The Relationship of Capillary Blood Flow Assessments with Real Time Myocardial Perfusion Echocardiography to Invasively Derived Microvascular and Epicardial Assessments

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Background: The basis for abnormal microvascular flow responses to demand stress in coronary artery disease (CAD) is affected by resistance changes at both the epicardial stenosis level and within the downstream capillary network. We hypothesized that abnormal microvascular perfusion (MVP) responses during demand stress in patients with intermediate coronary stenoses occur when fractional flow reserve (FFR) across the epicardial stenosis is normal, because of increased microvascular resistance.

Methods: In 49 coronary arteries of 41 patients with intermediate stenoses (40%-80%) who were referred for both coronary angiography and demand stress MVP assessment, invasive coronary hemodynamics were obtained across the stenosis to measure FFR, coronary flow reserve (CFR), and hyperemic microvascular resistance (HMR) during adenosine infusion. MVP in each coronary artery territory (CAT) during demand stress was evaluated by an independent expert reviewer blinded to clinical and angiographic data.

Results: Thirty-four of the 49 CATs with intermediate stenoses exhibited abnormal MVP. Although the sensitivity of MVP was high for detecting abnormal FFR (100%), FFR < 0.8 was observed in only 15 of the 34 vessels that exhibited abnormal MVP (positive predictive value 44%). However, HMR was abnormal in 32 of 34 vessels (94%) with abnormal MVP (positive predictive value, 94%).

Conclusions: Although abnormal MVP has high sensitivity for detecting abnormal FFR, MVP is frequently abnormal when FFR is normal. In a large percentage of these patients, invasive assessments of microvascular resistance are abnormal. (J Am Soc Echocardiogr 2019;32:1095-101.)

Keywords: Contrast echocardiography, Microvascular resistance, Flow reserve

Over the last decade, there has been a paradigm shift in the approach to revascularization of patients with stable intermediate coronary artery disease (CAD). Contrary to the seminal COURAGE trial,[1] it has been shown that patients with intermediate epicardial stenosis (40%-80%) who have abnormal fractional flow reserve (FFR) and undergo revascularization have improved outcomes compared with optimal medical therapy alone.[2,3] As such, the strategy for revascularization of stable intermediate CAD focuses on vessels that supply an area with proven hemodynamically significant ischemia, which is reflected in the current American and European guidelines.[4,5] The burden of ischemia, however, is measured both noninvasively and invasively by heterogenous methods in clinical practice. With FFR assessments, the value largely reflects the resistance contributed by the epicardial lesion and assumes downstream resistance during hyperemia is minimal. However, microvascular dysfunction alone, in the absence of epicardial stenoses, has been shown to cause angina and to be associated with worse clinical outcomes.[6,7] Factors that predispose to CAD, such as hyperlipidemia, cigarette smoking, and diabetes, also predispose to microvascular dysfunction and have been shown to cause microvascular dysfunction early in the disease process.[8-10] FFR is a point-of-care tool that allows immediate stratification of intermediate lesions at the time of angiography. Theoretically, adenosine results in minimized microvascular resistance (MVR), allowing isolation of the epicardial stenosis and quantification of the ischemia resulting from each lesion. Minimal MVR is achieved and assumed using a continuous intravenous adenosine infusion. However, downstream MVR and flow have been shown to be variable with adenosine administration during the measurement of FFR.[11-14]

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Abbreviations

CAD = Coronary artery disease

CAT = Coronary artery territory

CFR = Coronary flow reserve

FFR = Fractional flow reserve

HMR = Hyperemic microvascular resistance

HSR = Hyperemic stenosis resistance

MVP = Microvascular perfusion

MVR = Microvascular resistance

PPV = Positive predictive value

QCA = Quantitative coronary angiography

RTMCE = Real-time myocardial contrast echocardiography

WM = Wall motion

Microvascular perfusion (MVP), analyzed with real-time myocardial contrast echocardiography (RTMCE), examines capillary blood volume and flow changes during hyperemic stress.[10,15,16] The contrast intensity observed during hyperemic stress reflects capillary resistance, in that increased resistance correlates with decreased myocardial contrast intensity. In the setting of an intermediate coronary stenosis, both capillary and epicardial stenosis resistance play a role in regulating coronary blood flow.[15] Therefore, the FFR across the stenosis may reflect only a portion of the overall resistance changes that occur during stress. While we have previously shown that abnormal capillary blood flow has a high sensitivity for detecting intermediate vessels with an FFR value < 0.8,[17] FFR values were normal in a large proportion of patients who exhibited abnormal MVP during demand stress testing. The mechanism for this discrepancy in humans has not been elucidated. We hypothesized in this study that MVR, which can be derived from epicardial measurements of downstream flow and pressure, will be abnormal despite normal FFR across stenoses of intermediate severity. Subsequently, we prospectively investigated, in patients with a clinical suspicion for CAD referred for both RTMCE and coronary angiography, whether invasive assessments of pressure and flow velocity could detect microvascular abnormalities in vessels with normal FFR.

METHODS

Study Population

The University of Nebraska Medical Center Institutional Review Board approved this prospective study (IRB493-15-FB), and informed consent was obtained for all subjects. Eighty-three patients with a suspicion for significant CAD based on symptoms, who subsequently had an RTMCE and were referred for coronary angiography, gave consent and were enrolled. Of these patients, only those with intermediate CAD defined by quantitative coronary angiography (QCA) of between 40% and 80% ($n = 41$ patients, 49 coronary arteries) underwent invasive coronary hemodynamic assessment with a Doppler tipped pressure and flow wire (Volcano ComboWire; Philips). Exclusion criteria included patients who were pregnant or breast feeding, had known hypersensitivities to contrast agents, presented with acute ST elevation myocardial infarction, had coronary bypass grafts subtending the coronary artery territory (CAT) of interest, or had acute renal dysfunction that precluded angiography. No patients with clinical evidence of heart failure were enrolled given the prolonged procedural time required for coronary hemodynamic assessment.

Quantitative Coronary Angiography

Coronary angiography was performed as per normal institutional protocol from the radial or femoral artery. Patients with an intermediate stenosis underwent blinded QCA analysis by an experienced interventional cardiologist who was unaware of the results of the RTMCE. Measurements were expressed as the percentage stenosis using the diameter of the nearest normal-appearing region as reference. An intermediate stenosis for the purposes of the study was defined as between 40% and 80%, to reflect the range of stenosis examined in FFR outcome studies.[1,3] Percent diameter stenosis and lesion length were determined with Philips software (Xcelera version).

Invasive Coronary Hemodynamics

Caffeine and all food products were held for 12 hours prior to the procedure. Intracoronary nitroglycerin (100 μg) was administered to minimize spasm after access to the left main or right coronary artery was obtained with coronary guide catheters.

Following angiography, the ComboWire was calibrated and equalized to aortic pressure, and identification of an adequate left main Doppler flow velocity signal was performed prior to the wire being advanced 10 mm distal to the stenosis being interrogated. Resting flow velocity, pressure, and Doppler signals were obtained. Then intravenous adenosine was administered (140 μg/kg/minute). At steady state hyperemia, pressure, flow velocity, and Doppler signals were all obtained. The hemodynamic data obtained were then independently reviewed at a later point to adjudicate measures of coronary flow reserve (CFR), FFR, hyperemic MVR (HMR), and hyperemic stenosis resistance (HSR) as described elsewhere.[18] FFR was defined as the ratio of mean distal to mean aortic pressure during maximal hyperemia, CFR as the ratio of hyperemic to baseline average peak flow velocity, and HMR as the mean distal coronary pressure to mean distal flow velocity ratio. HSR was defined as the ratio of the average stenosis pressure gradient to the average peak flow during hyperemia (normal <0.8 mm Hg/cm/sec). A normal CFR was defined as >2.0, and an abnormal HMR was defined as an absolute value of >1 mm Hg/cm/sec during hyperemic stress. Normal FFR was defined as >0.8.

Real-Time Myocardial Contrast Echocardiography

The contrast agent used for the study was the commercially available lipid-encapsulated ultrasound-enhancing agent Definity (Lantheus Medical Imaging, North Billerica, MA).

This agent was administered as a 3% intravenous continuous infusion at 4 to 6 mL/minute under resting conditions and stress, with the infusion beginning 1 minute before acquisition of stress images. RTMCE was performed using ultrasound scanners equipped with very low mechanical index real-time pulse sequence schemes.[19] This used a mechanical index of <0.2, frame rates of 20 Hz, time gain compensation higher in the near field, focus at the mitral valve plane or below, and overall gain setting adjusted so that brief high mechanical index impulses uniformly clear the myocardium segments of any signals.[19,20]

The decision to perform dobutamine or exercise treadmill test echocardiography was made by the referring physician based on the patient's ability to exercise. In either case, patients were instructed

HIGHLIGHTS

- Microvascular perfusion is frequently abnormal with normal fractional flow reserve.
- Abnormal measurements of microvascular resistance are frequently seen with normal FFR.
- Microvascular perfusion correlates better with hemodynamic microvascular resistance.

to discontinue beta blockers 24 hours before the stress test. Patients undergoing dobutamine stress echocardiography received intravenous dobutamine at a starting dose of 5 μg/kg per minute, followed by increasing doses of 10, 20, 30, 40, and up to a maximal dose of 50 μg/kg per minute, in 3-minute stages.

Atropine (up to 2.0 mg) was injected in patients not achieving 85% of the predicted maximal heart rate. Treadmill testing was performed with symptom-limited Bruce protocols with perfusion assessments obtained within 90 seconds of completion of the stress test.[21]

MVP Analysis with RTMCE

All RTMCE studies were analyzed by an independent experienced reviewer (F.X.) who was blinded to angiographic and invasive coronary hemodynamic data, as well as clinical history. Perfusion and wall motion were assessed using the 17-segment model with CAT assignments made based on current guidelines.[22] Both MVP and wall motion (WM) were analyzed simultaneously during the replenishment phase of contrast after brief high mechanical index impulses, as per current guidelines recommendations[19,20] at baseline and at peak exercise (defined as >85% of predicted maximal heart rate for age). An MVP abnormality during stress imaging was defined as a delay in subendocardial or transmural myocardial enhancement of >2 seconds after a high mechanical index impulse that was observed in at least two contiguous segments and that exhibited normal replenishment under resting conditions.

Statistical Analysis

All data were presented as mean +/- SD if normally distributed. If not normally distributed, the data were presented as median values with ranges. The binary analysis of blinded MVP assessment within a given abnormal CAT by RTMCE was compared with three invasively derived parameters (FFR, CFR, and HMR) in the vessel subtending that territory using contingency tables. A χ^2 statistic was used to compare proportional agreement of MVP with each invasive parameter. The positive predictive value (PPV), sensitivity, and specificity of MVP for the detection of abnormal FFR, CFR, and HMR were also analyzed. To determine inter- and intraobserver variability, 15 studies were read independently by a second expert reviewer (T.P.) to determine agreement on (1) study normal versus abnormal and (2) CAT assignment as normal versus abnormal. Intraobserver variability was determined in 15 separate studies where the primary reviewer reanalyzed a study over 3 months after the original interpretation, and again blinded to all clinical data and previous analyses. Statistical analysis was performed using SigmaPlot V13.0 (Systat Software, San Jose, CA) and an established statistical web site (http://www.physics.csbsju.edu/stats/).

Table 1 Patient characteristics/demographics

Parameter	*N* (%)
Age, years	63 ± 14
Female	17 (41)
Family history of CAD	19 (46)
Cigarette smoker	25 (61)
Hyperlipidemia	28 (68)
Diabetes	16 (39)
Hypertension	33 (80)
Left ventricular mass, g/m^2	82
Left ventricular hypertrophy	6 (15)
Previous percutaneous intervention	4 (10)
Ejection fraction, %	56 ± 8
Medications	
Beta blockers	25 (61)
Nitrates	7 (17)
Aspirin	36 (88)
WMSI rest	1.0 ± 0.2
WMSI stress	1.2 ± 0.2
RTMCE resting HR, per minute	72 ± 12
RTMCE stress HR, per minute	143 ± 15
RTMCE resting systolic/diastolic BP, mm HG	142 ± 27/78 ± 11
RTMCE stress systolic/diastolic BP, mm HG	159 ± 31/82 ± 12
Invasive resting HR, per minute	74 ± 12
Invasive hyperemic HR, per minute	69 ± 12
Invasive resting systolic/diastolic BP, mm HG	144 ± 26/83 ± 11
Invasive hyperemic resting systolic/diastolic BP, mm HG	129 ± 23/75 ± 11
Hemoglobin, g	13.5 ± 1.6

BP, Blood pressure; *HR*, heart rate. Data are all mean +/- SD.

RESULTS

A total of 49 vessels and corresponding CATs were evaluated. Patient characteristics are summarized in Table 1. All 41 patients achieved 85% of maximal HR via exercise (n = 25) or dobutamine (n = 16) demand stress testing. Thirty-four of the 49 CATs (69%) with intermediate stenoses at QCA had abnormal MVP during demand stress (25 subendocardial, nine transmural defects). Of these, 31 (91%) also had inducible WM abnormalities. In only one patient did we see a WM abnormality with normal MVP. In that case there was global hypokinesis in all three CATs despite normal MVP. In all other intermediate stenoses, MVP was observed alone or with a WM abnormality. Differences in FFR, CFR, HMR, and HSR in WM and MVP abnormal versus normal CATs are displayed in Table 2. In nine of the patients, we observed an MVP defect (six subendocardial, three transmural) in a CAT that had <40% diameter stenoses. Invasive hemodynamics were not analyzed in these vessels. Intraobserver agreement on MVP within CATs was 93%, and interobserver agreement was 89%.

Table 2 Invasive hemodynamic comparisons between WM and MVP normal versus abnormal segments

Parameter	WM abnormal, *n* = 31	WM normal, *n* = 18	MVP abnormal, *n* = 34	MVP normal, *n* = 15
% Diameter stenosis	60 ± 10	54 ± 20	58 ± 14	57 ± 17
FFR	0.81 ± 0.13*	0.89 ± 0.07	0.82 ± 0.12*	0.89 ± 0.06
CFR	2.1 ± 0.83*	2.5 ± 0.74	2.1 ± 0.84	2.5 ± 0.74
HMR	2.1 ± 1.11	2.0 ± 0.89	2.0 ± 1.04	2.2 ± 1.0
HSR	0.29 ± 0.25*	0.14 ± 0.11	0.27 ± 0.24	0.15 ± 0.11

*P < .05 compared with normal group.

Table 3 Comparisons of MVP assessments with invasive hemodynamics

Parameter	MVP abnormal, *n* = 34	MVP normal, *n* = 15	Agreement. % (PPV, sensitivity/ specificity)
FFR < 0.8 (abnormal)	15	0	
FFR > 0.8	19	15	61 (44, 100, 44)
CFR < 2 (abnormal)	21	3	
CFR > 2	13	12	67% (62, 88, 48)
HMR > 1 (abnormal)	32	12	
HMR < 1	2	3	
HSR > 0.8	2	0	71 (94*, 73, 67)
HSR < 0.8	32	15	4 (100, 6, 100)

*P = .001; χ^2 compared with CFR and FFR PPV.

QCA and Coronary Hemodynamic Assessment

Mean QCA-derived stenosis diameter in all vessels analyzed was 60% + 17%. Lesion length averaged 17 + 10 mm. Of the 49 vessels with an intermediate stenosis, 30 involved the left anterior descending artery, 10 were in the circumflex artery, and nine were in the right coronary artery. FFR values ranged from 0.36 to 0.99 with a mean of 0.83. Thirty-four of the 49 stenoses (69%) interrogated had an FFR > 0.8. Mean resting coronary velocity was 22 cm/sec (10-48 cm/sec), while peak velocities were 47 cm/sec (range, 14-98 cm/sec). Mean CFR value was 2.2 + 0.9 (range, 1.2-4.8). Mean HMR value was 1.9 + 0.9. Although HSR was higher in abnormal MVP segments (Table 2), it was elevated above normal (>0.8) in only two of the stenoses (Table 3). Assuming arteriolar resistance was minimal, this would indicate capillary resistance was the major regulator of coronary blood flow in these vessels during hyperemia.

MVP Correlation with Invasive Coronary/Microvascular Hemodynamics

All vessels with an abnormal FFR had abnormal MVP within their respective CAT during demand stress (sensitivity of MVP to detect abnormal FFR 100%; Table 3). Despite the high test sensitivity, FFR was <0.8 in only 15 of the 34 vessels (44%) that exhibited abnormal MVP during demand stress. The sensitivity of MVP for detecting abnormal CFR was also good (88%), but again MVP was frequently abnormal when CFR was normal, resulting in a low specificity (48%), and low PPV (62%). MVP had the closest agreement with HMR (71%) and the highest PPV (94%, $P = .001$ compared with both FFR and CFR). HMR was abnormal in 32 of the 34 vessels with abnormal MVP but was also abnormal in 12 of the 15 vessels with normal MVP. In the 34 vessels with intermediate stenoses and normal FFR, CFR was abnormal in 13 (10 with abnormal MVP) and HMR was abnormal in 31 (19 with abnormal MVP). Figures 1 and 2 (see Video 1; available at www.onlinejase.com) demonstrate examples of CATs with abnormal MVP during stress imaging that exhibited elevated HMR during invasive hemodynamic assessments despite normal FFR values (the patient in Figure 1 had both normal FFR and normal CFR).

DISCUSSION

We have previously demonstrated that patients with abnormal MVP during demand stress who subsequently are found to have 40%-80% stenoses at coronary angiography frequently have normal FFR values.[17] This is the first study to date to examine the relationship between other invasively derived parameters of coronary and MVR and MVP assessments obtained during demand stress. As has been demonstrated in animal models, an increase in invasively derived MVR was in close agreement with decreased MVP in vessels with both normal and abnormal FFR values.

Animal studies in which epicardial stenoses similar to those examined in this study were examined have demonstrated that capillary resistance is the major regulator of coronary blood flow.[15] While CFR <2 has been able to identify this better than FFR,[11] hyperemic MVR, by measuring the actual pressure required to increase flow velocity downstream from the stenosis when arteriolar resistance is minimal, more accurately measures this capillary resistance. HMR is measured exclusively during hyperemia and correlates directly to resistance (index of both flow and pressure) during this period, whereas CFR is potentially influenced by both the level of resting resistance and the variable response of the microvasculature to adenosine. Beyond 80% stenosis severity, the resistance across the stenosis became the dominant regulator of flow. Therefore, there appears to be a dynamic interplay between the epicardial stenosis and capillary perfusion bed during hyperemic stress, in which the capillaries play the significant role when the epicardial stenosis is moderate in severity. Others have demonstrated the dynamics of this interplay following percutaneous coronary intervention, where an immediate reduction in HMR is observed following the reduction in stenosis severity.[23] This was reflected in the agreement between MVP and HMR in this study and confirms that microvascular abnormalities frequently exist when FFR is still normal. Furthermore, since wall motion abnormalities frequently accompanied the MVP defects in our patients, it emphasizes that abnormal MVR is contributing to ischemia in a large proportion of these patients even when FFR is still normal.

Previous Comparisons of Microvascular Hemodynamics with FFR

Our study confirms previous human investigations that have detected abnormal MVP in a high percentage of patients with an FFR value >0.8.[17] This has also been observed in invasive hemodynamic comparisons. Sen *et al.*[13] demonstrated that stenosed vessels with intermediate ranges of FFR (0.6-0.9) exhibited increased MVR, indicating

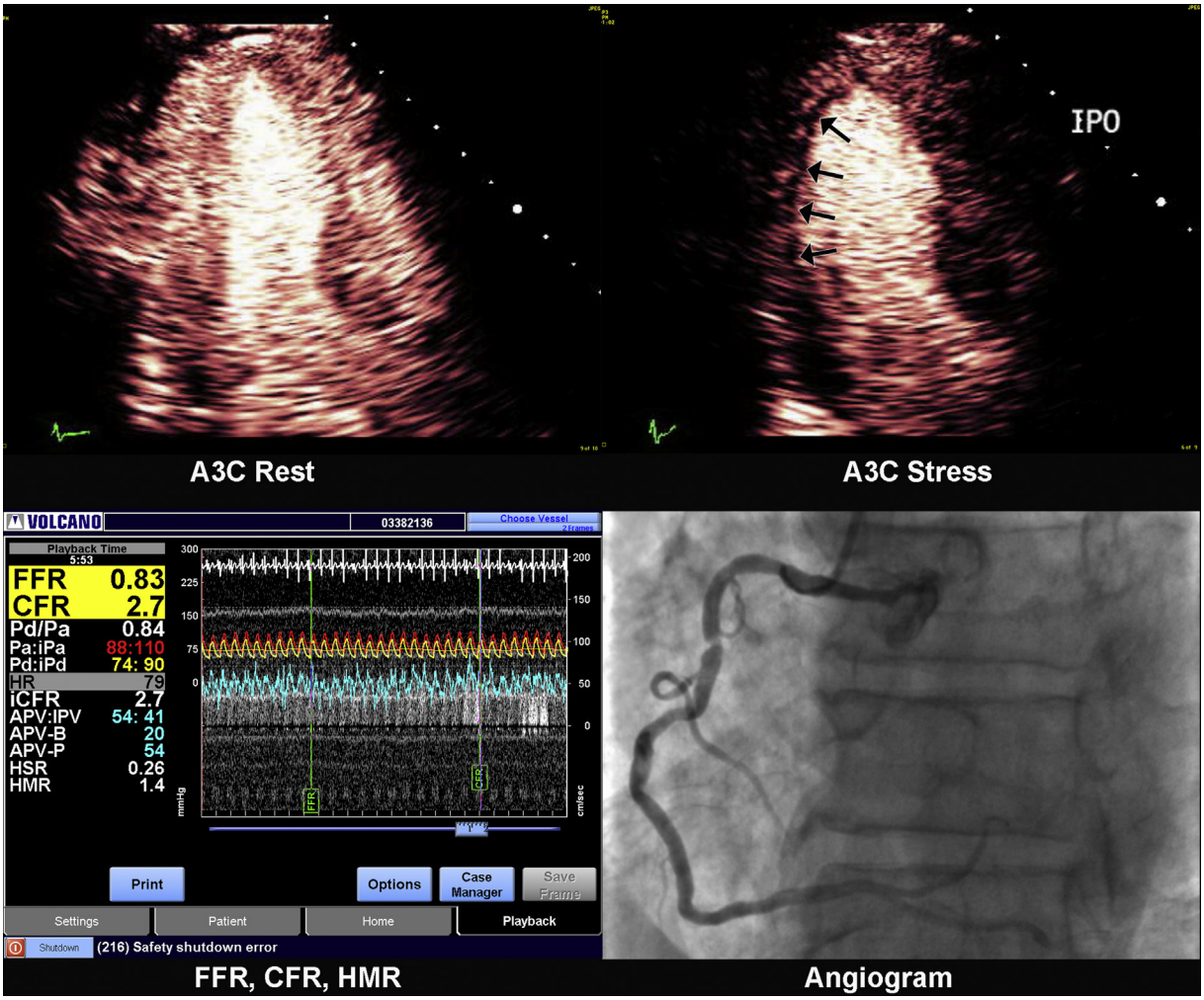

Figure 1 An MVP abnormality during dobutamine stress in the right CAT (*black arrows*). End-systolic images were obtained at 2 seconds following the high mechanical index impulse. Right coronary artery (RCA) stenosis severity by QCA was 61% *(white arrow)*. The subsequent FFR value in the RCA stenosis was 0.83, CFR was 2.7, but HMR was abnormal at 1.4. Wall thickening was abnormal in this CAT as well; see Video 1 (available at www.onlinejase.com). The RCA was a dominant vessel giving off the posterolateral branch (*arrowheads*) and thus was considered the vessel supplying this CAT (see Video 1; available at www.onlinejase.com). *A3C*, Apical three-chamber; *IPO*, immediate post-exercise.

a variable reduction in downstream resistance in response to adenosine. This variability was also seen in studies comparing FFR with CFR, where reductions in flow reserve were observed despite normal FFR values.[12] In our study, we found that HMR was actually elevated during adenosine infusion in nearly all patients with CAD. Although CFR detected these abnormalities in resistance better than FFR, we observed that over 40% of the vessels with CFR >2 still exhibited elevated MVR and reduced MVP (Table 2). Hence, abnormal MVR detected by noninvasive imaging or invasive hemodynamics is still observed when CFR is normal, indicating CFR may not be as sensitive of a marker as HMR and MVP for detecting microvascular dysfunction.

Previously published large randomized control trials using FFR have shown that it identifies patients at highest risk for events[1,3] as it clearly identifies lesions on the most severe spectrum of disease that appear to benefit from revascularization.

However, patients with a normal FFR value (>0.8) in these trials continued to have relatively high 12-month primary event rates (death, nonfatal myocardial infarction, and urgent revascularization) of 3%,[3] which is significantly higher than that of the 1% annual event rates seen with normal MVP during RTMCE in large clinical trials.[20,24] Detecting patients with elevated MVR despite normal FFR in this setting may identify a subgroup of patients who are more likely to have events despite normal FFR values. In preliminary studies, patients with normal FFR and abnormal MVP were more likely to have medically refractory symptoms or require revascularization because of refractory symptoms.[17] Further prospective clinical outcome trials are necessary to examine the potential benefit of revascularization, or more intensive medical therapy, in patients with microvascular disease demonstrated by MVP despite normal FFR.

Study Limitations

This was a single-center prospective study looking only at noninvasive and invasive parameters of coronary flow dynamics, so direct correlation to clinical outcomes cannot be made. Since these patients were referred for both stress MVP and angiography, the patients represent those with high pretest probability of physiologically relevant CAD,

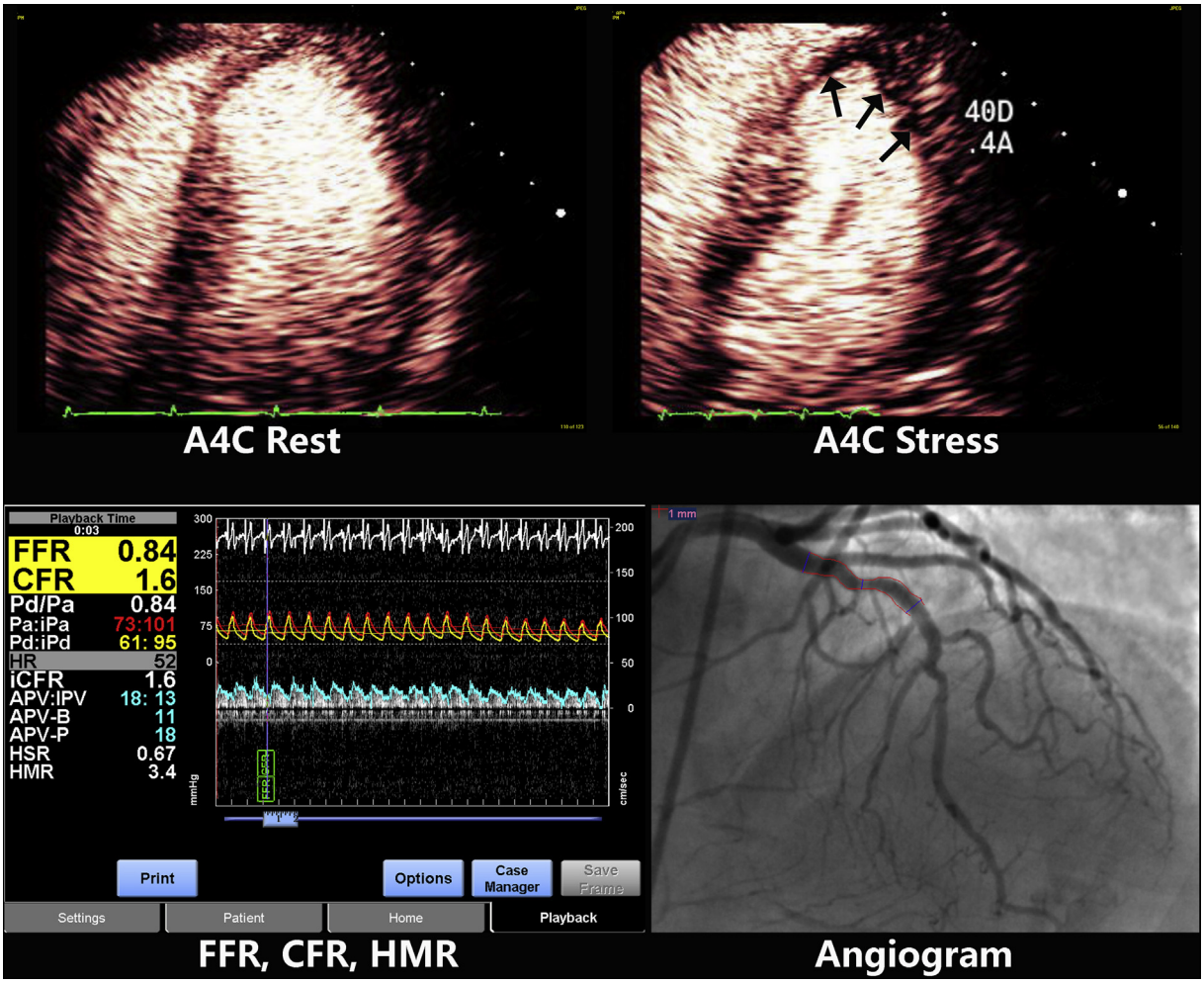

Figure 2 An MVP abnormality obtained at end systole during dobutamine stress in the left anterior descending (LAD) territory (delineated by *black arrows*). At subsequent coronary angiography, there was a 49% diameter stenosis in the LAD by QCA (*white arrow*) and FFR was 0.84. HMR, however, was elevated to 3.4. *A4C*, Apical four-chamber.

resulting in referral bias that may affect test specificity since the number of patients with normal MVR was low. The high pretest probability may also explain the high prevalence of abnormal HMR.

Abnormal MVP by expert visual analysis using RTMCE was seen in only 32 of the 44 vessels with HMR > 1.0. A quantitative evaluation of myocardial blood flow may have improved the agreement between techniques,[25] or techniques, which improve system dynamic range.[26]

The comparative data included were obtained from two different methods for achieving hyperemia, thus attempts to correlate flow and resistance by different stress methods are limited. Vasodilator and demand stress have different effects on red blood cell velocity and myocardial blood volume.[27] Nonetheless, most stress echo methods are demand stress, and intracoronary hemodynamic measurements are done with vasodilator stress, and thus our results compare to what is currently the standard of care.

CONCLUSION

Abnormal MVP during demand stress RTMCE correlates with invasive indices of MVR in vessels subtended by intermediate coronary stenoses. There was a high PPV for abnormal MVP to detect abnormal MVR despite a frequent discordance with FFR findings. Therefore, patients with intermediate epicardial stenoses and concomitant microvascular disease may be misclassified by FFR alone in terms of assessing the total burden of ischemia present in each individual myocardial territory supplied by the respective vessel. Further consideration of this requires that prospective outcome studies be performed to examine the effects of pharmacologic and interventional procedures in this patient subset.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2019.04.424.

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