.49 (36.08)	P = 0.122
Vessel Wall Area	24.41 ± 3.88 (24.45)	42.33 ± 11.55 (40.58)	P < 0.001
Vessel Wall Ratio ($\times 10^{-6}$)	13.18 ± 1.90 (13.74)	20.75 ± 6.02 (21.12)	P < 0.001
Ascending Aorta			
Outer Lumen	883.36 ± 203.09 (917.15)	1063.16 ± 175.51 (1032.90)	P = 0.021
Inner Lumen	725.06 ± 194.45 (751.20)	762.49 ± 142.81 (745)	P = 0.558
Vessel Wall Area	158.30 ± 23.40 (148.60)	300.68 ± 66.40 (279.50)	P < 0.001
Vessel Wall Ratio ($\times 10^{-6}$)	85.38 ± 8.54 (88.46)	147 ± 31.36 (141.24)	P < 0.001

Comparison of Healthy subjects (left column) and Diabetic patients (right column). Data expressed as mean ± standard deviation. Values in brackets represent median values.

differed between the groups: VD was 3.10 ± 1.75 $mmHg^{-1} \times 10^3$ in patients without CAD (no-CAD) vs. 1.44 ± 0.91 $mmHg^{-1} \times 10^3$ in CAD patients, P = 0.007. No such difference was observed for the carotid VD (2.82 ± 0.83 vs. 3.20 ± 1.73 $mmHg^{-1} \times 10^3$, P = 0.507) or aortic VD (3.61 ± 2.14 vs. 3.60 ± 2.71 $mmHg^{-1} \times 10^3$, P = 0.996), respectively. Compared to T2DM patients without CAD, the VWA and VWR were significantly increased in T2DM patients with CAD: 273.77 ± 56.21 vs. 334.31 ± 62.72 mm^2, P < 0.018 and 134.14 ± 27.15 vs. 163.08 ± 29.40 $\times 10^{-6}$, P = 0.017.

Age-matched T2DM patients: In an age-matched sub-group of ten T2DM patients (53 ± 5 years) the coronary artery VD differed significantly compared to the controls: 2.12 ± 1.09 vs. 6.74 ± 2.59 $mmHg^{-1} \times 10^3$, P < 0.001.

In this group, carotid VWR (13.18 ± 1.90 vs. 20.75 ± 6.02 $\times 10^{-6}$, P < 0.001) and aortic VWR (85.38 ± 8.54 vs. 147 ± 32.23 $\times 10^{-6}$, P < 0.001) were significantly lower in the healthy volunteer group. **Table 4** provides an overview of the aortic areas, vascular distensibility (VD), and vessel wall ratio (VWR) in the corresponding vessels.

Intra- and inter-observer variability: Repeat evaluations of 10 patients demonstrated excellent intra- and inter-observer agreement for distensibility and vessel wall thickness measurements in all 3 vessel territories (**Table 5**).

Discussion

The present study investigated the effects of T2DM on vascular function and anatomy by CMR in a group of thirty-one diabetic patients and nine controls. The following major findings were made: (i) Among T2DM patients, a significant reduction in coronary VD, as well as an increase in carotid and aortic VWR, was found

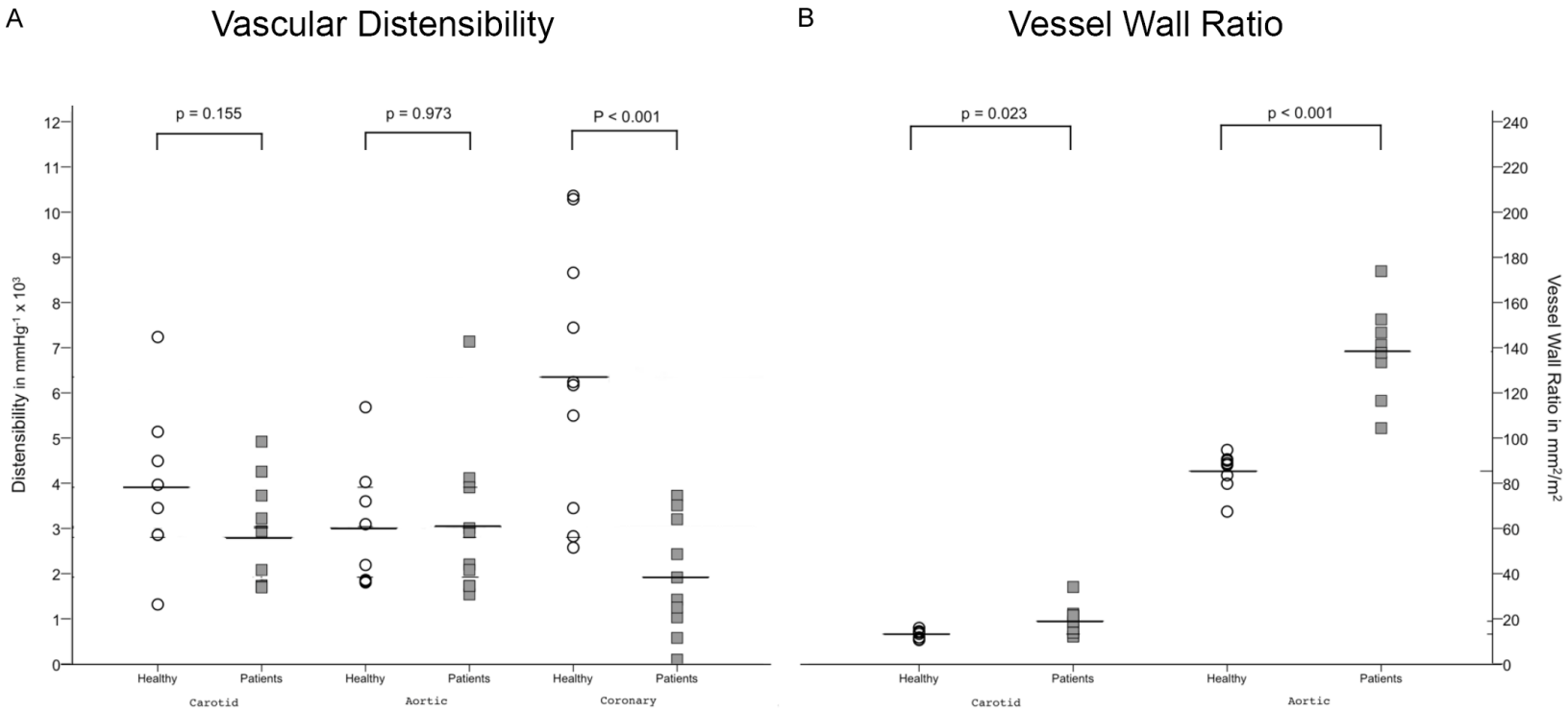

Figure 3. Comparison of carotid, aortic and coronary vascular distensibility (A) and carotid, aortic and coronary vessel wall ratio (B) between healthy controls and diabetic patients.

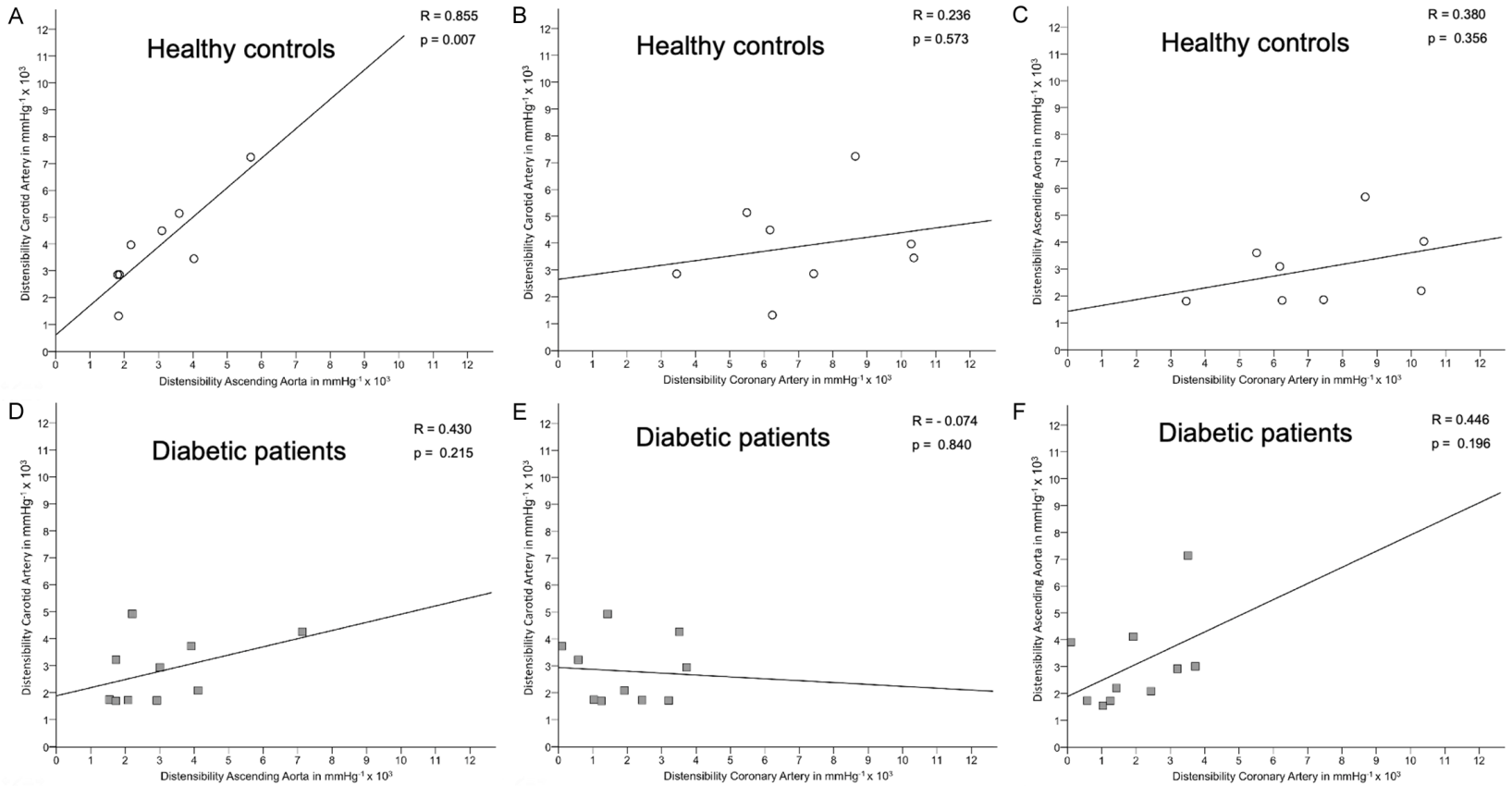

Figure 4. Correlation of Carotid and Aortic Vascular Distensibility (A, D); Correlation Carotid and Coronary Vascular Distensibility (B, E); Correlation of Aortic and Coronary Distensibility (C, F). Upper graphs illustrating Healthy controls; Lower graphs illustrating Diabetic patients.

Table 3. CMR findings of cross-sectional luminal areas, vascular distensibility, and vessel wall areas

Characteristics	Diabetic patients no CAD (n = 18)	Diabetic patients with CAD (n = 13)	*P*-value
Cross-sectional area measurements (mm^2)			
Common Carotid Artery			
Lumen max	45.13 ± 10.13 (39.81)	48.35 ± 10.48 (51.06)	P = 0.208
Lumen min	37.61 ± 9.20 (35.89)	38.89 ± 10.15 (42.65)	P = 0.737
Ascending Aorta			
Lumen max	909.94 ± 176.28 (926.15)	899.84 ± 175.96 (838.06)	P = 0.885
Lumen min	769.06 ± 160.41 (715.46)	749.30 ± 143.25 (716.95)	P = 0.703
Coronary Artery			
Lumen max	17.51 ± 4.90 (17.87)	16.02 ± 3.73 (14.84)	P = 0.900
Lumen min	15.01 ± 3.96 (15.02)	14.82 ± 3.61 (13.24)	P = 0.660
Vascular distensibility ($mmHg^{-1} \times 10^{-3}$)			
Common Carotid Artery	2.82 ± 0.83 (2.76)	3.20 ± 1.73 (2.56)	P = 0.507
Ascending Aorta	3.61 ± 2.14 (3.00)	3.60 ± 2.71 (3.10)	P = 0.996
Coronary Artery	3.10 ± 1.75 (3.15)	1.44 ± 0.91 (1.36)	P = 0.007
Vessel Wall Area (mm^2)			
Common Carotid Artery			
Outer Lumen	77.08 ± 19.83 (74.40)	83.30 ± 17.73 (79.90)	P = 0.395
Inner Lumen	35.87 ± 10.36 (33.98)	39.29 ± 7.54 (40.35)	P = 0.320
Vessel Wall Area	41.21 ± 11.60 (38.98)	44.00 ± 11.28 (43.15)	P = 0.533
Vessel Wall Ratio ($\times 10^{-6}$)	20.33 ± 6.22 (20.66)	21.39 ± 5.65 (21.44)	P = 0.653
Ascending Aorta			
Outer Lumen	1074.73 ± 171.21 (1032.90)	1048.71 ± 179.69 (1037.70)	P = 0.715
Inner Lumen	800.95 ± 134.94 (770.00)	714.40 ± 137.72 (706.80)	P = 0.123
Vessel Wall Area	273.77 ± 56.21 (263.00)	334.31 ± 62.72 (318.30)	P = 0.018
Vessel Wall Ratio ($\times 10^{-6}$)	134.14 ± 27.15 (133.54)	163.08 ± 29.40 (164.40)	P = 0.017

Comparison of Diabetic patients without Coronary artery disease (left column) and Diabetic patients with Coronary artery disease (right column). Data expressed as mean ± standard deviation. Values in brackets represent median values.

compared to controls. (ii) The findings were more severe in T2DM patients with CAD. (iii) In healthy participants, we found a significant correlation between aortic and carotid VD. This was not the case in T2DM patients. (iv) Coronary-, Aortic- and Carotid vascular distensibility (VD) and Aortic- and Carotid vessel wall ratio (VWR) can be obtained easily and reproducibly by CMR.

The long-term systemic effects of diabetes mellitus include stiffening of the arterial wall [23]. Specifically, the atherosclerotic process in T2DM is highly complex and has to be interpreted within the spectrum of metabolic syndrome. An altered glucose metabolism causes overproduction of reactive oxygen species (ROS) and glycemic end-products, ultimately leading to inflammation of the vessel wall [24, 25]. In combination with specific dyslipidemia in T2DM, mainly characterized by high triglycerides and low high-density lipoprotein (HDL), this process causes premature atherosclerosis resulting in major cardiovascular events [24, 25].

We investigated to what extent different vascular territories are affected by the atherosclerotic process and whether it was feasible to assess this process in one CMR examination. Previous studies indicated carotid and aortic vessels to stiffen earlier than femoral or brachial arteries [26]. In general, vascular aging is more prominent in central vessels closer to the heart with higher pressure differences. CMR is very well suited to detect vascular function and vascular anatomy simultaneously [27]. In line with previous studies, we found that aortic and carotid VWR were significantly higher in patients with T2DM, reflecting atherosclerotic changes

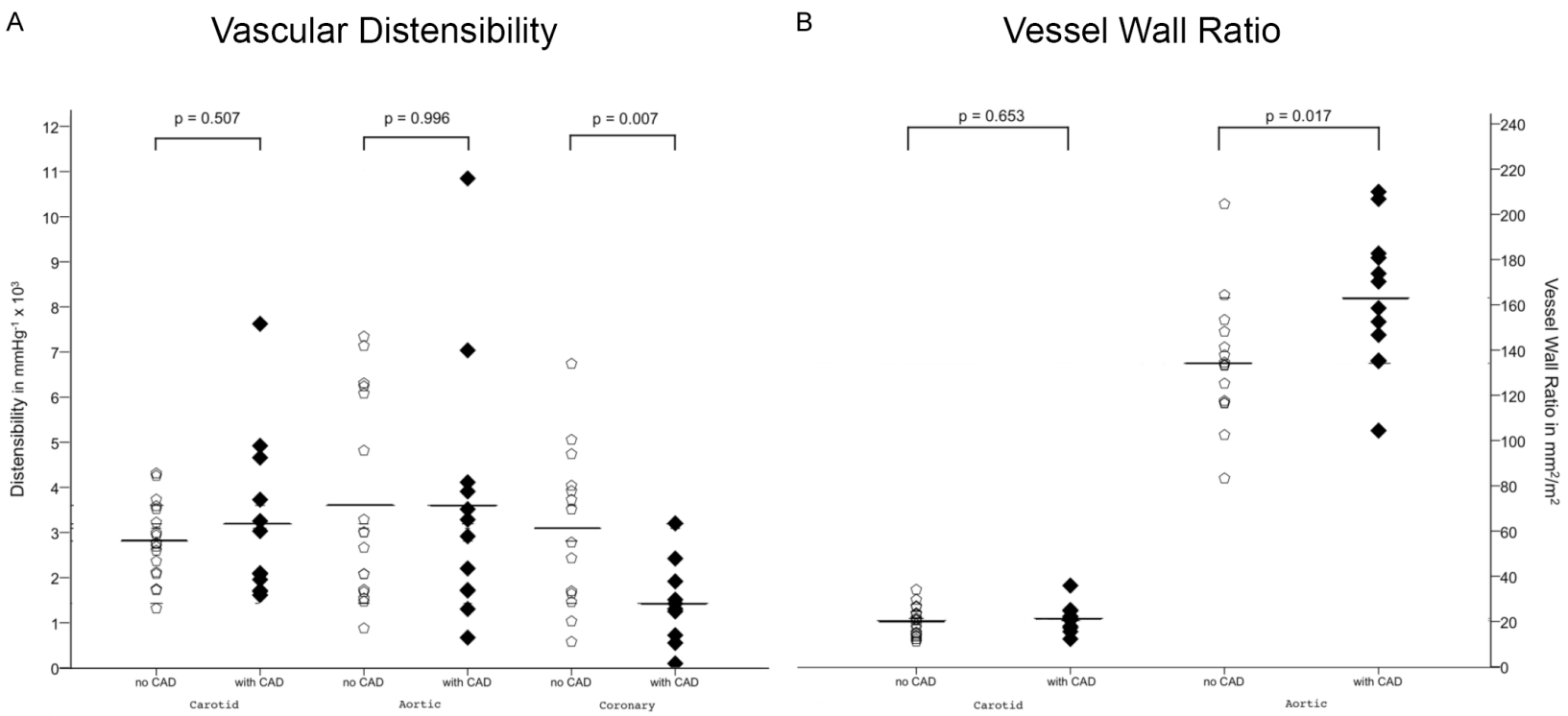

Figure 5. Comparison of Carotid, Aortic and Coronary Vascular Distensibility (A) and Carotid, Aortic and Coronary Vessel Wall Ratio (B) in Diabetic patients without and with Coronary Artery Disease (CAD).

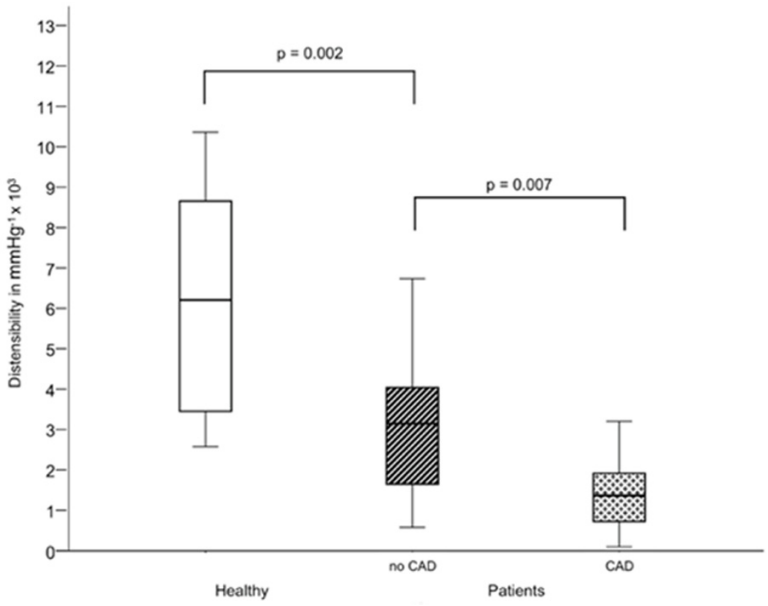

Figure 6. Comparison of Coronary Vascular Distensibility between Healthy Controls and Diabetic patients without and with Coronary Artery Disease (CAD).

in these vessels in T2DM. VWR of the coronary artery could not be obtained due to its small size. However, coronary VD was significantly altered in T2DM, regardless of pre-existing coronary stenosis or intervention. Even in the absence of CAD, the mean values of coronary VD were halved compared to the healthy volunteers of this study (3.10 ± 1.75 vs. 6.35 ± 2.87 $mmHg^{-1} \times 10^3$, P = 0.012).

Remodeling in small vessels begins early in T2DM, and CAD likely represents only the final stage of the progressive atherosclerotic cascade over years. In addition, the age-related process of vascular stiffening is accelerated in diabetic patients, even more in long-standing disease and insulin therapy [28]. However, prior studies pointed out that a loss of elasticity can be partially reversible even at an advanced age, especially with regular physical activity [29]. The mean age of this group was 53 years, and the respective VD and VWR values were already significantly compromised. This underlines that the reported vascular alterations in T2DM patients are not simply triggered by the age difference of our two cohorts.

Previous studies described a correlation between the severity of coronary atherosclerosis and increased CIMT measured by ultrasound. A correlation of aortic wall thickening and increased lifetime risk of cardiovascular events was found when CT was used to assess the aorta [30, 31]. We found a significant correlation between the coronary VD and the carotid and aortic VWR in the patient group. Thickened carotid walls might indicate increased coronary risk in T2DM. In healthy participants, aortic and carotid VD correlated well with each other, whereas this was not the case in T2DM patients.

It remains unanswered whether glycemic control in T2DM patients improves arterial stiffness, independent of antihypertensive therapy. Long-term effects of hyperglycemia on aortic stiffness have previously been reported in Type 1 Diabetes (DMT1) [32]. As no follow-up data is included in this work, we cannot report on this in our T2DM patients. A mean HbA1c of 6.96% suggests however a considerably low long-term risk of complications and probably less accelerated stiffing. We suggest that future studies should address the effects of therapeutic agents and therapeutic adherence on atherosclerosis in T2DM.

A recent study found that regular physical activity might improve arterial stiffness in T2DM patients [33]. Unfortunately, no information regarding physical activity was available in this study.

Among the major limits of this study is the relatively modest sample size. Small differences between groups might therefore have been missed. Due to the limited spatial resolution of the images, the SD in the VD values is high. Another limitation is the use of non-invasive peripheral blood pressure to obtain VD in the aorta and coronaries. The invasiveness though clearly limits the feasibility of these central measurements. The results have furthermore not been compared with other imaging modalities. Concerning the common carotid artery, ultrasound-derived CIMT measurements would have allowed a valid comparison to a standard technique of daily clinical practice. Also, a com-

Table 4. CMR findings of cross-sectional luminal areas, vascular distensibility, and vessel wall areas

Characteristics	Healthy subjects (n = 9)	Age-matched Diabetic patients (n = 10)	*P*-value
Cross-sectional area measurements (mm^2)			
Common Carotid Artery			
Lumen max	38.78 ± 11.04 (38.17)	47.12 ± 10.76 (50.10)	P = 0.124
Lumen min	33.62 ± 10.65 (32.09)	41.36 ± 9.97 (43.39)	P = 0.131
Ascending Aorta			
Lumen max	823.38 ± 215.32 (877.86)	875.78 ± 176.08 (836.75)	P = 0.587
Lumen min	737.00 ± 210.79 (774.10)	763.96 ± 181.61 (687.24)	P = 0.779
Coronary Artery			
Lumen max	18.06 ± 5.95 (15.64)	15.22 ± 3.07 (15.18)	P = 0.201
Lumen min	14.23 ± 5.19 (13.07)	13.89 ± 2.83 (13.90)	P = 0.860
Vascular distensibility ($mmHg^{-1} \times 10^{-3}$)			
Common Carotid Artery	3.91 ± 1.78 (3.71)	2.80 ± 1.20 (2.51)	P = 0.507
Ascending Aorta	3.01 ± 1.38 (2.64)	3.04 ± 1.70 (2.56)	P = 0.973
Coronary Artery	6.35 ± 2.87 (6.20)	1.92 ± 1.26 (1.67)	P < 0.001
Vessel Wall Area (mm^2)			
Common Carotid Artery			
Outer Lumen	55.63 ± 12.31 (54.35)	78.31 ± 20.94 (74.28)	P = 0.012
Inner Lumen	31.23 ± 9.07 (29.75)	38.52 ± 9.30 (37.10)	P = 0.114
Vessel Wall Area	24.41 ± 3.88 (24.45)	39.79 ± 12.37 (38.10)	P = 0.003
Vessel Wall Ratio ($\times 10^{-6}$)	13.18 ± 1.90 (13.74)	18.93 ± 6.54 (18.36)	P = 0.023
Ascending Aorta			
Outer Lumen	883.36 ± 203.09 (917.15)	1061.80 ± 143.28 (1074.10)	P = 0.064
Inner Lumen	725.06 ± 194.45 (751.20)	767.50 ± 142.55 (754.90)	P = 0.628
Vessel Wall Area	158.30 ± 23.40 (148.60)	294.30 ± 52.78 (285.95)	P < 0.001
Vessel Wall Ratio ($\times 10^{-6}$)	85.38 ± 8.54 (88.46)	138.30 ± 21.36 (139.49)	P < 0.001

Comparison of Healthy subjects (left column) and age-matched Diabetic patients (right column). Data expressed as mean ± standard deviation. Values in brackets represent median values.

Table 5. Intra- and Interobserver measurements

Characteristics	Intra-observer agreement (ICC; 95% CI)	Inter-observer agreement (ICC; 95% CI)
Vascular distensibility		
Common Carotid Artery	0.99 (0.98/0.99); P < 0.001	0.98 (0.94/0.99); P < 0.001
Ascending Aorta	0.86 (0.45/0.97); P = 0.001	0.86 (0.45/0.96); P = 0.004
Coronary Artery	0.87 (-0.02/0.97); P < 0.001	0.83 (0.37/0.96); P = 0.006
Vessel Wall Ratio		
Common Carotid Artery	0.95 (0.37/0.98); P < 0.001	0.99 (0.97/0.99); P < 0.001
Ascending Aorta	0.95 (0.51/0.99); P < 0.001	0.96 (0.86/0.99); P < 0.001

CI: Confidence interval; ICC: Intra-class correlation.

parison with CT would have been of high interest, but radiation exposure did not justify the use of this technique in our cohort. Moreover, our CMR sampling selected only limited segments of an artery when measuring the lumen. Such measurements reflect the ability to distend only at a single position and limit the significance of the overall atherosclerotic burden that may be regionally heterogeneous in the coronary artery vasculature.

Conclusions

Our findings suggest that CMR allows a simultaneous evaluation of the structure and function of three important vascular territories to detect

vascular remodeling in T2DM patients. T2DM patients showed significant reductions in coronary artery VD and increases in aortic VMR, potentially reflecting atherosclerotic remodeling. The alterations were more pronounced in T2DM patients with CAD than those without. CMR assessed VD and VMR might therefore serve as early markers for cardiovascular remodeling in diabetic patients and aid in the diagnosis, risk stratification, and therapy of cardiovascular disease. Potentially, a combination of CMR and CT to assess the calcific burden of the vasculature could improve this prediction.

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Address correspondence to: Sebastian Kelle, Department of Cardiology, Angiology and Intensive Care Medicine, Deutsches Herzzentrum der Charité, Berlin, Germany; DZHK (German Center for Cardiovascular Research), Partner Site Berlin, Germany. E-mail: sebastian.kelle@dhzc-charite.de

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