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Type 2 diabetes mellitus is associated with increased left ventricular mass independent of coronary artery volume

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AIM: To determine the relationship of left ventricular mass (LVM) and coronary artery volume in diabetic patients and the controls.

MATERIALS AND METHODS: This work included 448 consecutive patients (206 patients with diabetes and 242 non-diabetic participants) who underwent coronary computed tomography angiography (CTA) for evaluation of coronary artery disease (CAD). The whole coronary artery tree and the LVM were analysed using a cardiac imaging workstation. Multivariable logistic regression analysis was used to determine the independent association with coronary artery lumen volume to LVM ratio (V/M).

RESULTS: The total coronary artery cumulative volume and the coronary cumulative length showed no differences between groups ($p>0.05$); however, the LVM in patients with diabetes was significantly greater than that in controls (132.46±45.04 versus 115.82±29.13, $p=0.006$), and the total epicardial coronary arterial lumen volume to LVM ratio (V/M) was significantly lower in the diabetic group than in the non-diabetic group (2.02 cm^3/100±0.73 g versus 2.31 cm^3/100±0.82 g, $p=0.024$). In multivariate logistic regression analysis, diabetes was associated with V/M (odds ratio [OR] 2.027, 95% confidence interval [CI]: 1.462–2.728, $p=0.001$), and hypertension was not associated with V/M (OR 1.191, 95% CI: 0.978–1.451, $p=0.081$).

CONCLUSION: Patients with diabetes demonstrated a significantly lower coronary CTA-derived coronary V/M than controls. V/M may have an important role as a global measure of coronary vasculature in diabetic patients.

Introduction

Diabetes mellitus significantly increases the risk of coronary artery disease (CAD) in patients. Early effective identification and treatment of CAD in diabetic patients is recommended.[1,2] In addition to traditional clinical risk factors, such as hypertension, smoking and age, geometrical factors proved to be important in the development of atherosclerotic plaques.[3] Diabetes is characterised by a diffuse coronary plaques and is associated with increased left ventricular mass (LVM), a potent predictor of cardiovascular disease outcome. Several coronary studies have reported that epicardial coronary artery remodelling (positively remodelling or negatively remodelling) is

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characteristic of patients with diabetes[4]; however, the change in coronary artery size may not adequately indicate the severity of CAD. The relationship between coronary artery volume and LVM in diabetic patients remains unknown. Whether diabetes increases LVM independently of coronary artery volume has never been investigated. A new indicator of the coronary artery lumen volume to LVM ratio (V/M) has been successfully used in evaluating primary microvascular angina, fractional flow reserve in patients with CAD and quantification of coronary diffuse disease severity.[5,6] The indicator of low V/M, which may indicate hypoperfusion could be a novel potential clinical method for quantitatively evaluating the progression of CAD in diabetes. The purpose of this study was to investigate the relationship between V/M ratio in patients with and without diabetes using computed tomography angiography (CTA).

With the development of radiological technology, contrast-enhanced CTA has been routinely used for coronary plaque detection and coronary artery remodelling quantification. Coronary geometry reconstruction has been improved by new imaging techniques, such as planar reconstruction using CTA. To the authors' knowledge, the use of coronary CTA to non-invasively evaluate total coronary artery volume and LVM in at-risk diabetic patients has not yet been investigated. It was hypothesised that CTA can detect early coronary artery and ventricular mass scaling changes in diabetic patients without prior known CAD compared to those without diabetes.

Materials and methods

Patients

The present study was carried out as a retrospective case–control study from 1 January 2016 to 31 December 2017 in the Fourth Affiliated Hospital of Chinese Medical University and was approved by the Clinic Institutional Review Board of the hospital in accordance with the principles of the Helsinki Declaration. All patients provided written informed consent to be included in this study. Patients with at least a 5-year history of diabetes who underwent coronary CTA because of chest pain were included in the study. Diabetes was diagnosed according to the criteria recommended by the American Diabetes Association[7] comprising (1) a fasting blood glucose level of $\geq$7.1 mmol/l, or (2) symptoms of diabetes and a random blood glucose level of $\geq$11.1 mmol/l, or (3) treatment with hypoglycaemic medications or insulin. Type of angina was classified as being typical and atypical.[8] Participants were excluded if they had one of the following symptoms: (1) known coronary heart disease by history; (2) congenital heart disease; (3) presence of heart failure or cardiomyopathy; (4) known serious valve disease or serious arrhythmia; (5) other exclusion criteria included chronic inflammatory disorders, chronic kidney disease, and those with severe thyroid dysfunction and malignancy. Patients with anomalous coronary artery and severe segmental stenoses (stenosis diameter >50% or stenosis area >75%) were excluded from the study. Patients on statin therapy were also excluded because statins would affect coronary artery plaque volume.[9] All patients received a general health questionnaire survey. The questionnaire covered demographic background and medical history.

Data collection and selection of variables

All patients received blood tests before coronary tomography scanning. Blood samples were collected after fasting overnight for laboratory tests. The laboratory tests were conducted by certified experimental specialists using standard protocols at the hospital's Department of Diagnostics. Biomarkers were selected from the routine check-ups, including fasting plasma glucose level (FPG), fasting lipid profile, low-density lipoprotein level, high-density lipoprotein level, triglycerides level, haemoglobin A_{1c} (HbA_{1c}) level, and serum creatinine (Scr) level. Other data, such as age (years), sex (men/women), height, body weight, body mass index (BMI), history of hyperlipidaemia, blood pressure, history of hypertension, smoking history, and history of diabetes, were collected from patient records for clinical variables. BMI was calculated from the weight and height of each patient. Hypertension was defined as a systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg or use of antihypertensive drugs. Cigarette smoking was defined as smoking at least one cigarette per day for $\geq$1 years.[10,11]

Image acquisition

All patients with diabetes and the controls underwent coronary tomography due to clinical suspicion of CAD. The coronary angiography was performed with a 256-detector row Philips (Brilliance iCT 256, Philips Healthcare, The Netherlands) CT machine between 2016 and 2017. Each participant received a bolus of iodinated contrast material injected quickly through an arm vein. A helical scan protocol with electrocardiographic gating was applied. Patients with heart rate >65 beats/min were treated with oral β-blockers (metoprolol, 50 or 100 mg, single dose, 1 hour prior to the examination), and no nitroglycerine was given to any patient prior to the CT examination. To synchronise the contrast medium injection with scanning, bolus tracking was used. The image dataset was initially reconstructed at the diastolic phase of the R-R interval (75% of the R-R interval). Participants whose CTA examinations had poor coronary image quality were excluded from the study.

Image analysis

The CT image analysis was performed on a workstation with dedicated software (Philips Intellispace portal v6.0, PHILIPS Healthcare, The Netherlands). Image analysis was performed by an experienced imaging specialist blinded to the patient's clinical information. The epicardial coronary artery tree and left ventricle were segmented and extracted using the automatic and manual segment tool supplied by the workstation. As shown in Fig 1, the coronary artery geometry parameters (such as lengths, cross-sectional area, centrelines, and volume) were extracted from CTA images obtained from

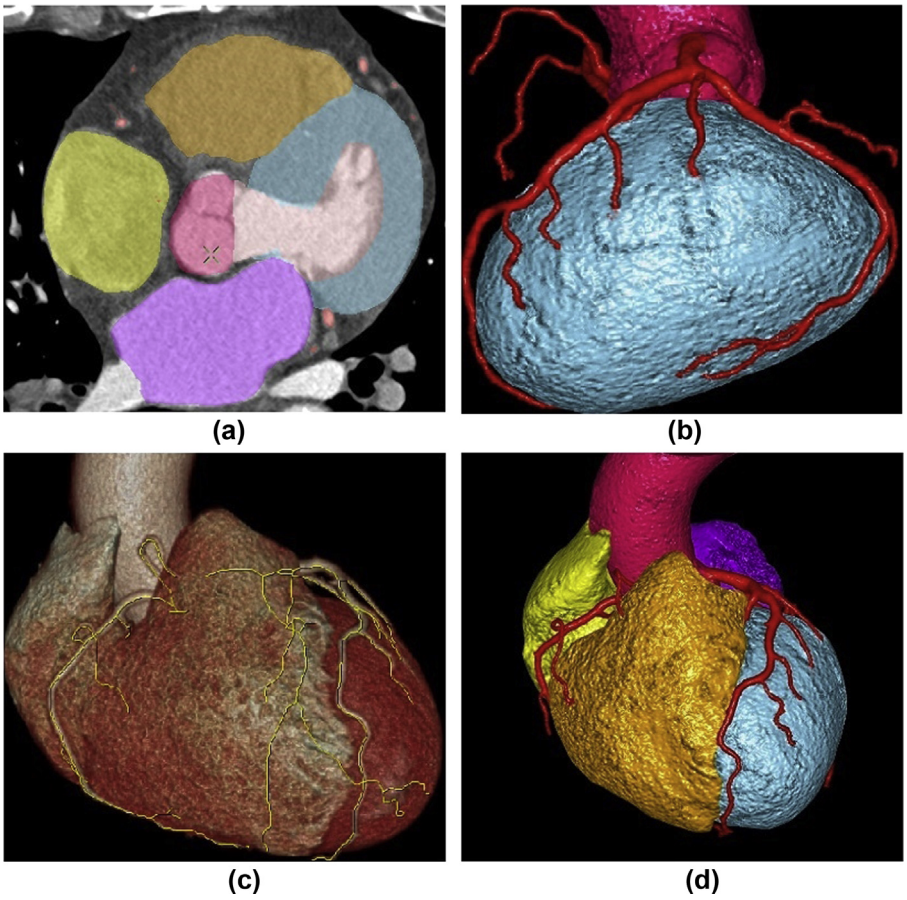

Figure 1 Representation of the total coronary artery and left ventricular segmentation. The process included: heart and left ventricular isolation (a, b), skeletonisation and coronary artery extraction (c), and 3D reconstruction of the coronary tree (d).

all patients. All automated contouring of the internal lumen was reviewed based on sections. When there was an obvious bias of the automated workstation's ability to properly determine true vessel boundaries, manual operation was performed for contouring the centreline and luminal boundaries. In the analysis, only vessels with a diameter of at least 1 mm were included. The lumen cross-section in the analysis was measured every 0.43 mm along the length of the coronary vessels, starting at the ostium.

Volume to mass calculation

Once the entire vessel was reconstructed, summed coronary artery branch lengths (L) and summed total coronary artery lumen volumes (V) in each patient were calculated. The volume of the myocardium was extracted from imaging data and multiplied by an average value for myocardial tissue density to calculate the LVM. Last, the ratio of the total epicardial coronary arterial lumen volume to LVM was computed.

$$V/M = V_c/LVM$$

L_c was defined as the sum of the lengths of each vessel segment in the entire crown coronary artery, V_c was defined as the sum of the intravascular volume of the left and right coronary artery segment detectable with coronary CTA.

Statistics

Microsoft Excel 2007 (Microsoft Corp, Redmond, WA, USA) software was used for data collection. All statistical calculations were performed with Stata 12.0 (StataCorp, College Station, TX, USA). The results are presented as the mean±SD (standard deviation) or frequency (%) of patients. The means of normally distributed continuous variables between the two groups were compared by two tailed, unpaired Student's *t*-tests. Multiple logistic regression analysis was used to determine the independent association with low or high V/M. The Pearson coefficient was used to evaluate the correlation of V/M and cardiovascular risk factors. Statistical significance was defined at $p<0.05$.

Results

Baseline characteristics

As shown in Fig 2, the present study recruited 576 consecutive asymptomatic and symptomatic patients with suspected CAD. One hundred and twenty-eight patients were excluded because of incomplete data, low image quality or because they did not align with the study protocol. Finally, a total of 448 patients (206 diabetes and 226

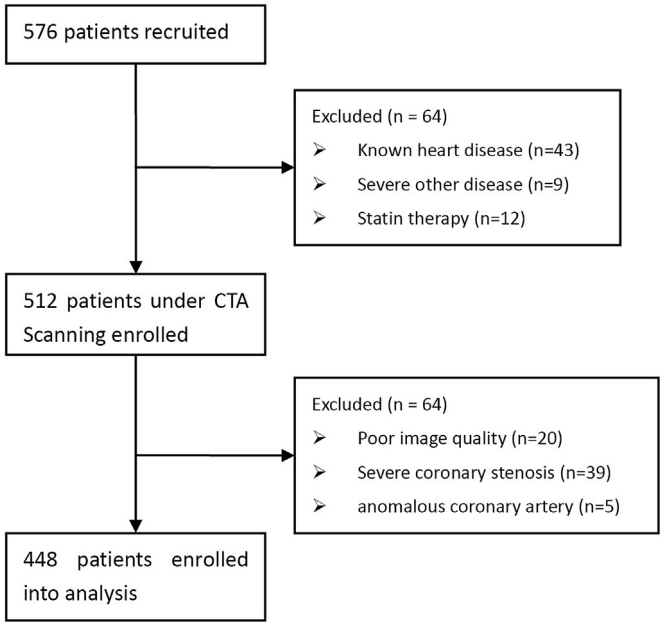

Figure 2 Flow chart of the study.

males) were enrolled, no one had type 1 diabetes. Table 1 lists the demographic and clinical characteristics of the patients with and without diabetes. The mean age of this study population was 58.91±8.89 years old. Among these characteristics, diabetic patients had greater HbA_{1c} (8.19±1.73% versus 6.03±0.56%, respectively; $p<0.001$) and FPG levels (9.09±3.25 versus 5.69±3.50 mmol/l, respectively; $p<0.001$). Diabetic patients were discernibly overweight compared the controls (BMI: 25.98±3.49 versus 24.63±3.42 kg/m^2, respectively; $p<0.01$). In addition, the total triglyceride, proportion of typical angina, proportion of hypertension, and systolic blood pressure were higher in diabetics than in non-diabetic patients ($p<0.05$). The age, sex, smoking history, and Scr levels showed no significant difference between the groups ($p>0.05$).

Table 1
Distribution of clinical characters with and without diabetes (means±SD).

Parameters	Diabetes (n=206)	Non-diabetics (n=242)	p-Value
Male, n (%)	114 (55.34%)	112 (46.28%)	0.213
Age (years)	59.15±9.16	58.52±8.41	0.577
Fasting glucose (mmol/l)	9.09±3.25	5.69±3.50	<0.001[a]
HbA_{1c} (%)	8.19±1.73	6.03±0.56	<0.001[a]
Hypertension, n (%)	127 (61.9%)	119 (49.1)	0.045[a]
SBP (mmHg)	145.9±25.27	134.5±19.56	<0.001[a]
DBP (mmHg)	85.2±12.3	81.4±11.8	0.025[a]
Smoker, n (%)	85 (41.26%)	82 (33.88%)	0.137
Typical angina, n (%)	90 (43.69%)	75 (30.99%)	0.035[a]
Hyperlipidaemia, n (%)	89 (43.2%)	79 (32.6%)	0.057
LDL (mmol/l)	2.80±1.03	2.65±0.80	0.597
HDL (mmol/l)	1.13±0.30	1.18±0.29	0.111
TC (mmol/l)	4.92±1.33	4.73±1.07	0.172
TG (mmol/l)	2.47±1.96	1.69±1.13	<0.001[a]
BMI (kg/m^2)	25.98±3.49	24.63±3.42	0.012[a]
Scr (mmol/l)	74.18±17.29	76.19±19.79	0.392

The diabetic group was with at least 5-year history of diabetes, and no patients was on statin therapy.
CAD, coronary artery disease; HbA_{1c}, haemoglobin A_{1c}; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; TC, total cholesterol level; TG, Triglyceride level; BMI, body mass index; Scr, serum creatinine.
[a] Statistical significance was defined at $p<0.05$.

Epicardial coronary artery morphological characteristics and LVM

Table 2 summarises the morphometric epicardial coronary arteries and body scaling parameters in the diabetic and control groups. No significant stenosis (>50%) of the coronary artery was presented in the present study. The overall lengths of the epicardial coronary arteries, measured from the beginning of the most proximal artery to the end of an approximately 1 mm diameter vessel, ranged from 38 to 62 mm, and showed no difference between the groups (p=0.771). There was no significant difference in the average vessel cross-sectional area or the mean diameter of the complete coronary artery tree (p=0.447 and p=0.674 respectively). The LVM was significantly higher in patients with diabetes than in controls (132.46±45.05 versus 115.84±29.14; p=0.006); however, the total cumulative intravascular volume of epicardial coronary artery tree in the diabetic group was not higher than that in the control group (2.66±1.06 versus 2.55±0.76 cm^3, p=0.542). The mean value of V/M was 2.15 cm^3/100±0.71 g. The median value was 2.13 cm^3/100 g, which defined the cut-off point between low and high V/M. The indicator V/M was much lower in patients with diabetes than in controls (2.02 cm^3/100±0.73 g versus 2.31 cm^3/100±0.82 g, respectively; p=0.024). In multivariable logistic regression analysis, V/M was associated with BMI (OR=1.354, 95% CI: 1.021–1.710, p=0.013), and diabetes (OR=2.027, 95% CI: 1.462–2.728, p=0.001; Table 3). Hypertension was not associated with V/M (OR=1.191, 95% CI: 0.978–1.451, p=0.081).

Discussion

The present study compared the novel concept of coronary V/M ratios between diabetic and non-diabetic

Table 2
Morphometric and scaling law results in epicardial coronary artery trees of diabetic and control groups.

Parameter	Diabetes (n=206)	Non-diabetics (n=242)	p-Value
Mean A_s (cm^2)	0.052±0.013	0.051±0.012	0.447
Maximum L_c (mm)	50.528±12.771	51.232±8.990	0.674
Maximum V_c (cm^3)	2.661±1.065	2.551±0.762	0.542
Coronary artery diameter (cm)	0.240±0.022	0.232±0.023	0.674
LVM (g)	132.461±45.047	115.824±29.137	0.006[a]
V/M (cm^3/100 g)	2.024±0.732	2.312±0.825	0.024[a]

A_s, cross-sectional area of the coronary artery tree; L_c, sum of vessel length of the entire epicardial coronary artery tree; V_c, sum of intravascular volume of the entire epicardial coronary artery tree; LVM, left ventricular mass; V/M, coronary artery lumen volume to left ventricular mass ratio.
[a] Statistical significance was defined at $p<0.05$.

Table 3
Multivariable logistic regression analysis of baseline characteristics associated with low and high V/M.

Parameter	OR	95% confidence interval	*p*-Value
Male	1.406	0.974–1.987	0.071
Age (years)	1.054	1.039–1.069	0.017
Smoking	1.152	0.954–1.581	0.193
Diabetes	2.027	1.462–2.728	0.001[a]
Hyperlipidaemia	1.253	0.972–1.671	0.045[a]
BMI	1.354	1.021–1.710	0.013[a]
Hypertension	1.191	0.978–1.451	0.081

BMI, body mass index; V/M, coronary artery lumen volume to left ventricular mass ratio.
[a] Statistical significance was defined at $p<0.05$.

patients. The main finding of this study proved the hypothesis that diabetic patients have lower V/M than the controls. This study presents a new quantitative assessment of vessel architecture of the coronary artery and ventricular scaling in diabetic patients. This is the first *in vivo* human patient study using the V/M method in the assessment of diabetic global heart and morphological features of the coronary artery.

LVM

Increased LVM is thought to increase the risk of CVD through a series of unfavourable metabolic, functional, and cardiac structural changes. An increased LVM has been shown to be an independent risk factor for cardiovascular mortality.[12] Many studies have shown that type 2 diabetes mellitus was associated with an increased LVM and LVM index, independent of various factors.[13–15] The present study showed that the LVM is significantly larger in diabetics than in controls in the early stages of CAD using an multidetector CT technique. Measuring the LVM using magnetic resonance imaging (MRI) is considered the reference standard method. Echocardiography typically overestimates LVM compared to CT and cardiac MRI. Additionally, LVM measurements derived from MDCT examinations showed no significant difference compared to MRI data sets and ultrasound.[16–19] Therefore, in this study the method of using the MDCT to measure LVM was a relatively precise method.

Coronary artery volume

Diabetes is characterised by diffuse coronary artery atherosclerosis and diffuse luminal remodelling. Coronary artery remodelling is defined by changes in vessel size and plaque burden.[20] Manifestations of vascular remodelling are considered to be active modifications of the vessel wall in response to changes in its milieu, and studies have showed that diabetes promotes impaired arterial remodelling; however, there is controversy as to whether coronary artery remodelling is associated with diabetes mellitus. Some studies have shown that type 2 diabetes is associated with vascular positive remodelling,[21,22] whereas other studies have shown that diabetes is associated with coronary artery vessel shrinkage (negative remodelling).[23,24] The present study showed that diabetic patients have slightly larger cumulative volume, which may be due to the positive remodelling. The morphology and changes in the remodelled coronary wall have not been comprehensively investigated in diabetic patients and is in need of further research.

V/M

Recent CTA studies have shown an association between low coronary lumen V/M and lower fractional flow reserve values, independent of coronary plaque measurements in patients.[25] Another study showed that the V/M is significantly lower in patients with a primary microvascular angina[26]; however, some other study results are inconsistent. One previous study showed that the total cumulative length is longer in CAD patients, whereas the total cumulative volume was similar between groups.[27] In another study, the coronary artery volume to length increased more significantly in CAD group than control group.[28] The present study showed that diabetic patients have a significantly lower coronary CTA-derived coronary V/M than controls. Studies have shown that coronary volume is linearly associated with the LVM[6,29]; however, in this study, coronary volume did not increase in correlation with LVM in diabetic patients.

The mechanism of diabetes associated pathological progression in coronary atherosclerosis is not fully understood. Diabetes increases microvessel resistance, which causes a reduced coronary flow reserve (CFR).[30] A previous study showed that diabetic rats have a decreased CFR along with decreased density of microvessels early in the course of CAD.[31] Widespread endothelial injury, endothelial and smooth muscle dysfunction, modification of the basement membranes, altered production of vasoactive substances, and superoxide are believed to play a decisive role in the vascular complications observed in diabetes.[32] In contrast to other conditions, the role of shear stress on the endothelium in combination with the effects of circumferential wall stress, metabolic factors and conducted responses are important factors in vascular network and remodelling. In a diabetic patient, the increased stiffness, extracellular matrix changes and calcifications can be observed in both atherosclerotic and non-atherosclerotic parts of the arterial tree.[33] Such long-term alterations in the vascular structure have been linked to the development of atherosclerotic cardiovascular diseases.[34] Optimal physiological vascular remodelling involves a finite volume of blood that must be metabolically exchanged over a very large area. Features of vascular scaling remodelling are expected to quantitatively evaluate the progression of cardiovascular diseases. Therefore, the combination of coronary artery volume and ventricular mass could serve as new biomarkers and will be useful for determining the mechanism of CAD in diabetes. This study is innovative in that it shows that even in the very early stages of CAD cardiac vascular changes may be used as a predictive tool for CAD disease progression.

Scientific basis and clinical implications of V/M

Vascular volume is fundamentally significant to the function of the cardiovascular system. Pathophysiological factors, such as hyperglycaemia, hypertension, myocardium ischaemic, and chemical factors affect the intravascular volume to regulate the blood pressure and flow in the body. Many structural and functional features are found to have a power-law (scaling) relation to organ size, metabolic rates, etc. Therefore, the concept of the V/M ratio has its origin in allometric scaling laws relating biological variables to size. The importance of coronary artery volume normalisation to LVM is well recognised. Coronary size is related to regional myocardial mass; it is known that $V \propto M$ (M is the mass perfused by the vessel, and V is the volume of the vessel) from the allometric scaling law.[35] The present study showed that diabetic patients have a similar cumulative length and cumulative volume compared to non-diabetic patients; however, the diabetic patients had an increased LVM and a mismatched coronary artery volume to LV mass. The enlarged left ventricular wall will increase myocardial oxygen consumption, so patients with diabetes are more likely to have an inadequate cumulative volume of major epicardial coronary arteries.

The heart is highly vascularised and has a complex geometric network due to elevated oxygen and nutrient demand.[36] The coronary artery system provides the basic structure to transport the blood within the heart. On the principle of minimum energy, coronary arterial circulation requires treating the coronary tree structure as an integrated whole and acts as an optimisation network to deliver nutrients and oxygen to cells. It is unclear whether the vascular arterial tree obeys scaling constraints during high blood level environment in humans. Features of V/M analysis are expected to serve as a novel means to detect early subclinical diabetic macrovasculopathy and help us to improve the understanding of the pathophysiological pathways of early coronary artery structural alterations in diabetes. Assessing the geometry of the coronary arteries and ventricular mass in diabetic patient may help us to better understand CAD development.

Study limitations and future directions

The present study has several limitations. First, the participants in the present study were patients from a single site from northeast of China who underwent CTA for clinically suspected CAD. In addition, the diabetic patients included were only hospital-referred patients whose blood glucose levels were poorly controlled; they were not recruited from the community. Therefore, it is impossible to avoid the selection bias on evaluation. Second, not only capillary vessels but also smaller arteries in the distal segments were not included in the calculation of coronary volume because of the limitations of resolution of currently available CT machines. Despite these limitations, the coronary CTA techniques for the first time revealed the full coronary artery and the LVM scaling relationship in these diabetic patients with use of non-invasive methods. At present, coronary CTA can routinely and non-invasively capture the full anatomical map of the coronary arteries and heart structure in a single heartbeat with a low radiation dose. In addition, further larger scale studies are needed to compare V/M and the risk of CAD using coronary CTA.

Conflict of interest

The authors declare no conflict of interest.

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