



Universiteit
Leiden
The Netherlands

Cardiac computed tomography-derived coronary artery volume to myocardial mass

Ihdayhid, A.R.; Fairbairn, T.A.; Gulsin, G.S.; Tzimas, G.; Danehy, E.; Updegrove, A.; ... ; Norgaard, B.L.

Citation

Ihdayhid, A. R., Fairbairn, T. A., Gulsin, G. S., Tzimas, G., Danehy, E., Updegrove, A., ... Norgaard, B. L. (2022). Cardiac computed tomography-derived coronary artery volume to myocardial mass. *Journal Of Cardiovascular Computed Tomography*, 16(3), 198-206.
doi:10.1016/j.jcct.2021.10.007

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/3567755>

Note: To cite this publication please use the final published version (if applicable).



Cardiac computed tomography-derived coronary artery volume to myocardial mass

Abdul Rahman Ihdahid^a, Timothy A. Fairbairn^b, Gaurav S. Gulsin^{c,d}, Georgios Tzimas^{d,e}, Edward Danehy^f, Adam Updegrave^g, Jesper M. Jensen^h, Charles A. Taylor^g, Jeroen J. Baxⁱ, Stephanie L. Sellers^d, Jonathon A. Leipsic^{d,*}, Bjarne L. Nørgaard^h

^a Department of Cardiology, Fiona Stanley Hospital, Harry Perkins Institute of Medical Research, University of Western Australia, Perth, Australia

^b Department of Cardiology, University of Liverpool, Liverpool Heart and Chest Hospital, Liverpool, United Kingdom

^c University of Leicester and the Leicester NIHR Biomedical Research Centre, Department of Cardiovascular Sciences, Glenfield Hospital, Leicester, United Kingdom

^d Department of Medicine and Radiology, University of British Columbia, Vancouver, British Columbia, Canada

^e Department of Heart Vessels, Cardiology Service, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

^f Radiology Regional, Naples, FL, USA

^g HeartFlow, Inc., Redwood City, CA, USA

^h Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

ⁱ Leiden University, Department of Medicine, Leiden, Netherlands

ARTICLE INFO

Keywords:

Coronary computed tomography angiography
Coronary volume/mass
Fractional flow reserve derived from computed tomography

ABSTRACT

In the absence of disease impacting the coronary arteries or myocardium, there exists a linear relationship between vessel volume and myocardial mass to ensure balanced distribution of blood supply. This balance may be disturbed in diseases of either the coronary artery tree, the myocardium, or both. However, in contemporary evaluation the coronary artery anatomy and myocardium are assessed separately. Recently the coronary lumen volume to myocardial mass ratio (V/M), measured noninvasively using coronary computed tomography angiography (CTCA), has emerged as an integrated measure of myocardial blood supply and demand *in vivo*. This has the potential to yield new insights into diseases where this balance is altered, thus impacting clinical diagnoses and management.

In this review, we outline the scientific methodology underpinning CTCA-derived measurement of V/M. We describe recent studies describing alterations in V/M across a range of cardiovascular conditions, including coronary artery disease, cardiomyopathies and coronary microvascular dysfunction. Lastly, we highlight areas of unmet research need and future directions, where V/M may further enhance our understanding of the pathophysiology of cardiovascular disease.

1. Introduction

A fundamental principle of biology describes that increased metabolic demands must be matched by increased blood supply.¹ In cardiac physiology, the amount of myocardium subtended by the coronary arterial tree drives adaptive changes in the feeding vascular bed until the calibers of the coronary arteries are adequate to supply the requisite blood flow. The volume of the coronary vessels therefore relates to the extent of subtended myocardium.¹

In patients with chronic coronary artery disease (CAD), progressive reductions in coronary lumen volume by atherosclerosis potentiates a mismatch between coronary blood supply and myocardial oxygen demand, forming the basis for the clinical symptoms and sequelae associated with myocardial ischemia.² Non-invasive functional tests such as myocardial perfusion imaging can quantify myocardial ischemia, although without directly visualising the coronary anatomy.³ Conversely, invasive coronary angiography (ICA) can provide a detailed assessment of epicardial coronary geometry, but as an anatomical test may overlook diffuse atherosclerotic plaque burden and ascribes little

* Corresponding author. Department of Medicine and Radiology, University of British Columbia.

E-mail addresses: absnet@iinet.net.au (A.R. Ihdahid), timothy.fairbairn@lhch.nhs.uk (T.A. Fairbairn), gaurav.gulsin@nhs.net (G.S. Gulsin), Georgios.Tzimas@chuv.ch (G. Tzimas), aupdegrave@heartflow.com (A. Updegrave), jesper.m.jensen@auh.rm.dk (J.M. Jensen), taylor@heartflow.com (C.A. Taylor), j.j.bax@lumc.nl (J.J. Bax), Stephanie.Sellers@hli.ubc.ca (S.L. Sellers), jleipsic@providencehealth.bc.ca (J.A. Leipsic), bnorgaard@dadlnet.dk (B.L. Nørgaard).

<https://doi.org/10.1016/j.jcct.2021.10.007>

Received 17 July 2021; Received in revised form 27 September 2021; Accepted 25 October 2021

Available online 29 October 2021

1934-5925/© 2021 The Authors. Published by Elsevier Inc. on behalf of Society of Cardiovascular Computed Tomography. This is an open access article under the CC

BY license (<http://creativecommons.org/licenses/by/4.0/>).

List of abbreviations

CAD	coronary artery disease
CTCA	coronary computed tomography angiography
FFR	fractional flow reserve
HCM	hypertrophic cardiomyopathy
ICA	invasive coronary angiography
INOCA	ischemia and no obstructive coronary artery disease
LV	left ventricle
MBF	myocardial blood flow
MI	myocardial infarction
MVA	microvascular angina
PET	positron emission tomography
STEMI	ST elevation myocardial infarction
V/M	coronary artery lumen volume to myocardial mass

significance to visually “mild” luminal narrowing even when this subtends a large proportion of the total myocardium.

With the advent of physiology guided assessment using invasive fractional flow reserve (FFR), it is increasingly evident that stenosis severity alone is not enough to identify hemodynamically significant CAD, with mismatch observed in up to a 1/3 of lesions.^{4,5} The absence of stenotic CAD on ICA may fail to appreciate the impact of diffuse atherosclerotic plaque burden on epicardial vasodilatory capacity.^{6,7} Furthermore, patients with isolated microvascular dysfunction in the absence of CAD can also present with angina and abnormalities in myocardial perfusion.⁸ This had led to increasing recognition for the need of an integrated assessment of physiological supply versus demand. Coronary artery lumen volume to myocardial mass ratio (V/M) bridges the gap between the epicardial coronary arteries and underlying myocardium, providing insights into the ability of the coronary arteries to adequately match myocardial demand.

Computed tomography coronary angiography (CTCA) is uniquely capable for non-invasive measurement of V/M. A standard CTCA acquisition offers the ability to extract both a detailed patient-specific three-dimensional model of the coronary geometry and an accurate volumetric assessment of left ventricular (LV) mass.^{9,10} In this review, we describe early studies identifying V/M via invasive assessment followed by subsequent development of techniques to derive V/M from CTCA. This is followed by an appraisal of recent clinical studies utilising CTCA-derived V/M across a range of cardiovascular conditions including CAD, cardiomyopathies and coronary microvascular dysfunction. Lastly, we highlight areas of unmet research need and future directions, where V/M may further enhance our understanding of the pathophysiology of cardiovascular diseases.

1.1. Early studies with invasive coronary angiography

The notion of assessing CAD in tandem with subtended myocardial mass was considered in early studies using ICA. In the first of these, cardiac catheterization was employed to measure the area of the proximal right and left coronary arteries, with ventriculography for calculation of myocardial mass.¹¹ In 27 subjects (6 with normal coronary arteries, 9 with minor CAD, 10 with valvular heart disease and 2 with cardiomyopathy), a linear increase in coronary artery area with LV mass was observed, posited to be an adaptive response to maintain adequate perfusion of hypertrophied myocardium. Although the small sample size did not permit comparison of the patients with various cardiac conditions, it highlighted that there exists a close relationship between coronary artery and myocardium dimensions. A subsequent study compared patients with ($n = 17$) and without ($n = 12$) evident CAD on ICA using quantitative coronary angiography to determine the ratio of coronary artery lumen area, branch lengths and branching patterns, to regional myocardial mass.¹² Patients

with angiographically normal coronary arteries had a proportional increase in coronary lumen area and regional myocardial mass. By contrast, in patients with CAD there was a 30–50% relative reduction in coronary artery lumen area to regional myocardial mass, highlighting a phenomenon of disproportionate vascular insufficiency in this group.¹² Haskell et al. also demonstrated the importance of physical activity on coronary vascular health and subsequent luminal dimensions.¹³ Physically active individuals had a significantly greater capacity to vasodilate their coronary arteries compared to sedentary individuals,¹³ underscoring the importance of non-atherosclerotic contributors to V/M. Invasive approaches to V/M calculation are limited by basic 2-dimensional angiographic measures of coronary artery area and myocardial mass with a high degree of error.^{14,15} The rapid advancement of CTCA and its ability to provide accurate 3-dimensional evaluation of cardiac anatomy has since made the non-invasive assessment of the V/M ratio both feasible and advantageous, obfuscating the requirement for ICA in calculation.

2. Scientific rationale and methodology

The relationship of CT-derived coronary luminal volume to coronary flow is fundamentally based on allometric scaling laws.¹⁶ Allometric scaling is a universally observed logarithmic relationship linking size and function in life science and describes the variation of biological parameters with scale.¹⁷ Coronary luminal volume demonstrates a proportional relationship to coronary flow and a strong linear relationship to myocardial mass, a concept that has been validated in both animal and human studies.^{1,18} These scientific principles form the basis for the overarching hypothesis that patients with low V/M ratio are at higher risk of ischemia under stress conditions due to inadequate coronary supply for a given myocardial tissue demand. In more specific detail, patients with low V/M are potentially characterised by 1) larger resting pressure gradients due to increased epicardial resistance despite normal resting flow, 2) lower FFR values, and 3) lower hyperemic perfusion as compared to patients with high V/M.

The V/M ratio can be readily computed from a standard CTCA (Fig. 1). First, the coronary artery luminal boundaries are extracted, i.e. segmented, from the CTCA image. This involves deep learning based centreline and lumen boundary image analysis methods to tracing the vessel paths of epicardial coronary arteries down to approximately 1 mm in diameter extracted from the image data¹⁹ and is processed within a matter of minutes, although semi-automated luminal segmentation using standard CT image processing software is also feasible.²⁰ Once the vessel tree centreline tree is obtained, the coronary luminal boundary can be segmented and ‘V’, the volume inside the coronary luminal surface can be calculated. Second, the LV myocardial mass, M, is calculated. The LV myocardial volume is segmented (area x slice thickness) from cardiac CT images. The LV myocardial volume is subsequently converted to LV mass, M, by multiplying with an assumed constant tissue density of myocardial tissue density (1.05 g/cc). Finally, the V/M ratio is calculated by dividing the coronary artery luminal volume by the LV myocardial mass. It should be noted that the computation of the coronary artery luminal volume is dependent on the image analysis methods used to segment the coronary arteries and the extent of the tree that is resolved. The first-generation V/M algorithms utilized image segmentation methods that derived the coronary luminal volume as a combination of the segmented epicardial vasculature in addition to the volume of a synthetic tree simulating the microvasculature.²¹ Consequently, this early methodology reported higher values for V/M.²¹ Refinement of the V/M quantification method subsequently removed such mathematical construction of the microvasculature and is based solely on the CT-derived epicardial coronary lumen volume extracted from vessels >1 mm in size.¹⁹

3. Clinical evidence to date

The linear relationship between vessel volume and myocardial mass may be disturbed in disease of the coronary artery tree (such as

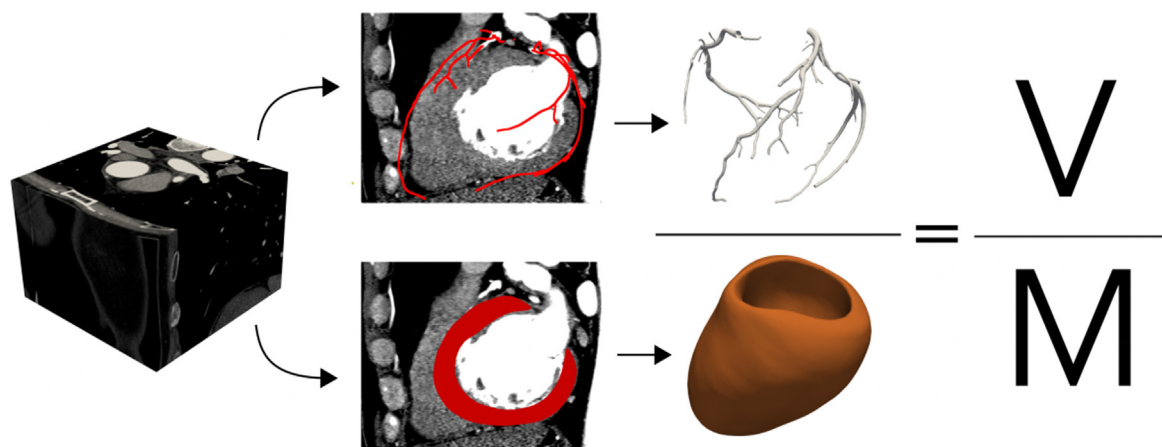


Fig. 1. Methodology for computing V/M ratio. Computed tomography coronary angiography (CTCA) data is used to compute the epicardial lumen volume subsequent to extracting the centerline of the coronary arteries and then segmenting the luminal surface along the vessel paths. The myocardial mass is calculated by first extracting the left ventricular myocardial volume from the CCTA data and multiplying it by a constant tissue density of 1.05 g/cc.

endothelial dysfunction, diffuse intimal thickening and/or arteriosclerosis), the myocardium (such as in aortic stenosis or hypertrophic obstructive cardiomyopathy), or both, and may be influenced by blood pressure, heart rate, hypoxia etc. Given that V/M ratio serves as an integrated measure of resting myocardial blood supply and demand *in vivo*, it has the potential to yield new insights into diseases where this balance is altered, thus impacting clinical diagnoses and management. With this aim, several studies have explored V/M in disease states (Table 1).

3.1. Epicardial coronary artery disease

Chronic CAD may cause a syndrome of recurrent angina pectoris, typically occurring due to flow-limiting lesions and is the archetypal state of supply-demand mismatch in myocardial perfusion.²² There is a well-recognised discordance between the anatomical severity of coronary stenosis and the presence of ischemia or physiological significance,^{4,5} which is particularly relevant for intermediate stenoses estimated to be

Table 1

Key studies evaluating coronary lumen volume to myocardial mass ratio in various cardiovascular disease populations.

Study	Subject group(s)	N	Age (years)	Sex (% female)	Assessment(s)	Key findings
Taylor et al., JCCT, 2017 ¹⁹	Stable CAD (stenosis $\leq 50\%$ on QCA)	238	64	38	FFR _{CT} and QCA.	Patients with low V/M ratio ($<18.57 \text{ mm}^3/\text{g}$) had greater diameter stenosis, higher total plaque volume and lower FFR _{CT} than those with high V/M. V/M independently associated with FFR ≤ 0.80 .
Gaur et al., JACC: CVI, 2017 ²¹	STEMI undergoing PCI Stable CAD	60 254	61 64	17 36	FFR _{CT} and ICA.	V/M ratio lower in STEMI vs. stable CAD patients (53 vs. $65 \text{ mm}^3/\text{g}$, $p = 0.009$). Baseline V/M ratio lowest in subset ($n = 8$) who required unplanned ICA within 12 months.
Grover et al., JCCT, 2017 ⁷¹	MVA Controls Groups matched for BMI, CV risk factors, physical activity and atherosclerotic burden.	30 32	55 61	92 91	FFR _{CT}	V/M ratio lower in MVA vs. controls (25.6 ± 5.9 vs. $30.0 \pm 6.5 \text{ mm}^3/\text{g}$, $p = 0.007$). V/M ratio predominantly driven by lower left coronary lumen volume in MVA vs. controls (1117 ± 80 vs. $1750 \pm 98 \text{ mm}^3$, $p < 0.001$).
Sellers et al., JCCT, 2018 ⁴⁰	HCM (hypertrophy distribution: 19% apical, 75% septal, 3% concentric, 3% mixed) Controls (matched for BMI, CV risk factors and plaque burden)	37 37	57 58	27 35	FFR _{CT}	V/M ratio lower in HCM vs. controls (23.8 ± 5.9 vs. $26.5 \pm 5.3 \text{ mm}^3/\text{g}$, $p = 0.0026$). Lowest V/M ratio in those with septal HCM ($22.4 \pm 5.1 \text{ mm}^3/\text{g}$).
Van Diemen et al., JCCT, 2019 ³³	Stable CAD (overall prevalence 103/431 (24%) obstructive coronary lesions)	152	58	39	SPECT, PET, FFR _{CT} and ICA.	Greater proportion of patients with V/M below median had abnormal hyperemic MBF and lower FFR _{CT} .
Fairbairn et al., JACC: CVI, 2020 ²⁹	Stable CAD	4737	66	34	FFR _{CT}	Females vs. males: lower coronary lumen volume (2548 ± 768 vs. $3226 \pm 977 \text{ mm}^3$, $p < 0.001$), lower myocardial mass (100 ± 23 vs. $133 \pm 30 \text{ g}$, $p < 0.001$) and higher V/M ratio (26.2 ± 7.6 vs. $24.8 \pm 7.2 \text{ mm}^3/\text{g}$, $p < 0.001$). Low V/M independently associated FFR _{CT} , sex, stenosis severity and multivessel disease.
Ithdayhid et al., JCCT, 2020 ⁵⁴	Suspected CAD: South Asians Caucasians East Asians Groups matched for BMI and diabetes.	100 100 100	58 59 59	49 49 49	FFR _{CT}	V/M ratio highest in East Asians ($29.3 \text{ mm}^3/\text{g}$) vs. Caucasians ($25.3 \text{ mm}^3/\text{g}$) vs. South Asians ($25.3 \text{ mm}^3/\text{g}$), $p < 0.001$.

Abbreviations: BMI = body mass index; CAD = coronary artery disease; CV = cardiovascular; FFR_{CT} = fractional flow reserve computed tomography; HCM = hypertrophic cardiomyopathy; ICA = invasive coronary angiography; JACC:CVI = Journal of the American College of Cardiology: Cardiovascular Imaging; JCCT = Journal of Cardiovascular Computed Tomography; MVA = microvascular angina; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; STEMI = ST-segment elevation myocardial infarction; V/M = coronary lumen volume to myocardial mass.

50–90% by visual assessment.²³ The evaluation of ischemia or flow by both non-invasive and invasive techniques remains central to guiding risk stratification and clinical decision making.²⁴ However, assessment of ischemia alone does not explain which factors led to the supply and demand imbalance (e.g. vascular tone, microvascular function, myocardial demand and environmental factors).²⁵ This may in part explain why not all patients with angina have demonstrable ischemia,²⁶ and why there is frequently a discordance between physiologically significance by invasive FFR and anatomical significance on ICA.^{4,5}

Anatomical assessment has the ability to discern atheroma but in the presence of lower-grade or diffuse atherosclerosis may under-diagnose ischemia. Functional testing may diagnose focal ischemia but has reduced sensitivity for a global reduction in blood flow and cannot identify atherosclerosis, which remains a key driver of cardiovascular risk.^{27,28} Given that atheroma and ischemia may potentially be overlooked by all tests, a test that incorporates measures of atherosclerotic burden, lesion-specific ischemia and subtended myocardial mass is desirable.

Several studies have examined the relationship between myocardial demand and supply using the V/M ratio in patients with stable CAD (Table 1). The first of these was a secondary analysis of the *NeXt sSteps* (NXT) trial (NCT01757678)¹⁹ performed using the first-generation V/M algorithms. In this study including 238 patients, those with a V/M ratio below the median value of 18.57 mm³/g had greater overall diameter stenosis by quantitative coronary angiography (38 vs. 31%, $p < 0.001$), higher total plaque volume (593 vs. 392 mm³, $p < 0.001$), and lower invasive FFR (0.80 vs. 0.87; $p < 0.001$) than those with V/M above the median. In patients with non-obstructive CAD (diameter stenosis $\leq 50\%$ by quantitative coronary angiography, $n = 202$), the prevalence of vessel specific FFR values ≤ 0.80 was increased in patients with a low V/M ratio (Fig. 2). Lastly, V/M ratio was associated with FFR ≤ 0.80 independent of sex, BMI, stenosis severity and plaque characteristics.¹⁹ These findings highlight the potential for the V/M ratio to improve the discrimination of CAD physiological significance over traditional ICA and CTCA markers, and potentially refine the risk stratification of ‘non-obstructive’ stenosis.

The largest study to date evaluating V/M in patients with chronic CAD was the ADVANCE registry.²⁹ In this group of 3110 symptomatic patients with evidence of at least 30%-degree stenosis CAD, the mean coronary epicardial lumen volume was 3003 mm³ and ranged from a minimum of 493 mm³ to a maximum of 7891 mm³ with a median value of 2873 mm³. The mean LV myocardial mass was 122 g and ranged from

a minimum of 55 g to a maximum of 357 g with a median value of 118 g. Mean V/M was 25.2 mm³/g and ranged from a minimum of 5.6 mm³/g to a maximum of 62.5 mm³/g with a median value of 24.8 mm³/g (Fig. 3).

Fig. 4 shows two patients with low V/M, the first due to normal LV mass but small epicardial coronary artery volume and the second with normal epicardial coronary artery volume but high LV mass. In both cases, the accompanying FFR_{CT} results exhibit a gradual decline in value along the length of the left anterior descending artery, ultimately falling below 0.7. In both cases, the combination of epicardial disease and an inadequate caliber vessel for the size of the myocardium results in functional limitations to coronary artery blood flow.

Myocardial blood flow (MBF) as measured by positron emission tomography (PET) or stress perfusion cardiovascular magnetic resonance imaging is a well-established prognostic marker in patients with CAD.^{30,31} As a potential measure of a mismatch between coronary ‘supply’ and myocardial ‘demand’, the relationship of V/M with MBF was investigated in a substudy of the PACIFIC trial (Prospective Comparison of Coronary CT Angiography, single-photon emission computed tomography, PET, and Hybrid Imaging for the Diagnosis of Ischemic Heart Disease Determined by Fractional Flow Reserve, NCT01521468).³² Patients with suspected CAD and preserved LV ejection fraction underwent assessment with CTA and PET prior to ICA with invasive FFR. In total, 152 subjects were included comprising 431 epicardial coronary vessels. There was a numerically lower vessel specific resting MBF in patients with low versus high V/M (1.06 vs. 1.13 mL/min/g, respectively, $p = 0.056$), but no difference in vessel specific hyperemic MBF (3.27 vs. 3.51 mL/min/g, $p = 0.125$) or coronary flow reserve (3.20 vs. 3.22, $p = 0.806$) between groups. However, a higher proportion of patients with low V/M had vessel specific abnormal hyperemic MBF (categorised as ≤ 2.30 mL/min/g) (34 vs. 19%, respectively, $p = 0.009$) and invasive FFR ≤ 0.80 (20 vs. 9%, respectively, $p = 0.004$). A weak correlation was observed between V/M and vessel specific ($R = 0.148$, $p = 0.027$) or global ($R = 0.179$, $p = 0.027$) hyperemic MBF and global CFR ($R = 0.163$, $p = 0.045$).³³ The relationship of V/M with global resting measures myocardial blood flow were not reported in this study. Future iterations of the V/M technique which permit derivation of regional V/M according to subtended coronary territory may potentially demonstrate improved correlation with vessel specific measures of myocardial and coronary blood flow and warrants further evaluation.¹⁸

In contrast to studies in stable CAD, only one has evaluated V/M in patients in the setting of acute coronary syndrome.²¹ Sixty patients

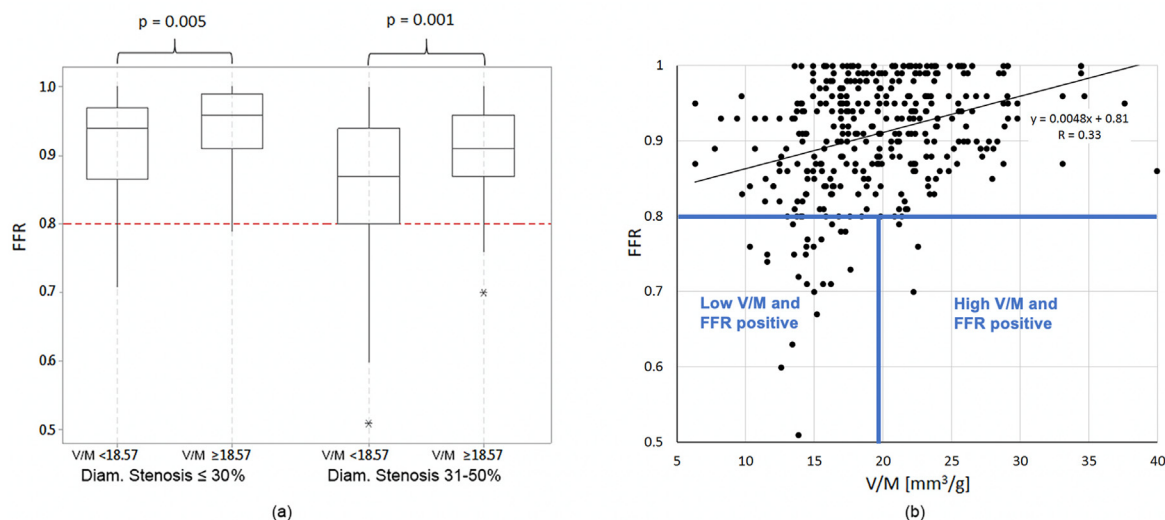


Fig. 2. (a) Relationship between diameter stenosis (by quantitative coronary angiography, QCA) and measured FFR for low and high V/M. (b) FFR vs. V/M for lesions with QCA diameter stenosis 50%. Lower values of V/M are associated with greater frequency of measured FFR values ≤ 0.8 , whereas higher values of V/M are infrequently associated with FFR ≤ 0.80 for vessels with 50% diameter stenosis by QCA. A positive correlation between FFR and V/M was observed with a Pearson's correlation coefficient of 0.33 ($p < 0.001$). Reproduced with permission from Taylor et al. JCCT 2017(19).

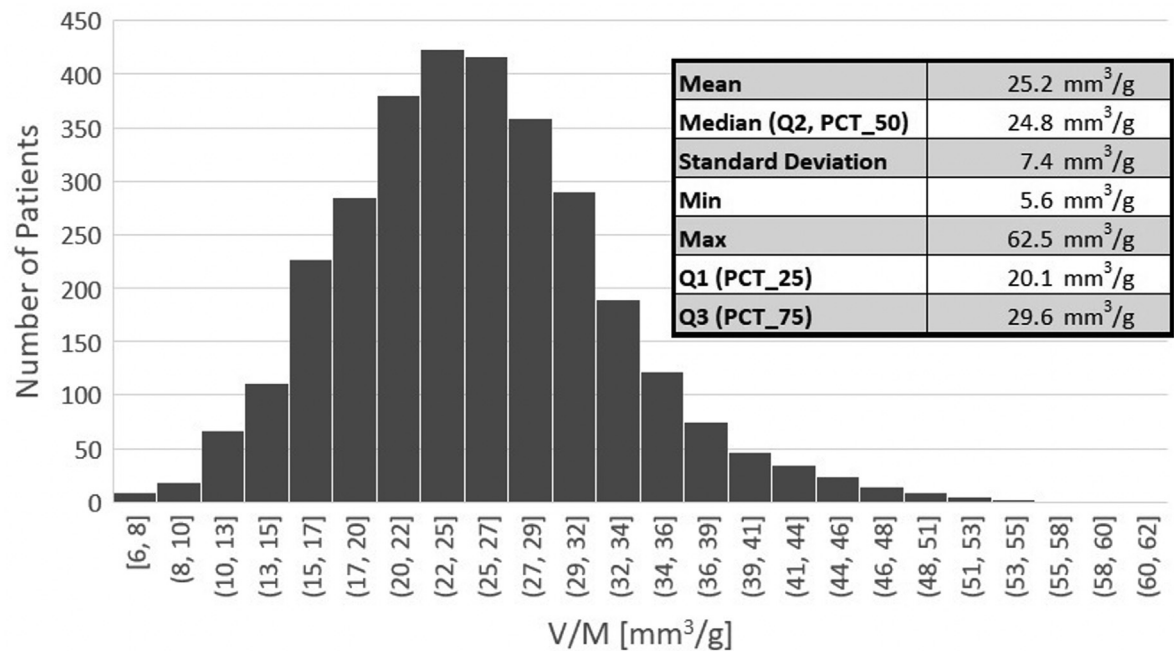


Fig. 3. Histogram of V/M ratio among 3110 patients with symptoms concerning for coronary artery disease and atherosclerosis on CCTA included in the ADVANCE registry. The median value of V/M was 24.8 mm³/g.

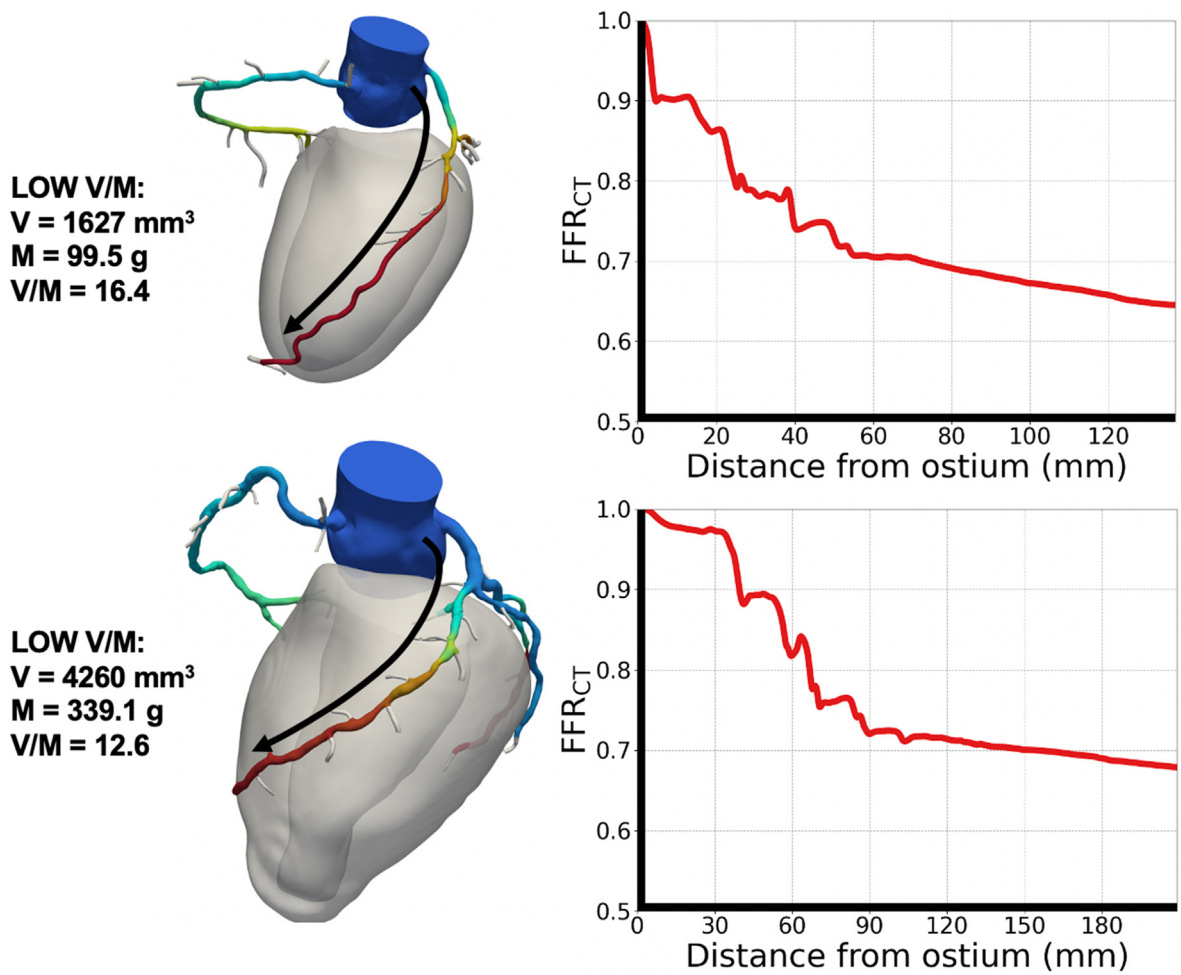


Fig. 4. Gradual decline in FFR_{CT} along the length of vessels due to an inadequate relationship of physiological supply and demand. Top: A low coronary volume causes low V/M. Bottom: A large myocardial mass causes low V/M.

presenting with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention with residual CAD ($\geq 50\%$ stenosis) in at least one non-culprit artery were included. FFR_{CT} was performed at one month after STEMI and was compared to a cohort with the stable CAD from the NXT trial. Median V/M was lower in patients following STEMI compared to those with stable CAD (53 vs. 65 mm³/g, $p = 0.009$). Furthermore, median V/M was lower still (40 mm³/g) in eight patients (13%) who underwent unplanned percutaneous coronary intervention over 12 months of follow-up.²¹ Notably, the V/M values in this study are higher than others reported in the prevailing literature, as they utilized the first-generation V/M methodology which composed of both the CTCA-derived epicardial lumen volume and the volume of a synthetic tree simulating the microvasculature. Nevertheless, these findings in small numbers are hypothesis generating and warrant further investigation to determine the role of V/M in improving identification of high-risk patients at on-going risk following MI.

From these studies in patients with CAD, it appears that V/M may be an integrated measure of myocardial oxygen supply to demand, is associated with invasive and non-invasive measures of FFR but not necessarily vessel specific MBF and may provide additional risk-stratification in patients with both stable CAD and recent acute coronary syndrome.

3.2. Coronary microvascular dysfunction

Patients with angina and no obstructive coronary artery stenoses account for half of patients with angina undergoing ICA.³⁵ Amongst these important subset are patients with microvascular angina (MVA), who suffer symptoms of chest pain in the absence of flow-limiting CAD but with objective evidence of myocardial ischemia and/or coronary microvascular dysfunction.²⁵ V/M as an index of myocardial oxygen supply-demand may provide non-invasive insight into microvascular function from a standard CTCA acquisition. It is recognised that endothelial dependent and independent mechanisms of vasodilation in the microvasculature directly impact the vasodilatory capacity of epicardial vessels and therefore the coronary luminal volume.^{36,37} In a cohort of patients with primary MVA, V/M was significantly lower compared to matched controls (25.6 ± 5.9 vs. 30.0 ± 6.5 , $p < 0.001$).¹⁶ This was driven predominantly by lower total coronary lumen volume in MVA patients (2302 ± 109 vs. 2978 ± 134 mm³, $p < 0.001$), highlighting that the vasodilatory capacity of the epicardial vessels (i.e. coronary luminal volume) is potentially related to microvascular function. Similarly, in the V/M analysis of STEMI patients, the coronary luminal volume was significantly lower compared to controls with stable CAD.²¹ Studies have indicated that endothelial dysfunction can occur beyond the culprit territory and also affect the remote myocardium with an impaired vasodilator response observed up to 6 months following MI.^{38,39}

3.3. Cardiomyopathy

Two studies have linked V/M with the pathophysiology of heart muscle disease, both in the context of hypertrophic cardiomyopathy (HCM) (Table 1). The first of these was a retrospective case-control analysis comparing 37 HCM patients with 37 controls matched to age, sex, cardiovascular risk factor and atherosclerotic plaque burden.⁴⁰ Unsurprisingly myocardial mass was greater in patients with HCM than controls (176 ± 84 vs. 119 ± 27 g, $p < 0.001$). Interestingly, whilst total coronary artery luminal volume was also higher in HCM (4112 ± 1139 vs. 3290 ± 924 mm³, $p < 0.001$) with equal contribution from the right and left coronary systems, these patients had lower overall V/M (23.8 ± 5.9 vs. 26.5 ± 5.3 mm³/g, $p = 0.026$) and lower nadir FFR_{CT} values (indicative of globally abnormal coronary physiology). The lowest V/M was observed in those patients with a septal pattern of hypertrophy. It is possible that the higher coronary luminal volume observed in HCM represents a physiological adaptation attempting to meet the increased myocardial oxygen demand of hypertrophied myocardium, albeit insufficiently in comparison to V/M in matched controls.⁴¹

The second study compared patients with primary (HCM, $n = 55$) and secondary (hypertension or aortic stenosis, $n = 176$) myocardial hypertrophy, to ascertain whether V/M could distinguish between causes of LVH.⁴² In patients with secondary hypertrophy, V/M decreased proportionally with increases in LV mass, whereas in HCM V/M was disproportionately lower for any given LV mass. These observations could indicate that the rate of myocyte hypertrophy in HCM exceeds the capacity for coronary artery remodelling and capillary angiogenesis, leading to relative increased myocardial oxygen supply-demand mismatch compared to secondary hypertrophy. Alternatively, low V/M in HCM may be the consequence of a higher burden of myocardial fibrosis and/or extracellular matrix expansion, resulting in capillary rarefaction.

These early studies in HCM highlight the potential value of V/M in patients with cardiomyopathy and there are a wealth of opportunities to employ V/M in other cardiomyopathies. For example, in ischemic cardiomyopathy, where V/M may elucidate mechanisms contributing to LV dysfunction in the absence of focal obstructive CAD. In patients with heart failure and preserved ejection fraction (HFpEF), who account for half of all patients hospitalised with heart failure^{43,44} and which is commonly accompanied by concentric LV hypertrophy and microvascular dysfunction/capillary rarefaction,^{45,46} it is possible that low V/M contributed to myocardial fibrosis and hence diastolic dysfunction. Or in dilated cardiomyopathy, in which microvascular dysfunction has been associated with the degree of LV impairment and may therefore be an additional adverse prognostic marker.⁴⁷ These are undoubtedly avenues of enquiry that will be explored once the utility of V/M is more widely recognised.

3.4. Sex and ethnic differences in V/M

The effects of sex and ethnicity on prevalence, severity and outcomes of CAD,^{48,49} as well as upon cardiac geometry,^{50,51} are widely recognised. Assessment of V/M presents a unique opportunity to provide an assessment of the interplay between epicardial coronary arteries and the myocardium in populations from different sex and ethnic backgrounds.

In the largest study employing V/M to date, male ($n = 3134$ [66%], mean age 65.0 years) and female ($n = 1603$ [34%], mean age 68.3 years) patients from the ADVANCE registry who underwent CTA with FFR_{CT} were compared to identify sex differences in coronary physiology and microvascular disease.²⁹ Despite their older age and higher overall symptom burden, females had lower prevalence of obstructive CAD (65.5 vs. 74.7%, $p < 0.001$) and higher overall FFR_{CT} (0.76 vs. 0.73, $p < 0.001$) compared with males. Although both total coronary artery luminal volume (2548 vs. 3226 mm³, $p < 0.001$) and myocardial mass (99.5 vs. 133.2g, $p < 0.001$) were lower in females compared with males, overall V/M was higher (26.2 vs. 24.8 mm³/g, $p < 0.001$), driven predominantly by their relative lower LV mass. In multivariate regression analyses, female sex, stenosis severity, multivessel disease and FFR_{CT} were independently associated with V/M. Importantly, higher V/M was independently associated with a reduced likelihood of revascularisation within 90 days, which may explain lower rates of revascularisation in females.²⁹ The impact of sex differences in V/M on symptoms and long-term cardiovascular outcomes warrants further investigation, in particular conditions that promote adverse LV remodelling (e.g. hypertension, obesity and diabetes) and disturb this balance, a reduction in V/M may be a key driver of poorer cardiovascular outcomes in females^{52,53} by promoting a greater predisposition towards microvascular dysfunction.

Similarly, Ithayhid et al. undertook a comparison of V/M in 300 Caucasian, South Asian and East Asian patients with chest pain referred for CTCA, who were well-matched for age-, sex-, cardiovascular risk factors and atherosclerotic burden.⁵⁴ Interestingly, the highest V/M was observed in East Asians (29.2 mm³/g), a group who had the highest overall total coronary luminal volume but similar indexed LV mass to Caucasians. Although South Asians had the lowest overall coronary luminal volumes, myocardial mass was also comparatively lower in this group and overall V/M was similar to Caucasians (25.5 vs. 25.3,

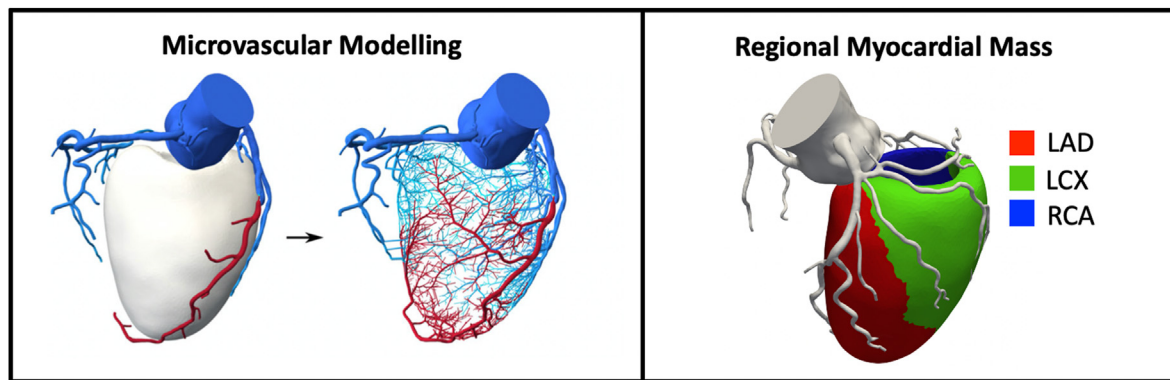


Fig. 5. The future of assessing myocardial ischemic burden non-invasively. Left: The generation of microvascular networks to measure the impacted perfusion of the myocardium. Right: Breakdown of myocardial mass and V/M per territory to assess vessel-specific health.

$p = 0.98$). These findings may partly explain why, relative to Caucasians, East Asians have lower observed cardiovascular risk whereas South Asians are at higher risk (especially in the context of obesity, diabetes and hypertension).⁵⁵ Similar to what has been posited in females, it is possible that diseases which drive LV remodelling and thereby increase myocardial oxygen demand cause relatively reduced capillary density and myocardial perfusion in the context of lower luminal volumes (i.e. ‘coronary supply’) in South Asians.

The sex and ethnic differences in V/M may have implications for the non-invasive estimation of coronary blood flow and therefore FFR derived from CTCA. The estimation of coronary flow from CTCA is based on allometric scaling laws, which describes the variation of biological parameters with scale.¹ The FFR_{CT} technique derives resting coronary blood flow from the allometric scaling of CT-derived LV mass (Coronary Flow $\propto$ myocardial mass^{3/4}). It is well established that sex-differences exist, with both invasive and PET studies highlighting that women have a higher resting myocardial flow compared to men.^{56,57} Indeed, this higher resting flow per unit tissue for women vs men is predictable from a $\frac{3}{4}$ power scaling law, given the fact that women are, on average, smaller than men and have a smaller sized heart. Overall given the diversity of human biology; variations of allometric scaling within the human heart in relation to age, sex, ethnicity and pathology may exist and their impact on the accuracy of CT-derived coronary flow is as yet undefined. The patient-specific characterisation of V/M may potentially allow for improved modelling of coronary flow and therefore refine the diagnostic accuracy of FFR_{CT}.

3.5. Summary of clinical evidence to date

Although existing clinical studies are predominantly retrospective, observational case-control analyses, they highlight the potential value of V/M as an easily derived measure that may shed light on drivers of hyperemic pressure loss and angina in the absence of stenotic coronary disease. In CAD, V/M correlates with invasive (FFR) and non-invasive (FFR_{CT}) markers of physiology, may be linked to quantitative MBF. In patients with microvascular dysfunction, V/M may unmask contributory mechanisms such as LV hypertrophy or reduced coronary luminal volume that could be targets for intervention. There is real potential for V/M in elucidating supply-demand mismatch in patients with cardiomyopathy, as has been elegantly demonstrated in hypertrophic cardiomyopathy. And a relatively simple and intuitive metric as V/M may help enhance our understanding of drivers of cardiovascular disease in populations with heightened risk.

4. Future directions

Although the theory of V/M is not new, the ability to accurately quantify it on a non-invasive test is. This provides us with many potential

avenues of future clinical use to improve the diagnosis, prognostication and management of both non-obstructive and obstructive CAD and complements the anatomical and functional information currently obtained from CTCA, FFR_{CT} and CT-myocardial perfusion. Ischemia with no obstructive coronary artery disease (INOCA) is an increasingly recognised condition related to coronary microvascular dysfunction and spasm.⁸ INOCA is not without risk and is associated with adverse prognosis, significant symptomatic limitation and impairment to quality of life.⁵⁸ Given the relationship of endothelial function with epicardial coronary vasoreactivity³⁷ and therefore luminal dimensions, CCTA in combination with V/M data could provide further personalised risk assessment for patients with no-evident or non-obstructive CAD. Improved risk assessment could augment management strategies such as intensifying existing treatments (low – high intensity statins), monitoring the physiological response to pharmacotherapies (e.g. angiotensin converting enzyme inhibitors) or improving patient selection and cost-effectiveness for the use of expensive therapies (PCSK9 inhibitors). Similarly, in patients with obstructive CAD, the integration of V/M with other emerging CTCA metrics such as plaque morphology,⁵⁹ FFR_{CT},⁶⁰ wall shear stress⁶¹ and myocardial territory at risk,⁶² may also improve the identification of patients that will receive the greatest benefit from a revascularisation strategy as compared to medical therapy alone.

The reporting of V/M remains limited to being a per-patient measure of total coronary luminal volume and total LV myocardial mass. Given that disease states such as atherosclerosis and hypertension are systemic processes, it is commonly understood that microvascular dysfunction globally affects the myocardium.⁶³ However, global measures of microvascular dysfunction may fail to identify the increasingly recognised variations in coronary flow, endothelial function and myocardial perfusion that can exist within coronary territories.^{64,65} For example, a patient with diffuse coronary atherosclerosis limited to the right coronary artery may still have normal global coronary flow reserve, despite endothelial dysfunction and reduced perfusion in the right coronary territory. Therefore, as it stands, the global measure of V/M is limited in identifying the regional heterogeneity of ‘vascular health’.

The ability to determine regional V/M has been limited by the lack of validated CT techniques to quantify fractional myocardial mass in relation to patient-specific coronary anatomy. The essential step in establishing this relationship lies in efforts to validate the hypothesis of myocardial mass being proportional to myocardial perfusion. Several methods have been previously proposed, however are limited to studies in animals or single-vessel human validation.^{66,67} More recently, Keulards et al. invasively measured myocardial perfusion in all three major coronary territories and demonstrated that there was a high agreement with CT-derived fractional mass for the relative perfusion territory.¹⁸ These findings provide an important foundation for the development of future techniques to quantify fractional myocardial mass and V/M. The ability to appreciate regional differences in V/M may offer improved

patient-specific diagnosis, risk stratification and disease monitoring (Fig. 5).

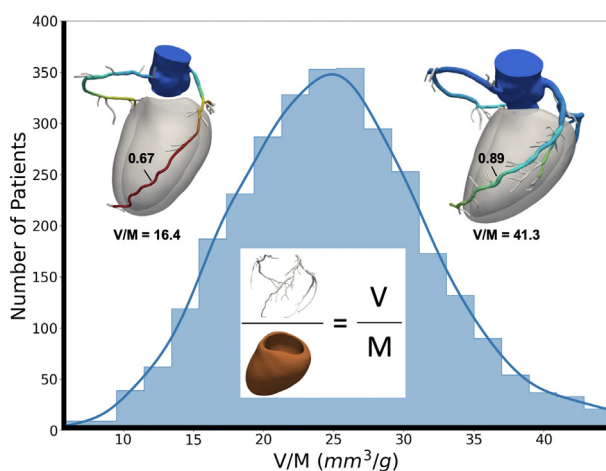
Future modifications to V/M also extend to refining the quantification of coronary luminal volume. Improvements in CTCA image quality with routine nitroglycerin and heart-rate control, in addition to advances in post-imaging data analysis have been important in optimizing the calculation of coronary luminal volume.⁶⁸ However, the spatial resolution of CTCA remains an intrinsic limitation and prohibits the complete visualization of the coronary vasculature.¹⁹ Recently, algorithms have been developed that allow for the generation of synthetic patient-specific coronary vascular networks from the segmented epicardial vessels down to the microvascular arterioles.⁶⁹ This has significant potential to not only improve the quantification of V/M but also advance the non-invasive CT-modelling of coronary flow, microvascular function and myocardial perfusion.⁷⁰

5. Conclusion

Coronary volume to mass ratio is a promising investigational measure providing insight into vascular health and mechanisms of abnormal physiology. V/M has been investigated in a number of clinical scenarios as highlighted in this review. With the concept established, future studies will need to explore whether V/M is modifiable through alterations in medical management and cardiac rehabilitation and whether improvements in V/M are associated with improved clinical outcomes.

Declaration of competing interest

BLN has received institutional unrestricted research grants from Siemens and HeartFlow. JL is a consultant and holds stock options in Circle CVI and Heartflow, research grants from GE and modest speaker fees from GE and Philips. AI has received consulting fees from Canon, Artrya Medical and Boston Scientific. CT and AU are employees of HeartFlow Inc.



Central illustration. V/M links the epicardial arteries to the myocardium in a simple, integrated measure. Low V/M indicates a poor epicardial vessel supply for the size of the myocardium.

References

- Choy JS, Kassab GS. Scaling of myocardial mass to flow and morphometry of coronary arteries. *J Appl Physiol.* 2008;104:1281–1286.
- Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation.* 2003;107:2900–2907.
- Salerno M, Beller GA. Noninvasive assessment of myocardial perfusion. *Circ Cardiovasc Imaging.* 2009;2:412–424.
- Toth G, Hamilos M, Pyxaras S, et al. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. *Eur Heart J.* 2014;35:2831–2838.
- Curzen N, Rana O, Nicholas Z, et al. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain?: the RIPCORDER study. *Circ Cardiovasc Interv.* 2014;7:248–255.
- Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. *Circulation.* 2004;109:III27–32.
- De Bruyne B, Hersbach F, Pijls NH, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "Normal" coronary angiography. *Circulation.* 2001;104:2401–2406.
- Ford TJ, Yli E, Sidik N, et al. Ischemia and No obstructive coronary artery disease: prevalence and correlates of coronary vasomotion disorders. *Circ Cardiovasc Interv.* 2019;12, e008126.
- Luo T, Wischgoll T, Kwon Koo B, Huo Y, Kassab GS. IVUS validation of patient coronary artery lumen area obtained from CT images. *PLoS One.* 2014;9, e86949.
- Raman SV, Shah M, McCarthy B, Garcia A, Ferketich AK. Multi-detector row cardiac computed tomography accurately quantifies right and left ventricular size and function compared with cardiac magnetic resonance. *Am Heart J.* 2006;151:736–744.
- Lewis BS, Gotsman MS. Relation between coronary artery size and left ventricular wall mass. *Br Heart J.* 1973;35:1150–1153.
- Seiler C, Kirkeeide RL, Gould KL. Basic structure-function relations of the epicardial coronary vascular tree. Basis of quantitative coronary arteriography for diffuse coronary artery disease. *Circulation.* 1992;85:1987–2003.
- Haskell WL, Sims C, Myll J, Bortz WM, St Goar FG, Alderman EL. Coronary artery size and dilating capacity in ultradistance runners. *Circulation.* 1993;87:1076–1082.
- Molloy S, Kassab GS, Zhou Y. Quantification of coronary artery lumen volume by digital angiography: in vivo validation. *Circulation.* 2001;104:2351–2357.
- Devereux RB, Pini R, Aurigemma GP, Roman MJ. Measurement of left ventricular mass: methodology and expertise. *J Hypertens.* 1997;15:801–809.
- Min JK, Taylor CA, Achenbach S, et al. Noninvasive fractional flow reserve derived from coronary CT angiography: clinical data and scientific principles. *JACC Cardiovasc Imaging.* 2015;8:1209–1222.
- Lindstedt SL, Schaeffer PJ. Use of allometry in predicting anatomical and physiological parameters of mammals. *Lab Anim.* 2002;36:1–19.
- Keulards D, Fournier S, van't Veer M, et al. Computed tomographic myocardial mass compared to invasive myocardial perfusion measurement. *Heart.* 2020;106:1489–1494. in press <https://heart.bmj.com/content/106/19/1489>.
- 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 Tomogr.* 2017;11:429–436.
- Sorensen SK, Kuhl JT, Fuchs A, et al. Volume and dimensions of angiographically normal coronary arteries assessed by multidetector computed tomography. *J Cardiovasc Comput Tomogr.* 2017;11:295–301.
- Gaur S, Taylor CA, Jensen JM, et al. FFR derived from coronary CT angiography in nonculprit lesions of patients with recent STEMI. *JACC Cardiovasc Imaging.* 2017;10:424–433.
- Ford TJ, Corcoran D, Berry C. Stable coronary syndromes: pathophysiology, diagnostic advances and therapeutic need. *Heart.* 2018;104:284–292.
- 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.
- Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J.* 2020;41:407–477.
- Ford TJ, Berry C. Angina: contemporary diagnosis and management. *Heart.* 2020;106:387–398.
- Steg PG, Greenlaw N, Tendera M, et al. Prevalence of anginal symptoms and myocardial ischemia and their effect on clinical outcomes in outpatients with stable coronary artery disease: data from the International Observational CLARIFY Registry. *JAMA Intern Med.* 2014;174:1651–1659.
- Burrell S, MacDonald A. Artifacts and pitfalls in myocardial perfusion imaging. *J Nucl Med Technol.* 2006;34:193–211. quiz 212–4.
- Nakanishi R, Gransar H, Slomka P, et al. Predictors of high-risk coronary artery disease in subjects with normal SPECT myocardial perfusion imaging. *J Nucl Cardiol.* 2016;23:530–541.
- Fairbairn TA, Dobson R, Hurwitz-Koweek L, et al. Sex differences in coronary computed tomography angiography-derived fractional flow reserve: lessons from ADVANCE. *JACC Cardiovasc Imaging.* 2020;13:2576–2587.
- Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation.* 2011;124:2215–2224.
- Knott KD, Seraphim A, Augusto JB, et al. The prognostic significance of quantitative myocardial perfusion: an artificial intelligence-based approach using perfusion mapping. *Circulation.* 2020;141:1282–1291.
- Danad I, Rajmakers 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 Cardiol.* 2017;2:1100–1107.
- van Diemen PA, Schumacher SP, Bom MJ, et al. The association of coronary lumen volume to left ventricle mass ratio with myocardial blood flow and fractional flow reserve. *J Cardiovasc Comput Tomogr.* 2019;13:179–187.
- Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med.* 2010;362:886–895.
- Gutierrez E, Flammer AJ, Lerman LO, Elizaga J, Lerman A, Fernandez-Aviles F. Endothelial dysfunction over the course of coronary artery disease. *Eur Heart J.* 2013;34:3175–3181.
- Gunawardena T, Merinopoulos I, Wickramarachchi U, Vassiliou V, Eccleshall S. Endothelial dysfunction and coronary vasoreactivity - a review of the history, physiology, diagnostic techniques, and clinical relevance. *Curr Cardiol Rev.* 2021;17:85–100.

38. Bax M, de Winter RJ, Koch KT, Schotborgh CE, Tijssen JG, Piek JJ. Time course of microvascular resistance of the infarct and noninfarct coronary artery following an anterior wall acute myocardial infarction. *Am J Cardiol.* 2006;97:1131–1136.
39. Uren NG, Crake T, Lefroy DC, de Silva R, Davies GJ, Maseri A. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. *N Engl J Med.* 1994;331:222–227.
40. Sellers SL, Fonte TA, Grover R, et al. Hypertrophic Cardiomyopathy (HCM): new insights into Coronary artery remodelling and ischemia from FFRCT. *J Cardiovasc Comput Tomogr.* 2018;12:467–471.
41. Rahman H, Demir OM, Khan F, et al. Physiological stratification of patients with angina due to coronary microvascular dysfunction. *J Am Coll Cardiol.* 2020;75: 2538–2549.
42. Hamdan A, Nassar M, Monakier D, et al. Differentiating primary from secondary hypertrophy based on the coronary lumen volume to myocardial mass relationship. *JACC Cardiovasc Imaging.* 2018;11:1926–1928.
43. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med.* 2006;355:260–269.
44. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med.* 2006;355:251–259.
45. D'Amario D, Migliaro S, Borovac JA, et al. Microvascular dysfunction in heart failure with preserved ejection fraction. *Front Physiol.* 2019;10:1347.
46. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation.* 2015;131:550–559.
47. Gulati A, Ismail TF, Ali A, et al. Microvascular dysfunction in dilated cardiomyopathy: a quantitative stress perfusion cardiovascular magnetic resonance study. *JACC Cardiovasc Imaging.* 2019;12:1699–1708.
48. Gupta A, Wang Y, Spertus JA, et al. Trends in acute myocardial infarction in young patients and differences by sex and race, 2001 to 2010. *J Am Coll Cardiol.* 2014;64: 337–345.
49. Budoff MJ, Yang TP, Shavelle RM, Lamont DH, Brundage BH. Ethnic differences in coronary atherosclerosis. *J Am Coll Cardiol.* 2002;39:408–412.
50. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex differences in cardiovascular pathophysiology: why women are overrepresented in heart failure with preserved ejection fraction. *Circulation.* 2018;138:198–205.
51. Kishi S, Reis JP, Venkatesh BA, et al. Race-ethnic and sex differences in left ventricular structure and function: the coronary artery risk development in young adults (CARDIA) study. *J Am Heart Assoc.* 2015;4, e001264.
52. Kee YK, Kim MH, Oh J, Oh HJ, Ryu DR. Sex differences in the blood pressure level associated with increased risks of cardiovascular events: a Korean nationwide population-based cohort study. *J Clin Hypertens.* 2020;22:1638–1646.
53. Peters SA, Huxley RR, Sattar N, Woodward M. Sex differences in the excess risk of cardiovascular diseases associated with type 2 diabetes: potential explanations and clinical implications. *Curr Cardiovasc Risk Rep.* 2015;9:36.
54. Ithdayhid AR, Thakur U, Yap G, et al. Ethnic differences in coronary anatomy, left ventricular mass and CT-derived fractional flow reserve. *J Cardiovasc Comput Tomogr.* 2020.
55. Owusu Adjah ES, Bellary S, Hanif W, Patel K, Khunti K, Paul SK. Prevalence and incidence of complications at diagnosis of T2DM and during follow-up by BMI and ethnicity: a matched case-control analysis. *Cardiovasc Diabetol.* 2018;17:70.
56. Murthy VL, Bateman TM, Beanlands RS, et al. Clinical quantification of myocardial blood flow using PET: joint position paper of the SNMMI cardiovascular council and the ASNC. *J Nucl Med.* 2018;59:273–293.
57. Kobayashi Y, Fearon WF, Honda Y, et al. Effect of sex differences on invasive measures of coronary microvascular dysfunction in patients with angina in the absence of obstructive coronary artery disease. *JACC Cardiovasc Interv.* 2015;8: 1433–1441.
58. Herscovici R, Sedlak T, Wei J, Pepine CJ, Handberg E, Bairey Merz CN. Ischemia and No obstructive coronary artery disease (INOCA): what is the risk? *J Am Heart Assoc.* 2018;7, e008868.
59. Chang HJ, Lin FY, Lee SE, et al. Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol.* 2018;71:2511–2522.
60. Ithdayhid AR, Norgaard BL, Gaur S, et al. Prognostic value and risk continuum of noninvasive fractional flow reserve derived from coronary CT angiography. *Radiology.* 2019;292:343–351.
61. Lee JM, Choi G, Koo BK, et al. Identification of high-risk plaques destined to cause acute coronary syndrome using coronary computed tomographic angiography and computational fluid dynamics. *JACC Cardiovasc Imaging.* 2019;12:1032–1043.
62. Ithdayhid AR, Norgaard BL, Achenbach S, et al. Ischemic myocardial burden subtended by computed tomography-derived fractional flow reserve (APPROACHFFRCT): an exploratory analysis on diagnostic performance. *JACC Cardiovasc Imaging.* 2020;13:2264–2267.
63. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med.* 2007;356: 830–840.
64. Gould KL, Johnson NP. Coronary physiology beyond coronary flow reserve in microvascular angina: JACC state-of-the-art review. *J Am Coll Cardiol.* 2018;72: 2642–2662.
65. Hays AG, Kelle S, Hirsch GA, et al. Regional coronary endothelial function is closely related to local early coronary atherosclerosis in patients with mild coronary artery disease: pilot study. *Circ Cardiovasc Imaging.* 2012;5:341–348.
66. Ide S, Sumitsuji S, Yamaguchi O, Sakata Y. Cardiac computed tomography-derived myocardial mass at risk using the Voronoi-based segmentation algorithm: a histological validation study. *J Cardiovasc Comput Tomogr.* 2017;11:179–182.
67. Murai T, van de Hoef TP, van den Boogert TPW, et al. Quantification of myocardial mass subtended by a coronary stenosis using intracoronary physiology. *Circ Cardiovasc Interv.* 2019;12, e007322.
68. Holmes KR, Fonte TA, Weir-McCall J, et al. Impact of sublingual nitroglycerin dosage on FFRCT assessment and coronary luminal volume-to-myocardial mass ratio. *Eur Radiol.* 2019;29:6829–6836.
69. Jaquet C, Najman L, Talbot H, et al. Generation of patient-specific cardiac vascular networks: a Hybrid image-based and synthetic geometric model. *IEEE Trans Biomed Eng.* 2019;66:946–955.
70. Papamanolis L, Kim HJ, Jaquet C, et al. Myocardial perfusion simulation for coronary artery disease: a coupled patient-specific multiscale model. *Ann Biomed Eng.* 2020.
71. Grover R, Leipsic JA, Mooney J, et al. Coronary lumen volume to myocardial mass ratio in primary microvascular angina. *J Cardiovasc Comput Tomogr.* 2017;11: 423–428.