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Research paper

The association of coronary lumen volume to left ventricle mass ratio with myocardial blood flow and fractional flow reserve

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ABSTRACT

Background: A diminished coronary lumen volume to left ventricle mass ratio (V/M) derived from coronary computed tomography angiography (CCTA) has been proposed as factor contributing to impaired myocardial blood flow (MBF) even in the absence of obstructive disease on invasive coronary angiography (ICA).

Methods: Patients underwent CCTA, and positron emission tomography (PET) prior to ICA. Matched global V/M, global, and vessel specific hyperaemic MBF (hMBF), coronary flow reserve (CFR), and, FFR were available for 431 vessels in 152 patients. The median V/M (20.71 mm^3/g) was used to divide the population into patients with either a low V/M or a high V/M.

Results: Overall, a higher percentage of vessels with an abnormal hMBF and FFR (34% vs. 19%, p = 0.009 and 20% vs. 9%, p = 0.004), as well as a lower FFR (0.93 [interquartile range: 0.85–0.97] vs. 0.95 [0.89–0.98], p = 0.016) values were observed in the low V/M group. V/M was weakly associated with vessel specific hMBF (R = 0.148, p = 0.027), and FFR (R = 0.156, p < 0.001). Among vessels with non-obstructive CAD on ICA (361 vessels), no association between V/M and vessel specific hMBF nor CFR was noted. However, in the absence of obstructive CAD, V/M was associated with (R = 0.081, p = 0.027), and independently predictive for FFR (p = 0.047).

Conclusion: Overall, an abnormal vessel specific hMBF and FFR were more prevalent in patients with a low V/M compared to those with a high V/M. Furthermore, V/M was weakly associated with vessel specific hMBF and FFR. In the absence of obstructive CAD on ICA, V/M was weakly associated with notwithstanding independently predictive for FFR.

1. Introduction

Visually gauging the severity of lumen narrowing during invasive coronary angiography (ICA) has long been the cornerstone for assessing the significance of coronary artery disease (CAD). Nowadays, auxiliary functional assessment by means of fractional flow reserve (FFR) interrogation has proven to guide revascularization strategy and outcome in a beneficial manner.[1] Since the introduction of FFR, a discrepancy between the diameter stenosis (DS) of lesion and its physiological consequences has been observed.[2–5] Up to one in five lesions with a DS of 70%–90%, prove to be functionally irrelevant when interrogated by FFR. Conversely, a substantial portion of lesions deemed non-obstructive on ICA have an FFR below the ischemic threshold.[2,4] A possible explanation for the observed discordancy in the latter group is the presence of diffuse atherosclerosis, which results in a continuous pressure drop along the length of an artery leading to a gradual decline of

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Abbreviations

CAD	Coronary Artery Disease
CCTA	Coronary Computed Tomography Angiography
CFR	Coronary Flow Reserve
CTO	Chronic Total Occlusion
DS	Diameter Stenosis
FFR	Fractional Flow Reserve
GEE	Generalized Estimating Equations
ICA	Invasive Coronary Angiography
IQR	Interquartile Range
MBF	Myocardial Blood Flow
PET	Positron Emission Tomography
SD	Standard Deviation
SPECT	Single-Photon Emission Computed Tomography
V/M	Coronary Lumen Volume to Left Ventricle Mass Ratio

FFR values.[5] Furthermore, a mismatch in global coronary lumen volume and myocardial demand due to a hampered vasodilator function of the epicardial vasculature has been proposed as contributing factor to impaired myocardial blood flow (MBF) even in the absence of obstructive CAD.[6] Indeed, diminished FFR values have been noted in patients with a low coronary lumen volume to left ventricle mass ratio (V/M) derived from coronary computed tomography angiography (CCTA). Moreover, a reduced V/M was found to be predict an FFR ≤ 0.80 independent of other CCTA characteristics.[6] However, to date the interplay between V/M and actual MBF has not yet been clarified. This study therefore sought to elucidate the relation between V/M and non-invasively obtained absolute MBF by means of $[^{15}O]H_2O$ positron emission tomography (PET), as well as invasive FFR measurements.

2. Methods

2.1. Study population

This is a substudy of the Prospective Comparison of Coronary CT Angiography, single-photon emission computed tomography (SPECT), PET, and Hybrid Imaging for the Diagnosis of Ischemic Heart Disease Determined by Fractional Flow Reserve (PACIFIC) trial, in which patients with a preserved left ventricular ejection fraction without previously documented CAD underwent CCTA, SPECT, and PET prior to ICA in conjunction with interrogation of all major coronary arteries by FFR regardless of DS severity. (NCT01521468).[7] A more elaborate description of the study design, and in- and exclusion criteria are presented in the main article.[7] For the present study patients who did not undergo rest and stress PET, did not receive nitroglycerine prior to CCTA acquisition, had a chronic total occlusion (CTO), or in whom FFR measurements could not be obtained were excluded. The study protocol was approved by the institutional Medical Ethics Committee and complied with the Declarations of Helsinki. All study subjects provided written informed consent.

2.1.1. Coronary CTA

Coronary CTA acquisition and plaque analysis were performed as previously described.[7,8] In short, CCTA scans were obtained in accordance with the guidelines of the society of cardiovascular computed tomography using a 256-slice CT scanner (Philips Brilliance iCT, Philips Healthcare, Best, the Netherlands).[9] Nitroglycerine was administered prior to acquisition, metoprolol was only given to achieve a heart rate of < 65 beats per minute. Core laboratories (Dalio Institute of Cardiovascular Imaging, New York-Presbyterian Hospital, New York, United States of America and St Paul's Hospital, Vancouver, British Columbia, Canada) visually assessed coronary arteries with a diameter of > 2 mm for the presence of obstructive lesions ($\geq$50% DS). Plaque analysis were performed using semi-automated software (Comprehensive Cardiac Analysis, Philips Healthcare). The atherosclerotic burden was automatically quantified within manually designated regions, total plaque length, and volume were calculated by the summation of separate plaques along each coronary artery. The total non-calcified, and calcified volumes were calculated by applying a scanner specific threshold of 150 Hounsfield units to denote non-calcified, and calcified plaque tissue.

2.1.2. volume to mass analysis

HeartFlow Inc. (Redwood City, California, United States of America) computed the ratio between coronary arterial lumen volume and left ventricle mass, V/M, blinded to clinical parameters. the sequential steps required for V/M analysis have previously been described by Taylor et al.[6] In summary, a patient-specific anatomic epicardial model of the coronary vasculature is segmented from CCTA images.[10] The total coronary lumen volume is obtained by the summation of all the segmented coronary arteries, while the volume of the myocardium extracted from CCTA was multiplied by an average value for myocardial tissue density resulting in the left ventricle myocardial mass. Lastly, the total coronary lumen volume was divided by the left ventricular mass to obtain a patient specific V/M ratio in mm^3/g.

2.2. $[^{15}O]H_2O$ PET

Attaining PET MBF parameters using a hybrid PET/CT device (Philips Gemini TF64, Philips Healthcare, Best, The Netherlands) has previously been reported.[7] Briefly, an injection of 370 MBq of $[^{15}0]H_2O$ during resting as well as during hyperaemic conditions (infusion of 140 μg/kg/min adenosine) allowed for quantification of MBF in ml/min/g of myocardial tissue on a global and vascular level. Vascular territories were defined according to the standardized 17-segment model of the American Heart Association.[11] Coronary flow reserve (CFR) was calculated by dividing hyperaemic MBF (hMBF) by resting MBF. A blinded core laboratory (Turku University Hospital, Turku, Finland) assessed PET scans for the presence of ischemia using quantitative perfusion values wherein a hMBF of $\leq$2.30 mL/min/g or CFR of $\leq$2.5 in at least 2 adjacent segments was considered abnormal.[12]

2.3. ICA and FFR measurements

Invasive assessment of the coronary vasculature was performed using best clinical practices and reported previously.[7] In summary, at least two orthogonal views per evaluated coronary segment were obtained. Nitroglycerine (0.2 ml) was used to induce epicardial vasodilation. All major coronary arteries were interrogated by FFR regardless of DS, except for occluded or subtotal lesions in which wire passage was not deemed possible. Hyperaemia was achieved by intravenous (140 μg/kg/min) or intracoronary (150 μg) infusion of adenosine. Lumen narrowing defined as DS% was assessed using quantitative coronary angiography. An FFR $\leq$0.80 defined significant CAD, while a lesion with a DS $\geq$50% was deemed obstructive.

2.4. Statistical analysis

Continuous variables are presented as mean values ± standard deviation (SD) when normally distributed or as median with [interquartile range (IQR)] when a non-normal distribution was observed. Categorical variables are expressed as frequencies with corresponding percentages. The median V/M was used to divide the study population into patients with a low or high V/M. Statistical significance of the differences between the low, and high V/M group were calculated using generalized estimating equations (GEE) analysis to account for multiple measurements within the same patient. An exchangeable working

correlation structure was used and if needed dependent variables were log-tranformed prior to GEE analysis. The correlation between V/M and global PET MBF parameters was assessed using Pearson R correlations, and presented as scatter plots with regression line, corresponding formula, correlation coefficient, and p-value. GEE analyses were used to assess the association of V/M and hMBF, CFR, and FFR on a per vessel level. The associations on a per vessel level are graphically represented as scatter plots with regression line, formula obtained through GEEs, and corresponding p-value. An indicative correlation coefficient is presented, however this coefficient is not corrected for multiple measurements. Candidate predictors of vessel specific hMBF, CFR, and FFR were identified using an univariable GEE analysis. A log transformation was applied to account for the leftward skew of FFR. Variables with a $p < 0.10$ were subsequently included in a multivariable GEE analysis with backward selection to determine a set of independent predictors for myocardial blood flow parameters and FFR. A p-value of < 0.05 was deemed statistically significant. All analyses were performed using IBM SPSS software package (IBM SPSS Statistics 22.0, Chigago, IL, USA).

3. Results

3.1. Patient characteristics

A total of 204 patients underwent CCTA, and PET prior to ICA. Three patients underwent stress PET only, and four participants did not receive nitroglycerine prior to CCTA acquisition. Leaving 197 patients of which 22 had at least one CTO, while in two patients the presence of subtotal lesions prohibited FFR measurements. Computation of V/M was successful in 152 of the remaining 173 patients constituting the present study population. The median V/M of 20.71 mm^3/g among the 152 patients was used to divide the study population into 76 patients with a low V/M ($< 20.71\ mm^3/g$) and 76 patients with high V/M ($\geq 20.71\ mm^3/g$). Table 1 displays the characteristics of included study subjects. Participants with a low V/M were younger (56 vs. 59 years, p = 0.040), and more frequently male (70% vs. 51%, p = 0.020) compared to patients with a high V/M. Fig. 1 depicts a case example of a patient with a low V/M.

3.2. Overall study population

In total, 431 vessels with a DS ranging from 0% to 95% were interrogated by FFR. Nearly half (49%) of the included vessels belonged to patients with a low V/M. Coronary CTA, PET, and ICA characteristics of all vessels included in the present study specified according to either a low or high corresponding patient specific V/M are presented in Table 2.

3.2.1. Coronary CTA

Obstructive lesions (33% vs. 16%, $p < 0.001$) on CCTA were more frequently observed among vessels of patients with a low V/M (Table 2). The prevalence of plaques did not differ between the two groups (p = 0.571). Furthermore, atherosclerotic burden parameters, plaque length (p = 0.790), plaque volume (p = 0.306), non-calcified volume (p = 0.251), and calcified volume (p = 0.128) were comparable between both groups (Table 2).

3.2.2. Myocardial blood flow parameters

On a per vessel level, resting MBF (1.06 vs. 1.13 ml/min/g, p = 0.056) tended to be lower among vessels of patients with a low V/M, while vessel specific hMBF (p = 0.125) and CFR (p = 0.806) were similar in both groups (Table 2). Notwithstanding, the percentage of vessels with an abnormal hMBF was significantly higher in the low V/M group compared to the high V/M group (34% vs. 19%, p = 0.009), whereas an abnormal vessel specific CFR was observed equally (p = 0.268) among both groups (Table 2). Furthermore, V/M was significantly albeit weakly associated with vessel specific hMBF (R = 0.148, p = 0.027) but not with vessel specific CFR (R = 0.090, p = 0.143) (Fig. 2). CCTA derived obstructive lesions and plaque length were identified as independent predictors of vessel specific hMBF, while plaque length and calcified volume were independent predictors of vessel specific CFR (Table 3). No independent predictive value of V/M for either vessel specific hMBF or CFR was observed (Table 3). On a global level, a significant although weak correlation between V/M and hMBF (R = 0.179, p = 0.027), as well as CFR (R = 0.163, p = 0.045) was observed (Fig. 3).

Table 1
Patient characteristics.

Characteristics	N (%) / mean ± SD			
	Overall (N = 152)	Low V/M (N = 76)	High V/M (N = 76)	p-value
Male gender	92 (61)	53 (70)	39 (51)	**0.020**
Age, years	58 ± 9	56 ± 8	59 ± 9	**0.040**
BMI, kg/m^2	26.7 ± 3.5	26.8 ± 3.3	26.6 ± 3.7	0.743
V/M ratio, mm^3/g	21.43 ± 6.06	17.00 ± 2.71	25.86 ± 5.18	< **0.001**
Cardiovascular risk factors				
Diabetes mellitus	18 (12)	7 (9)	11 (14)	0.315
Hypertension	68 (45)	29 (38)	39 (51)	0.103
Hypercholesterolemia	54 (36)	32 (42)	22 (29)	0.090
History of Tabaco use	69 (45)	35 (46)	34 (45)	0.871
Family history of CAD	77 (51)	37 (49)	40 (53)	0.626
Number of CVRs	2 [1-3]	2 [1-3]	2 [1-3]	0.656
Medication				
Acetylic acid	130 (86)	65 (86)	65 (86)	1.000
β-blocker	95 (63)	46 (61)	49 (65)	0.615
Calcium channel blocker	42 (28)	22 (29)	20 (26)	0.717
Statin	112 (74)	57 (75)	55 (72)	0.713
Long acting nitrate	16 (11)	8 (11)	8 (11)	1.000
ACE-inhibitors	28 (18)	12 (16)	16 (21)	0.403
ARB	25 (16)	14 (18)	11 (15)	0.512
Symptoms				
Typical angina pectoris	53 (35)	26 (34)	27 (36)	0.865
Atypical angina pectoris	60 (40)	27 (36)	33 (43)	0.319
Non-specific chest pain	39 (26)	23 (30)	16 (21)	0.194

Abbreviations; SD: Standard Deviation, BMI: Body Mass Index, V/M ratio: Volume to Mass ratio, CAD: Coronary Artery Disease, CVRs: Cardiovascular Risk Factors, ARB: Angiotensin Receptor Blockers.

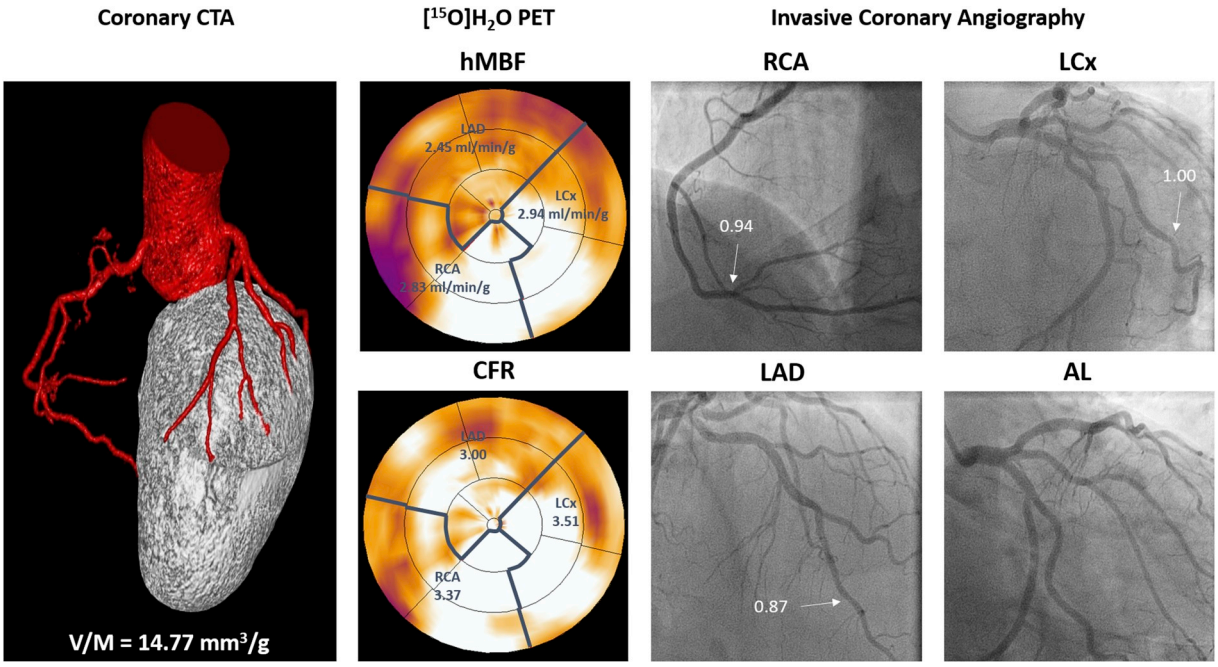

Fig. 1. Case example of a patients with a low V/M. Fig. 1 presents a case example of a patient with a low V/M. Quantitative [^{15}O]H_2O PET revealed a normal hMBF, and CFR in all coronary territories. Invasive assessment of the coronary vasculature confirmed non-obstructive and non-significant CAD, as defined by FFR, in all vessels.

Abbreviations: V/M: Volume to Mass ratio, PET: Positron Emission Tomography, hMBF: Hyperaemic Myocardial Blood Flow, CFR: Coronary Flow Reserve, CAD: Coronary Artery Disease, FFR: Fractional Flow Reserve, CTA: Computed Tomography Angiography, RCA: Right Coronary Artery, LCx: Left Circumflex Artery, LAD: Left Anterior Descending, AL: Anterolateral artery.

Table 2

A per vessel analysis of CCTA, PET, and ICA characteristics of all coronary arteries included in present study stratified according to either a low or high corresponding patient specific V/M.

Characteristics	N (%) / mean ± SD / median [IQR]			
	Overall (N = 431)	Low V/M (N = 210)	High V/M (N = 221)	p-value
CCTA				
Obstructive lesion	103 (24)	70 (33)	35 (16)	< **0.001**
Plaque features*				
≥1 plaque present	278 (65)	131 (62)	147 (67)	0.571
Length, mm	27 [12-43]	31 [12-50]	25 [13-39]	0.790
Volume, mm^3	135 [52-263]	147 [45-292]	125 [56-244]	0.306
Non calcified volume, mm^3	28 [7-68]	38 [11-80]	23 [6-54]	0.251
Calcified volume, mm^3	86 [35-179]	86 [22-183]	85 [41-177]	0.128
PET				
Resting MBF (ml/min/g)	1.10 ± 0.32	1.06 ± 0.31	1.13 ± 0.31	0.056
hMBF (ml/min/g)	3.39 ± 1.26	3.27 ± 1.39	3.51 ± 1.11	0.125
Abnormal hMBF	113 (26)	72 (34)	41 (19)	**0.009**
CFR	3.22 ± 1.30	3.20 ± 1.45	3.22 ± 1.12	0.806
Abnormal CFR	132 (31)	71 (34)	61 (28)	0.268
ICA				
DS%	24 [14-39]	23 [14-43]	25 [14-37]	0.733
Obstructive lesion	70 (16)	43 (21)	27 (12)	**0.038**
FFR	0.94 [0.87–0.98]	0.93 [0.85–0.97]	0.95 [0.89–0.98]	**0.016**
FFR ≤0.80	60 (14)	41 (20)	19 (9)	**0.004**

* Presented plaque features are quantitative measurements of vessels with at least one plaque.

Abbreviations; CCTA: Coronary Computed Tomography Angiography, ICA: Invasive Coronary Angiography, PET: Positron Emission Tomography, DS: Diameter Stenosis, V/M ratio: Volume to Mass ratio, SD: Standard Deviation, IQR: Interquartile Range, FFR: Fractional Flow Reserve, hMBF: Hyperaemic Myocardial Blood Flow, CFR: Coronary Flow Reserve.

3.2.3. *Invasive coronary angiography*

Median DS% did not differ between vessels of the low or high V/M group (p = 0.733). Obstructive lesions on ICA were however more prevalent among vessels in the low V/M group (21% vs. 12%, p = 0.038) (Table 2). FFR of vessels in the low V/M group was significantly lower (0.93 vs. 0.95, p = 0.016), with a higher percentage of positive FFR measurements (20% vs. 9%, p = 0.004) noted when compared to vessels in the high V/M group (Table 2). Furthermore, V/M was weakly associated with FFR (R = 0.156, p < 0.001) (Fig. 2). Although all tested CCTA characteristics, including V/M, were predictive of FFR in a univariable analysis, obstructive lesions and non-calcified volume were found to be the only independent predictors of

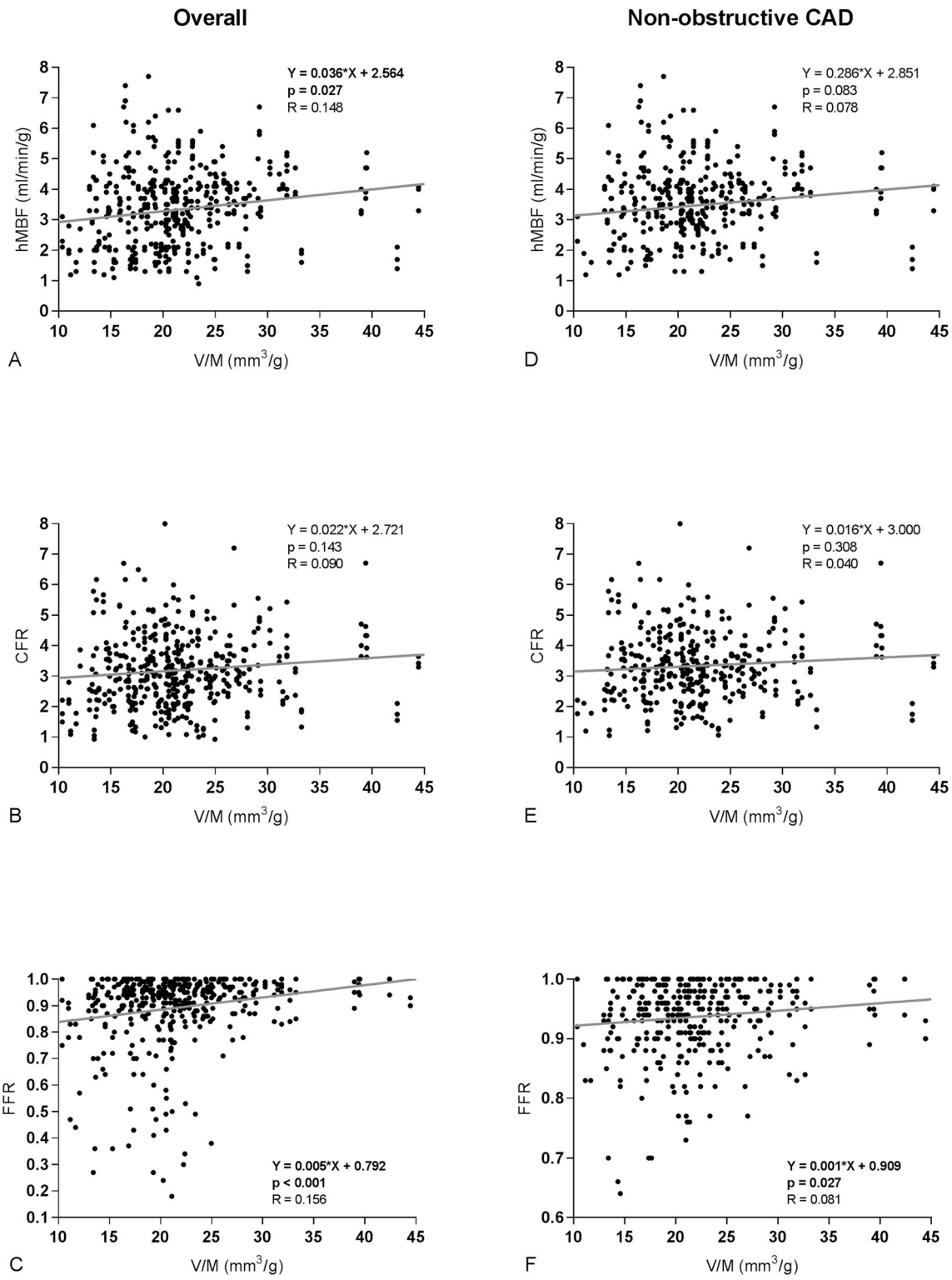

Fig. 2. Scatterplots demonstrating the association of patient specific V/M with vessel specific hMBF, CFR, and FFR, specified for all vessels included in the present article as well as for vessel with non-obstructive CAD on ICA. Fig. 2 presents the association of patient specific V/M with vessel specific hMBF (A), CFR (B), and FFR (C) overall and in vessels with non-obstructive CAD on ICA (D–F).
Abbreviations: ICA: Invasive Coronary Angiography, other abbreviations as in Fig. 1.

FFR (Table 3).

3.3. Non-obstructive CAD

A total of 361 (84%) coronaries had no or non-obstructive lumen narrowing (DS < 50%) on ICA. Of these vessels 167 (46%) were related to patients with a low V/M. Table 4 presents CCTA, PET, and ICA characteristics of non-obstructed vessels stratified according to either a low or high patient specific V/M.

Table 3
Uni- and multivariable GEE analysis of CCTA characteristics for the prediction of vessel specific hMBF, CFR and FFR, in the overall study population, and in vessels with non-obstructive CAD on ICA.

hMBF								
CCTA characteristics	**Overall**				**Non-obstructive CAD**			
	Univariable		**Multivariable**		**Univariable**		**Multivariable**	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**
Obstructive lesion	−0.264 (-0.443 to −0.085)	**0.004**	−0.207 (−0.380 to −0.035)	**0.018**	0.065 (−0.102 - 0.233)	0.444		
Plaque features								
Length (per 10 mm)	−0.081 (-0.113 to −0.048)	< **0.001**	−0.072 (−0.104 to −0.040)	< **0.001**	−0.041 (-0.072 to −0.009)	**0.012**	−0.041 (−0.072 to −0.009)	**0.012**
Non-Calcified volume (per 100 mm^3)	−0.199 (−0.357 to −0.040)	**0.014**	–	–	−0.026 (−0.131 - 0.078)	0.622		
Calcified volume (per 100 mm^3)	−0.188 (−0.175 to −0.062)	< **0.001**	–	–	−0.063 (-0.115 to −0.011)	**0.018**	–	-
V/M (mm^3/g)	0.036 (0.004–0.067)	**0.027**	-	-	0.029 (−0.004 - 0.061)	**0.083**	-	–
CFR								
CCTA characteristics	**Overall**				**Non-obstructive CAD**			
	Univariable		**Multivariable**		**Univariable**		**Multivariable**	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**
Obstructive lesion	−0.348 (-0.672 to −0.023)	**0.036**	–	-	0.036 (-0.419 - 0.490)	0.878		
Plaque features								
Length (per 10 mm)	−0.138 (-0.186 to −0.090)	< **0.001**	−0.225 (−0.346 to −0.105)	**0.001**	−0.118 (-0.178 to −0.057)	< **0.001**	−0.118 (−0.178 to −0.057)	< **0.001**
Non-Calcified volume (per 100 mm^3)	−0.439 (−0.611 to −0.268)	< **0.001**	–	-	−0.352 (−0.569 to −0.135)	**0.001**	–	-
Calcified volume (per 100 mm^3)	−0.201 (−0.273 to −0.128)	< **0.001**	0.187 (0.008–0.366)	**0.040**	−0.171 (-0.256 to −0.087)	< **0.001**	–	–
V/M (mm^3/g)	0.022 (−0.007 - 0.051)	0.143			0.016 (-0.014 - 0.045)	0.308		
FFR								
CCTA characteristics	**Overall**				**Non-obstructive CAD**			
	Univariable		**Multivariable**		**Univariable**		**Multivariable**	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**
Obstructive lesion	−0.221 (−0.296 to −0.146)	< **0.001**	−0.158 (−0.225 to −0.091)	< **0.001**	−0.032 (−0.057 to −0.006)	**0.015**	–	–
Plaque features								
Length (per 10 mm)	−0.037 (−0.048 to −0.026)	< **0.001**	-	–	−0.016 (−0.021 to −0.011)	< **0.001**	−0.010 (−0.016 to −0.004)	**0.001**
Non-Calcified volume (per 100 mm^3)	−0.203 (−0.279 to −0.127)	< **0.001**	−0.167 (−0.240 to −0.095)	< **0.001**	−0.074 (−0.098 to −0.051)	< **0.001**	−0.035 (−0.064 to −0.006)	**0.018**
Calcified volume (per 100 mm^3)	−0.056 (-0.081 to −0.032)	< **0.001**	-	–	−0.027 (-0.038 to −0.016)	< **0.001**	–	–
V/M (mm^3/g)	0.006 (0.004–0.009)	< **0.001**	-	–	0.001 (0.001–0.003)	**0.023**	0.001 (0.001–0.002)	**0.047**

Abbreviations; GEE: Generalized Estimating Equations, CCTA: Coronary Computed Tomography Angiography, ICA; Invasive Coronary Angiography, hMBF: Hyperaemic Myocardial Blood Flow, CFR: Coronary Flow Reserve, FFR: Fractional Flow Reserve, CI; Confidence Interval, V/M; volume to mass ratio.

3.3.1. Coronary CTA

CCTA derived obstructive lesions were more frequently observed among vessels in the low V/M group (25% vs. 9%, p < 0.001) (Table 4). The prevalence of plaques was similar in both groups (p = 0.303). Vessels of the low V/M group had a significantly lower calcified volume (56 vs. 78 mm^3, p = 0.020), while non-calcified volume did not differ between the low and high V/M group (p = 0.520) (Table 4).

3.3.2. Myocardial blood flow parameters

On a per vessel level, resting MBF (p = 0.171), hMBF (p = 0.296), and CFR (p = 0.852) were similar between vessels of the low and high

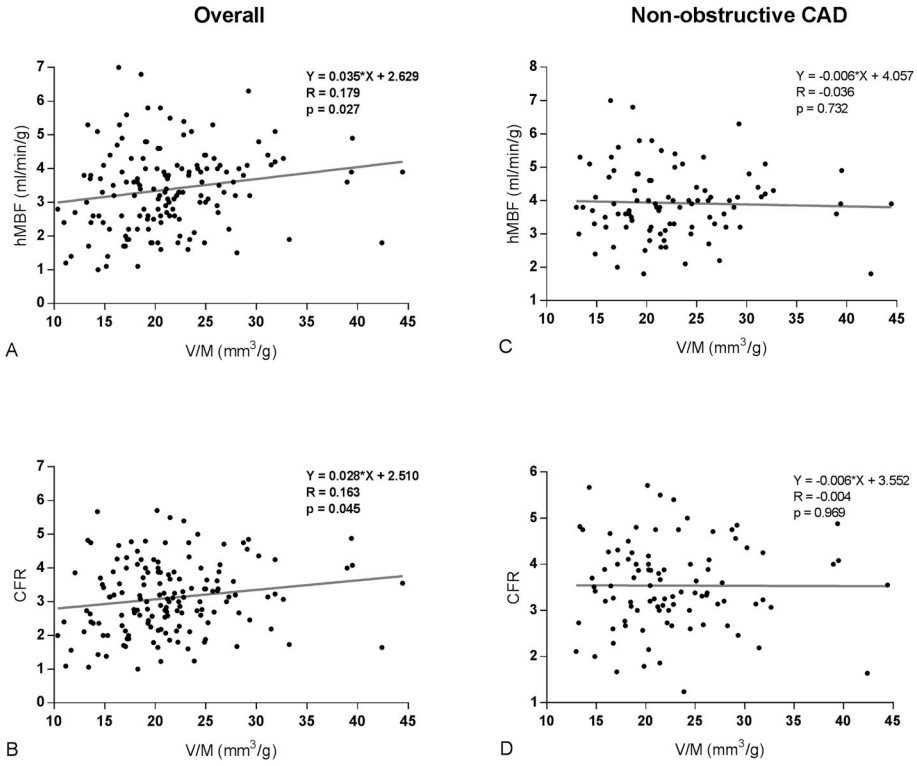

Fig. 3. Correlation of patient specific V/M with global hMBF and global CFR, overall and in patients with solely non-obstructive CAD on ICA. Fig. 3 presents the correlation of V/M with global hMBF (A), and CFR (B) overall as well as in patients with solely non-obstructive CAD observed during ICA (C–D). Abbreviations as in Figs. 1 and 2.

Table 4
A per vessel analysis of CCTA, PET, and ICA characteristics of non-obstructed vessel on ICA stratified according to either a low or high patient specific V/M.

	N (%)/ mean ± SD / median [IQR]			
Characteristics	Overall (N = 361)	Low V/M (N = 167)	High V/M (N = 194)	p-value
CCTA				
Obstructive lesion	60 (17)	42 (25)	18 (9)	< **0.001**
Plaque features*				
≥1 plaque present	210 (58)	89 (53)	121 (62)	0.303
Length, mm	22 [10-39]	23 [8-42]	22 [12-37]	0.222
Volume, mm^3	106 [40-210]	104 [23-215]	107 [48-208]	0.082
Non calcified volume, mm^3	22 [5-50]	25 [6-56]	21 [5-45]	0.520
Calcified volume, mm^3	72 [25-158]	56 [14-143]	78 [37-168]	**0.020**
PET				
Resting MBF (ml/min/g)	1.11 ± 0.32	1.09 ± 0.33	1.14 ± 0.32	0.171
hMBF (ml/min/g)	3.61 ± 1.19	3.58 ± 1.33	3.64 ± 1.05	0.296
Abnormal hMBF	61 (17)	35 (21)	26 (13)	0.079
CFR	3.41 ± 1.27	3.46 ± 1.45	3.36 ± 1.08	0.852
Abnormal CFR	84 (23)	41 (25)	43 (22)	0.441
ICA				
DS%	20 [13-30]	18 [13-29]	22 [13-31]	0.322
FFR	0.95 [0.91–0.99]	0.95 [0.90–0.99]	0.96 [0.91–0.99]	0.243
FFR ≤0.80	12 (3)	6 (4)	6 (3)	0.778

* Presented plaque features are quantitative measurements of vessels with at least one plaque.
Abbreviations; CCTA: Coronary Computed Tomography Angiography, ICA: Invasive Coronary Angiography, PET: Positron Emission Tomography, DS: Diameter Stenosis, V/M ratio: Volume to Mass ratio, SD: Standard Deviation, IQR: Interquartile Range, FFR: Fractional Flow Reserve, hMBF: Hyperaemic Myocardial Blood Flow, CFR: Coronary Flow Reserve.

V/M group (Table 4). Notwithstanding, a trend towards a higher percentage of vessels with an abnormal hMBF among the low V/M group compared to the high V/M group (21% vs. 13%, p = 0.079) was observed, while the prevalence of an abnormal vessel specific CFR was similar in both groups (p = 0.441) (Table 4). There was no significant association between patient specific V/M and vessel specific hMBF (R = 0.078, p = 0.083) or vessel specific CFR (R = 0.040, p = 0.308) (Fig. 2). Multivariable analysis revealed CCTA derived plaque length as the only independent predictor of vessel specific hMBF and CFR in the absence of obstructive CAD (Table 3). On a global level, there was no correlation between V/M and hMBF (p = 0.732) nor CFR (p = 0.969) (Fig. 3).

3.3.3. *Invasive coronary angiography*

DS percentage (p = 0.322), FFR values (p = 0.243), and number of positive FFR measurements (p = 0.778) did not differ between the two studied groups (Table 4). Notwithstanding, a significant but rather poor association of V/M with FFR (R = 0.081, p = 0.027) was observed (Fig. 2). Nevertheless, multivariable analysis demonstrated V/M to be an independent predictor of FFR, alongside plaque length, and non-

calcified plaque volume in this subset of vessels (Table 3).

4. Discussion

This is the first study to assess the association of V/M with non-invasively obtained MBF parameters in patients suspected of having obstructive CAD. Secondly, the present study evaluated the relation of V/M with invasive FFR measurements. Overall, a higher percentage of vessels with an abnormal hMBF and FFR were observed among patients with a low V/M in comparison to those with a high V/M. Furthermore, patient specific V/M was associated with vessel specific hMBF and FFR, however when corrected for other CCTA variables V/M was not independently predictive of vessel specific MBF parameters or FFR. In the absence of obstructive CAD on ICA, V/M proved not to be associated with vessel specific hMBF nor CFR. Nonetheless, in this subset of vessel V/M was associated with and independently predictive of FFR.

Allometric scaling laws form the foundation for the concept of V/M. These laws provide a model to predict structural and functional properties of the cardiovascular system of mammals.[13] Choy et al. applied allometric scaling laws to the porcine heart, and demonstrated a very tight linear relationship between coronary artery lumen volume and myocardial mass.[14] As such, a mismatch in coronary artery lumen volume and the subtended myocardial mass might lead to an inadequate perfusion. V/M is obtained after achieving vasodilation of the epicardial coronaries by means of nitroglycerin prior to CCTA acquisition, therefore V/M is a possible marker of the ability of the coronary vasculature to dilate in response to increased flow. Patients with a diminished V/M are expected to use some of their natural vasodilatory reserve to maintain resting flow, and subsequently possess a diminished vasodilatory reserve in case of hyperaemic conditions potentially leading to lower a hMBF and CFR.[6]

To date, the study of Taylor et al. is the only one exploring the possible role of V/M in patients with suspected CAD, studying the effect of V/M on FFR.[6] FFR defined ischemia (FFR $\leq$0.80) was more frequently observed in patients with a low V/M compared to those with a high V/M in the overall study population and interestingly also in the absence of obstructive lesions (DS < 50%) on ICA.[6] Secondly, a significant (weak) correlation between V/M and FFR measured in non-obstructed vessels was observed.[6] In the present study obstructive CAD on ICA was more prevalent among patients with a low V/M. Obstructive CAD is an important factor contributing to diminished FFR values and abnormal MBF.[15–17] As such the present study shows that, similarly to Taylor et al., patients with a low V/M have a higher prevalence of vessels with an FFR $\leq$0.80 compared to patients with a high V/M. We extent the findings of Taylor et al., by demonstrating that a higher percentage of vessels with an abnormal hMBF is present in patients with a low V/M. However, in contrast to Taylor et al., in the absence of obstructive CAD on ICA the number of vessels with an abnormal hMBF, CFR, or FFR did not differ between patients with a low or high V/M. Notwithstanding, V/M was significantly although weakly associated with FFR. Striking difference between the present study and of Taylor et al. is the number of vessels with an FFR $\leq$0.80 among non-obstructed vessels, being 3% in the present study vs. 10% in the study of Taylor et al. The present study might therefore not observe a significant difference in the prevalence of vessels with an FFR $\leq$0.80 among non-obstructed vessels as they are very few in number.

The value of CCTA derived parameters for predicting ischemia defined by either myocardial perfusion imaging or FFR has been well established.[8,18] Taylor et al. explored the additive value of V/M on top of CCTA derived atherosclerotic parameters for predicting an FFR $\leq$0.80.[6] V/M was found to be an independent predictor of an FFR $\leq$0.80 when separately corrected for non-calcified plaque volume, plaque length, epicardial coronary lumen volume, and left ventricle mass, in the overall study population as well as in vessels with non-obstructive CAD on ICA.[6] Contrary to Taylor et al. the present study does not show an independent predictive value of V/M for FFR nor MBF parameters when all vessel are taken into account. Importantly, the present study assessed the predictive value of V/M when corrected for multiple plaque parameters in one multivariable analysis and did not assess the predictive value of V/M in subsequent separate analysis with one other variable as Taylor et al. did. The fact that V/M is weakly associated with hMBF and FFR but not independently predictive of either variable in the overall study population can in part be explained by the presence of obstructive lesions when considering all vessels. Myocardial blood flow, and pressure loss over a stenosis as assessed with PET and FFR are inversely correlated with the diameter stenosis of a lesion observed on ICA.[15–17] The detrimental effect of obstructive disease on MBF as determined by myocardial perfusion imaging techniques has been demonstrated in abundance by studies reporting on the diagnostic performance of PET and SPECT to detect obstructive CAD on ICA.[19] Furthermore, despite the discrepancy between DS% and FFR, primarily observed in lesions with a DS around the cut-off defining obstructive disease, the majority of lesions deemed obstructive have corresponding FFR values below the threshold defining ischemia.[2,3] Lastly, CCTA derived DS% exhibits excellent diagnostic capabilities to detect obstructive disease on ICA.[20] As such, CCTA parameters linked to the presence of obstructive lesions on ICA are important independent predictors of MBF parameters, and FFR and might therefore trump the possible predictive value of V/M when all vessels including vessel with obstructive disease are taken into account.

Interestingly, the present study does shows that in the absence of obstructive lesions on ICA V/M is independently predictive for FFR while not being predictive of MBF parameters. An explanation for the observed discrepancy might be attributable to the coronary compartment assessed by either measurement. Whereas FFR solely assesses the epicardial coronaries are MBF parameters the cumulative result of blood flow through both the epicardial arteries and microvasculature.[21,22] Discordant FFR and MBF results provide insight in where the problem within the vasculature might lie. A normal FFR with reduced MBF points towards a problem in the microvasculature, whereas an abnormal FFR with normal MBF indicates a epicardial stenosis without a significant effect on myocardial perfusion due to a sufficient microvascular vasodilatory reserve.[23] V/M takes into account the ability of the epicardial coronaries to dilate after administration of nitroglycerin. Therefore, as seen in the present study a low V/M might lead to diminished FFR values as measurement of the epicardial coronaries. However, V/M does not take into account the microvasculature status of the patient. The PACIFIC-trial included patients without a cardiac history with a relatively healthy microvasculature as seen by the mean vessel specific hMBF (3.61 ml/min/g) and CFR (3.41) among vessels with non-obstructive disease. As such, the reserve capabilities of the microvasculature might prevent diminished MBF parameters due to a low V/M.

4.1. Limitations

As V/M is a relatively new parameter the range of V/M values from healthy subjects to patients with CAD has not been established. In the present study, low and high V/M were therefore defined by the median V/M of the current study population. These results may therefore not be extrapolated to other patients cohorts. Furthermore, V/M was calculated on a per patient level, implying all coronary arteries are equally affected by an diminished vasodilatory function of the coronaries. However, we cannot exclude the possibility that within one patient the V/M per coronary territory might vary and in fact one territory might be defined as having a low V/M while another as having a high V/M. Vessel specific V/M might therefore prove to be more insightful. Lastly, PET derived MBF per vascular territory was obtained using the standardized American Heart Association (AHA) 17-segment model and not matched with CCTA derived coronary anatomy. However, Bom et al. recently demonstrated that differences between MBF parameters obtained using an individualized CCTA approach compared to the AHA

17-segment model are negligible.[24]

5. Conclusion

The present study demonstrates that, overall, an abnormal vessel specific hMBF and FFR are more prevalent among vessels of patients with a low V/M compared to patients with a high V/M. Furthermore, V/M is weakly associated with vessel specific hMBF and FFR but not independently predictive of either measurement. Interestingly, in the absence of obstructive disease on ICA V/M is associated with and independently predictive of FFR. Importantly, the present study observes weak associations between V/M, MBF parameters and FFR with a wide scatter of data points. As such, further research is needed to assess the incremental role of V/M for the individual patient suspected of having CAD.

Conflicts of interest

Dr. James K. Min receives funding from the Dalio Foundation, National Institutes of Health, and GE Healthcare, serves on the scientific advisory board of Arineta and GE Healthcare, and has an equity interest in Cleerly. Dr. Leipsic has received research grants from GE Healthcare; and holds stock options in and serves as a consultant to Circle CVI and HeartFlow. Dr Knuuti reported receiving support from the Academy of Finland Centre of Excellence in Molecular Imaging in Cardiovascular and Metabolic Research, Helsinki, Finland, and receiving grant support from Gilead Inc and serving as a consultant to Lantheus Inc. C. Taylor is an employee of and shareholder in HeartFlow Inc. and receives royalties from Stanford University. Dr. Knaapen has received research grants from HeartFlow Inc.. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

References

1. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med.* 2018. https://doi.org/10.1056/NEJMoa1803538.
2. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol.* 2010;55:2816–2821. https://doi.org/10.1016/j.jacc.2009.11.096.
3. Toth G, Hamilos M, Pyxaras S, et al. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. *Eur Heart J.* 2014;35:2831. https://doi.org/10.1093/eurheartj/ehu094.
4. Park SJ, Kang SJ, Ahn JM, et al. Visual-functional mismatch between coronary angiography and fractional flow reserve. *Jacc-Cardiovasc Inte.* 2012;5:1029–1036. https://doi.org/10.1016/j.jcin.2012.07.007.
5. De Bruyne B, Pijls NHJ, Smith L, Wievegg M, Heyndrickx GR. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but 'normal' coronary angiography (vol 104, pg 2003, 3001). *Circulation.* 2002;105. https://doi.org/10.1161/hh1002.106409 1256-1256.
6. Taylor CA, Gaur S, Leipsic J, et al. Effect of the ratio of coronary arterial lumen volume to left ventricle myocardial mass derived from coronary CT angiography on fractional flow reserve. *J Cardiovasc Comput.* 2017;11:429–436. https://doi.org/10.1016/j.jcct.2017.08.001.
7. Danad I, Raijmakers PG, Driessen RS, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for Diagnosis of ischemic heart disease determined by fractional flow reserve. *Jama Cardiology.* 2017;2:1100–1107. https://doi.org/10.1001/jamacardio.2017.2471.
8. Driessen RS, Stuijfzand WJ, Raijmakers PG, et al. Effect of plaque burden and morphology on myocardial blood flow and fractional flow reserve. *J Am Coll Cardiol.* 2018;71:499–509. https://doi.org/10.1016/j.jacc.2017.11.054.
9. Abbara S, Blanke P, Maroules CD, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the society of cardiovascular computed tomography guidelines committee endorsed by the north American society for cardiovascular imaging (NASCI). *J Cardiovasc Comput.* 2016;10:435–449. https://doi.org/10.1016/j.jcct.2016.10.002.
10. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *J Am Coll Cardiol.* 2013;61:2233–2241. https://doi.org/10.1016/j.jacc.2012.11.083.
11. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart - a statement for healthcare professionals from the cardiac imaging committee of the council on clinical cardiology of the American heart association. *Circulation.* 2002;105:539–542. https://doi.org/10.1161/hc0402.102975.
12. Danad I, Uusitalo V, Kero T, et al. Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease: cutoff values and diagnostic accuracy of quantitative [(15)O]H2O PET imaging. *J Am Coll Cardiol.* 2014;64:1464–1475. https://doi.org/10.1016/j.jacc.2014.05.069.
13. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. *Science.* 1997;276:122–126. https://doi.org/10.1126/science.276.5309.122.
14. Choy JS, Kassab GS. Scaling of myocardial mass to flow and morphometry of coronary arteries. *J Appl Physiol.* 2008;104:1281–1286. https://doi.org/10.1152/japplphysiol.01261.2007.
15. Dicarli M, Czernin J, Hoh CK, et al. Relation among stenosis severity, myocardial blood-flow, and flow reserve in patients with coronary-artery disease. *Circulation.* 1995;91:1944–1951. https://doi.org/10.1161/01.Cir.91.7.1944.
16. Ryzhkova DV, Nifontov EM, Kornushina MK, Krasilnikova LA, Nikiforov AA. The relation between myocardial blood flow and severity of coronary artery stenosis: a study wiith PET and [13N]-ammonia. *Eur J Nucl Med Mol Imaging.* 2007;34 S268-S268.
17. Uren NG, Melin JA, Debruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood-flow and the severity of coronary-artery stenosis. *N Engl J Med.* 1994;330:1782–1788. https://doi.org/10.1056/Nejm199406233302503.
18. Gaur S, Ovrehus KA, Dey D, et al. Coronary plaque quantification and fractional flow reserve by coronary computed tomography angiography identify ischaemia-causing lesions. *Eur Heart J.* 2016;37:1220–1227. https://doi.org/10.1093/eurheartj/ehv690.
19. Mc Ardle BA, Dowsley TF, deKemp RA, Wells GA, Beanlands RS. Does rubidium-82 PET have superior accuracy to SPECT perfusion imaging for the Diagnosis of obstructive coronary disease? A systematic review and meta-analysis. *J Am Coll Cardiol.* 2012;60:1828–1837. https://doi.org/10.1016/j.jacc.2012.07.038.
20. Hamon M, Biondi-Zoccai GGL, Malagutti P, et al. Diagnostic performance of multislice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography - a meta-analysis. *J Am Coll Cardiol.* 2006;48:1896–1910. https://doi.org/10.1016/j.jacc.2006.08.028.
21. Camici PG, d'Amati G, Rimoldi O. Coronary microvascular dysfunction: mechanisms and functional assessment. *Nat Rev Cardiol.* 2015;12:48–62. https://doi.org/10.1038/nrcardio.2014.160.
22. Camici PG, Crea F. Medical progress - coronary microvascular dysfunction. *N Engl J Med.* 2007;356:830–840. https://doi.org/10.1056/NEJMra061889.
23. van de Hoef TP, van Lavieren MA, Damman P, et al. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. *Circ-Cardiovasc Inte.* 2014;7:301–311. https://doi.org/10.1161/Circinterventions.113.001049.
24. Bom MJ, Schumacher SP, Driessen RS, et al. Impact of individualized segmentation on diagnostic performance of quantitative positron emission tomography for haemodynamically significant coronary artery disease. *Eur Heart J Cardiovasc Imaging.* 2018. https://doi.org/10.1093/ehjci/jey201.