Journal of Cardiovascular Computed Tomography xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Cardiovascular Computed Tomography

journal homepage: www.JournalofCardiovascularCT.com

Research paper

Cardiac computed tomography-derived coronary artery volume to myocardial mass in patients with severe coronary artery disease

Shigetaka Kageyama [a,1], Charles A. Taylor [b,1], Adam Updegrove [b], Scot Garg [3], Shinichiro Masuda [a], Pruthvi Chenniganahosahalli Revaiah [a], Momoko Kageyama [a], Tsung-Ying Tsai [a], Kotaro Miyashita [a], Akihiro Tobe [a], Kaoru Tanaka [d], Johan De Mey [e], Mark La Meir [e], Ulrich Schneider [f], Torsten Doenst [f], Ulf Teichgräber [g], Mushtaq Saima [h], Giulio Pompilio [h,i], Daniele Andreini [j,k], Gianluca Pontone [h,i], John D. Puskas [l], Himanshu Gupta [m], Marie-Angele Morel [a], Patrick W. Serruys [a,**], Yoshinobu Onuma [a,*]

[a] University of Galway, Galway, Ireland
[b] HeartFlow, California, USA
[c] Department of Cardiology, Royal Blackburn Hospital, Blackburn, United Kingdom
[d] Department of Radiology, University Hospital Brussels, Belgium
[e] Universitair Ziekenhuis Brussel, VUB, Brussels, Belgium
[f] Department of Cardiothoracic Surgery, University Hospital Jena, Germany
[g] Department of Radiology, University Hospital Jena, Germany
[h] Centro Cardiologico Monzino, IRCCS Monzino, Italy
[i] Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milano, Italy
[j] Division of Cardiology and Cardiac Imaging, IRCCS Galeazzi Sant'Ambrogio, Milan, Italy
[k] Department of Biomedical and Clinical Sciences, University of Milan, Italy
[l] Department of Cardiothoracic Surgery, Emory University Hospital Midtown, USA
[m] Department of Radiology, The Valley Hospital, Ridgewood, NJ, USA

ARTICLE INFO

Keywords:
Volume to myocardial mass
CABG
Coronary computed tomography angiography (CCTA)
Fractional flow reserve derived from CCTA (FFR_{CT})
Non-invasive coronary angiography

ABSTRACT

Background: Coronary artery lumen volume (V) to myocardial mass (M) ratio (V/M) can show the mismatch between epicardial coronary arteries and the underlying myocardium.
Methods: The V, M and V/M were obtained from the coronary computed tomography angiography (CCTA) of patients in the FAST-TRACK CABG study, the first-in-human trial of coronary artery bypass grafting (CABG) guided solely by CCTA and fractional flow reserve derived from CCTA (FFR_{CT}) in patients with complex coronary artery disease (CAD). The correlations between V/M ratios and baseline characteristics were determined and compared with those from the ADVANCE registry, an unselected cohort of historical controls with chronic CAD.
Results: The V/M ratio was obtained in 106 of the 114 pre-CABG CCTAs. Mean age was 65.6 years and 87% of them were male. The anatomical SYNTAX score from CCTA was significantly higher than the functional SYNTAX score derived using FFR_{CT} [43.1 (15.2) vs 41.1 (16.5), $p < 0.001$]. Mean V, M, and V/M were 2204 mm^3, 137 g, and 16.5 mm^3/g, respectively. There were weak negative correlations between V and anatomical and functional SYNTAX scores (Pearson's $r = -0.26$ and -0.34). V and V/M had a strong correlation ($r = 0.82$). The V/M ratio in the current study was significantly lower than that in the ADVANCE registry (median 16.1 vs. 24.8 [1st quartile 20.1]).

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; FFR_{CT}, fractional flow reserve derived from coronary computed tomography angiography; ICA, invasive coronary angiogram; PET, positron emission tomography; PPGI, pullback pressure gradient index; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery; V/M, The coronary lumen volume to myocardial mass ratio.

* Corresponding author. Department of Cardiology, University of Galway, University Road, Galway, H91 TK33, Ireland.
** Corresponding author. Department of Cardiology, University of Galway, University Road, Galway, H91 TK33, Ireland.
E-mail addresses: patrick.w.j.c.serruys@gmail.com (P.W. Serruys), yoshinobu.onuma@universityofgalway.ie (Y. Onuma).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.jcct.2024.06.010
Received 14 March 2024; Received in revised form 27 May 2024; Accepted 14 June 2024

Please cite this article as: Kageyama S et al., Cardiac computed tomography-derived coronary artery volume to myocardial mass in patients with severe coronary artery disease, Journal of Cardiovascular Computed Tomography, https://doi.org/10.1016/j.jcct.2024.06.010

Conclusion: Systematically smaller V/M ratios were found in this population with severe CAD requiring CABG compared to an unselected cohort with chronic CAD. The V/M ratio could provide additional non-invasive assessment of CAD especially when combined with FFR_{CT}.

1. Introduction

In patients with chronic coronary artery disease (CAD), progressive reductions in coronary lumen volume by atherosclerosis cause a mismatch between coronary blood supply and myocardial oxygen demand, resulting in clinical symptoms associated with myocardial ischemia, like angina.[1] Non-invasive functional tests of myocardial perfusion imaging obtained from scintigraphy and positron emission tomography (PET) can quantify myocardial ischemia, without directly visualizing the coronary anatomy.[2] Whole heart magnetic resonance imaging (MRI) allows both coronary anatomy and myocardial perfusion to be obtained, however, MRI is not able to separate impairments in blood flow from the epicardial vessels which are addressed with revascularization to the microcirculation and tales longer acquisition time.[3]

The evidence supporting physiology-guided assessment of coronary stenoses using invasive fractional flow reserve (FFR) has established that the diameter stenosis from invasive coronary angiography (ICA) is not enough in itself to identify significant CAD.[4] Furthermore, the impact of diffuse atherosclerotic plaque on the vasodilatory capacity of epicardial vessels may also fail to be appreciated with ICA. Finally, patients with isolated microvascular dysfunction in the absence of CAD can also present with angina and abnormalities in myocardial perfusion.[5] These deficiencies have led to increasing recognition of the need for an integrated assessment of physiological supply versus demand.

Coronary artery lumen volume to myocardial mass ratio (V/M) can show the mismatch between the epicardial coronary arteries and the underlying myocardium, providing information on the ability of the coronary arteries to adequately match the demands of the myocardium.

Coronary computed tomography angiography (CCTA) is uniquely capable of non-invasive measurement of V/M. A standard CCTA 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.[6]

This study aimed to determine whether any relationships exist between V/M ratios and baseline characteristics in a cohort of patients with severe CAD and also determine whether the V/M distribution differed among populations with different severities of CAD.

2. Study population and historical control

2.1. Study population

This study used data from patients enrolled in the FAST-TRACK CABG study, which is described in detail elsewhere.[7] In brief, this was an investigator-initiated single-arm, multicenter, prospective, proof-of-concept, first-in-human study, which explored the safety and feasibility of planning and performing coronary artery bypass grafting (CABG) with the sole guidance of CCTA and fractional flow reserve derived from CCTA (FFR_{CT}, HeartFlow, USA) in 114 patients with the three-vessel disease with or without the left main disease (NCT0414202). All the lesions which are visually assessed as % diameter stenosis $\geq$50% on the vessels $\geq$1.5 mm included anatomical SYNTAX score calculation. Furthermore, functional SYNTAX score is defined as including anatomical lesions only on the vessels which have a significant drop of FFR_{CT} value at the most distal part ($\leq$0.80).[8] Ethical approval from the ethics committee was obtained, and each patient provided written informed consent.

2.2. Historical controls

To compare with the current trial, the largest study to date evaluating V/M in patients with chronic CAD, the ADVANCE registry tabulated V/M in 3110 chronic CAD patients, and this was referred to regarding the V/M distribution.[9] Clinically stable patients being investigated for suspected cardiac chest pain or symptoms suggestive of underlying CAD with evidence of coronary atherosclerosis on CCTA were prospectively enrolled as part of the ADVANCE registry study. Eligibility criteria included age older than 18 years, ability to provide informed consent, and CAD >30% degree stenosis (DS) on site-based CCTA analysis. The V/M distribution was obtained by using WebPlotDigitizer.[6]

2.3. Methodology of calculating V/M ratio

The V/M ratio can be readily computed from a standard CCTA (Fig. 1). First, the coronary artery luminal boundaries are extracted, i.e. segmented, from the CCTA image. This involves deep learning-based centerline and lumen boundary image analysis methods to trace the paths of epicardial coronary arteries down to approximately 1 mm in diameter from the extracted imaging data,[10] which are then processed within a matter of minutes; although semi-automated luminal segmentation using standard CT image processing software is also feasible.[11] Once the vessel centerline tree was obtained, the coronary luminal boundary could be segmented and 'V', the volume inside the coronary luminal surface could be calculated. In this population, total occlusions (TO) were common, and vessel models terminated at the point of the occlusion detected by FFR_{CT}, with the lumen volume distal to the occlusion not included in the global assessment regardless of the visibility of the lumen behind. Greyed-out small vessels were included provided they could be reconstructed. Second, the left ventricular (LV) myocardial

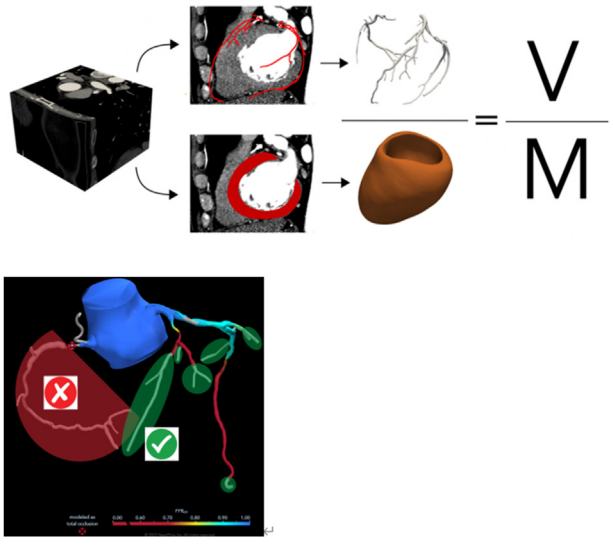


Fig. 1. Methodology for computing V/M ratio.
The V/M ratio is calculated by dividing the coronary artery luminal volume by the myocardial mass (upper). Vessel models were terminated at the point of total occlusion (TO) detected by FFR_{CT} and the lumen volume distal to the occlusion was not included in the global assessment, while grey-out small vessels are included as long as reconstructed (lower). This figure referred to Taylor CA et al. J Cardiovasc Comput Tomogr. 2017; 11 (6):429–436 and reproduced.

volume was segmented (area x slice thickness) from the CCTA images and subsequently converted to LV mass, 'M', by multiplying it by an assumed constant density of myocardial tissue (1.05 g/mm^3), which is assumed to be constant. Finally, the V/M ratio was calculated by dividing the coronary artery luminal volume by the LV myocardial mass. Refinement of the V/M quantification method is based solely on the CT-derived epicardial coronary lumen volume extracted from vessels >1 mm in size.[10] All the analyses and calculations were automatically performed in the latest software offline (HeartFlow Major Version 3). Minimum manual modification was done if needed and approved by the trained and certified analysts.

3. Statistical analysis

Continuous variables were presented as mean (standard deviation, SD) or median quartile, while categorical variables as absolute numbers and percentages. Student t-test was performed to compare continuous values between the groups. Comparison of 3 or more groups was evaluated by the Kruskal-Wallis test following the Mann-Whitney *U* test for pair-wise comparison with Bonferroni adjustment if needed. Testing for normality of the distribution of continuous values, Shapiro-Wilk test was performed. Correlation between 2 continuous values was evaluated by Pearson's r.

All statistical analyses were performed using R 4.1.1 (The R Foundation for Statistical Computing, Vienna, Austria). All reported *P*-values were two-sided, and $P < 0.05$ was considered statistically significant.

4. Results

4.1. Baseline characteristics

The FAST TRACK CABG trial enrolled 114 consecutive patients, of whom FFR_{CT} was analyzable in 106 patients, with V/M obtained in all cases. The main reason FFR_{CT} could not be analyzed was major motion artifacts or noise in the acquired CCTA, although, despite this, those cases could still be used to guide the strategy for surgery. Patient and lesion characteristics are presented in Tables 1 and 2. Mean age was 65.6 (8.9) years and 87% of them were male. Both anatomically and physiologically significant lesions were included in the functional SYNTAX score calculation, which was significantly lower than the anatomical SYNTAX score [43.1 (15.2) vs 41.1 (16.5), paired *t*-test $p < 0.001$].

Table 1
Baseline patient characteristics.

N = 106	
Age, year	65.6 (8.9)
Body mass index	26.9 (4.2)
Male, n (%)	92 (86.8%)
Prior myocardial infarction, n (%)	11 (10.4%)
Prior heart failure, n (%)	3 (2.8%)
Prior revascularization, n (%)	0 (0%)
Angina status	
Chronic coronary syndrome, n (%)	99 (93.3%)
Unstable angina, n (%)	7 (6.7%)
Chronic obstructive lung disease, n (%)	8 (7.6%)
Creatinine clearance, ml/min	89.2 (17.4)
Hypertension, n (%)	89 (84.0%)
Diabetes mellitus, n (%)	37 (34.9%)
Left ventricular ejection fraction, %	56.3 (7.7)
Left main disease, n (%)	29 (27.4%)
Three-vessel disease, n (%)	77 (72.6%)
Number of lesions per patient	6.04 (1.74)
CCTA-derived anatomical SYNTAX score	43.1 (15.2)
FFR_{CT}-derived functional SYNTAX score	41.1 (16.5)
EuroScore II	1.06 (0.62)
STS score	0.76 (0.50)

Abbreviations. CCTA, coronary computed tomography angiography; FFR_{CT}, fractional flow reserve derived from CCTA; STS, Society of Thoracic Surgery.

Table 2
Baseline lesion characteristics.

N = 666	
Aorto-ostial (%)	27 (4.1%)
Bifurcation (%)	196 (29.4%)
Angulation<70° (%)	74 (11.1%)
Trifurcation (%)	25 (3.8%)
Lesion length>20 mm (%)	161 (24.2%)
Severe calcification (%)	236 (35.4%)
Total occlusion (%)	75 (11.3%)
SYNTAX score per lesion	6.80 (6.52)

4.2. V/M distribution in the current trial

Mean values and SD of epicardial coronary volume, myocardial mass, and V/M in the current trial are 2203.9 (773.5) mm^3, 137.1 (29.5) g, and 16.5 (5.8) mm^3/g, respectively. The distribution of these valuables is presented in Fig. 2. Of note, M follows the normal distribution (Shapiro-Wilk test $p = 0.39$, skewness 0.374, Kutosis 0.042), while V and V/M do not ($p < 0.001$, $p = 0.04$, respectively). V/M had a bimodal distribution.

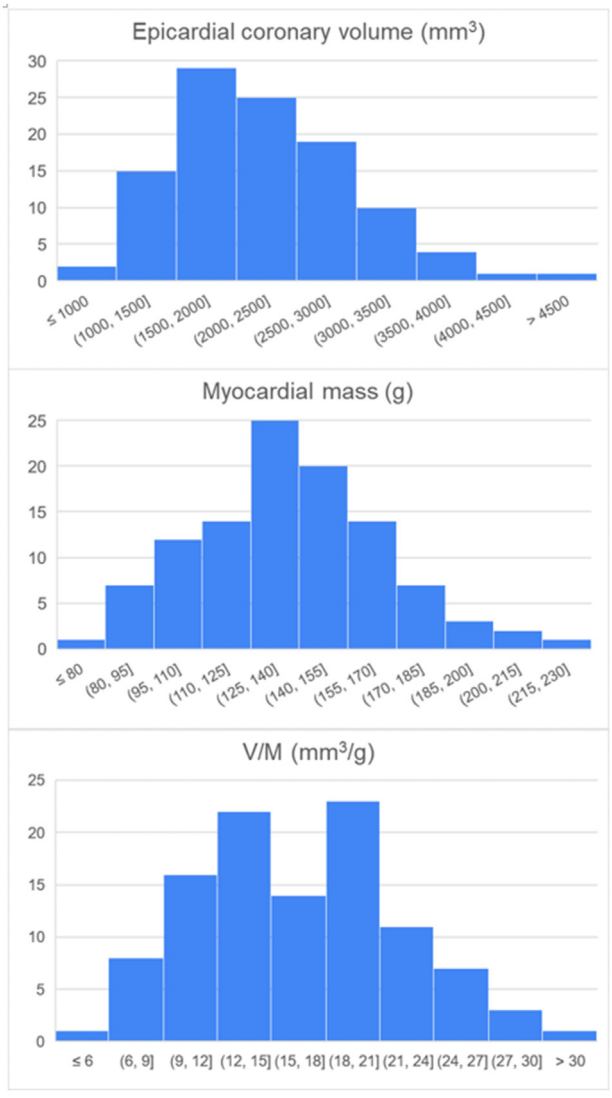


Fig. 2. Distribution of epicardial coronary artery volume, myocardial mass, and V/M in FAST TRACK CABG trial (n = 106)
Histogram of the epicardial coronary volume (V), myocardial mass (M), and volume to mass ratio (V/M) are presented in upper, middle, and lower panel, respectively.
Abbreviation: V/M, volume to mass ratio.

4.3. Correlation between baseline characteristics and V, M

There are weak negative correlations between V and anatomical and functional SYNTAX score (r = −0.26 and −0.34, Fig. 3A). The number of total occlusions did not relate significantly to V overall (Kruskal-Wallis test p = 0.09, Fig. 3D) but pair-wise comparisons become significant between no TO and two TOs (p = 0.03). M had a weak negative correlation with left ventricular ejection fraction (LVEF) (r = −0.35, Fig. 3B).

V/M correlated strongly to V (r = 0.82, Fig. 3C). The number of TOs related to the difference of V overall, and pair-wise comparisons of non-TO and one TO and non-TO and two TOs became significant (Kruskal-Wallis test p < 0.001, Fig. 3D).

4.4. Results of V/M distribution in the current trial and comparison of the previous ADVANCE registry

Compared to the ADVANCE registry (n = 3110), the current cohort had a lower median epicardial coronary volume (2038.2 vs. 2871.7 mm^3, p < 0.001) and conversely, a greater median myocardial mass (138.2 vs. 118.4 g, p < 0.001). Consequently, the V/M in the FAST TRACK CABG was much lower than that of the ADVANCE registry; in fact, the median V/M of FAST TRACK was lower than the 1st quartile of the ADVANCE registry (16.1 vs. 24.8, 1st quartile of V/M in ADVANCE 20.1, p < 0.001).[6] A comparison of the distribution of the V/M from both trials is presented in Fig. 4.

The histogram of V/M in the FAST TRACK CABG shows a bimodal distribution, which deviates to the left side compared to ADVANCE. These two peaks are also located within the 1st quartile of the ADVANCE registry. The distribution of V/M with TO in the FAST TRACK CABG population is shifted more to the left (median 13.0) compared to that without TO (median 19.2, Fig. 5).

5. Discussion

The main findings from this study are: (1) epicardial vessel lumen volume has a weak negative correlation with the SYNTAX score, (2) the existence and the number of TO contributed to different V and V/M values, (3) the V/M distribution in complex CAD was significantly lower than that in general CAD population.

5.1. Meaning of V and M, and correlation with baseline factors

As per the definition of V and M, V is expected to have a negative correlation with the SYNTAX score because it is based on segment weights (especially for a TO in the proximal part of a main coronary

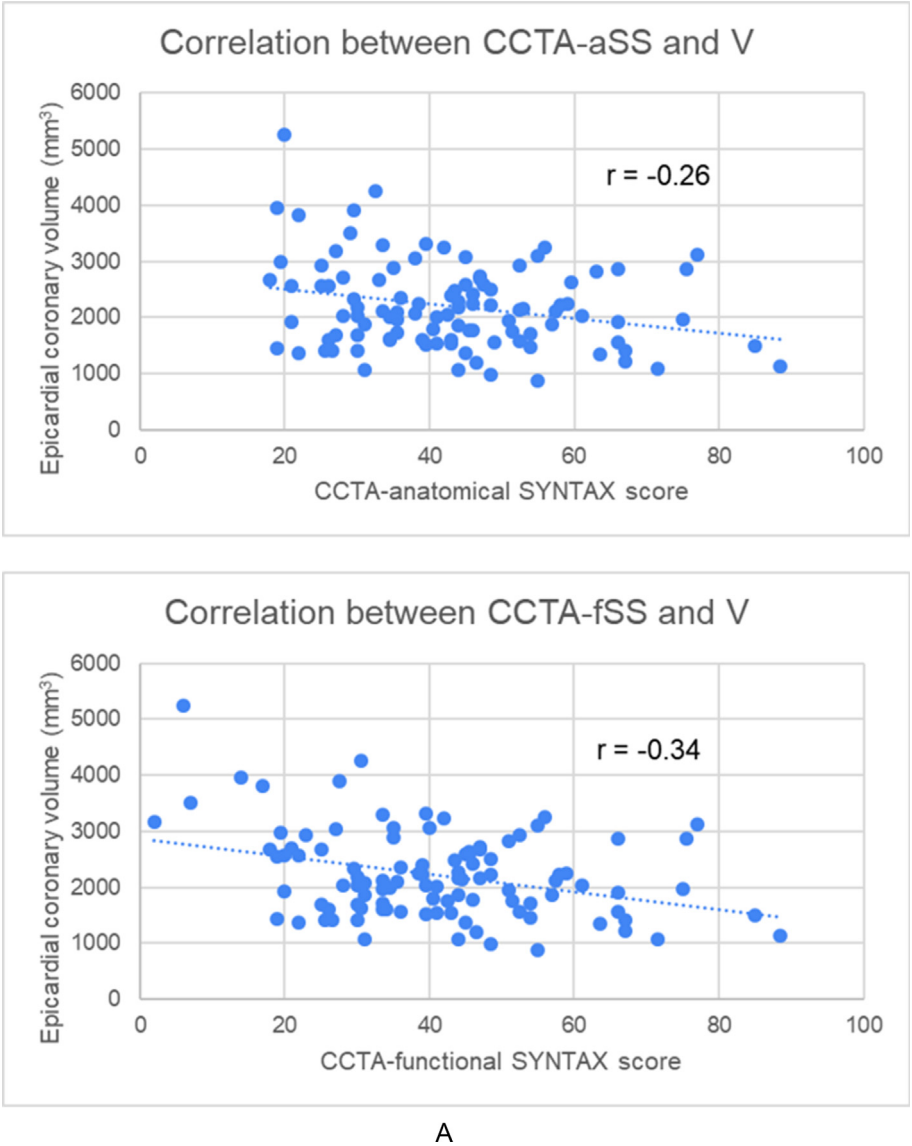
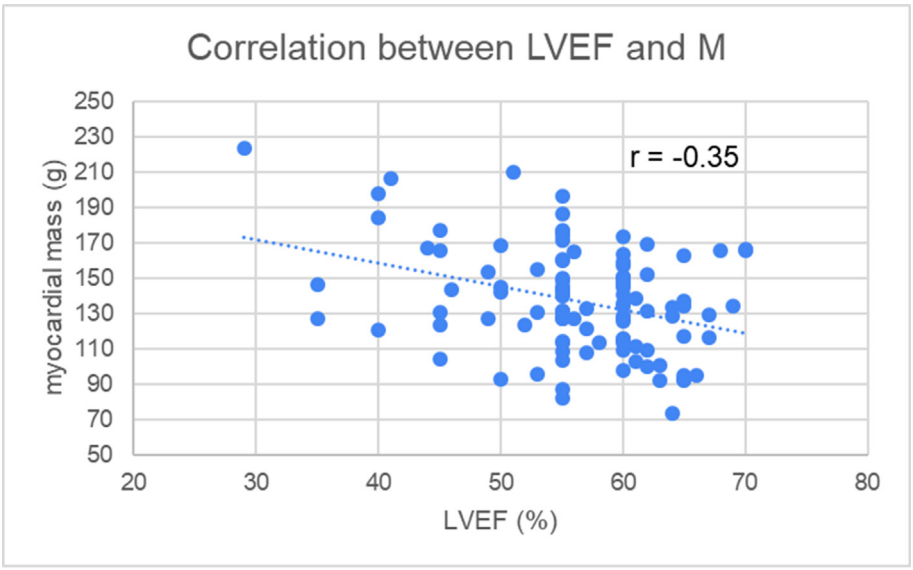
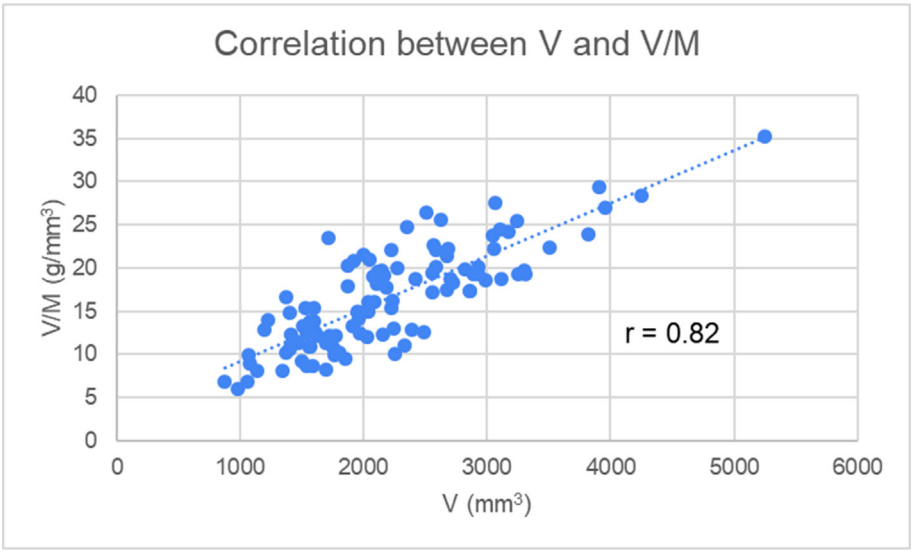


Fig. 3A. Correlation between V and anatomical/functional SYNTAX score. Trend lines and correlation coefficients are presented in the scatterplots. The upper panel shows the correlation between CCTA-derived anatomical SYNTAX score and epicardial coronary volume, and the lower panel shows the correlation between CCTA-derived functional SYNTAX score and epicardial coronary volume.
Abbreviations. CCTA, coronary computed tomography angiography; aSS, anatomical SYNTAX score; fSS, functional SYNTAX score; V, epicardial coronary vessel volume.



B

Fig. 3B. Distribution of M according to LVEF. Trend line and correlation coefficient are presented in the scatterplots.
Abbreviations. M, myocardial mass; LVEF, left ventricular ejection fraction.



C

Fig. 3C. Correlation between V and V/M. Correlation between epicardial vessel volume and volume to mass ratio is presented. Trend line and correlation coefficient are presented in the scatterplots.
Abbreviations. V, epicardial coronary vessel volume; V/M, volume to mass ratio.

artery, which receives a high score), lesion numbers, lesion length and the presence of diffuse disease. As expected, both anatomical and functional SYNTAX scores also have a negative correlation with V, with a stronger correlation seen with the functional SYNTAX score based on FFR_{CT} than the anatomical SYNTAX score based on CCTA. Calculating V per main epicardial conductance vessel (e.g. LAD) and its pullback pressure gradient index (PPGI)[12] derived from FFR_{CT}, would likely lead to an even stronger correlation. Indeed, V and V/M have a negative correlation to the total plaque volume per case (Fig. A). M has a normal distribution and only a weak correlation was seen with LVEF. A tenth of the population reported a previous myocardial infarction, however, the LVEF was preserved in most cases (mid-range 10, reduced 6).[13] Conversely, hypertension was the commonest comorbidity, being present in 84.0% of patients, and this can cause myocardial hypertrophy. The changes in cellular biology leading to the transition to systolic dysfunction are complex and probably due to multiple changes in gene expression.[14] In chronic pressure overload and extreme volume overload, subendocardial ischemia due to reduced coronary flow reserve probably plays a role in limiting exercise reserve and promoting myocardial fibrosis. Afterload excess, due to inadequate hypertrophy to normalize wall stress itself, reduces systolic ejection performance.[15] Diabetes mellitus occurred in just under a third of patients, and this can cause diabetic cardiomyopathy, which is usually asymptomatic in its early stages, with one of its earliest manifestations LV hypertrophy and decreased LV compliance, characterized by impaired early diastolic filling, increased atrial filling, and prolonged isovolumetric relaxation.[16] Hence, for the most part, myocardial hypertrophy tends to lower the LVEF from the normal range, and thereby results in a negative correlation between M

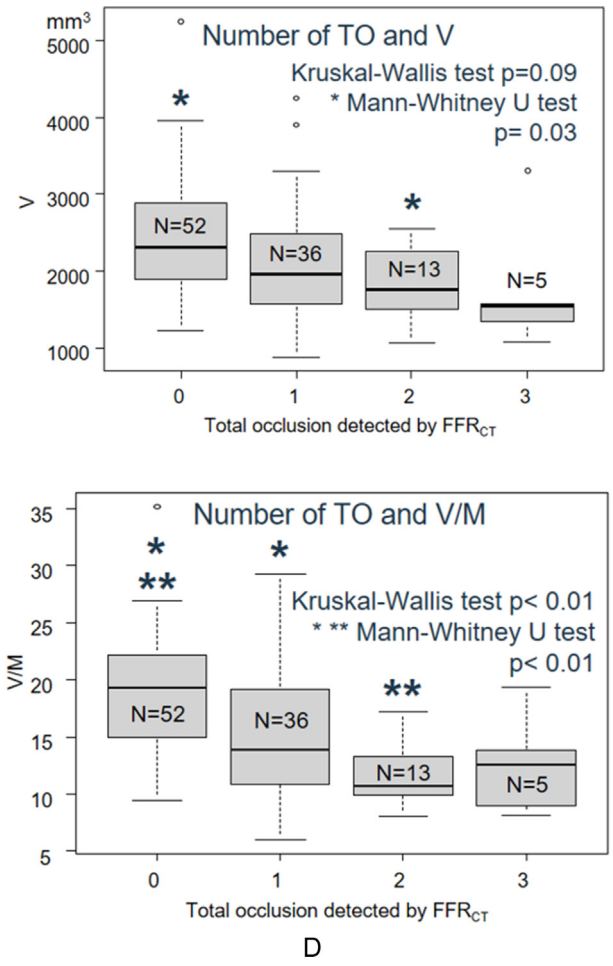


Fig. 3D. Number of total occlusion and V, V/M. Box and whisker plot are presented for epicardial coronary volume (upper panel) and volume to mass ratio (V/M) according to the number of total occlusions.
Abbreviations. V, epicardial coronary vessel volume; V/M, volume to mass ratio; TO, total occlusion.

and LVEF. It is well-known that patients with diabetes tend to have more diffuse and complex CAD compared to non-diabetic patients.[17] Considering all these factors, our findings regarding V, M, and V/M in the total and diabetic population are not unexpected. The comorbidity of hypertension and diabetes in the FAST TRACK CABG trial and ADVANCE trial was 84% vs 59.8% and 34.9% vs 21.9%, respectively. Both the denominator (high comorbidity related to myocardial hypertrophy) and numerator (severe CAD causes low V) seemed to affect the small V/M in the FAST TRACK CABG population compared to the ADVANCE registry.

The frequency distributions of angiographic indexes often superficially resemble the Gaussian distribution.[18,19] We previously assessed this using the Kolmogorov-Smirnov test, however, this time the Shapiro-Wilk test was used in view of the small sample size. Although the null hypothesis, that M follows a normal distribution could not be rejected with either test, it should be remembered that potency is reduced when the sample size is small.

5.2. V/M in severe epicardial conductance vessel disease

In our study, V/M showed a bimodal distribution as sometimes seen in angiographic measures.[20,21] As per the definition of creating a three-dimensional model of epicardial conductance vessels, the existence and number of TOs in each patient impacted V. The V/M ratios of patients with a TO (median 13.0) were lower than those without a TO (median 19.2). In the presence of a TO, the epicardial vessel volume distal to the lesion was not calculated, which may result in a potential underestimation of vessel volume if the distal vessel received blood supply via collaterals.

Several studies have examined the relationship between myocardial demand and supply using the V/M ratio in patients with stable CAD. The first of these was a secondary analysis of the NeXtsTeps (NXT) trial performed using first-generation V/M algorithms (Fig. B). In this study of 238 patients, those with a V/M ratio below the median value of 18.6 mm^3/g had greater overall diameter stenosis by quantitative coronary angiography (38% vs. 31%, $p < 0.001$), higher total plaque volume (593 mm^3 vs. 392 mm^3, $p < 0.001$), and lower invasive FFR (0.80 vs. 0.87, $p < 0.001$) than those with a V/M above the median. The V/M ratio was associated with an FFR $\leq$0.80 independent of sex, BMI, stenosis severity and plaque characteristics.[10] These findings highlight the potential for the V/M ratio to improve the discrimination of the physiological significance of CAD, over the evaluation of CCTA alone.

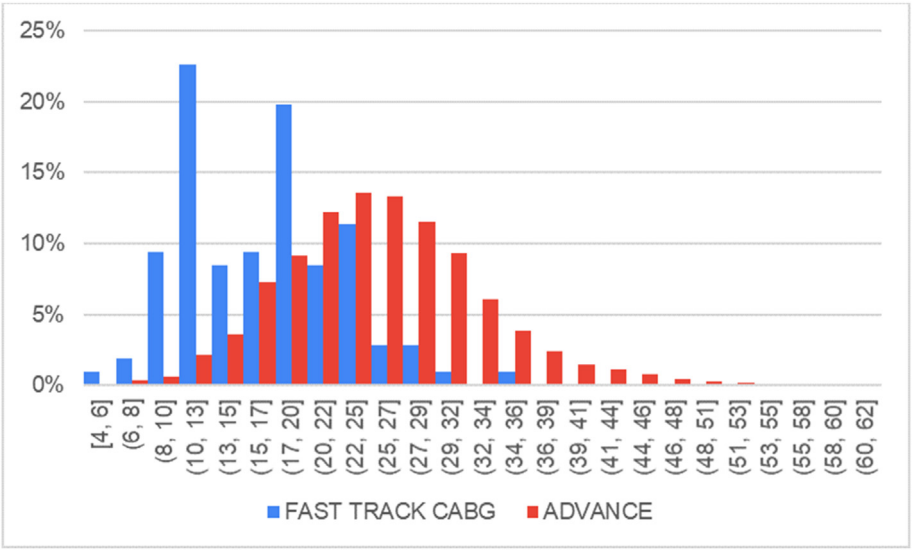


Fig. 4. Distribution of V/M in FAST TRACK CABG and ADVANCE trial.
The blue histogram shows the distribution of V/M of the FAST TRACK CABG trial and the red histogram shows the distribution of ADVANCE trial.
Abbreviation: V/M, volume to mass ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

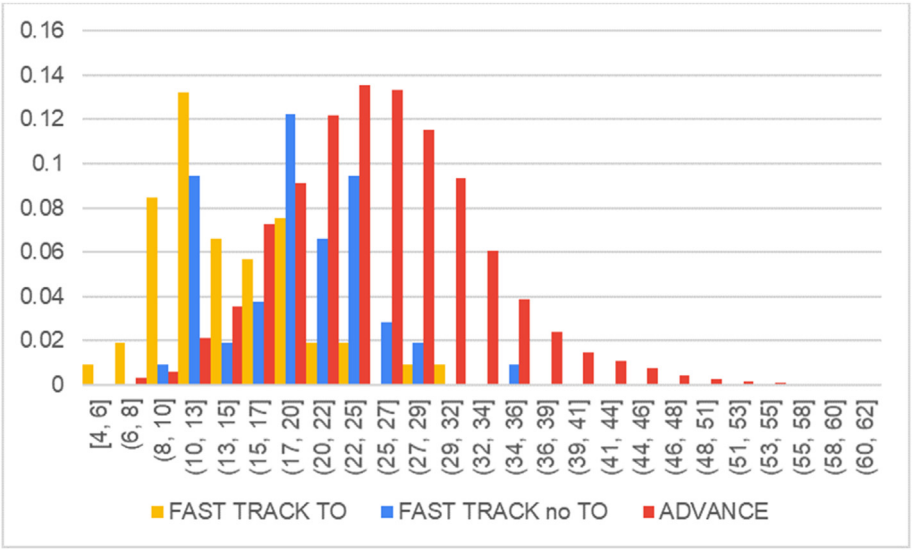


Fig. 5. Distribution of V/M in FAST TRACK CABG with or without total occlusion.
Difference of V/M distribution among three; with or without total occlusion in the FAST TRACK CABG trial and whole population of the ADVANCE trial.
Abbreviation. TO, total occlusion.

The largest study to date evaluating V/M ratio in patients with chronic CAD was the ADVANCE registry.[9] In this group of 3110 symptomatic patients with CAD with a diameter stenosis of ≥30%, the mean V was 3003 mm^3, with a range of 493 mm^3–7891 mm^3 and a median of 2873 mm^3. The mean M was 122g and ranged from 55g to 357g with a median of 118g. The mean V/M ratio was 25.2 mm^3/g and ranged from 5.6 mm^3/g to 62.5 mm^3/g, with a median of 24.8 mm^3/g. The histogram of V/M showed a typical normal distribution pattern.

Myocardial blood flow as measured by PET or stress perfusion cardiac magnetic resonance imaging is a well-established prognostic marker in patients with CAD.[22,23] As a potential measure of the mismatch between coronary supply and myocardial demand, the relationship between V/M ratio and myocardial blood flow was investigated in a sub-study of the PACIFIC trial.[24]

Future iterations of the V/M technique which permit derivation of regional V/M ratios according to the sub-tended coronary territory, may potentially improve correlation with vessel-specific measures of myocardial and coronary blood flow, and warrant further evaluation.[25]

A combination of regional V/M and FFR_{CT} including PPGI would contribute to a better understanding of the precise mechanism of myocardial perfusion in individual complex CAD patients. This future technology may become crucial for surgeons who currently need to select which lesions to graft using a limited amount of graft material, because they will then be able to clearly recognize non-invasively which bypass strategy minimizes residual ischemia, before the operation.

5.3. Other factors affect V/M in the current population

Previous studies mentioned that various factors can affect V/M such as sex, ethnicity, severity and outcomes of CAD, as well as cardiac geometry.[6] Another important factor which has not yet been discussed is coronary microvascular dysfunction. In a cohort of patients with primary microvascular angina, V/M was significantly lower compared to matched controls (25.6 ± 5.9 vs. 30.0 ± 6.5, $p < 0.001$),[26] which was predominantly driven by a lower V in patients with microvascular dysfunction (2302 ± 109 vs. 2978 ± 134 mm^3, $p < 0.001$), implying that the vasodilatory capacity of epicardial vessels is potentially related to microvascular function.

5.4. Limitations of this study

As this study is a first-in-human trial aiming to achieve safety and feasibility, the number of patients is small. However, the distribution of the V/M ratio is obviously different between the current trial and the ADVANCE trial. Also, there are only 30 days for clinical outcomes to prove that sole CCTA guidance CABG is safe; no middle to long-term clinical outcome that will relate to V/M distribution is not available in the study so far. Not only the hard endpoints but also the angina questionnaire will be useful to reveal the different distribution of V/M.

The V/M was missing in 8 patients due to the inability to analyze the FFR_{CT} due to major motion artifacts, despite the trial investigators strictly following the pre-defined CCTA acquisition protocol (Appendix).

It should also be noted that the computation of the coronary artery luminal volume is dependent on the image quality used to segment the coronary arteries and the extent of the tree that is involved.

6. Conclusion

In conclusion, systematically smaller V/M ratios were found in the patients with severe CAD who had already been referred for CABG compared to a large, unselected population with chronic CAD. The V/M ratio could provide additional non-invasive information to enable a better understanding of the mechanism of CAD, especially when combined with FFR_{CT}. A low V/M may reflect an intrinsic imbalance between blood supply and demand, that possibly could not be resolved by focal percutaneous treatment or a bypass strategy, and may therefore identify patients who would not necessarily benefit from revascularization.

Funding

Funded by the University of Galway, receiving grants from GE HealthCare (Chicago, IL, USA) and HeartFlow (Mountain View, CA, USA).

Declaration of competing interest

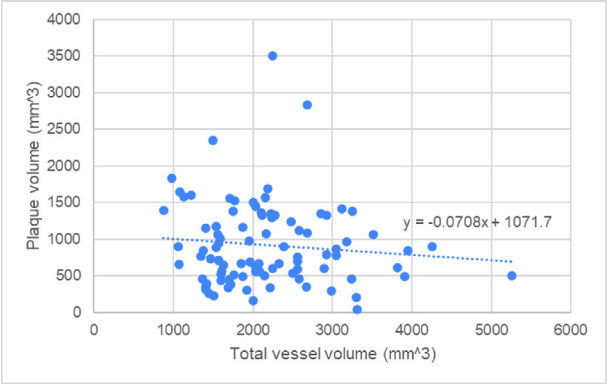
Dr Serruys has received consultancy fees from Philips/Volcano, SMT, Novartis, Xeltis, Merillife. Dr Garg receives consulting fee from

Biosensors. Dr Puskas reports consulting fees from Medtronic, Atricure, Medistim, Edwards Life Science, and royalty payments from Scanlan. Dr Gupta reports an institutional grant from Siemens Health Solutions. Dr Garg reported consulting fees from Biosensors. Dr Taylor and Dr Rogers are employees of HeatFlow Inc. including salary and equity. Dr Thomsen is an employee of GE HealthCare. Dr Pontone reports grants and consultant fees from GE HealthCare, Bracco, and HeartFlow, Payment honoraria from GE HealthCare and HeartFlow, and payment for expert testimony from GE HealthCare. All other authors have no conflict of interest to declare.

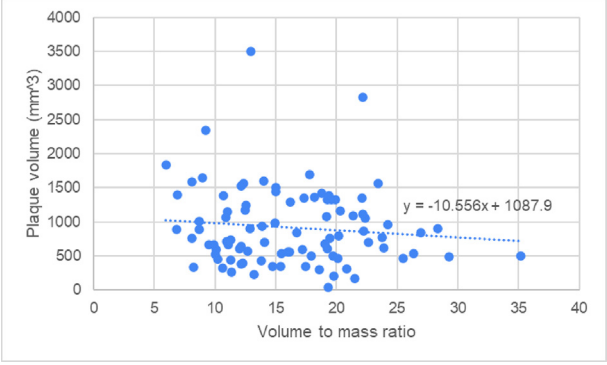
All other authors have no conflict of interest to declare.

Appendix

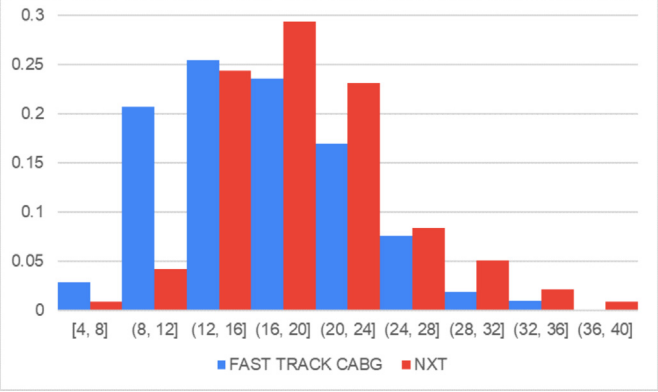
Fig. A. Scatter plot between V, V/M and total plaque volume per case
Scatter plot between total vessel volume of the coronary artery and plaque volume



Pearson's r = - 0.10
Scatter plot between volume to mass ratio and plaque volume



Pearson's r = -0.11
Fig. B. V/M distribution in FASTTRACK CABG and NXT trial.



Text A: Acquisition guideline of CCTA images of the FAST TRACK CABG trial (also presented in this manuscript)

CTA acquisition guidelines for CT prior to CABG.
Introduction.

- Before CABG procedure, CTA is performed to assess the native coronary arteries.

According to the local practice, mammary arteries may be assessed with additional imaging.

- Utilize 256-slice GE Revolution CT Scanner.
- Imaging the entire coronary tree allows for the most accurate FFRCT computation.
- These guidelines also including imaging of the mammary arteries and implications on image reconstruction.
- The full set of image data as well as raw scan data should be saved for each exam.

Preparation.

- Assess heart rate and rhythm. Heart rate control (below 65 beats per minute) reduces motion artifacts.
- Heart rate modulation for heart rates >60/min during breath holding.

Oral: metoprolol tartrate 100 mg, 1 h before the exam. Atenolol 50 mg, 1 h before the exam.
IV: metoprolol 5 mg, repeated up to 5 times.
Contraindications: conduction delays, hypotension, severe asthma, allergy to betablockers, reduced left ventricle ejection fraction.
Consider ivabradine for patients with contra-indications to betablockers (in case of ivabradine the dosage suggested is 5 mg twice a day for at least 3–4 days before the scan).

- Provide full explanation of exam, and practice breath hold. Ensure breath hold time will be sufficient for scan time. Evaluate impact of breath holds on heart rate.

Nitrates and FFRCT.

- Use NTG preferably 3 min prior to CT image acquisition;
- Use 1–2 sprays (0.4mg–0.8 mg)
- Use beta-blocker with it to avoid reflex tachycardia/vasoconstriction
- Additional Beta blockade may be given after nitroglycerin to counteract the reflex tachycardia
- Confirm absence of allergy to contrast media (consider prophylaxis for patients with doubtful or mild reactions to contrast in the past).

Patient installation:

- Attach ECG leads, avoid respiratory muscles, and check signal stability during breath hold.
- Placement of an IV catheter that allows a flow of at least 5 ml/s

Data acquisition:
Overview/scout of the entire chest.
Contrast enhancement:

- ≥300 g/L iodine contrast medium.
- Injection rate: 5–6 ml/s.
- Total amount depends on the patient size, the scan mode and the scan duration.

Contrast-scan timing:

- Test/Timing Bolus: 15–20 ml of contrast is injected, preferably followed by a bolus chaser. Place the localizer line 1 cm below the carina and just above the base of the heart, the optimal location to find the ascending aorta for a timed contrast injection. The time of (maximum) enhancement is used as the delay of the data acquisition after start of contrast injection.
- Bolus tracking/Smart Prep: arrival of the (entire) bolus is monitored in the ascending aorta. To avoid premature triggering of the scan the ROI should be sufficiently large and placed away from the superior vena cava. A saline bolus of ≥50 ml is injected after the contrast medium at the same rate.

Gating and phase acquisition:

ECG-triggered one-beat scan mode should be used. For HR < 65, 75% of the R–R cycle is appropriate. For HR > 65 or variable heart rates, 40–80% of the R–R cycle is appropriate with ECG mA modulation. Consider use of Auto-Gating functionality on the system.
Acquisition parameters:

- Thinnest detector collimation.
- Noise Index (NI) of 30 at ASIR-V 50%. May be adjusted depending on the size of the patient. If fixed tube current (mA) is used, it should be > 500 mA. For patients acquired in standard mode we suggest 100 kVp for BMI<25 and 120 kVp for BMI>25; for HD mode we suggest 100 kVp for BMI<20 and 120 kVp for BMI>20. Do not use a kVp less than 100 kVp.
- For patients with BMI >25, the x-large focal spot should be preferentially used. This can be achieved by either increasing the NI until the focal spot size change is reflected on the screen, or by switching to a fixed tube current scan mode.
- Additionally, if heart rate is well controlled (HR < 65) in these large patients, gantry rotation time of 0.35sec should be considered. This is pre-configured in the nominal
  Autogating profiles if Autogating is being utilized on the system.
- Scan range: from the apex of the lung until the caudal border of the heart. If more than one slab is required, the acquisition should be performed such that first the entire heart is captured in one axial slab, and then the table is moved to capture the remaining range in the cranial direction.
- High Definition Mode should be used preferably except in patients with BMI >25

Image reconstruction:
Two sets of reconstructions will be provided – one for assessing the heart and one for assessing the mammary arteries should be provided.
For assessment of the heart:

- 0.625 mm slice thickness

ASIR-V 50% in all cases should be provided. Additional ASIR-V levels may be provided if ASIR-V 50% is inadequate.
Field-of-view enclosing the entire heart (cover inferior carina to lower heart border) (approx. 18 × 18 cm).

- Standard kernel reconstructions. Depending on the scan protocol both diastolic and systolic reconstructions should be performed.
- Reconstructions should be optimized for the segments of interest (ROI). In case of suboptimal image quality other phases should be explored.
- Additional high-definition or sharp kernel reconstructions should be provided at the optimal phase(s). If High Definition mode was not performed, then Detail kernel reconstructions should be provided
- If motion artifacts persist in the optimal phase images, the standard and high definition

(or detail) reconstructions should be done with “Temporal Enhanced” enabled and SnapShot Freeze processing should be performed.
For assessment of the mammary arteries:

- 0.625 mm slice thickness
- ASIR-V 50% in all cases should be provided. Additional ASIR-V levels may be provided if ASIR-V 50% is inadequate.
- Field-of-view enclosing the entire chest cavity.
- The optimal phase as what was reconstructed for the coronary assessment should be reconstructed.
- Standard kernel reconstruction

NOTE: the above acquisition and reconstruction guidelines are subject to revision by the steering committee based on new software and hardware capabilities that may be available on the CT system during the course of this study.

TOC summary.

- Systematically smaller Volume to myocardial mass ratios were found in patients with severe coronary artery disease (CAD), who had already been referred for surgery, compared to an historical unselected population of patients with CAD.
- V/M ratios could provide additional non-invasive assessment of CAD especially if combined with FFR_{CT}.

References

1. 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(23):2900–2907.
2. Salerno M, Beller GA. Noninvasive assessment of myocardial perfusion. *Circ Cardiovasc Imaging*. 2009;2(5):412–424.
3. Moghari MH, Uecker M, Roujol S, Sabbagh M, Geva T, Powell AJ. Accelerated whole-heart MR angiography using a variable-density Poisson-disc undersampling pattern and compressed sensing reconstruction. *Magn Reson Med*. 2018;79(2):761–769.
4. 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(40):2831–2838.
5. Serruys PW, Kageyama S, Garg S, Onuma Y. In the beginning there was angina pectoris, at the end there was still angina pectoris. *JACC Cardiovasc Interv*. 2022;15(24):2519–2522.
6. Ihdayhid AR, Fairbairn TA, Gulsin GS, et al. Cardiac computed tomography-derived coronary artery volume to myocardial mass. *J Cardiovasc Comput Tomogr*. 2022;16(3):198–206.
7. Kawashima H, Pompilio G, Andreini D, et al. Safety and feasibility evaluation of planning and execution of surgical revascularisation solely based on coronary CTA and FFR(CT) in patients with complex coronary artery disease: study protocol of the FASTTRACK CABG study. *BMJ Open*. 2020;10(12):e038152.
8. Kageyama S, Serruys PW, Kotoku N, et al. *Coronary Computed Tomography Angiography-Based SYNTAX Score for Comprehensive Assessment of Advanced Coronary Artery Disease*. J Cardiovasc Comput Tomogr; 2023.
9. Fairbairn TA, Dobson R, Hurwitz-Koweek L, et al. Sex differences in coronary computed tomography angiography-derived fractional flow reserve. *Jacc-Cardiovasc Imag*. 2020;13(12):2576–2587.
10. 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(6):429–436.
11. 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(4):295–301.
12. Collet C, Sonck J, Vandeloo B, et al. Measurement of hyperemic pullback pressure gradients to characterize patterns of coronary atherosclerosis. *J Am Coll Cardiol*. 2019;74(14):1772–1784.
13. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129–2200.
14. Lorell BH, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. *Circulation*. 2000;102(4):470–479.

15. Gunther S, Grossman W. Determinants of ventricular function in pressure-overload hypertrophy in man. *Circulation*. 1979;59(4):679–688.
16. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. *Circ Res*. 2018;122(4):624–638.
17. Park SJ, Park DW. Diabetes in myocardial revascularization for left main coronary artery disease: predictor or decision maker? *J Am Coll Cardiol*. 2019;73(13): 1629–1632.
18. Lehmann KG, Melkert R, Serruys PW. Contributions of frequency distribution analysis to the understanding of coronary restenosis. A reappraisal of the Gaussian curve. *Circulation*. 1996;93(6):1123–1132.
19. Rensing BJ, Hermans WR, Deckers JW, de Feyter PJ, Tijssen JG, Serruys PW. Lumen narrowing after percutaneous transluminal coronary balloon angioplasty follows a near Gaussian distribution: a quantitative angiographic study in 1,445 successfully dilated lesions. *J Am Coll Cardiol*. 1992;19(5):939–945.
20. Latib A, Cosgrave J, Colombo A. Bimodal distribution of angiographic measures of restenosis: what does it mean? *Heart*. 2009;95(19):1556–1558.
21. Schomig A, Kastrati A, Elezi S, et al. Bimodal distribution of angiographic measures of restenosis six months after coronary stent placement. *Circulation*. 1997;96(11): 3880–3887.
22. 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(16):1282–1291.
23. Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation*. 2011;124(20):2215–2224.
24. 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 Cardiol*. 2017;2(10):1100–1107.
25. Keulards DCJ, Fournier S, van 't Veer M, et al. Computed tomographic myocardial mass compared with invasive myocardial perfusion measurement. *Heart*. 2020; 106(19):1489–1494.
26. 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(6):423–428.