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Journal of Cardiovascular Computed Tomography 16 (2022) 319–326

Contents lists available at ScienceDirect

Journal of Cardiovascular Computed Tomography

journal homepage: www.JournalofCardiovascularCT.com

Research paper

Coronary volume to left ventricular mass ratio in patients with diabetes mellitus

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ARTICLE INFO

Keywords:
Coronary volume
Left ventricular mass
Volume to mass ratio
Coronary computed tomography angiography
Coronary artery disease
Diabetes mellitus

ABSTRACT

Background: Diabetes mellitus is a major risk factor for coronary artery disease (CAD) and may provoke structural and functional changes in coronary vasculature. The coronary volume to left ventricular mass (V/M) ratio is a new anatomical parameter capable of revealing a potential physiological imbalance between coronary vasculature and myocardial mass. The aim of this study was to examine the V/M derived from coronary computed tomography angiography (CCTA) in patients with diabetes.

Methods: Patients with clinically suspected CAD enrolled in the ADVANCE (Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care) registry and known diabetic status were included. Coronary artery volume and left ventricular myocardial mass were analyzed from CCTA and the V/M ratio was calculated and compared between patients with and without diabetes.

Results: Of the 3053 patients (age 66 ± 10 years; 66% male) with known diabetic status, diabetes was present in 21.9%. Coronary volume was lower in patients with diabetes compared to those without diabetes (2850 ± 940 mm^3 vs. 3040 ± 970 mm^3, $p < 0.0001$), whereas the myocardial mass was comparable between the 2 groups (122 ± 33 g vs. 122 ± 32 g, $p = 0.70$). The V/M ratio was significantly lower in patients with diabetes (23.9 ± 6.8 mm^3/g vs. 25.7 ± 7.5 mm^3/g, $p < 0.0001$). Among subjects with obstructive CAD (n = 2191, 24.0% diabetics)

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https://doi.org/10.1016/j.jcct.2022.01.004
Received 16 July 2021; Received in revised form 24 January 2022; Accepted 25 January 2022
Available online 1 February 2022

and non-obstructive CAD (16.7% diabetics), the V/M ratio was significantly lower in patients with diabetes compared to those without (23.4 ± 6.7 mm^3/g vs. 25.0 ± 7.3 mm^3/g, $p < 0.0001$ and 25.6 ± 6.9 mm^3/g vs. 27.3 ± 7.6 mm^3/g, respectively, $p = 0.006$).

Conclusion: The V/M ratio was significantly lower in patients with diabetes compared to non-diabetics, even after correcting for obstructive coronary stenosis. The clinical value of the reduced V/M ratio in diabetic patients needs further investigation.

List of abbreviations

ADVANCE	Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary Care registry
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
FFR	Fractional flow reserve
FFR_{CT}	CCTA-derived fractional flow reserve
LV	Left ventricular
V/M	Coronary artery volume to left ventricular myocardial mass

1. Introduction

The ratio of the total epicardial coronary artery lumen volume to left ventricular (LV) myocardial mass (V/M) is a newly available anatomical parameter capable of revealing a potential physiological imbalance between the supply (coronary artery epicardial volume) and demand (myocardial mass).[1,2] Previous studies observed that low V/M ratios derived from coronary computed tomography angiography (CCTA) were related with more advanced CAD, reduced myocardial blood flow and lesion-specific fractional flow reserve (FFR) ≤0.80 suggesting ischemia.[2,3]

Diabetes mellitus is a major risk factor for CAD affecting millions of people worldwide.[4,5] Moreover, diabetes has been associated with increased total coronary artery plaque burden, more advanced coronary atherosclerosis, and increased risk of adverse cardiovascular events.[6–10] In addition, diabetes has been associated with abnormalities in the coronary circulation including microvascular dysfunction and reduced vasodilation capacity.[11]

The high rate of adverse events in diabetic patients with CAD has raised questions about the roles of anatomic and functional characteristics of diabetic coronary arteries. The V/M ratio might provide additional insight into the epicardial vascular characteristics and risk in patients with diabetes. However, data examining the V/M ratio in patients with diabetes are lacking. The aim of this study is to evaluate the association of the V/M ratio with the diabetic status using the data from a large multicenter registry comprising diabetic and non-diabetic subjects with clinically suspected CAD.

2. Methods

2.1. Study populations

Patients were selected from the *Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary Care* (ADVANCE) registry (NCT02499679). ADVANCE is an international multicenter, prospective registry designed to evaluate the utility of CCTA-derived Fractional Flow Reserve (FFR_{CT}) in the clinical setting. The design of the study has been described in detail previously.[12] In short, subjects were enrolled in 38 sites across North America, Europe, and Asia between July 2015–October 2017. Patients with clinically suspected CAD >18 years of age with documented atherosclerosis on CCTA and ability to provide written informed consent were included. The patients without CAD on CCTA, insufficient CCTA image quality, life expectancy <1 year and inability to comply with follow-up were excluded. In the present analysis, only patients with a) known diabetic status and b) coronary artery lumen volume and LV myocardial mass analysis were included. The study complied with the Declaration of Helsinki. All subjects provided written informed consent following local Institutional Review Board approval.

2.2. CCTA acquisition and image analysis

CCTA was performed in accordance with local and international guidelines using ≥64-row multidetector computed tomography scanners.[13,14] Sublingual nitrates were administered before scanning in all subjects and, if necessary, beta-blockers were administered in order to achieve a heart rate <60 bpm. All coronary arteries ≥2 mm diameter were evaluated for stenosis severity in accordance with current guidelines.[14] The strategy of visual CCTA assessment was left to the discretion of the local investigators of each site. CCTA images were submitted to a central core laboratory for FFR_{CT} and V/M analysis (HeartFlow Inc., Redwood City, California, USA) which has been described previously.[1,12,15–17] In brief, a 3-dimensional model of the coronary tree was derived from the CCTA datasets provided. For FFR_{CT} analysis, the luminal boundaries of all vessels >1 mm diameter were extracted, the total coronary flow was computed and coronary resistance under hyperemia was calculated. For V/M analysis, the total coronary arterial lumen volume and LV myocardial volume were measured.[18] The volume of the extracted myocardium was multiplied by 1.05 g/ml to calculate the myocardial mass. Subsequently, the ratio between the coronary arterial lumen volume and LV myocardial mass was calculated (Fig. 1).

2.3. Clinical endpoints

The diagnosis of diabetes was based on the medical history in the electronic case report forms. There was no sub-classification of Type 1 or 2 diabetes. Baseline patient characteristics, including cardiac risk factors and symptom status, and CCTA data were obtained and compared between patients with and without diabetes. In addition, the coronary volume and LV myocardial mass were separately analyzed among subjects with anatomically obstructive and non-obstructive CAD. Obstructive CAD was defined as any atherosclerotic lesion ≥50% diameter stenosis.

2.4. Statistical analysis

Continuous variables following a normal distribution are presented as mean ± standard deviation (SD). Continuous variables were compared using a 2-sample *t*-test with Satterthwaite approximation for the degrees of freedom. Categorical variables are presented as absolute numbers and percentages (%) and were compared using the $\chi 2$ test. Analysis of covariance (ANCOVA) models were used to correct for the potential confounding effect of age, body mass index, hypertension, hyperlipidemia, smoking status and the number of vessels with obstructive CAD on the coronary volume and LV myocardial mass as well as V/M ratio, and were used as covariates. The differences in coronary volume, LV myocardial mass and the V/M ratio between patients with and without diabetes in the ANCOVA models are presented as least square (LS) mean difference estimate with 95% confidence intervals (CI). A p-value <0.05 was considered significant. All statistical analysis were performed using SAS version 9.4 (SAS institute, Cary, North Carolina, USA).

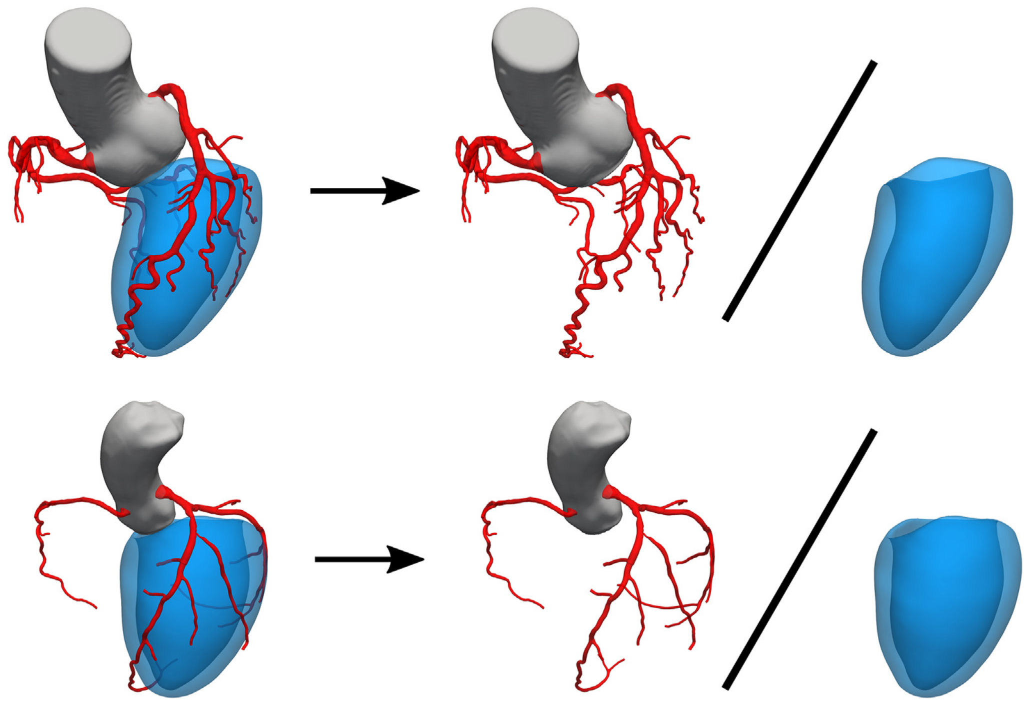

Figure 1. Graphical presentation of the coronary artery volume and left ventricular myocardial mass and the coronary volume to left ventricular mass ratio showing the difference between a non-diabetic (top of figure) and a diabetic patient (bottom of figure). Both subjects had non-obstructive coronary artery disease (0–30% diameter stenosis).

3. Results

3.1. Study population

A total of 5083 patients were enrolled in the ADVANCE registry. Of these, 3053 patients (age 66.4 ± 10.3 years; 66% male) with known diabetic status and measured V/M ratio were included in this analysis. A flowchart of patient enrolment and follow-up is shown in Fig. 2. Comparison of the patients included in the analysis versus those excluded due to missing V/M ratios is shown in the Supplemental Table 1. Diabetes was present in 670 patients (21.9%). Baseline patient demographic and clinical characteristics are summarized in

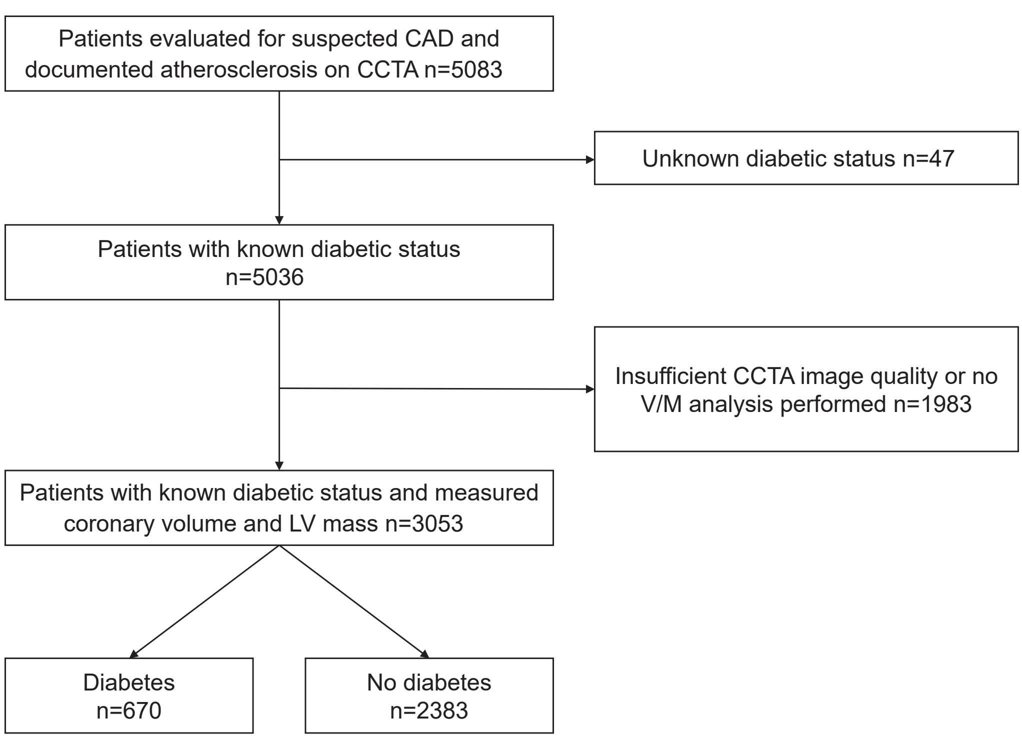

Figure 2. Flowchart study population. CAD = coronary artery disease, CCTA = coronary computed tomography angiography, LV = left ventricular, V/M = coronary volume and left ventricular mass.

Table 1. Patients with diabetes had a higher cardiovascular risk profile, were older (67.6 ± 9.8 vs 66.1 ± 10.4 years, p = 0.001), had a higher body mass index (BMI) (27.0 ± 5.2 vs 26.1 ± 4.7 kg/m^2, p < 0.0001) and were more likely to be current smokers (p = 0.039) as compared to patients without diabetes. In addition, hypertension and hyperlipidemia were more often present among patients with diabetes (both p < 0.0001).

3.2. CCTA parameters and coronary volume to mass ratio in diabetic and non-diabetic patients

The main CCTA characteristics are reported in Table 2. Patients with diabetes had more frequently obstructive CAD and severe stenosis by anatomical CCTA evaluation (both p < 0.0001). In the quantitative analysis, epicardial coronary artery volume was lower in patients with diabetes (2850 ± 940 mm^3 vs. 3040 ± 970 mm^3, p < 0.0001), whereas the LV myocardial mass was comparable between patients with and without diabetes (122 ± 33 g vs. 122 ± 32 g, p = 0.70). The V/M ratio was significantly lower in patients with diabetes (23.9 ± 6.8 mm^3/g vs. 25.7 ± 7.5 mm^3/g, p < 0.0001, Fig. 3).

Table 1
Baseline patient demographic and clinical characteristics of patients according to diabetic status.

	Total (n = 3053)	Diabetes (n = 670)	No diabetes (n = 2383)	p-value
Age, y	66.4 ± 10.3	67.6 ± 9.8	66.1 ± 10.4	0.001
Male sex, n (%)	2021 (66.2)	453 (67.6)	1568 (65.8)	0.38
Body mass index, kg/m^2	26.3 ± 4.8	27.0 ± 5.2	26.1 ± 4.7	<0.0001
Diamond Forrester CAD likelihood	51 ± 20	52 ± 20	51 ± 20	0.14
Hypertension, n (%)	1856 (60.8)	510 (76.1)	1346 (56.5)	<0.0001
Hyperlipidemia, n (%)	1851 (60.6)	482 (71.9)	1369 (57.4)	<0.0001
Tobacco use, n (%)				
Current smoker	496 (16.2)	131 (19.6)	365 (15.3)	0.039
Ex-Smoker	1046 (34.3)	230 (34.3)	816 (34.2)	
Never Smoked	1291 (42.3)	269 (40.1)	1022 (42.9)	
Unknown	220 (7.2)	40 (6.0)	180 (7.6)	
Angina status, n (%)				
Typical	597 (19.6)	131 (19.6)	466 (19.6)	0.042
Atypical	1098 (36.0)	228 (34.0)	870 (36.5)	
Dyspnea	343 (11.2)	68 (10.1)	275 (11.5)	
Non-cardiac Pain	181 (5.9)	31 (4.6)	150 (6.3)	
None	811 (26.6)	206 (30.7)	605 (25.4)	
Unknown	23 (0.8)	6 (0.9)	17 (0.7)	
CCS Angina class, n (%)				
Grade I	141/597 (23.6)	32/131 (24.4)	109/466 (23.4)	0.067
Grade II	334/597 (55.9)	69/131 (52.7)	265/466 (56.9)	
Grade II	62/597 (10.4)	20/131 (15.3)	42/466 (9.0)	
Grade IV	11/597 (1.8)	5/131 (3.8)	6/466 (1.3)	
Unknown	49/597 (8.2)	5/131 (3.8)	44/466 (9.4)	

Data are presented as mean ± SD or n (%). CAD = coronary artery disease; CCS = Canadian Cardiovascular Society.

3.3. Clinical and CCTA parameters and coronary volume to mass ratio in patients with obstructive CAD

Obstructive CAD was present in 2191 subjects (71.9%) of which 525 (24.0%) had diabetes. Baseline patient demographic and clinical characteristics for patients with obstructive CAD are shown in Table 3. In subjects with obstructive CAD, patients with diabetes were older (p = 0.03), had a higher BMI (p = 0.0003), had more frequently a history of hypertension and hyperlipidemia (p < 0.0001 for both), and were more likely to be current smokers (p = 0.045).

Coronary volume was significantly lower in patients with diabetes compared to non-diabetic patients who had obstructive coronary

Table 2
Coronary computed tomography angiography parameters of patients according to diabetic status.

	Total (n = 3053)	Diabetes (n = 670)	No diabetes (n = 2383)	p-value
CCTA anatomical stenosis, n (%)				
Non-obstructive stenosis <50%	856 (28.0)	143 (21.3)	713 (29.9)	<0.0001
Obstructive stenosis ≥50%	2191 (71.8)	525 (74.4)	1666 (69.9)	
Unknown	6 (0.2)	2 (0.3)	4 (0.2)	
Non-severe stenosis ≤70%	2069 (67.8)	388 (57.9)	1681 (70.5)	<0.0001
Severe stenosis >70%	978 (32.0)	280 (41.8)	698 (29.3)	
Unknown	6 (0.2)	2 (0.3)	4 (0.2)	
Degree stenosis, n (%)				
Normal (0%)	18 (0.6)	3 (0.4)	15 (0.6)	<0.0001
Minimal (0–30%)	158 (5.2)	22 (3.3)	136 (5.7)	
Mild (30–50%)	680 (22.3)	118 (17.6)	562 (23.6)	
Moderate (50–70%)	1213 (39.7)	245 (36.6)	968 (40.6)	
Severe (70–90%)	687 (22.5)	194 (29.0)	493 (20.7)	
Sub-total/occluded (≥90%)	291 (9.5)	86 (12.8)	205 (8.6)	
Unknown	6 (0.2)	2 (0.3)	4 (0.2)	
Number of vessels with anatomically obstructive CAD ≥50% DS, n (%)				
0	856 (28.0)	143 (21.3)	713 (29.9)	<0.0001
1	1355 (44.4)	290 (43.3)	1065 (44.7)	
2	557 (18.2)	137 (20.4)	420 (17.6)	
3	279 (9.1)	98 (14.6)	181 (7.6)	
4	0	0	0	
Unknown	6 (0.2)	2 (0.3)	4 (0.2)	
Rate of obstructive CAD per vessel, n (%)				
LAD stenosis <50%	1319 (43.2)	247 (36.9)	1072 (45.0)	0.0002
LAD stenosis ≥50%	1734 (56.8)	423 (63.1)	1311 (55.0)	
LCX stenosis <50%	2321 (76.0)	457 (68.2)	1864 (78.2)	<0.0001
LCX stenosis ≥50%	732 (24.0)	213 (31.8)	519 (21.8)	
RCA stenosis <50%	2213 (72.5)	448 (66.9)	1765 (74.1)	0.0002
RCA stenosis ≥50%	840 (27.5)	222 (33.1)	618 (25.9)	
Coronary volume – myocardial mass				
Epicardial coronary artery volume, mm^3	3000 ± 970	2850 ± 940	3040 ± 970	<0.0001
LV myocardial mass, g	122 ± 32	122 ± 33	122 ± 32	0.70
Coronary volume/ mass ratio, mm^3/g	25.3 ± 7.4	23.9 ± 6.8	25.7 ± 7.5	<0.0001

Data are presented as mean ± SD or n (%). CAD = coronary artery disease; CCTA = coronary computed tomography angiography; DS = diameter stenosis; LAD = left anterior descending artery; LCX = left circumflex artery; LV = left ventricular; RCA = right coronary artery.

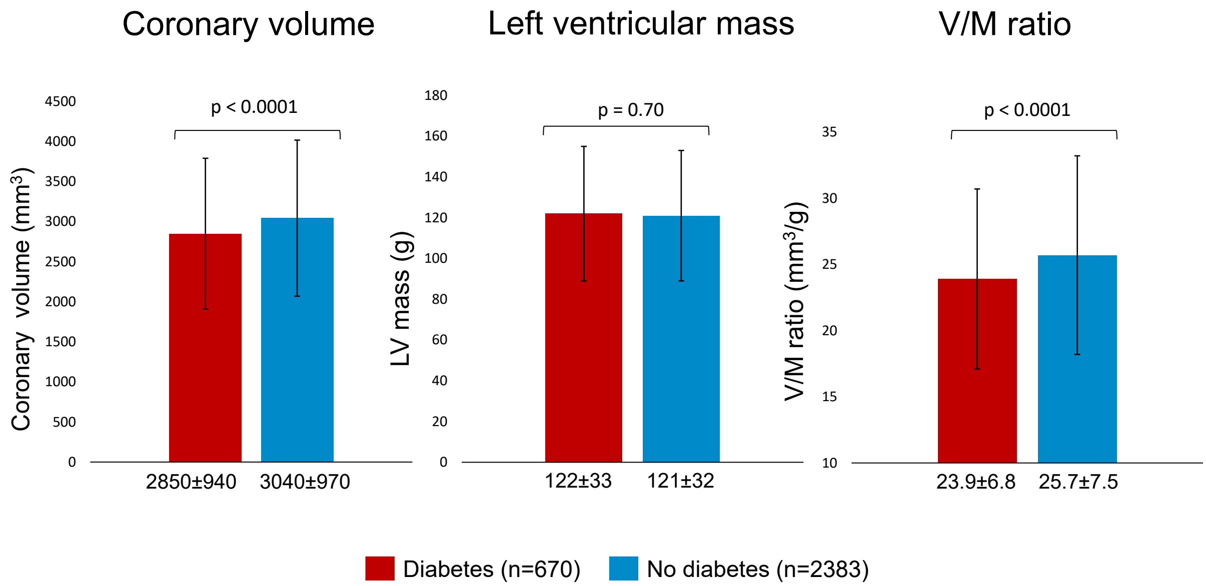

Figure 3. Bar chart showing the mean coronary artery volume, LV myocardial mass and V/M ratio for patients with and without diabetes.

disease (2800 ± 920 mm^3 vs. 2990 ± 950 mm^3, $p < 0.0001$). LV mass was not significantly different between groups (122 ± 31 g vs. 123 ± 32 g, respectively, $p = 0.63$). Accordingly, the V/M ratio was significantly lower in patients with diabetes (23.4 ± 6.7 mm^3/g vs. 25.0 ± 7.3 mm^3/g, $p < 0.0001$, Fig. 4).

3.4. Clinical and CTA parameters and coronary volume to mass ratio in patients with non-obstructive CAD

Diabetes was present in 143 out of 856 (16.7%) patients with non-obstructive CAD. Patients with diabetes were older ($p = 0.02$), had a

Table 3
Baseline patient demographic and clinical characteristics of patients with anatomically obstructive and non-obstructive CAD according to diabetic status.

	Obstructive CAD (≥50% DS)				Non-obstructive CAD (<50% DS)			
	Total (n = 2191)	Diabetes (n = 525)	No diabetes (n = 1666)	p-value	Total (n = 856)	Diabetes (n = 143)	No diabetes (n = 713)	p-value
Age, y	66.8 ± 10.1	67.7 ± 9.7	66.6 ± 10.3	0.03	65.3 ± 10.6	67.2 ± 10.1	64.9 ± 10.7	0.02
Male sex, n (%)	1526 (69.6)	374 (71.2)	1152 (69.1)	0.3637	492 (57.5)	78 (54.5)	414 (58.1)	0.44
Body mass index, kg/m^2	26.1 ± 4.6	26.8 ± 5.0	25.9 ± 4.5	0.0003	26.7 ± 5.3	27.9 ± 5.6	26.4 ± 5.2	0.005
Diamond Forrester CAD likelihood	53 ± 20	54 ± 20	53 ± 20	0.37	46 ± 19	46 ± 19	46 ± 19	0.95
Hypertension, n (%)	1365 (62.3)	397 (75.6)	968 (58.1)	<0.0001	487 (56.9)	111 (77.6)	376 (52.7)	<0.0001
Hyperlipidemia, n (%)	1332 (60.8)	372 (70.9)	960 (57.6)	<0.0001	514 (60.0)	108 (75.5)	406 (56.9)	<0.0001
Tobacco use, n (%)								
Current smoker	386 (17.6)	112 (21.3)	274 (16.4)	0.045	109 (12.7)	18 (12.6)	91 (12.8)	0.99
Ex-Smoker	758 (34.6)	182 (34.7)	576 (34.6)		286 (33.4)	48 (33.6)	238 (33.4)	
Never Smoked	896 (40.9)	202 (38.5)	694 (41.7)		393 (45.9)	67 (46.9)	326 (45.7)	
Unknown	151 (6.9)	29 (5.5)	122 (7.3)		68 (7.9)	10 (7.0)	58 (8.1)	
Angina status, n (%)								
Typical	500 (22.8)	118 (22.5)	382 (22.9)	0.032	96 (11.2)	13 (9.1)	83 (11.6)	0.74
Atypical	740 (33.8)	172 (32.8)	568 (34.1)		356 (41.6)	56 (39.2)	300 (42.1)	
Dyspnea	222 (10.1)	45 (8.6)	177 (10.6)		121 (14.1)	23 (16.1)	98 (13.7)	
Non-cardiac Pain	120 (5.5)	20 (3.8)	100 (6.0)		59 (6.9)	9 (6.3)	50 (7.0)	
None	594 (27.1)	166 (31.6)	428 (25.7)		216 (25.2)	40 (28.0)	176 (24.7)	
Unknown	15 (0.7)	4 (0.8)	11 (0.7)		8 (0.9)	2 (1.4)	6 (0.8)	
CCS Angina class, n (%)								
Grade I	117/500 (23.4)	27/118 (22.9)	90/382 (23.6)	0.048	23/96 (24.0)	5/13 (38.5)	18/83 (21.7)	0.64
Grade II	284/500 (56.8)	62/118 (52.5)	222/382 (58.1)		50/96 (52.1)	7/13 (53.8)	43/83 (5.8)	
Grade III	58/500 (11.6)	20/118 (16.9)	38/382 (9.9)		4/96 (4.2)	0/13	4/83 (4.8)	
Grade IV	10/500 (2.0)	5/118 (4.2)	5/382 (1.3)		1/96 (1.0)	0/13	1/83 (1.2)	
Unknown	31/500 (6.2)	4/118 (3.4)	27/382 (7.1)		18/96 (18.8)	1/13 (7.7)	17/83 (20.5)	
Coronary volume – myocardial mass								
Epicardial coronary artery volume, mm^3	2940 ± 950	2800 ± 920	2990 ± 950	<0.0001	3150 ± 1010	3030 ± 1000	3170 ± 1020	0.13
LV myocardial mass, g	123 ± 32	122 ± 32	123 ± 32	0.63	120 ± 33	122 ± 39	119 ± 32	0.31
Coronary volume/mass ratio, mm^3/g	24.6 ± 7.2	23.4 ± 6.7	25.0 ± 7.3	<0.0001	27.0 ± 7.5	25.6 ± 6.9	27.3 ± 7.6	0.006

Data are presented as mean ± SD or n (%). CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; LV = left ventricular.

higher BMI ($p = 0.005$), had more frequently a history of hypertension and hyperlipidemia ($p < 0.0001$ for both). Smoking status was similar between patients with and without diabetes in subjects with non-obstructive CAD ($p = 0.99$, Table 3) which was in contrast to those with obstructive coronary disease.

Coronary volume was not significantly different between patients with and without diabetes who did not have obstructive coronary disease (3030 ± 1000 mm^3 vs. 3170 ± 1020 mm^3, $p = 0.13$). Moreover, LV mass was comparable between groups (122 ± 39 g vs. 119 ± 32 g, respectively, $p = 0.31$). Still, the V/M ratio was significantly lower in patients with diabetes (25.6 ± 6.9 mm^3/g vs. 27.3 ± 7.6 mm^3/g, $p = 0.006$, Fig. 4).

Similar results were observed when correcting for the differences in baseline and CCTA characteristics between patients with and without diabetes: significantly lower coronary volume and V/M ratio in patients with diabetes versus those without (LS mean difference estimate: −209 (95% CI: −295,-123) mm^3, $p < 0.001$ and −1.4 (95% CI: −2.0, −0.8) mm^3/g, $p < 0.001$, respectively), whereas the myocardial mass was comparable in both groups (LS mean difference estimate: −2.3 (95% CI: −5.0, 0.5) g, $p = 0.19$).

4. Discussion

We examined the coronary V/M ratio in patients with and without diabetes in the multicenter ADVANCE registry comprising subjects with suspected stable CAD. We found that patients with diabetes had a significantly lower V/M ratio compared to those without diabetes. This difference was observed not only in diabetic patients with obstructive CAD but also among those with non-obstructive CAD or when corrected for differences in baseline characteristics.

The principle of the V/M ratio is based on allometric scaling laws and was first described by Gould et al. over 40 years ago.[19] More recently, CCTA proved to be an excellent noninvasive instrument capable to perform coronary volume and myocardial mass analysis. Previous studies including data from the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) and PACIFIC (Prospective Comparison of CCTA, SPECT, PET, and Hybrid Imaging for Diagnosis of Ischemic Heart Disease using FFR) trials reported that patients with a low V/M ratio had more extensive atherosclerosis and also reduced myocardial blood flow on positron emission tomography compared to patients with a high V/M ratio.[3] Furthermore, the V/M ratio was independently associated with an FFR ≤0.80.[2]

Diabetes has been linked with increased risk of atherosclerosis but also abnormalities in the coronary circulation including microvascular dysfunction and reduced vasodilation capacity.[11] We observed that the decreased V/M ratio in patients with diabetes was mainly driven by lower coronary artery volume while LV myocardial mass was comparable between the groups. As the presence of atherosclerosis has been linked with reduced coronary volume, we analyzed separately the patients with and without obstructive CAD. The V/M ratio in diabetic patients was found to be reduced in both groups.

The question arises why the V/M ratio is lower in patients with diabetes compared to non-diabetics. Since the LV mass is similar in both groups, the difference in the V/M ratio is explained by the lower coronary volume. There are several potential mechanisms by which the coronary volume - and thus the V/M ratio - is reduced in patients with diabetes. One explanation is that atherosclerosis is more advanced, even in the group without obstructive CAD. Patients with diabetes have shown increased plaque burden and more advanced atherosclerosis compared to non-diabetic patients with a subsequent augmented risk of adverse outcome.[7,20,21] Atherosclerosis may also reduce the coronary volume, not only directly via its lumen narrowing effect, but also as a result of impaired endothelial function with a subsequent reduction of vasodilator capacity.[22]

The vascular complications of diabetes independent of atherosclerosis might provide a second explanation for the lower V/M ratios in diabetic patients. As a result of insulin resistance, chronic hyperglycemia and autonomic dysfunction, diabetes may alter vascular structure and function. High glucose concentrations lead to endothelial dysfunction due to several pathophysiological mechanisms including an imbalance between nitric oxide bioavailability and accumulation of reactive oxygen species.[23] Accordingly, endothelial dysfunction results in reduced vasodilatation after the admission of nitrates. Moreover, this impaired response to hyperemia has been found even in the absence of atherosclerosis.[24]

Microvascular dysfunction has been linked with reduced V/M ratio in a retrospective case-control study by Grover et al.[1] that reported significantly lower V/M ratios in patients who met the criteria for microvascular angina as compared to their matched controls. This difference was mainly driven by lower coronary artery volumes. These results support the hypothesis that a lower V/M ratio could be linked with microvascular dysfunction in patients with diabetes, although no direct evidence for this was provided by the present study.

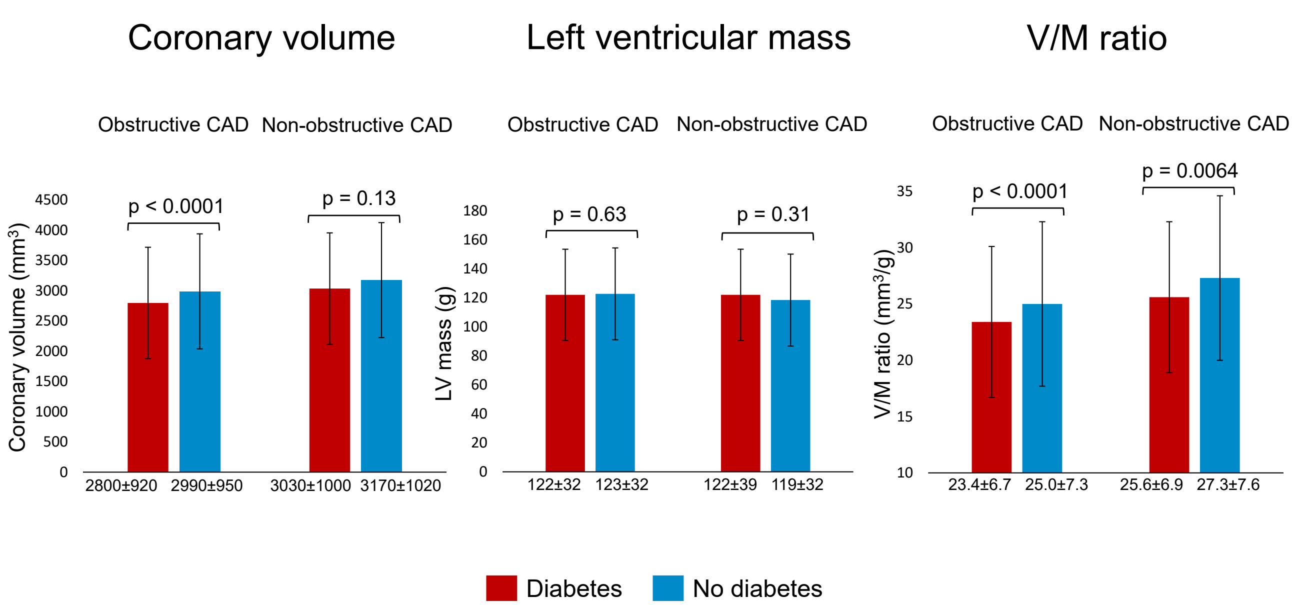

Figure 4. Bar chart showing the mean coronary artery volume, LV myocardial mass and V/M ratio for diabetic and non-diabetic patients in subjects with anatomically obstructive and non-obstructive CAD.

4.1. Limitations

This study has some limitations. First, the ADVANCE registry, as with all registries, may have been affected by referral bias. Second, of the total of 5083 subjects enrolled in the ADVANCE registry, diabetic status was unknown in 47 patients. In addition, the V/M ratio analysis was performed in only 3053 studies because of software development during the study time period. However, the patient characteristics of the population with measured V/M ratio were comparable with the total population in this registry (Supplemental Table 1). Fourth, this study lacked the ability to further characterize atherosclerosis. In addition, right ventricular mass was not measured in the current analysis. At last, the diagnosis of diabetes was based on medical history and detailed information about the severity and duration as well as type and treatment of the diabetes was lacking.

5. Conclusion

The coronary volume to myocardial mass ratio was significantly lower in patients with diabetes compared to non-diabetics, even after correcting for obstructive coronary stenosis and differences in baseline characteristics. Whether this is due to more advanced CAD in diabetics or diabetic-related changes in coronary structure and function remains unclear. These intriguing findings provide interesting data for future studies. The clinical value of the V/M ratio needs also further investigation.

Funding

This study was supported by HeartFlow Inc., Redwood City, CA, USA.

Declaration of competing interest

The department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands has received unrestricted research grants from Medtronic, Biotronik, Boston Scientific, and Edwards Lifesciences. Dr. Patel has received research grants from HeartFlow, Bayer, Janssen, and the National Heart, Lung, and Blood Institute; and has served on the advisory board for HeartFlow, Bayer, and Janssen. Dr. Nørgaard has received unrestricted institutional research grants from Siemens and HeartFlow. Dr. Fairbairn has served on the Speakers Bureau for HeartFlow. Dr. Nieman has received institutional research support from Siemens Healthineers, HeartFlow, GE Healthcare, and Bayer Healthcare. Dr. Berman has received unrestricted research support from HeartFlow. Dr. Hurwitz Koweek has received research support and speaking fees from HeartFlow and Siemens. Dr. Pontone has received institutional research grant and/or honorarium as consultant/speaker from GE Healthcare, Boehringer, Bracco, Medtronic, Bayer, and HeartFlow. Dr. Sonck has received research grant support from the Cardiopath PhD program. Dr. Rabbat has served as a consultant for HeartFlow. Dr. De Bruyne has received consulting fees from Abbott, Opsens, and Boston Scientific; and is a shareholder for Siemens, GE Healthcare, Bayer, Philips, HeartFlow, Edwards Lifesciences, and Sanofi. Dr. Rogers is employee of and owns equity in HeartFlow. Dr. Leipsic has received research grants from GE Healthcare and Edwards Lifesciences; and has served as a consultant for and holds stock options in Circle Cardiovascular Imaging and HeartFlow Inc. Dr. Bax has received speaker fees from Abbot Vascular. Dr. Knuuti has received consultancy fees from GE Healthcare and AstraZeneca and speaker fees from GE Healthcare, Bayer, Lundbeck, Boehringer-Ingelheim and Merck, outside of the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Acknowledgements

The authors would like to thank Ms. Amy Flynt (PharPoint Research), Ms. Whitney Huey and Ms. Sarah Mullen for their contribution towards data collection and analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2022.01.004.

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