Effect of the ratio of coronary arterial lumen volume to left ventricle myocardial mass derived from coronary CT angiography on fractional flow reserve

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ARTICLE INFO

Article history:
Received 5 February 2017
Received in revised form 14 June 2017
Accepted 1 August 2017
Available online 3 August 2017

Keywords:
Fractional flow reserve
Coronary computed tomography angiography
Coronary artery disease

ABSTRACT

Background: We hypothesize that in patients with suspected coronary artery disease (CAD), lower values of the ratio of total epicardial coronary arterial lumen volume to left ventricular myocardial mass (V/M) result in lower fractional flow reserve (FFR).

Methods: V/M was computed in 238 patients from the NXT trial who underwent coronary computed tomography angiography (CTA), quantitative coronary angiography (QCA) and FFR measurement in 438 vessels. Nitroglycerin was administered prior to CT, QCA and FFR acquisition. The V/M ratio was quantified on a patient-level from CT image data by segmenting the epicardial coronary arterial lumen volume (V) and the left ventricular myocardial mass (M). Calcified and noncalcified plaque volumes were quantified using semi-automated software.

Results: The median value of V/M (18.57 mm3/g) was used to define equal groups of low and high V/M patients. Patients with low V/M had greater diameter stenosis by QCA, more plaque and lower FFR (0.80 ± 0.12 vs. 0.87 ± 0.08; P < 0.0001) than those with high V/M. A total of 365 vessels in 202 patients had QCA stenosis ≥ 50% and measured FFR. In these patients, those with low V/M had higher percent diameter stenosis by QCA, greater total plaque volume and lower FFR (0.81 ± 0.12 vs. 0.88 ± 0.07; P < 0.0001) than those with high V/M. In multivariate logistic regression analysis, V/M was an independent predictor of FFR < 0.80 (all p-values < 0.001).

Conclusions: Patients with a low V/M ratio have lower FFR overall and in non-obstructive CAD, independent of plaque measures.

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The relationship between lumen stenosis and coronary blood flow was first elucidated in the experiments of Gould and...
colleagues more than 40 years ago.\textsuperscript{1} Gould et al. demonstrated that while resting flow could be maintained in vessels with up to 85% diameter stenosis due to compensatory reduction in microcirculatory resistance, hyperemic flow and coronary flow reserve started to fall at approximately 50% diameter reduction.\textsuperscript{1} However, more recent studies have demonstrated that the relationship between progressive lumen narrowing and reduction in either coronary flow reserve (CFR) or fractional flow reserve (FFR) is more complex in humans than in the original animal studies. Discordance between angiographic stenosis severity and functional significance was reported in the DEFER and FAME clinical trials with a majority of lesions with greater than 50% diameter stenosis being negative by measured FFR.\textsuperscript{2,3} In contrast, it has been demonstrated that a substantial proportion of FFR values are positive (FFR < 0.8) even in lesions with stenosis <50%.\textsuperscript{4-6}

Based on our recent experience with FFR\textsubscript{CT}, we have observed patients without focal lumen stenosis with gradual reductions in FFR\textsubscript{CT} along the length of the coronary arteries. For example, a recent case report of two patients without angiographic evidence of coronary artery disease, but with FFR\textsubscript{CT} and FFR values < 0.80, revealed small caliber vessels in addition to diffuse atherosclerosis.\textsuperscript{7} Based on such observations, we hypothesize that, in some patients, pressure losses measured in FFR may arise due to a mismatch between global coronary artery lumen dimensions following vasodilation and myocardial demand. The purpose of this study was to investigate the relationship between coronary artery lumen volume to left ventricle myocardial mass (V/M ratio) in patients with suspected coronary artery disease (CAD) and to determine whether low values of V/M are indicative of a patient phenotype predisposed to low FFR, independent of the presence of focal, obstructive CAD or plaque measures.

\subsection*{1. Methods}

\subsubsection*{1.1. Study population}

All 254 patients from the HeartFlow analysis of coronary blood flow using CT angiography: NeXt Steps (NXT) trial (NCT01757678) were considered for inclusion in the present analysis.\textsuperscript{8} The study population comprised patients with stable CAD who underwent coronary CTA within 60 days prior to clinically-indicated non-emergent invasive coronary angiography (ICA). Exclusion criteria included recent myocardial infarction, prior stent implantation or coronary bypass surgery, contraindications to beta blockers, nitrates or adenosine, acute coronary syndrome, significant arrhythmia, and body mass index >35 kg/m\textsuperscript{2}. The study complied with the Declaration of Helsinki. The ethics committees at each site approved the study protocol. All patients provided written informed consent.

\subsubsection*{1.2. Coronary CTA acquisition}

Coronary CTA was performed using CT scanners with \(\geq 64\) detector rows.\textsuperscript{8} Beta-blockers were administered if necessary targeting a heart rate <60 beats per minute. Sublingual nitrates were administered prior to scanning in all patients. Details of scanning parameters have previously been presented.\textsuperscript{8}

\subsubsection*{1.3. Plaque analysis in coronary CTA}

Coronary segments \(\geq 2\) mm were analyzed using semi-automated software (AutoPlaq version 9.7, Cedars-Sinai Medical Center, Los Angeles, CA, USA). Plaque analyses was performed on a per-vessel basis.\textsuperscript{8} In brief, calcified and non-calcified plaques were identified using scan-specific thresholds. Low-density non-calcified plaque (LD-NCP) was defined as plaque with attenuation < 30 Hounsfield units. Plaque analysis was performed on a per-vessel basis. Aggregate plaque volume (APV %) was computed as \((\text{total plaque volume/vessel volume}) \times 100\%\).

\subsubsection*{1.4. Invasive coronary angiography and FFR measurements}

Quantitative coronary angiography (QCA) and FFR were performed according to standard practice.\textsuperscript{8} Importantly, the angiogram was performed subsequent to intracoronary administration of a minimum 0.2 mg of isosorbide dinitrate. Stenosis severity was assessed in all coronary segments \(\geq 2\) mm at a core lab and the highest per-vessel diameter stenosis was registered. Coronary stenosis >50% was considered obstructive. FFR measurements were performed in 438 vessels with a stenosis ranging from 0 to 89%. The sensor of the FFR pressure-wire was positioned at least 20 mm distal to the stenosis in vessel segments with a reference diameter \(\geq 2\) mm. Hyperemia was induced by intravenous adenosine \((140–180 \mu\text{g/kg/min})\). FFR \(\leq 0.80\) defined a positive test.

\subsubsection*{1.5. Volume to mass calculation}

The coronary artery lumen volume to left ventricle myocardial mass ratio was computed as shown in Fig. 1. First, the three-dimensional patient-specific anatomic model of the epicardial coronary arteries was segmented from imaging data.\textsuperscript{10} Arteries were truncated distal to diseased regions in a location where the average area of the vessel was fairly constant. Branches off the main epicardial coronary arteries identified in the coronary CTA data greater than 1 mm in diameter were included. Second, the total arterial lumen volume of the segmented epicardial coronary arteries was calculated. Third, the volume of the myocardium extracted from imaging data was multiplied by an average value of myocardial tissue density to calculate the left ventricle myocardial mass. Fourth, the ratio of the total arterial lumen volume to the left ventricle myocardial mass (V/M) was computed.

\subsubsection*{1.6. Statistical analysis}

Demographic information and plaque characteristics were described using means and standard deviations for continuous variables and counts and percentages for categorical variables. Definitions of low and high V/M were derived from the median V/M in the entire data set. Comparisons between low and high V/M

\begin{table}[h]
\centering
\begin{tabular}{|l|c|}
\hline
\textbf{Abbreviations} & \\
\hline
CFR & coronary flow reserve \\
CTA & Computed tomography angiography \\
FFR & invasive fractional flow reserve \\
FFRCT & coronary CT angiography-derived fractional flow reserve \\
PCI & percutaneous coronary intervention \\
V/M & ratio of coronary arterial volume to left ventricle myocardial mass \\
\hline
\end{tabular}
\end{table}
groups were done using a Wilcoxon Signed Rank Test for continuous variables and Chi-squared testing for categorical variables. Data were analyzed first by dividing the patients into two equal groups using the median value, low V/M and high V/M patients. Quantities such as percent diameter stenosis, plaque volume, and FFR were analyzed on a per-vessel basis and are only reported for vessels where all three quantities were available. Diameter stenoses were the worst measurement along the vessel, plaque volumes and plaque length were the total along the vessel, and FFR values the lowest value in each vessel. Diameter stenoses, plaque volumes, plaque lengths and FFR values were averaged across vessels for patients in the low V/M or high V/M groups.

Univariate logistic regression was run using FFR < 0.80 as the binary threshold. Odds Ratios were computed and p-values quantified to show significance of coefficients effect on the model. Variables that showed a statistical difference in the univariate logistic regression analysis were tested individually in separate multivariate logistic regression models including V/M to determine whether V/M was an independent predictor of FFR < 0.80. The odds ratio were based on binary division of low vs. high V/M patients. A p-value < 0.05 was considered statistically significant. All analyses were performed using SAS software version 9.3 (SAS Institute, Inc., Cary, NC, USA).

2. Results

The clinical characteristics of the patient population have been described elsewhere. Among the 254 patients, 16 had at least one occluded vessel and were excluded from further analysis. A histogram of V/M is shown in Fig. 2 for the remaining 238 patients. The mean value of V/M was 19.4 ± 5.6 mm³/g. The median value was 18.57 mm³/g which defined the cut-point between low and high V/M.

Baseline characteristics of patients with low and high V/M are shown in Table 1. Low V/M patients were more frequently male, and had higher BMI and updated Diamond-Forrester risk scores as compared to patients with high V/M. There were no other differences in patient characteristics between the groups. Two representative patients with similar left ventricular myocardial masses, but different values of V/M are shown in Fig. 3.

Table 2 provides the data for anatomic and plaque characteristics as well as FFR values for patients with low and high V/M. Notably, patients with low V/M have greater mean percent diameter stenosis by QCA, higher calcified, non-calcified, and total plaque volumes, as well as lower FFR values and more vessels with FFR < 0.80.

2.1. V/M in non-obstructive CAD

A total of 365 vessels in 202 patients had QCA stenosis ≤ 50% and measured FFR. Patients with low V/M had vessels with lower FFR values than those with high V/M for lesions with percent stenosis by QCA ≤ 30% and 31–50%, respectively (Fig. 4a). The frequency of measured FFR values ≤ 0.80 with QCA diameter stenosis ≤ 30% was 10% for low V/M and 1% for high V/M, and with QCA diameter stenosis 31–50% was 26% for low V/M and 6% for high V/M. Lower values of V/M were associated with a greater frequency of measured FFR values ≤ 0.8, whereas higher values of V/M were infrequently associated with FFR ≤ 0.80 for vessels with ≤ 50% diameter stenosis by QCA (Fig. 4b). V/M was analyzed as a continuous variable and a positive correlation between FFR and V/M was observed with a Pearson’s correlation coefficient of 0.33 (p < 0.001).

Table 3 provides the per-vessel data for anatomic and plaque characteristics as well as FFR values for patients with low and high V/M who had QCA maximum stenosis ≤ 50% in at least one vessel and measured FFR. Notably, patients with low V/M have higher percent diameter stenosis by QCA, higher non-calcified, low-density non-calcified and total plaque volumes and more vessels with FFR ≤ 0.80 despite QCA maximum stenosis ≤ 50%.
Table 1
Baseline characteristics of patients. Patients were divided into two equal groups of 119 patients using the median value of V/M = 18.57 mm$^3$/g.

<table>
<thead>
<tr>
<th></th>
<th>All (N = 238)</th>
<th>Low V/M (&lt;18.57 mm$^3$/g) (n = 119)</th>
<th>High V/M (≥18.57 mm$^3$/g) (n = 119)</th>
<th>p-value (Low vs. high V/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>64 ± 9</td>
<td>63 ± 9</td>
<td>65 ± 10</td>
<td>0.12</td>
</tr>
<tr>
<td>Male</td>
<td>148 (62)</td>
<td>91 (76)</td>
<td>57 (48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>56 (24)</td>
<td>33 (28)</td>
<td>23 (19)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hypertension</td>
<td>164 (69)</td>
<td>85 (71)</td>
<td>79 (66)</td>
<td>0.40</td>
</tr>
<tr>
<td>Hypertension</td>
<td>185 (78)</td>
<td>90 (76)</td>
<td>95 (80)</td>
<td>0.49</td>
</tr>
<tr>
<td>Current smoker</td>
<td>42 (18)</td>
<td>23 (19)</td>
<td>19 (16)</td>
<td>0.50</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>4 (2)</td>
<td>3 (2.5)</td>
<td>1 (0.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>Symptoms*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical angina</td>
<td>93 (51)</td>
<td>52 (44)</td>
<td>41 (34)</td>
<td>0.24</td>
</tr>
<tr>
<td>Atypical angina</td>
<td>70 (38)</td>
<td>34 (16)</td>
<td>36 (30)</td>
<td>0.51</td>
</tr>
<tr>
<td>Nonanginal chest pain</td>
<td>9 (5)</td>
<td>3 (3)</td>
<td>6 (5)</td>
<td>0.26</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11 (6)</td>
<td>6 (5)</td>
<td>5 (4)</td>
<td>0.84</td>
</tr>
<tr>
<td>Angina within the past month</td>
<td>182 (76)</td>
<td>94 (79)</td>
<td>88 (74)</td>
<td>0.36</td>
</tr>
<tr>
<td>Updated Diamond-Forrester risk score, %</td>
<td>57 ± 22</td>
<td>63 ± 18</td>
<td>51 ± 24</td>
<td>0.0005</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>25 ± 4</td>
<td>26 ± 4</td>
<td>25 ± 4</td>
<td>0.024</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.40</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>62 ± 7</td>
<td>62 ± 7</td>
<td>62 ± 7</td>
<td>0.78</td>
</tr>
</tbody>
</table>

If not stated otherwise values are mean (±SD), n (%), or % (±SD).

Fig. 3. Coronary CTA, invasive angiography and FFR in a patient with low V/M, V/M = 9.7 mm$^3$/g, M = 126 g (Top) and a patient with high V/M ratio, V/M = 26 mm$^3$/g, M = 117 g (Bottom). Neither patient had angiographic stenoses >30% by QCA. The patient with lower V/M has noticeably smaller coronary arteries. The patient with low V/M had FFR of 0.70 in the distal LAD. The patient with high V/M had a mild mid-LAD lesion and FFR of 0.96.
Table 2  
Anatomic, plaque, and FFR characteristics of patients with low vs. high V/M.

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Low V/M. (&lt;18.57 mm³/g)</th>
<th>High V/M. (≥18.57 mm³/g)</th>
<th>p-value (Low vs. High V/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent diameter stenosis by QCA</td>
<td>34% ± 18%</td>
<td>38% ± 18%</td>
<td>31% ± 17%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with QCA maximum stenosis &gt;50%</td>
<td>65 (27%)</td>
<td>40 (34%)</td>
<td>25 (21%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Total non-calcified plaque volume (mm³)</td>
<td>426 ± 316</td>
<td>512 ± 312</td>
<td>341 ± 298</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total calcified plaque volume (mm³)</td>
<td>66 ± 94</td>
<td>81 ± 109</td>
<td>51 ± 74</td>
<td>0.019</td>
</tr>
<tr>
<td>Total low density non-calcified plaque volume (mm³)</td>
<td>73 ± 63</td>
<td>91 ± 67</td>
<td>55 ± 53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total plaque length (mm)</td>
<td>272 ± 21.8</td>
<td>33.7 ± 23.9</td>
<td>21.6 ± 18.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total plaque volume (mm³)</td>
<td>493 ± 382</td>
<td>593 ± 395</td>
<td>392 ± 341</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aggregate Plaque Volume (%)</td>
<td>50 ± 17</td>
<td>54 ± 16</td>
<td>45 ± 16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FFR</td>
<td>0.84 ± 0.11</td>
<td>0.80 ± 0.12</td>
<td>0.87 ± 0.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with FFR &lt;0.80</td>
<td>64 (27%)</td>
<td>50 (42%)</td>
<td>14 (12%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vessels with FFR &lt;0.80</td>
<td>73 (17%)</td>
<td>56 (25%)</td>
<td>17 (8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with FFR &lt;0.80 in &gt;1 vessel</td>
<td>8 (3%)</td>
<td>8 (6.7%)</td>
<td>0 (0%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

If not stated otherwise values are mean (±SD), n (%), or % (±SD). QCA: Quantitative coronary angiography; FFR: Fractional flow reserve.

2.2. V/M as a predictor of FFR <0.80

Table 4 provides data for univariate regression analysis. Male gender was a predictor of FFR <0.80 in the overall and QCA ≤50% stenosis group. BMI was only significant for the QCA ≤50% stenosis group. All plaque variables excluding calcified plaque volume were predictors of FFR <0.80 in univariate analysis in the overall and QCA ≤50% stenosis groups. Coronary arterial lumen volume, V, was a predictor of FFR <0.80 in univariate analysis in the overall and QCA ≤50% stenosis groups, but the left ventricle myocardial mass, M, was not. V/M was a predictor of FFR <0.80 for the overall and QCA ≤50% stenosis group. Increased V/M is associated with lower odds of FFR <0.8.

When controlled for diameter stenosis, gender, BMI, V, M, or any and all of the plaque variables examined, based on multivariate logistic regression, V/M ratio remained a significant predictor of FFR <0.8 in the overall patient population and in the QCA ≤50% stenosis group. For example, Table 5, shows the odds ratio for V/M computed using separate multivariate logistic regression models controlling for diameter stenosis, low-density noncalcified plaque (previously shown to be predictive of ischemia^5), total plaque length, V, and M, for the overall patient group and the QCA stenosis ≤50% group. Note that in all cases, V/M remains an independent predictor of FFR <0.8.

3. Discussion

The main finding of this study proved the hypothesis that patients with low coronary artery lumen volume to left ventricle myocardial mass ratios (V/M) following coronary vasodilation mediated by nitrates were much more likely to have FFR values ≤ 0.80 than patients with high V/M regardless of the presence or absence of focal stenosis. Among patients in the lower half of V/M, 42% had an FFR value ≤ 0.80, compared to only 12% of patients with a V/M above the median. Importantly, while subjects with a low V/M were found to have significantly greater atherosclerosis than patients with high V/M, V/M was found to be an independent predictor of FFR <0.80.

3.1. Scientific basis of V/M

The concept of the volume-to-mass ratio has its origin in...
Values are mean ± SD, range, n (%), or %. QCA: Quantitative coronary angiography; FFR: Fractional flow reserve.

Table 3
Anatomic, plaque and FFR characteristics of patients with low vs. high V/M and QCA diameter stenosis ≤50%

<table>
<thead>
<tr>
<th></th>
<th>Overall (N = 238 patients and 438 vessels)</th>
<th>Stenosis ≤50% (n = 202 patients and 365 vessels)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>2.323 (1.457, 3.075)</td>
<td>0.0004</td>
</tr>
<tr>
<td>BMI</td>
<td>0.958</td>
<td>0.14</td>
</tr>
<tr>
<td>Total plaque length (mm)</td>
<td>1.031 (0.904, 1.015)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Plaque volume (mm³)</td>
<td>1.002 (1.001, 1.002)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aggregate plaque volume (%)</td>
<td>1.021 (1.008, 1.035)</td>
<td>0.002</td>
</tr>
<tr>
<td>Calcified Plaque Volume (mm³)</td>
<td>1.001 (0.999, 1.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Noncalcified plaque volume (mm³)</td>
<td>1.002 (1.001, 1.003)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low Density Noncalcified plaque volume (mm³)</td>
<td>1.013 (1.009, 1.017)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epicardial coronary artery lumen volume, V (mm³)</td>
<td>1.004 (0.999, 1.000)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricle myocardial mass, M (g)</td>
<td>1.005 (0.998, 1.012)</td>
<td>0.18</td>
</tr>
<tr>
<td>V/M</td>
<td>0.869 (0.827, 0.913)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

3.2. Potential mechanisms of low V/M

Seiler et al., in a seminal paper, characterized structure-function relationships of the epicardial coronary arteries and noted that patients with coronary artery disease had lumen areas too small for the distal myocardial bed size.14 Molloy et al. described the quantification of coronary artery lumen volume from invasive angiography and the possibility of using this information for quantification of diffuse coronary artery disease.15 Huo et al. studied the relationship between epicardial coronary artery lumen volume and the summed branch lengths of the arteries in an effort to describe diffuse atherosclerosis.16 Diffuse atherosclerosis was also proposed by De Bruyne et al. as the explanation for positive FFR values in vessels with no focal lesions or angiographic evidence of disease.4 Gould et al. further described the role diffuse atherosclerosis may have in reducing coronary flow reserve in patients without focal stenosis.17

In the present study, low V/M in patients with QCA diameter stenosis ≤50% was associated with a higher coronary plaque burden. It is important to note that V/M was quantified at a patient level implying all vessels may be affected. In addition to, or because of, diffuse atherosclerosis, low V/M may be related to impaired vasodilation of the epicardial coronary arteries even after the administration of nitroglycerin. Nitroglycerin can have a profound effect on the caliber of epicardial coronary arteries. The diameter of coronary arteries can increase by 10% or more for large coronary arteries and 50% for small branches in response to nitroglycerin.18 Diffuse intimal...
thickening may provide a mechanism for impaired vasodilation of the coronary arteries. An impaired response to nitrates would result in smaller caliber coronary arteries for a given amount of myocardium to be perfused with resulting pressure loss along the entire length of the coronary tree under resting and hyperemic conditions independent of focal stenoses.

Previous studies have assessed the relationship between fitness level and caliber and vasodilation capacity of the epicardial coronary arteries. Haskell et al. demonstrated that endurance runners had the same baseline coronary artery lumen size and myocardial mass as normal control subjects, but a much greater ability to vasodilate with sublingual nitroglycerin. During cardiac catheterization, endurance runners experienced an almost 60% increase in the total cross-sectional area of the proximal arteries after administration of nitroglycerin, thereby accommodating up to a 2.5-fold increase in coronary flow without a significant pressure gradient. In contrast, for a patient unable to dilate their epicardial vessels, any increase in flow would result in a proportional increase in pressure gradient along the length of the vessel.

3.3. Clinical implications of low V/M

We postulate that the V/M ratio value is a measure of the ability of the epicardial coronary arteries to supply blood in relation to myocardial demand. This ratio is easily extracted from models created from coronary CT angiography for noninvasive fractional flow reserve analysis and could therefore be used as an additional metric of coronary circulatory function.

The findings in this study may also offer an explanation for why some patients with positive noninvasive stress tests have an absence of significant obstructive coronary artery disease at the time of cardiac catheterization. Patients with a low V/M ratio would be expected to use some of their vasodilatory reserve to maintain resting flow and, as a result, have lower CFR values as well as lower absolute hyperemic flow.

Exercise may provide a mechanism to increase V/M. Blood vessels adapt in response to flow and endothelial-dependent and endothelial-independent vasodilation improves with exercise. It is reasonable to expect that regular exercise which induces vasodilation of the coronary arteries may, in turn, increase the vasodilatory capacity of the coronary arteries and increase the V/M ratio.

Finally, in a recent study examining the functional significance of nonculprit lesions in patients with prior STEMI, Gaur et al. found V/M to be significantly lower as compared to that of patients with stable CAD. These findings are intriguing and motivate the calculation of V/M in other patient populations.

3.4. Limitations

This study was a post-hoc analysis of the NXT trial including patients with suspected CAD. The range of V/M values for normal subjects with no CAD or subjects with more severe disease than assessed in this patient population is unknown. There are patients that have elevated FFR values despite having low V/M. It may be speculated that at least some of these patients have a lower vasodilatory capacity and hence higher microvascular resistance. However, in this study we did not measure coronary flow reserve or microvascular resistance so this possibility should be investigated in subsequent studies.

Epicardial coronary volume is extracted from coronary CTA data and hence can be affected by the quality of the image data. Due to limits in spatial resolution, motion artifacts, and poor opacification of the coronary arteries, it may be difficult to determine the size of smaller caliber vessels or identify them in the first place. In the methods presented herein, epicardial vessel segments were truncated based on trimming rules related to the ability to visualize the distal coronary arteries. It is unknown how these truncation rules affect the coronary volume calculations. In a previous investigation describing low V/M in patients with prior STEMI from the present study group, we used morphometric rules to generate a model of the arterial tree beyond the limits of the epicardial model. Thus, the values for V/M reported in the present study, which only include the epicardial tree segmented from the CT data are lower than in that prior study. While either method for computing the coronary artery lumen volume would result in similar conclusions, we opted for the simpler, epicardial-based method in the current investigation.

V/M was reported on a patient-level, i.e. the entire epicardial coronary artery lumen volume and the entire left ventricle myocardial mass was computed. While the strength of this approach is it may identify a patient-phenotype predisposed to ischemia, it may also be of interest to relate a regional coronary artery lumen volume to the fraction of the myocardial mass subtended by the vessel territory. This fractional myocardial mass could be computed by one of several methods previously described, but this approach requires several assumptions to assign a portion of the myocardium to each vessel. In the present study, we could not exclude the possibility that one territory exhibited a small vessel volume relative to its subtended myocardium while another may have exhibited a large ratio of vessel volume to subtended myocardium. In assessing the relationship between V/M and FFR in vessels with QCA ≤50%, we did not exclude patients that may have had a high grade stenosis somewhere else in the coronary tree.

Table 5

<table>
<thead>
<tr>
<th>V/M when controlled for the following variables</th>
<th>Overall</th>
<th>Stenosis ≤50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent diameter stenosis by QCA</td>
<td>0.884 (0.841, 0.929)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low Density Noncalciﬁed plaque volume (mm³)</td>
<td>0.901 (0.857, 0.948)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total plaque length (mm)</td>
<td>0.982 (0.972, 0.991)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epicardial coronary artery lumen volume, V (mm³)</td>
<td>0.887 (0.841, 0.935)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left ventricle myocardial mass, M (g)</td>
<td>0.869 (0.816, 0.907)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>


QCA: Quantitative coronary angiography; FFR: Fractional flow reserve.
Finally, the plaque burden was not normalized by the vessel length, which should be considered for future investigations.

4. Conclusion

Patients with low V/M were found to have lower FFR values than those with high V/M with or without focal coronary stenoses >50%. V/M remained an independent predictor of FFR<0.80. Whether low V/M is due to small caliber epicardial coronary arteries which dilate normally with nitroglycerin or normal caliber epicardial arteries with abnormal vasodilatory capacity is unclear and would be important to determine in future investigations.

Conflicts of interest

C. Taylor is an employee of and shareholder in HeartFlow and receives royalties from Stanford University. J. Leipsic has received speaker’s honorarium from GE, and is consultant to and has received institutional research support from HeartFlow. D. Berman and D. Dey have received royalties for software licensing from Cedars-Sinai Medical Center. J. Jensen has received speaker’s honorarium from Bracco Imaging. S. Khem, H. Kim, A. Wilk, and C.K. Zarins are employees of and shareholders in HeartFlow. F. St. Goar reports equities of HeartFlow. B. De Bruyne reports institutional research grants from Abbott, St. Jude Medical, Medtronic, Boston Scientific, institutional consultancies from St. Jude Medical, Opsens and Boston Scientific and equities of Omega Pharma, Siemens, GE, Sanofi, HeartFlow. B. Nørgaard has received institutional research support from Edwards Lifesciences. Siemens and HeartFlow. S. Achenbach, A. Ahmadi, H. Bøtker, H. Bezerra, S. Gaur, B. Ko, J. Lesser, J. Narula, K. Øvrehus, report no conflicts.

Acknowledgments

The HeartFlow analysis of coronary blood flow using CT angiography: NEXT steps (NXT trial) (NCT01757678) was funded by HeartFlow, Inc.

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