JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 15, 2016
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ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.04.008

Physiological Severity of Coronary Artery Stenosis Depends on the Amount of Myocardial Mass Subtended by the Coronary Artery

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ABSTRACT

OBJECTIVES This study investigated the role of fractional myocardial mass (FMM), a vessel-specific myocardial mass, in the evaluation of physiological severity of stenosis. Using computed tomography angiography, the study investigated fractional myocardial mass, a concept of myocardial mass subtended by specific vessel, which could reduce anatomical-physiological mismatch.

BACKGROUND Discordance between anatomical stenosis and physiological severity is common but remains poorly understood.

METHODS This multicenter study enrolled 463 patients with 724 lesions, who underwent coronary computed tomography angiography (CCTA) and invasive coronary angiography with fractional flow reserve (FFR) measurement. FMM was assessed by allometric scaling analysis of arterial tree length and myocardial mass from CCTA.

RESULTS FFR $<$0.80, a criteria for vessel-specific physiological stenosis, was found in 281 vessels (39%). FMM decreased consistently according to the vessel downstream ($p < 0.001$, all). The frequency of FFR $<$0.80 increased in proportion to FMM and inverse proportion to angiographic minimal luminal diameter (MLD) ($p < 0.001$). In per-vessel analysis, FMM per MLD (FMM/MLD) showed good correlation with FFR ($r = 0.61$) and was superior to diameter stenosis (DS) for FFR $<$0.80 by receiver operating characteristic and reclassification analysis (C-statistics = 0.84 versus 0.74, net reclassification improvement [NRI] = 0.63, integrated discrimination improvement [IDI] = 0.18; $p < 0.001$, all). The optimal cutoff of FMM/MLD was 29 g/mm, with sensitivity = 75%, specificity = 77%, positive predictive value = 68%, negative predictive value = 83%, and accuracy = 77%. Addition of FMM/MLD to DS could further discriminate vessels with FFR $<$0.80 (C-statistic = 0.86 vs. 0.84, NRI = 0.34, IDI = 0.03; $p < 0.005$, all). In per-range classification analysis, agreement between FFR and FMM/MLD maintained $>$80% when the severity of disease was away from cutoff.

CONCLUSIONS FMM/MLD could find physiological severity of coronary artery with higher accuracy than anatomical stenosis. FMM may explain the anatomical-physiological discordance. (J Am Coll Cardiol Intv 2016;9:1548–60)
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Evaluation of myocardial ischemia or physiological severity of coronary artery disease is the most important criterion for predicting prognosis and decision of revascularization. Coronary angiography (CAG) is being used as a standard for decision of treatment strategy or revascularization in daily practice. However anatomical stenosis visualized by CAG is a poor predictor of physiological severity and frequently underestimates or overestimates physiological severity of stenosis. Fractional flow reserve (FFR) <0.80, a widely accepted gold standard of vessel-specific physiologically significant stenosis which may evoke myocardial ischemia, is identified in less than one-half of vessel with significant stenosis defined by diameter stenosis (DS) ≥50%. This discordance between anatomical stenosis and physiological severity is found in as high as 40% of stenotic coronary arteries but is still poorly understood (1). Hence physiology-guided revascularization is considered superior to anatomy-guided revascularization in terms of improved clinical outcome and saving medical cost (2,3), understanding and reducing anatomical-physiological discordance has important implications for performing appropriate revascularization procedure.

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FFR can be described as a pressure gradient across stenotic segment during maximal myocardial blood flow. Anatomical stenosis, myocardial mass, and microvascular resistance are major constituents of FFR value (4). The major unknowns in anatomical measurement are myocardial mass and microvascular resistance. Therefore, we reasoned that the anatomical-physiological discordance can be reduced by addition of downstream myocardial mass to anatomical stenosis of the supplying artery. We developed fractional myocardial mass (FMM), a concept defined by vessel-specific myocardial mass, and investigated its implication in the anatomical-physiological discordance.

METHODS

STUDY DESIGN. This study was a prospective multicenter registry of 5 university teaching hospitals in Korea. From January 2010 to May 2015, the study enrolled 466 patients who underwent clinically indicated coronary computed tomography angiography (CCTA) and followed elective CAG with physiological assessment without intervening coronary events. Patients with ST-segment elevation myocardial infarction (MI), uncompensated heart failure, bypass surgery with patent graft, contraindication to adenosine therapy, complex structural or congenital heart disease, prosthetic valves, or any clinical instability or life-threatening disease were not included. The study protocol was approved by the institutional review board at each institute. All data were anonymized and independently analyzed by core laboratory in Samsung Medical Center.

ABBREVIATIONS AND ACRONYMS

CAG = coronary angiography
CCTA = computed tomography angiography
DS = diameter stenosis
FFR = fractional flow reserve
FMM = fractional myocardial mass
MLD = minimal luminal diameter
QCA = quantitative coronary angiography
RD = reference diameter

FFR AND QCA. CAG and FFR measurements were made according to the standard protocol of each institute as described previously (5). Briefly, a minimum of 2 optimized projections were obtained for each major coronary artery after administration of intracoronary nitroglycerin. FFR was measured using a pressure wire (PressureWire Certus, St. Jude Medical Systems, San Francisco, California; ComboWire, Philips Healthcare, Baltimore, Maryland) under adenosine-induced maximal hyperemia. An FFR value <0.80 was considered physiologically significant stenosis. Quantitative coronary angiography (QCA) was performed by independent experienced technicians who were told of the location of FFR measurement but were blinded to the result of FFR and the other data. A computer-assisted automatic arterial contour detection system (Centricity CA-1000, GE Healthcare, Little Chalfont, United Kingdom) was used. Lesion length, DS, and minimal luminal diameter was measured in the end-diastolic angiographic image with optimal projection showing minimal foreshortening of the lesion. Decision to revascularize was made by agreement of attending physician and interventional cardiologist.

ACQUISITION AND ANALYSIS OF CCTA. CCTA was performed using multivendor CT scanners equipped with 64 or more detectors (Aquilion One or Aquilion 64, Toshiba Medical Systems, Tokyo, Japan; Somatom Definition, Siemens Medical Solution, Austin, Texas; Lightspeed VCT, GE Healthcare). Oral nitroglycerin and metoprolol were administered before subjects were scanned, if required. Prospective or retrospective

Biomedical Research Institute grant GL1B33211, and by the Heart Vascular and Stroke Institute of Samsung Medical Center. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 28, 2015; revised manuscript received March 25, 2016, accepted April 7, 2016.

electrocardiographic gating was used, and radiation dose reduction strategy was applied in accordance with Society of Cardiovascular Computed Tomography guidelines. Image data were reconstructed by 0.5- or 0.6-mm slices. A dedicated workstation (iNtuition, Terarecon, Foster City, California) was used by 2 experienced imaging specialists blinded to other data. Three-dimensional entire coronary arterial tree model was constructed and segmented according to the modified American Heart Association classification of coronary artery anatomy. All major epicardial coronary arteries and first-order branches ≥1.0 mm in diameter were tracked from ostium to distal end. Vessel central axis was determined manually with assistance of automatic tracking function and was confirmed by reviewing all cross-sectional images. A total of 8,259 vessel segments were evaluated. Left ventricular (LV) myocardial mass was also measured using a dedicated software module.

CALCULATION OF FMM. FMM was computed using a stem-and-crown model established by Huo and Kassab (6), which is based on allometric scaling between length of coronary arterial tree and LV myocardial mass. Allometric scaling law is a simple and universally observed logarithmic relationship among size, function, and energy expenditure in life science (6). Energy efficient provision of materials such as oxygen in hierarchical fractal-like network of branching tubes plays a key role in the mechanism of living organism (7). Based on the principle of efficiency or minimum energy loss, stem-and-crown models which describe scaling power between structures and functions have been developed theoretically and validated experimentally in both animal and human studies (8,9). Therefore we reasoned that the allometric scaling between cumulative vessel length (L) and myocardial mass (M) found in mammalian heart, $M = k \cdot L^{(4/3)}$ can be applied in human heart (10).

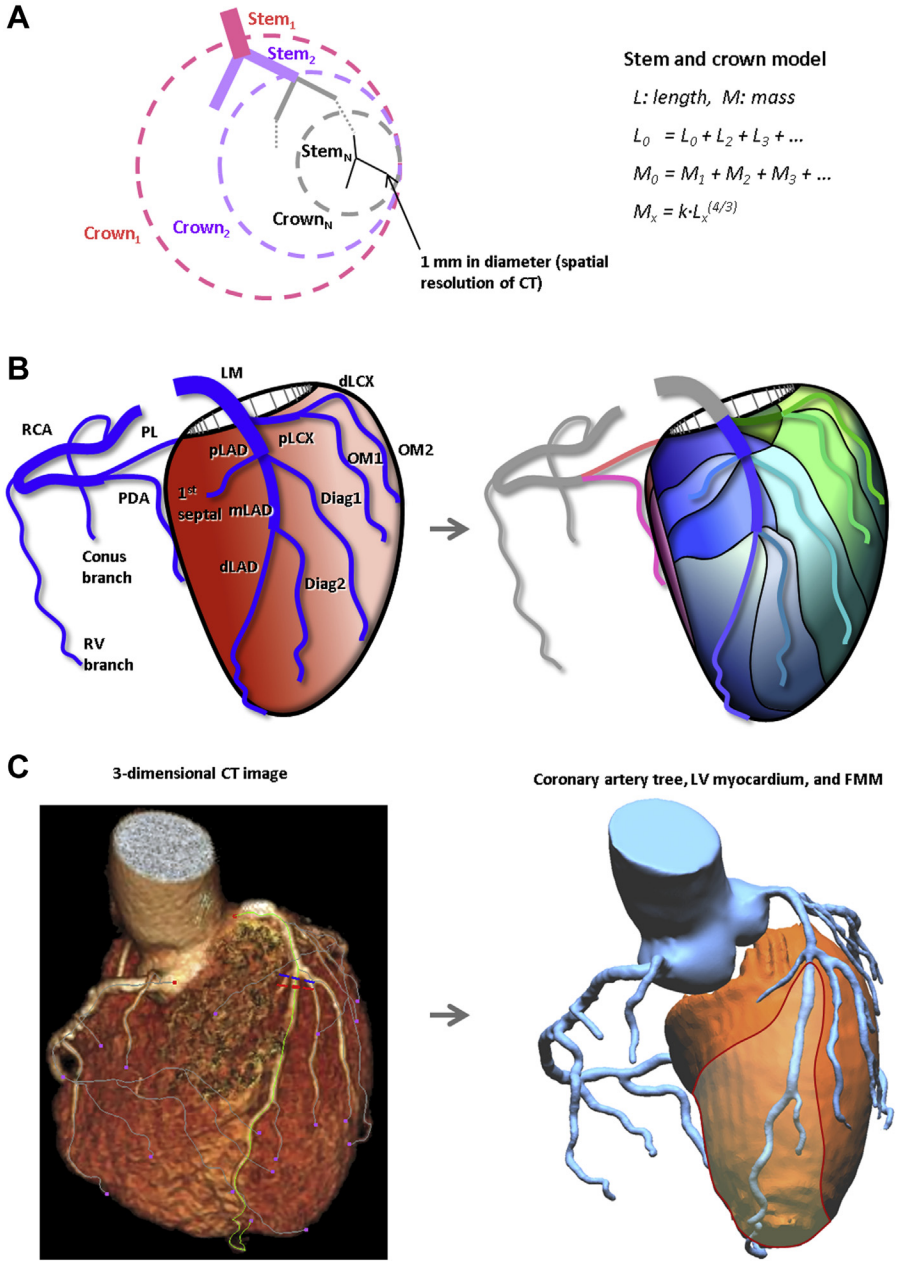
A vessel segment was defined as a stem. Arterial tree distal to stem was defined as a crown (**Figure 1A**) (9). Before myocardium was segmented, arterial segments that did not directly perfuse LV myocardium were excluded, which were right coronary artery (RCA) segments from ostium to distal RCA, right ventricular branches, and left main segment (**Figure 1B**, gray vessels). First, FMM of left coronary artery and RCA were determined by dividing the whole LV myocardial mass proportionately to each arterial tree length to the power of four thirds. Next, FMM of left coronary artery was divided into proximal left anterior descending artery (LAD), proximal left circumflex artery (LCX), and ramus artery if present proportionally to the 4/3rd power of each arterial tree length. The same method was applied recursively along vessel downstream in each bifurcations; mid LAD and first diagonal branch, distal LAD and second diagonal branch, mid LCX and first obtuse marginal (OM) branch, distal LCX and second OM, posterolateral artery and posterior descending artery so that vessel-specific myocardial mass is proportional to the 4/3rd power of the summed length of subtending arterial tree (**Figures 1B and 1C**).

STATISTICAL ANALYSIS. Analysis was done on both per-vessel and per-patient basis. In per-patient analysis, the representative vessel was selected based on the lowest FFR or the longest length in case of vessels with same FFR. Data were not normally distributed and nonparametric statistics were applied. Categorical variables are presented as frequencies and percentages. Continuous variables are shown as median values with first and third quartiles in parentheses. FFR and QCA data were treated on a continuous scale. FFR <0.80, DS ≥ 50%, FMM/MLD ≥28.8 g/mm, and MLD ≤1.29 mm were used as dichotomized parameters for physiologically significant stenosis or optimal cutoff for discrimination. Dose-response relationship between FMM and vessel location or QCA parameters were assessed by Cochran-Armitage test for trend. Correlations among variables were assessed by the Pearson method and are shown with standard error. Diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated as proportions with 95% confidence intervals (CIs). Performance of discrimination was quantitated by receiver operating characteristics using the DeLong method and reclassification analyses including net reclassification improvement (NRI) and integrated discrimination improvement (IDI). Per-range agreement was assessed by plotting the diagnostic accuracy against the average of FFR and FMM/MLD normalized with FFR, using 15 equal sized groups (11). A 2-tailed p value of <0.05 was considered statistically significant. R version 3.2.3 software (R Foundation, Vienna, Austria) was used for computational analyses.

RESULTS

STUDY POPULATION AND CLINICAL CHARACTERISTICS. A total of 466 patients with 729 vessels were enrolled. One vessel from a patient was excluded due to poor CCTA quality. Three vessels from 2 patients were excluded due to prior interventional procedures in the same vessel. Finally a total of 724 vessels from 463 patients were included in the

FIGURE 1 Concept of Fractional Myocardial Mass

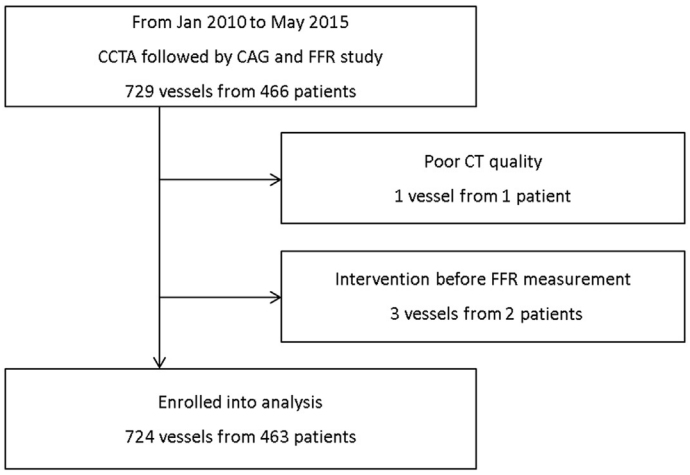


(A) Stem and crown model by Huo and Kassab (9). **(B)** Schematic illustration showing the concept of FMM. **(C)** CCTA image and calculation of FMM subtended by mid LAD lesion. FMM = fractional myocardial mass; CCTA = coronary computed tomography angiography; LAD = left anterior descending artery.

analysis (Figure 2). Baseline clinical characteristics are shown in Table 1. A majority of patients (83%) had symptomatic angina. The median interval between CCTA and CAG was 17 (first and third quartiles, 7 to 37) days.

QCA AND FMM. Per-vessel and per-patient prevalence rates of vessels with FFR <0.80 was 39% (281 vessels) and 52% (n = 228), respectively. In both per-vessel and per-patient analyses, vessels with FFR <0.80 showed higher diameter stenosis (DS),

FIGURE 2 Study Enrollment



lower reference diameter (RD), and lower minimal luminal diameter (MLD) than vessels with FFR ≥0.80 ($p < 0.001$, all). The median of total LV myocardial mass and FMM was 107 g (94 to 129 g) and 36 g (21 to 51 g), respectively, and were significantly higher in vessels with FFR <0.80 than in vessels with FFR ≥0.80 ($p < 0.01$, all) (Table 2).

TABLE 1 Demographics

Age, yrs	64 (58-70)
Male	352 (76)
Body mass index, kg/m^2	24.6 (23.0-26.4)
Diagnosis	
Stable angina	320 (69.2)
Silent ischemia	53 (11.4)
Unstable angina	90 (19.4)
Diabetes	174 (37.6)
Hypertension	283 (61.1)
Dyslipidemia	129 (27.9)
Prior history of smoking	183 (39.5)
Family history of coronary artery disease	30 (6.4)
Prior myocardial infarction	40 (8.6)
Prior percutaneous coronary intervention	69 (14.9)
Prior coronary bypass surgery*	1 (0.2)
Chronic kidney disease	5 (0.1)
Prior stroke	7 (1.5)
Left ventricular ejection fraction, %†	65 (59-69)
Hemoglobin, g/dl	14.0 (12.9-14.7)
Creatinine, mg/dl	0.93 (0.79-1.01)
Total cholesterol, mg/dl	170 (137-202)
LDL-cholesterol, mg/dl	102 (73-129)
HDL-cholesterol, mg/dl	48 (42-57)
Triglyceride, mg/dl	111 (76-147)

Values are or median (interquartile range) or n (%). *A patient with prior bypass surgery but completely occluded graft vessel. †Echocardiography was assessed in 250 patients.

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

FMM OF EACH CORONARY ARTERY SEGMENT. FMM consistently decreased according to the vessel downstream ($p < 0.001$, all). The median FMM was 91 g (75 to 103 g) in left main, 53 g (42 to 61 g) in proximal LAD, and 43 g (34 to 53 g) in mid LAD, which correspond to 80%, 49%, and 40% of LV myocardial mass, respectively. Median FMM was 35 g in distal LAD and proximal to mid LCX, and 19 g in RCA. Median FMMs of side branches including diagonal, OM, posterior descending artery, posterolateral artery, and ramus were 11 g (6 to 19 g), which corresponded to 11% (5% to 15%) of LV myocardial mass (Figure 3, Online Table 1).

IMPACT OF FMM ON THE RELATIONSHIP BETWEEN ANATOMICAL STENOSIS AND PHYSIOLOGICAL SEVERITY. Overall, DS showed moderate diagnostic performance for FFR <0.80; sensitivity = 78% (95% confidence interval [CI]: 72% to 82%), specificity = 48% (95% CI: 43% to 53%), PPV = 49% (95% CI: 44% to 53%), NPV = 77% (95% CI: 72% to 82%), and accuracy = 60% (95% CI: 56% to 63%). The correlation between %DS and FFR was modest ($r = 0.49$, $p < 0.001$) (Figures 4A and 4B).

At the given DS, vessels with higher FMM showed lower FFR and higher frequency of FFR <0.80 than vessels with lower FMM ($p < 0.001$, all) (Figures 4C and 4D). Also, at the given FMM, vessels with higher DS or lower MLD showed lower FFR and higher frequency of FFR <0.80 than vessels with lower DS or higher MLD ($p < 0.001$, all) (Figures 4E to 4H). Elaborately, the frequency and cutoff of MLD for FFR <0.80 increased consistently according to FMM.

Therefore, we reasoned that the FMM-to-MLD (FMM/MLD) ratio, which represents the ratio of myocardial blood flow demand to maximal blood supply, can be a novel anatomical index for physiologically significant stenosis having FFR <0.80 (Figures 4I to 4J). Intriguingly, FMM/MLD showed a good correlation with FFR ($r = -0.61$; $p < 0.001$) (Figure 4K).

IMPROVED DISCRIMINATION FOR FFR <0.80 BY FMM/MLD COMPARED TO ANGIOGRAPHIC STENOSIS. In per-vessel analysis, FMM/MLD was superior to DS (C-statistics = 0.84 [95% CI: 0.81 to 0.87] vs. 0.74 [95% CI: 0.70 to 0.78], $p < 0.001$) for discrimination of vessel with FFR <0.80. The optimal cutoff of FMM/MLD was 28.8 g/mm, with sensitivity = 75% (95% CI: 70% to 80%), specificity = 77% (95% CI: 73% to 81%),

PPV = 68% (95% CI: 62% to 73%), NPV = 83% (95% CI: 79% to 87%), and accuracy = 77% (95% CI: 73% to 80%). With this cutoff value, FMM/MLD could correctly reclassify 123 vessels (17.0%; NRI = 0.626 [95% CI: 0.485 to 0.767]; IDI = 0.178 [95% CI: 0.138 to 0.217]). Also, addition of FMM/MLD to DS further discriminated vessel with FFR <0.80 (C-statistics = 0.86 [95% CI: 0.83 to 0.88] vs. 0.84 [95% CI: 0.81 to 0.87]; NRI = 0.339 [95% CI: 0.192 to 0.486]; IDI = 0.031 [95% CI; 0.018 to 0.044]; p < 0.005, all) (**Figures 5A and 5B**, **Table 3**). Per-patient analysis showed consistent results (**Figures 5C and 5D**, **Table 3**).

CLASSIFICATION AGREEMENT OF FFR AND FMM/MLD. Per-range classification agreement between FFR and FMM/MLD was >80% in most ranges of averages of FFR and normalized FMM/MLD. The gray zone in which classification agreement <80% was not wide, 0.78 to 0.86, and similar to the published per-range agreement between FFR and second FFR or iFR (instantaneous wave-free ratio) (11) (**Figures 6A to 6C**).

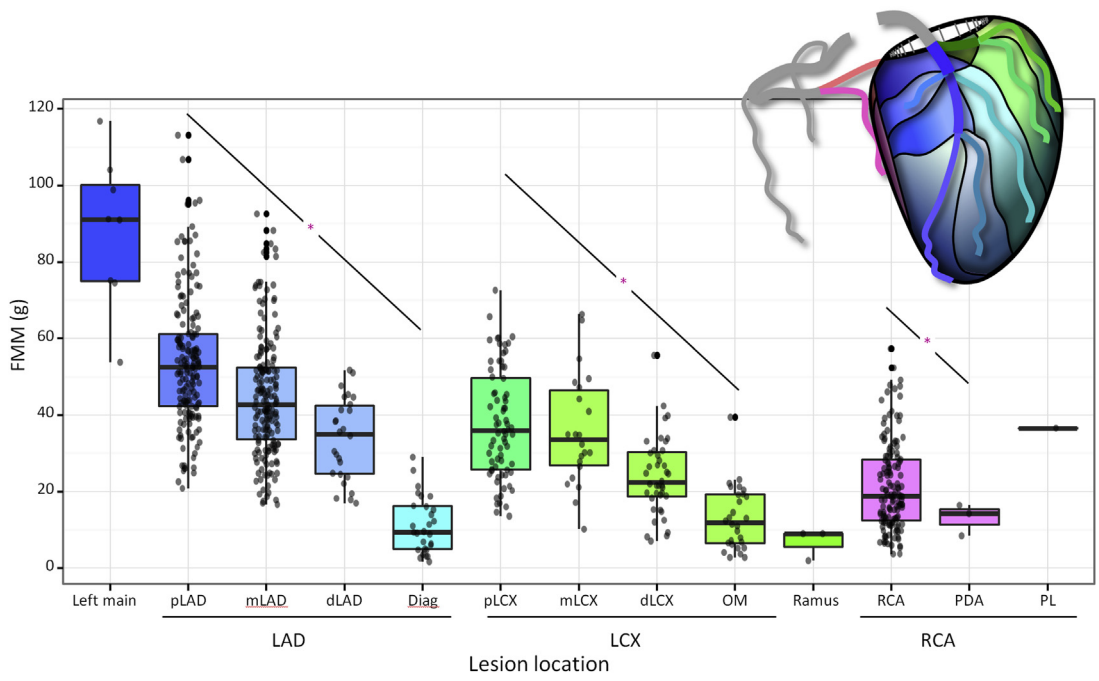
TABLE 2 QCA and FMM

	All	FFR <0.8	FFR ≥0.8	p Value
Per-vessel analysis				
n	724 (100)	281 (38.8)	443 (61.2)	–
FFR	0.83 (0.74-0.90)	0.71 (0.64-0.75)	0.88 (0.84-0.93)	<0.001
DS, %	54.0 (44.9-64.1)	61.3 (51.2-70.9)	50.9 (40.9-58.2)	<0.001
RD, mm*	3.09 (2.67-3.57)	3.00 (2.55-3.40)	3.14 (2.74-3.65)	<0.001
MLD, mm	1.38 (1.06-1.78)	1.13 (0.84-1.39)	1.58 (1.21-1.94)	<0.001
Length, mm	15.3 (10.7-20.6)	16.7 (12.0-22.6)	14.0 (9.5-19.6)	<0.001
Total LV mass, g	107.0 (94.4-128.8)	111.8 (96.9-131.8)	105.2 (92.9-125.0)	<0.001
FMM, g	36.0 (21.3-51.1)	44.8 (30.0-57.9)	30.8 (17.4-44.2)	<0.001
Per-patient analysis				
n	439 (100)	228 (51.9)	221 (48.1)	
FFR	0.79 (0.69-0.86)	0.69 (0.63-0.75)	0.87 (0.83-0.89)	<0.001
DS, %	56.1 (48.4-67.4)	62.9 (522.5-71.8)	52.0 (42.1-57.4)	<0.001
RD, mm*	3.12 (2.70-3.61)	3.05 (2.59-3.43)	3.23 (2.81-3.75)	<0.001
MLD, mm	1.31 (0.98-1.72)	1.10 (0.81-1.37)	1.60 (1.25-1.98)	<0.001
Length, mm	16.4 (11.4-22.5)	17.5 (11.9-23.3)	15.8 (10.8-20.9)	0.050
Total LV mass, g	107.0 (93.0-126.8)	109.3 (96.7-131.0)	103.7 (90.1-122.0)	<0.001
FMM, g	40.1 (26.7-53.7)	45.0 (30.2-58.0)	36.2 (23.1-46.8)	0.006

Values are n (%) or median (interquartile range). *Average of proximal and distal RD except in case of ostial stenoses.

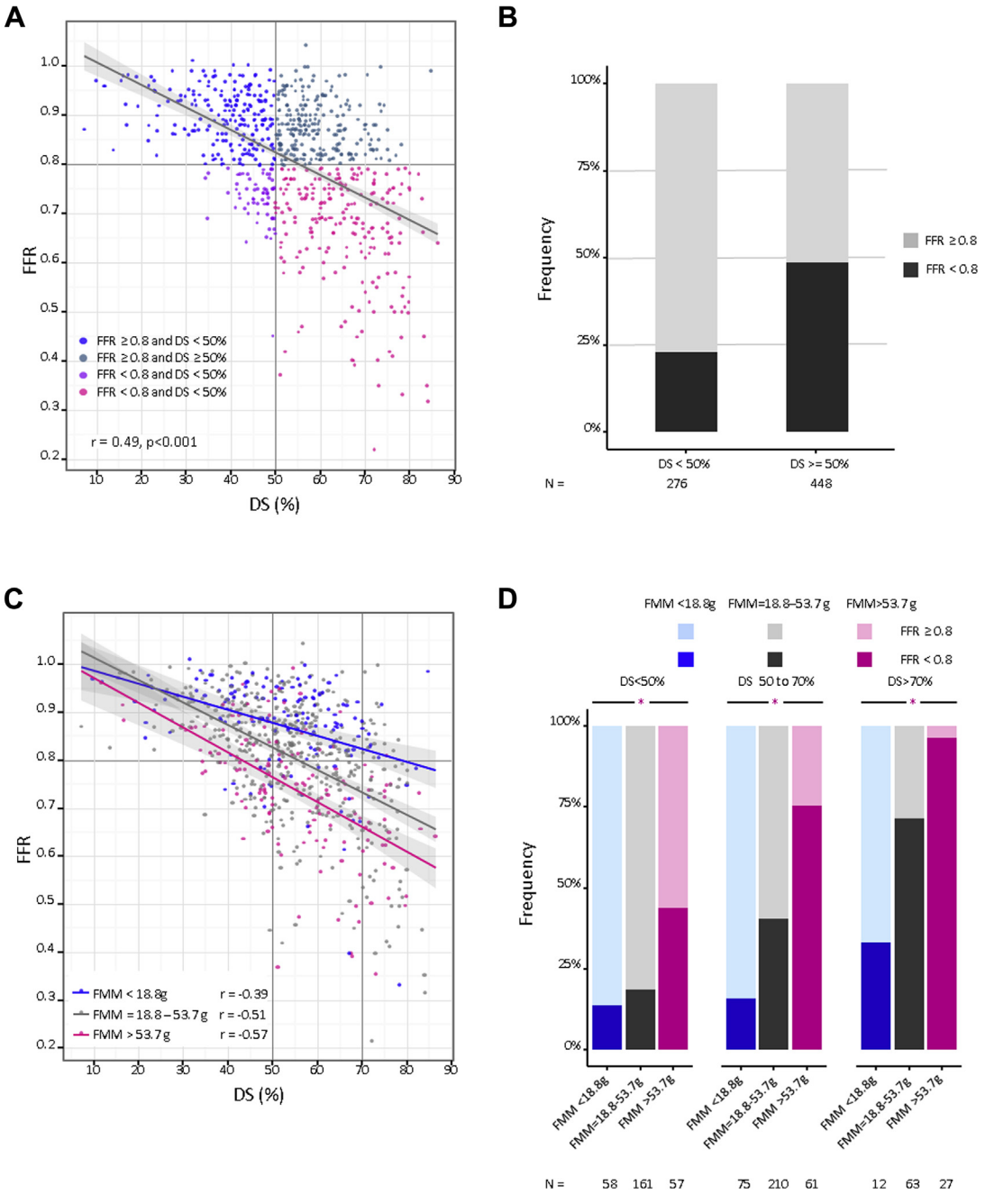
DS = diameter stenosis; FFR = fractional flow reserve; FMM = fractional myocardial mass; LV = left ventricular; QCA = quantitative coronary angiography; RD = reference diameter.

FIGURE 3 FMM in Major Coronary Artery and Its Branches



Per-vessel analysis. *p < 0.001 by Cochran-Armitage test for trend in LAD, LCX, and RCA. LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

FIGURE 4 Impact of FMM on the Relationship Between Anatomical and Functional Stenosis



All data are per-vessel analyses. *p < 0.01 by Cochrane-Armitage test for trend. **(A)** Plot of DS versus FFR showing true positive **(red dots)**, true negative **(blue dots)**, false positive **(green dots)**, false negative **(violet dots)**. **(B)** DS ≥ 50% showed moderate performance for predicting FFR <0.80. **(C)** Plot in **A** is reconstituted according to the <20, 20 to 80, and >80 percentiles of FMM. **(D)** The higher the FMM and/or DS, the higher the frequency of FFR <0.80. **(E)** Plot of FMM versus FFR reconstituted according to <50%, 50% to 70%, and >70% of DS. **(F)** The higher the FMM and/or DS, the higher the frequency of FFR <0.80. **(G)** Plot of FMM versus FFR reconstituted according to MLD tertile. **(H)** The higher the FMM and/or the lower MLD, the higher the frequency of FFR <0.80. **(I)** Plot of MLD versus FMM. Vessels with FFR <0.80 **(red dots)** showed higher FMM/MLD than vessels with FFR ≥0.80 **(blue dots)**. **(J)** Optimal cutoff of FMM/MLD (≥28.9 g/mm) showed better discrimination than DS. **(K)** FMM/MLD showed good correlation with FFR (r: −0.61). Notice shift of **green dots** to **left side**, which reflects decreased false positive and increased accuracy compared with **A**. DS = diameter stenosis; FFR = fractional flow reserve; FMM = fractional myocardial mass; MLD = minimal luminal diameter.

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FIGURE 4 Continued

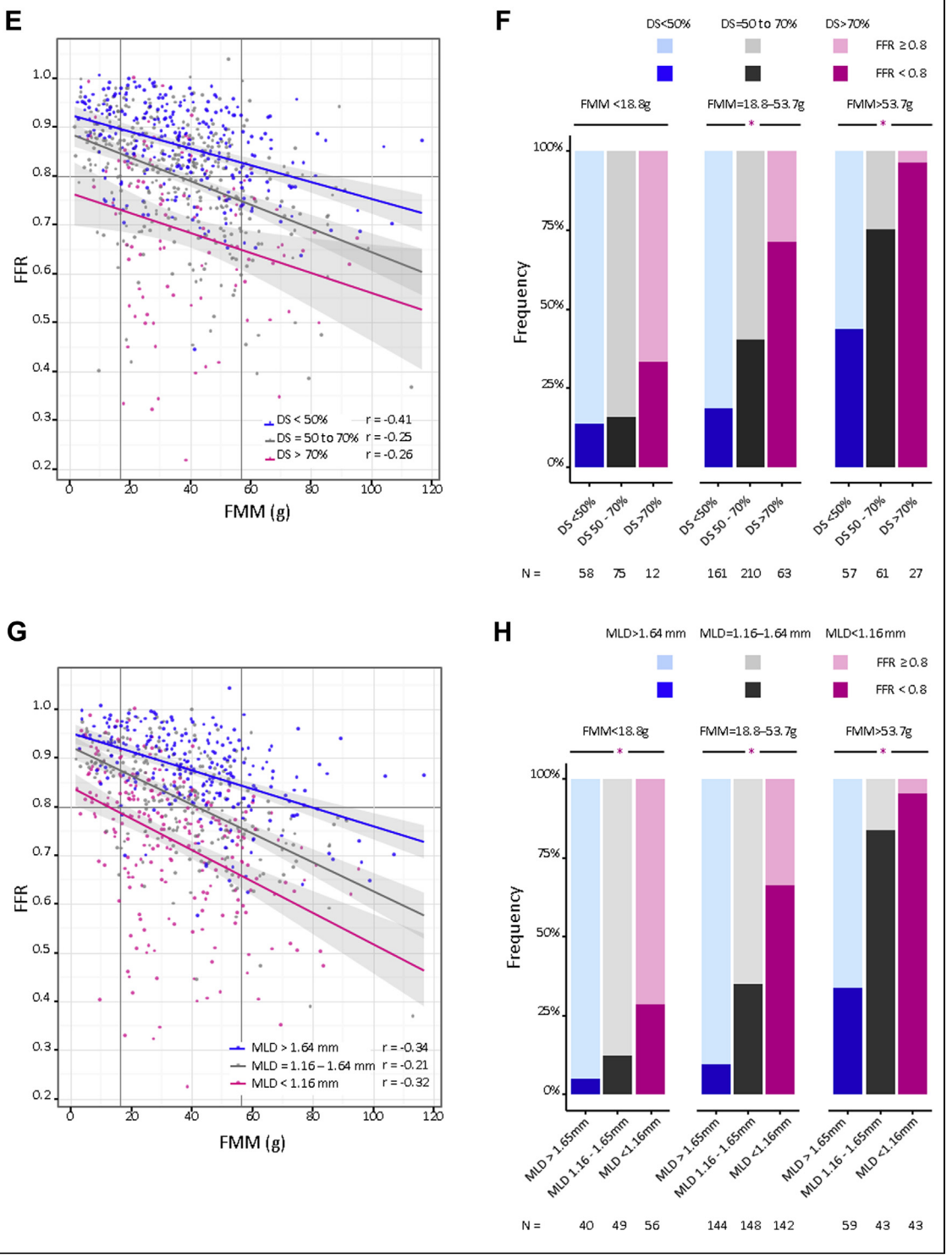

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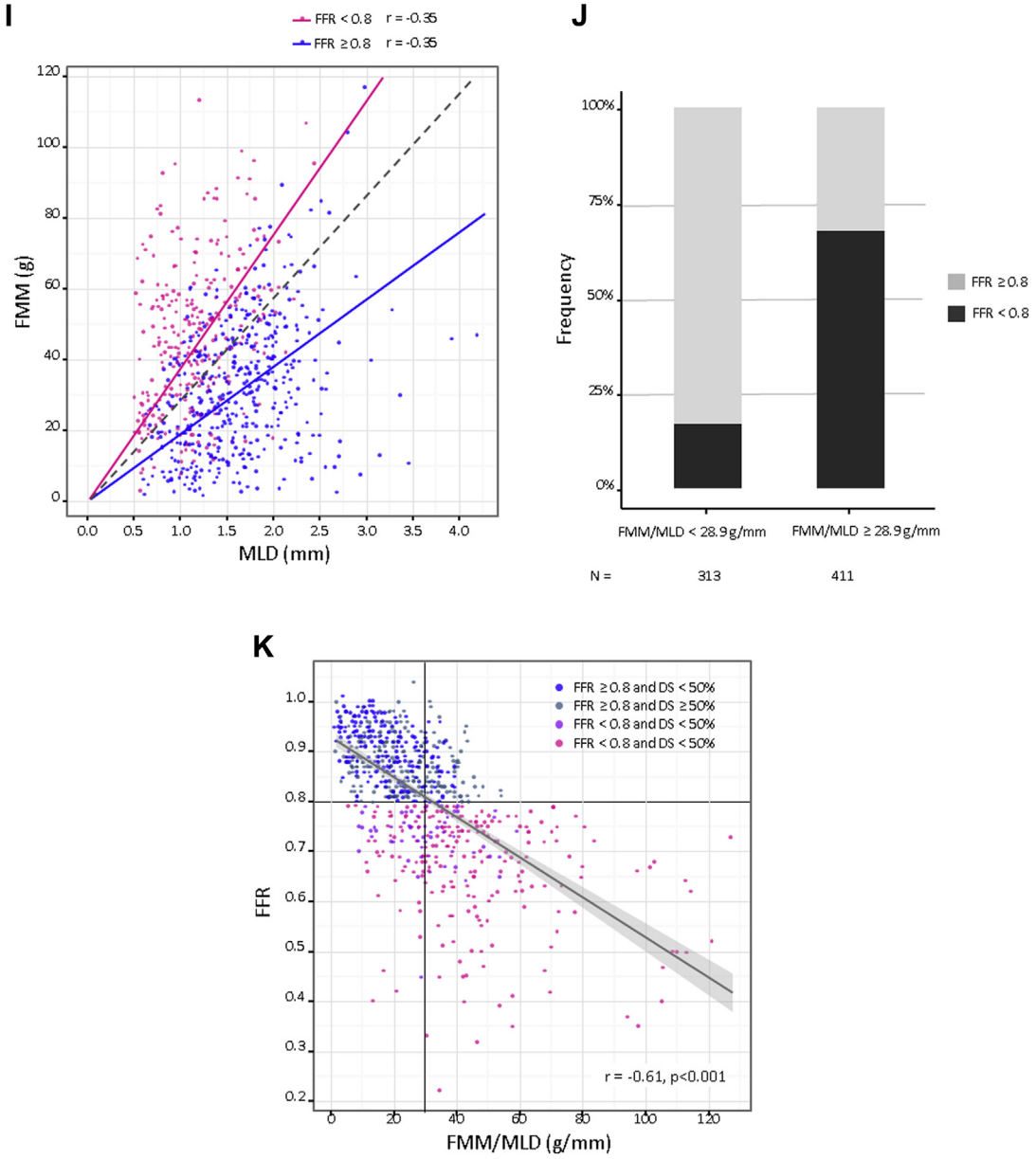
FIGURE 4 Continued

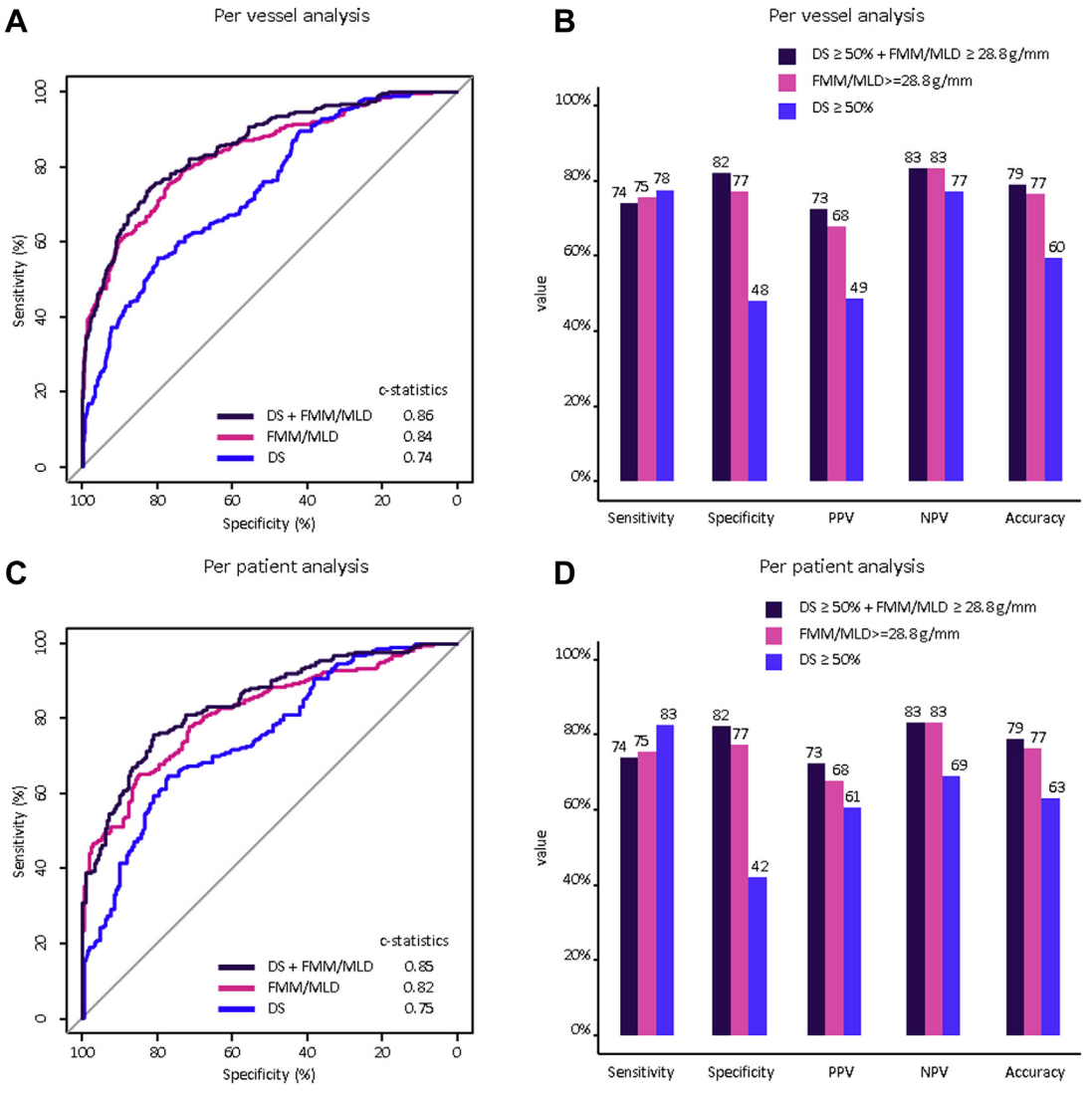


DISCUSSION

In this multicenter study, FMM/MLD discovered vessels with FFR <0.80 and vessels with FFR ≥0.80 better than anatomical stenosis. Also FMM/MLD additively improved the accuracy of DS. Results were consistent at the patient level as well as at the vessel level. Applying the concept of FMM to anatomical dimension could significantly reduce anatomical-physiological discordance. To our knowledge, this study is the first systematic demonstration with robust quantitative data that shows improved discriminative performance of anatomical stenosis for physiological severity using solely anatomical measurements.

FMM MAY BE A MISSING LINK IN ANATOMICAL-PHYSIOLOGICAL DISCORDANCE. The mechanism underlying anatomical-physiological discordance has been poorly understood. Angiographic or

FIGURE 5 Diagnostic Performance of FMM/MLD for FFR <0.80 Compared With Diameter Stenosis



$p < 0.05$ among C-statistics in both per-vessel and per-patient analyses.

physiological conditions including calcification, ruptured plaque, remodeling, diffuse disease, ostial or bifurcation disease, foreshortening or overlap of arterial segment, age-related myocyte loss or individual variation in vasodilator response has been proposed as the mechanism of discordance (1,12,13).

Based on the physiological principle that the myocardial mass to be perfused affects the physiological severity of stenosis. This intuitive model has been suggested by previously studies but without quantitatively robust data (14,15). In addition to anatomical stenosis, myocardial mass and microvascular resistance also contribute to physiological severity of stenosis represented by FFR (4). Therefore, addition of myocardial mass or microvascular resistance to anatomical stenosis may reduce the discordance between anatomical stenosis and physiological severity. We reasoned that vessel-specific myocardial mass can be calculated based on allometric scaling law, which governs relationships among structure and function in life science (6–8,10). Our result showed that FMM, a vessel-specific myocardial mass subtended by the artery, may be one of the major missing links needed to explain the anatomical-physiological discordance.

TABLE 3 Diagnostic Performance of FMM/MLD for FFR <0.80 Compared to Angiographic Stenosis

	DS	FMM/MLD	FMM/MLD + DS
Per-vessel analysis			
Sensitivity, %	78 (72–82)	75 (70–80)	74 (68–79)
Specificity, %	48 (43–53)	77 (73–81)	82 (78–86)
PPV, %	49 (44–53)	68 (62–73)	72 (67–78)
NPV, %	77 (72–82)	83 (79–87)	83 (79–87)
Accuracy, %	60 (56–63)	77 (73–80)	79 (76–82)
c-statistics	0.74 (0.70–0.78)	0.84 (0.81–0.87)*	0.86 (0.83–0.88)†
NRI (categorical)	–	0.025 (-0.004 to 0.054), p = 0.09	0.063 (0.035 to 0.092), p < 0.001
NRI (continuous)	–	0.626 (0.485 to 0.767), p < 0.001	0.339 (0.192 to 0.486), p < 0.001
IDI	–	0.178 (0.138 to 0.217), p < 0.001	0.031 (0.018 to 0.044), p < 0.001
Per-patient analysis			
Sensitivity, %	82 (77–87)	78 (72–83)	74 (68–79)
Specificity, %	42 (35–49)	72 (65–78)	82 (78–86)
PPV, %	61 (55–66)	75 (69–80)	72 (67–78)
NPV, %	69 (60–77)	75 (69–81)	83 (79–87)
Accuracy, %	63 (58–68)	75 (71–79)	79 (76–82)
c-statistics	0.75 (0.71–0.80)	0.82 (0.78–0.86)*	0.85 (0.81–0.88)†
NRI (categorical)	–	0.019 (-0.004 to 0.042), p = 0.10	0.038 (0.012 to 0.064), p = 0.004
NRI (continuous)	–	0.761 (0.588 to 0.934), p < 0.001	0.387 (0.203 to 0.570), p < 0.001
IDI	–	0.165 (0.130 to 0.200), p < 0.001	0.049 (0.029 to 0.069), p < 0.001

Sensitivity, specificity, PPV, NPV, and accuracy were calculated against fixed cut-off values; DS ≥50%, FMM/MLD ≥28.8 g/mm, predictive value of FMM/MLD + DS ≥0.39. *p < 0.001 between DS and FMM/MLD. †p < 0.001 between DS and FMM/MLD + DS, p = 0.001 between FMM/MLD and FMM/MLD + DS (p = 0.24 between DS and MLD).

IDI = integrated discrimination improvement; NPV = negative predictive value; NRI = net reclassification improvement; PPV = positive predictive value; other abbreviations as in Table 2.

CLINICAL IMPLICATIONS OF VESSEL-SPECIFIC MYOCARDIAL MASS ENABLED BY FMM. Scaling of size or function in cardiovascular structure is commonplace in pediatric cardiology. However such factors have been less appreciated in adult cardiology with coronary artery disease (7). In this study, vessels with FFR <0.80 could be better discriminated by scaling of myocardial burden against size of arterial lumen compared to anatomical stenosis. Such application in scaling of size or function may lead to better diagnostic and therapeutic decision making in cardiovascular medicine, including the following clinical issues.

Supply and demand (type 2) MI is a common clinical entity but is still poorly defined. The concept of FMM or FMM/MLD can be applied for adjudicating type 2 MI (16).

Despite many large clinical trial results, there are still a lot of debates about the appropriateness and optimal threshold of revascularization. FMM enables direct assessment of the amount of ischemic myocardium as well as myocardium to be revascularized, which has been estimated semi-quantitatively by angiographic scoring systems. As the FFR could reclassify the need of revascularization based on the presence of ischemia, FMM might reclassify the strategy of revascularization based on the amount of ischemic myocardium to be saved. (2,3,17–21).

FMM can explain why aggressive treatment of bifurcation side branch and chronic total occlusion has not translated into significant clinical benefit (22). The benefit of revascularization is known to be significant when ischemic burden is larger than 12% to 15% of myocardium (20,23). In this study, side branches interrogated by FFR represented clinically meaningful vessels but supplied approximately 11% of myocardium (**Figure 3**, Online Table 1). Therefore, FMM can explain low frequency of FFR <0.80 and limited benefit of aggressive side branch treatment (24,25). Most chronic total occlusion shows FFR <0.5, but supplies myocardium scarred from prior MI, which limits the benefit of revascularization (15,26).

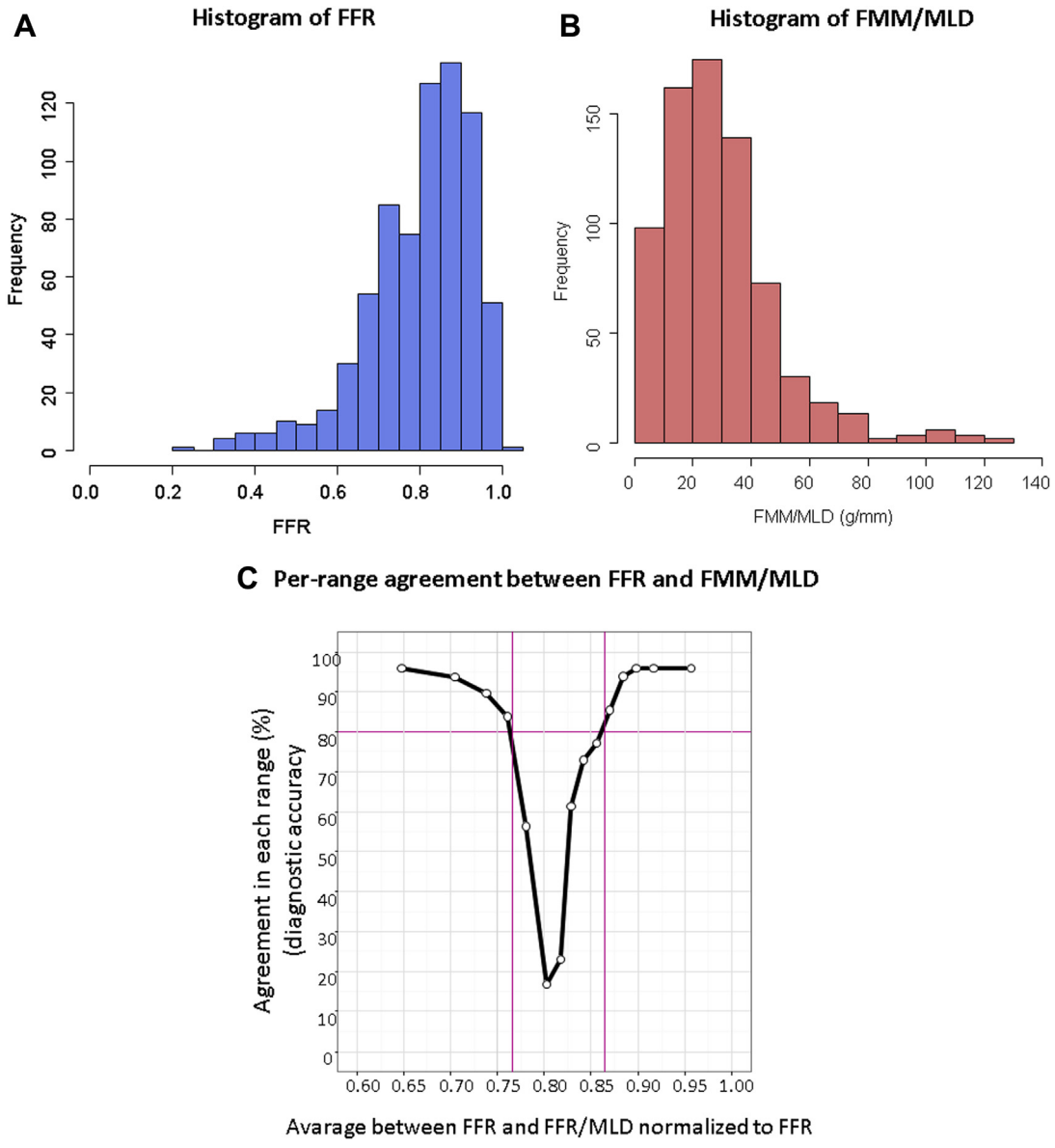
STUDY LIMITATIONS. FMM is an intuitive concept based on biophysics and experimental studies but is derived from a limited hierarchy of stem-and-crown models and assumes the arterial segment as a cylindrical tube without compliance and flow turbulence, which may be different in actual arteries. Also microvascular function, which is one of the key factors in coronary hemodynamics, was not covered but might be included by additional analysis of regional LV hypertrophy which is linked to be associated with impaired function of coronary resistance vessels (27).

Not every vessel was tested for FFR. Vessels without stenosis or extremely stenotic vessels were excluded because such vessels do not benefit from FFR for therapeutic decision, although inclusion of such vessels would increase further the accuracy of FMM/MLD.

The accuracy of FMM/MLD for FFR <0.8 was approximately 80% except near cutoff. In addition to the decreased reproducibility of FFR measurement in the functionally intermediate stenosis (28), biological factors which cannot be reflected in the lesion-specific anatomical assessments including the extent of maximal hyperemia, LV diastolic filling pressure, or presence of multiple or diffuse disease might affect the accuracy of FMM/MLD.

As a proof-of-concept study, the severity of stenosis was assessed by CAG. Current spatial resolution of CCTA is still limited for precise evaluation of stenosis. An advanced CT scanner with higher

FIGURE 6 Distribution and Per-Range Agreement Between FFR and FMM/MLD



(A,B) Distribution frequency of FFR and FMM/MLD. Abbreviations are as shown in Figure 4. **(C)** In this per-vessel analysis, FMM/MLD was normalized to FFR by correlation coefficients. The averages of FFR and normalized FMM/MLD were divided into 15 equal size groups delimited by 0.648, 0.705, 0.739, 0.762, 0.781, 0.802, 0.818, 0.829, 0.842, 0.857, 0.871, 0.885, 0.898, 0.917, and 0.957. Agreement or diagnostic accuracy falls lower than 80% in ranges between 0.781 and 0.857 **(purple lines)**.

spatial resolution and refined imaging software would be required for CCTA-based FMM/MLD that enables one-stop assessment of the severity of ischemia and amount of ischemic myocardium.

Finally, the prognostic implication of FMM or FMM/MLD was not investigated but is currently under investigation.

CONCLUSIONS

We established FMM, a vessel-specific myocardial mass subtended by coronary artery stenosis. Addition of FMM to MLD, an anatomical measurement improved the accuracy of anatomical measurement for physiological severity compared with anatomical

diameter stenosis alone. FMM may explain the discordance between anatomical stenosis and physiological severity.

ACKNOWLEDGEMENTS The authors thank Seon A. Jeong and So Hyeon Park for excellent and devotional contribution.

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PERSPECTIVES

WHAT IS KNOWN? Angiographic stenosis is a poor predictor of myocardial ischemia.

WHAT IS NEW? FMM, a concept of vessel-specific myocardial mass, explains the discordance between anatomical stenosis and physiological severity.

WHAT IS NEXT? FMM may reduce anatomical-physiological discordance and integrate it with the ischemic myocardial burden, which may lead to better comprehensive evaluation of coronary artery disease.

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KEY WORDS anatomical-physiological discordance, coronary artery physiology, fractional flow reserve, fractional myocardial mass

APPENDIX For a supplemental table, please see the online version of this article.