Comparison of Fractional Flow Reserve Assessment With Demand Stress Myocardial Contrast Echocardiography in Angiographically Intermediate Coronary Stenoses

Juefei Wu, MD; David Barton, MD; Feng Xie, MD; Edward O’Leary, MD; John Steuter, MD; Gregory Pavlides, MD; Thomas R. Porter, MD

Background—Real-time myocardial contrast echocardiography (RTMCE) directly measures capillary flow (CBF), which in turn is a major regulator of coronary flow and resistance during demand or hyperemic stress. Although fractional flow reserve (FFR) was developed to assess the physiological relevance of an epicardial stenosis, it assumes maximal microvascular vasodilation and minimal resistance during vasodilator stress. Therefore, we sought to determine the relationship between CBF assessed with RTMCE during stress echocardiography and FFR in intermediate coronary lesions.

Methods and Results—Sixty-seven vessels with 50% to 80% diameter stenoses by quantitative coronary angiography in 58 consecutive patients were examined with FFR and RTMCE (mean age, 60±13 years). RTMCE was performed using an incremental dobutamine (n=32) or exercise (n=26) stress protocol, and myocardial perfusion was assessed using a continuous infusion of ultrasound contrast. The presence or absence of inducible perfusion defects and wall motion abnormalities were correlated with FFR. Mean percent diameter stenosis was 60±9%. Eighteen stenoses (27%) had an FFR ≤ 0.8. Although 17 of the 18 stenoses that were FFR+ had abnormal CBF during RTMCE, 28 of the 49 stenoses (57%) that were FFR had abnormal CBF, and 24 (49%) had abnormal wall motion in the corresponding coronary artery territory during stress echocardiography.

Conclusions—in a significant percentage of intermediate stenoses with normal FFR values, CBF during demand stress is reduced, resulting in myocardial ischemia. (Circ Cardiovasc Imaging. 2016;9:e004129. DOI: 10.1161/CIRCIMAGING.116.004129.)

Key Words: coronary artery disease ■ coronary angiography ■ dobutamine ■ myocardial ischemia ■ perfusion imaging

Maximal hyperemic coronary flow begins to decrease as stenosis severity exceeds 50% in diameter.¹ At this point, a coronary stenosis is considered functionally significant. Although one might assume that the regulation of hyperemic coronary flow in this setting is primarily controlled by stenosis, it is also regulated by microvascular and capillary resistance.²⁻³ Detection of functionally significant coronary artery disease (CAD) has become increasingly important, as large clinical trials have demonstrated outcome (death, nonfatal myocardial infarction, and need for urgent revascularization) is related to functional significance of a stenosis and not anatomic appearance.⁵⁻⁶ However, detecting functional significance requires a technique that can accurately examine and quantify the mediators of coronary flow during stress. Real-time myocardial contrast echocardiography (RTMCE) is a technique that utilizes ultrasound contrast for the simultaneous analysis of myocardial perfusion and wall motion (WM) during stress echocardiography.⁷⁻⁸ This perfusion technique measures capillary blood flow (CBF) and volume, and thus can indirectly assess capillary microvascular resistance.²⁻³ Previous studies have shown that the detection of CBF abnormalities identified with RTMCE during stress echocardiography improve the ability of echocardiography to predict patient outcome during both demand and vasodilator stress.⁹⁻¹⁰

See Editorial by Kern and Seto
See Clinical Perspective

Intracoronary pressure–derived fractional flow reserve (FFR) provides physiologically relevant information in determining the functional significance of a coronary stenosis, but provides no data regarding CBF.⁵⁻¹¹⁻¹² An FFR-guided approach for revascularization is associated with improved clinical outcomes in multivessel CAD,⁶ and abnormal values with this technique clearly identify a higher risk subgroup of patients. Although they do not seem to benefit from

Received January 26, 2016; accepted June 23, 2016.
From the Department of Cardiology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China (J.W.); Department of Cardiology, Internal Medicine, University of Nebraska Medical Center, Omaha (D.B., F.X., E.O’L., G.P., T.R.P.); and Nebraska Heart, Lincoln (J.S.).
Correspondence to Thomas R. Porter, MD, Division of Cardiology, 982265 Nebraska Medical Center, Omaha, NE 68198. E-mail tporter@unmc.edu
© 2016 American Heart Association, Inc.

Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org
DOI: 10.1161/CIRCIMAGING.116.004129

Downloaded from http://circimaging.ahajournals.org/ by NARESH KUMAR on September 13, 2016
percutaneous coronary interventions, patients with normal values for FFR (>0.8) in these studies still had relatively high event rates, with death and nonfatal myocardial infarction rates of ≈2% at ≤1-year follow up and 4% requiring revascularization. These event rates are worse than those observed after negative RTMCE stress studies.9,10 With noncritical coronary stenoses during hyperemic stress, capillary resistance has been shown to play a greater role than stenosis resistance in regulating coronary blood flow.2 Because RTMCE can visualize abnormalities in capillary resistance as perfusion defects during hyperemic stress,3 we hypothesized that these perfusion abnormalities may be observed in patients during stress imaging despite having FFR values that would still be considered normal. The purpose of this project was to determine the frequency with which FFR and demand stress measurements of myocardial blood flow and function are discrepant in a selected group of patients with intermediate coronary stenoses at quantitative coronary angiography (QCA).

Methods

Study Population
The University of Nebraska Medical Center Institutional Review Board approved this retrospective study (IRB493-15-FB) and informed consent was waived. Fifty-eight consecutive patients who underwent both stress RTMCE and coronary angiography with FFR measurement within 1 month at the University of Nebraska Medical Center from Jan 2007 to June 2015 were analyzed. All patients were referred first for an exercise or dobutamine stress RTMCE for suspicion of significant CAD based on the patient’s symptoms. The decision to proceed to angiography was based on both symptoms and the results of the RTMCE study. Subsequent angiograms all had to have one 50% to 80% stenosis in a major epicardial artery as determined by QCA. Exclusion criteria included those with known hypersensitivity to contrast agents, pregnancy or breast feeding, or inadequate apical windows to analyze myocardial perfusion in 2 contiguous segments of the selected coronary artery territory. We reviewed all clinically available records to ensure that patients with prior myocardial infarction based on cardiac biomarker criteria were excluded and excluded any coronary artery territory that had a resting WM abnormality detected during the resting contrast infusion.

Quantitative Coronary Angiography and FFR
Coronary angiography was performed as per standard practice via either femoral or radial approach. The pressure wire (Pressure Wire 5; Radi Medical Systems, Uppsala, Sweden) was calibrated and electronically equalized with the aortic pressure before being placed in the distal third of the coronary artery being interrogated. Intracoronary ni troglycerin (100 μg) was injected before adenosine infusion to prevent vasospasm. Intravenous adenosine was administered (140 μg/kg per minute) through an intravenous line in the antecubital fossa. At steady-state hyperemia, FFR was recorded on the RadiAnalyzer Xpress (Radi Medical Systems), calculated by dividing the mean coronary pressure measured with the pressure sensor placed distal to the stenosis by the mean aortic pressure measured through the guide catheter. This procedure was repeated for all major epicardial arteries with ≥50% stenoses. An FFR value of ≤0.8 was chosen as the cut off for abnormal based on previous multicenter studies.9 Caffeine and all food products were held in patients for 12 hours before FFR measurements.

Quantitative Coronary Angiography
Quantitative coronary analysis was performed by an experienced interventional cardiologist (E.O. or D.B.) unaware of the results of the stress echocardiogram. Any visually evident stenosis was measured using a handheld electronic caliper (Tesa SA, Renes, Switzerland) operated with custom-developed software. Measurements were expressed as the percentage diameter narrowing using the diameter of the nearest normal-appearing region as the reference. An intermediate coronary stenosis for this study was defined as ≥50% to 80% luminal diameter stenosis in one major coronary artery or one of its major epicardial branches, which were the majority of stenoses studied by FAME II investigators.6

Imaging Techniques With Ultrasound Contrast
The contrast agent used for the study was the commercially available lipid-encapsulated microbubble, Definity (Lantheus Medical Imaging, North Billerica, MA). This agent was administered as a 3% intravenous continuous infusion at 4 to 6 mL/min under resting conditions and during stress, with the infusion beginning 1 minute before acquisition of stress images. RTMCE was performed using ultrasound scanners equipped with low mechanical index real-time pulse sequence schemes.5–11 This utilized a mechanical index of ≤0.2, frame rates of 20 to 25 Hz, time gain compensation higher in the near field, focus at the mitral valve plane or below, and overall gain settings adjusted so that brief high mechanical index impulses uniformly clear the myocardial segments of any signals.

The decision to perform dobutamine or exercise treadmill stress echocardiography was made by the referring physician based on patient’s ability to exercise. In either case, patients were instructed to discontinue β-blocker drugs 24 hours before the stress test. Patients undergoing treadmill stress underwent maximal symptom-limited exercise according to the Bruce protocol. 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, up to a maximal dose of 50 μg/kg per minute, in 3- to 5-minute stages. Atropine (up to 2.0 mg) was injected in patients not achieving 85% of the predicted maximal heart rate. Only coronary artery territories with inducible defects but normal resting WM and CBF were used for comparisons with FFR measurements.

CBF Analysis With RTMCE
All RTMCE studies were analyzed by independent experienced reviewers (T.R.P. or F.X.) who were blinded to angiographic and FFR data. These experienced reviewers have interpreted over 1000 RTMCE studies. Perfusion and WM were both assessed using a 17-segment model with coronary artery territory assignments based on the same consensus model.11 Both CBF and WM were analyzed simultaneously during the replenishment phase of contrast after brief high mechanical index impulses, as previously described,9,10 at baseline and at peak stress (defined as >85% of predicted maximum heart rate). A CBF abnormality during stress imaging was defined as a delay in subendocardial or transmural myocardial contrast replenishment of >2 seconds after a high mechanical index impulse that was in 2 contiguous segments, and which exhibited normal replenishment under resting conditions.

Statistical Analysis
All values for FFR and stenosis severity are presented as means±SD. No adjustments were made for multiple vessels within individuals in the per-vessel analysis. Sensitivity and specificity of CBF analysis with RTMCE were analyzed for detecting stenoses with FFR values of ≤0.8. Differences in stenosis severity between vessels with abnormal versus normal FFR values were compared with unpaired t testing. Contingency tables were constructed to determine if the proportion of times an abnormal FFR study was associated with an abnormal RTMCE study was significantly different than the proportion of times a normal FFR study was associated with a normal RTMCE study. A Fisher exact test was used for this comparison. In all comparisons, a P<0.05 was considered significant.

Results
A total of 67 vessels in 58 patients with 1 stenosis defined by quantitative angiography to be 50% to 80% diameter were
Wu et al  Comparing Stress Perfusion Imaging With FFR

evaluated (mean age, 60±13 years; 22 women). Patient characteristics are summarized in Table 1.

Real-Time Myocardial Contrast Echocardiography

Of the 67 vessels with 50% to 80% diameter stenoses, 45 (67%) exhibited abnormal CBF in the subtended coronary artery territory with RTMCE. CBF abnormalities in multiple coronary artery territories were evident in 2 patients (Table 2). Thirty-six of the 45 coronary artery territories with inducible perfusion defects (80%) also had inducible WM abnormalities (ischemia). Thirty-one territories involved the left descending artery, 9 involved left circumflex artery territories, and 5 involved the right coronary artery. Mean QCA-derived stenosis severity in the territories that were abnormal with RTMCE was 60±9%, whereas it was 59±9% in the territories that were negative with RTMCE (P=0.82).

Fractional Flow Reserve and Quantitative Angiography

FFR readings ranged from 0.55 to 1.00 (mean, 0.86±0.11). A total of 18 vessels (27%) had FFR values ≤0.8, 15 in the left anterior descending coronary artery, and 3 in the right coronary artery territories. Figure 1 demonstrates how percent diameter stenosis severity by quantitative angiography correlated with FFR results. Mean QCA stenosis severity in the territories that were positive with FFR was 63±10% and 58±8% in the territories that were negative with FFR, respectively (P=0.029).

RTMCE Versus FFR

Seventeen of the 18 vessels (93%) with abnormal FFR values had abnormal CBF (Table 3). However, in 28 vessels (57%), FFR was considered normal despite the presence of an induced perfusion defect in the territory (examples are shown in Figures 2 and 3 for the right coronary and left anterior descending territories, respectively). Inducible WM abnormalities (ischemia) were observed in 24 of these 28 territories. The FFR values in the vessels with abnormal perfusion but normal WM (0.85±0.10) were not different from those with both abnormal perfusion and WM (0.84±0.12; P=0.71). In the FFR vessels that had values ≤0.80, there were no differences in FFR values for those with normal RTMCE studies versus abnormal RTMCE studies (Figure 4). There was a significant difference in the proportion of times an abnormal FFR study was associated with an abnormal RTMCE study and the proportion of times a normal FFR study was associated with a normal RTMCE study (P=0.003, Fisher exact test).

Follow-up was possible in 26 of the 27 patients (total of 28 vessels) who had abnormal CBF with RTMCE but had negative FFR values at the time of the corresponding angiogram. Median duration of follow-up was 2 months (range, 1–16 months). One patient could not be reached by phone and medical records were unavailable. Sixteen patients (59%) still had Canadian Cardiovascular Functional Class II–III symptoms or had revascularization of the coronary artery because of compelling symptoms. Ten patients remained asymptomatic on medical therapy.

Discussion

This is the first study to examine the relationship between CBF assessments during demand stress in myocardial territories supplied by coronary arteries with exclusively intermediate

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Family Hx of CAD</td>
</tr>
<tr>
<td>Smoker</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>HTN</td>
</tr>
<tr>
<td>Previous PTCA</td>
</tr>
<tr>
<td>Ejection fraction</td>
</tr>
</tbody>
</table>

Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total Patients (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blockers</td>
<td>40 (69%)</td>
</tr>
<tr>
<td>ACE inhibitors or ARB</td>
<td>31 (53%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>47 (81%)</td>
</tr>
<tr>
<td>Statin</td>
<td>40 (69%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>10 (17%)</td>
</tr>
</tbody>
</table>

**Stress echo data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total Patients (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak heart rate, bpm</td>
<td>142±16</td>
</tr>
<tr>
<td>Peak systolic blood pressure, mmHg</td>
<td>156±36</td>
</tr>
<tr>
<td>Peak rate pressure product</td>
<td>22219±6116</td>
</tr>
</tbody>
</table>

**Angiographic data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total Patients (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients Single-vessel stenoses</td>
<td>50</td>
</tr>
<tr>
<td>No. of patients two-vessel stenoses</td>
<td>7</td>
</tr>
<tr>
<td>No. of patients three-vessel stenoses</td>
<td>1</td>
</tr>
</tbody>
</table>

*Values presented are mean and percentages for continuous variables, and n (%) for categorical variables.
ACE indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; CAD, coronary artery disease; HTN, hypertension; and PTCA, percutaneous transluminal coronary angioplasty.

<table>
<thead>
<tr>
<th>Table 2. RTMCE and FFR Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTMCE Test Results</td>
</tr>
<tr>
<td>Total patients (territories)</td>
</tr>
<tr>
<td>Abnormal territory result</td>
</tr>
<tr>
<td>Normal territory result</td>
</tr>
<tr>
<td>Location of I Abnormal Territories</td>
</tr>
<tr>
<td>LAD</td>
</tr>
<tr>
<td>RCA</td>
</tr>
<tr>
<td>LCX</td>
</tr>
<tr>
<td>FFR results</td>
</tr>
<tr>
<td>Total patients (vessels)</td>
</tr>
<tr>
<td>FFR &gt; 0.8 (vessels)</td>
</tr>
<tr>
<td>FFR ≤0.8 (vessels)</td>
</tr>
</tbody>
</table>

FFR indicates fractional flow reserve; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; and RTMCE, real-time myocardial contrast echocardiography.
sténoses (50%–80% by quantitative angiography) and a range of both normal and abnormal FFR values. It confirms that abnormal CBF during demand stress RTMCE not only has high sensitivity for detecting a significant pressure gradient across a coronary stenosis but also demonstrates that abnormal CBF and WM occur in a sizable percentage of cases where FFR of the supplying vessel is considered normal.

Previous studies have demonstrated the incremental diagnostic value of myocardial perfusion imaging over WM analysis during stress in both the detection of angiographic disease by angiography and in predicting patient outcome.9,10 These clinical studies have validated animal studies which demonstrated that CBF changes become visually evident with myocardial contrast echocardiography earlier in the stress test than WM.12 During stress imaging, CBF, as measured by RTMCE, is a major regulator of coronary flow in the upstream circuit, which includes epicardial vessels, prearterioles and arterioles. Although intuitively one would think that epicardial stenosis is the primary location of coronary blood flow regulation during stress, it has actually been shown to be more related to the microvascular resistance at the capillary level when an intermediate stenosis is present.2–4 Sen et al13 demonstrated that in ranges of intermediate FFR values (0.6–0.9), microvascular resistance was more variable when compared with Instantaneous Wave-Free Ratio suggesting a variable response to adenosine by the arterioles or an inability to achieve true hyperemia in this setting. This variability has also been observed in studies comparing FFR to coronary flow reserve, where reductions in flow reserve occurred in instances where FFR values were normal.4,16 In these studies, low coronary flow with increased microvascular resistance was observed in vessels that had discordantly high or normal FFR values. Abnormalities in coronary blood flow reserve measured with transthoracic Doppler have been observed in patients with intermediate stenoses (5±65%) who had FFR values >0.8.17 On the contrary, quantitative measurements of coronary blood flow reserve in patients have correlated closely with CBF changes, both in the presence or absence of intermediate epicardial stenoses.18 Therefore, we hypothesize that in some instances where microvascular resistance is not minimized, or potentially increased, that FFR measurements may be falsely negative in patients with clinically relevant demand ischemia. This suggests that the distal pressure measured with FFR is influenced not only by the gradient across the epicardial stenosis but also by the resistance of the downstream vessels. Only with more severe forms of epicardial stenoses does FFR become less variable likely because of a more uniform resistance within the microvasculature.2,16 In our study, we did note that stenosis severity was worse in those with abnormal FFR values (Figure 1).

This may explain why an abnormal FFR value has been shown to identify patients at highest risk for events,6,11,12 as it clearly identifies the most severe spectrum of obstructive lesions from a functional standpoint. However, a normal FFR value, when defined as >0.8, may underestimate the physiological and clinical relevance of anatomically less severe stenoses. As our study showed, there was even inducible ischemia (ie, WM abnormality) in the coronary artery territories subtended by vessels that had FFR values >0.8 and a 50% to 80% diameter stenosis by quantitative angiography. This failure of FFR to identify certain physiologically relevant intermediate coronary stenoses may explain the differences in clinical outcome observed in trials utilizing FFR to guide CAD management versus those utilizing RTMCE. The large multicenter studies examining FFR as a guide to management in patients with stable angina still had annual event rates of 3% in their normal registries,6 which are significantly higher than the 1% annual event rates in similar patients after normal stress RTMCE studies.9,10

**Correlation With Other Comparative Studies**

When examining noninvasive correlations with FFR, magnetic resonance imaging (MRI) utilizing first-pass bolus injections of gadolinium contrast have demonstrated excellent sensitivities and specificities for detecting vessels with FFR values < 0.75.19 However, these studies included > over 40% of patients without angiographic CAD, as well as patients having coronary vessels in which there was a subtotal or total occlusion. Other adenosine magnetic resonance studies examining correlations of myocardial perfusion reserve with FFR exclusively in vessels that were >50% stenosed have demonstrated similar findings to the current study (93% sensitivity, 57% specificity in the study by Costa et al20). Chiribiri et al21 did improve specificity for detection

---

**Table 3. Concordance Between RTMCE and FFR in Vessels With Coronary Stenoses Between 50% to 80% Diameter by Quantitative Angiography**

<table>
<thead>
<tr>
<th></th>
<th>FFR+</th>
<th>FFR–</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTMCE+</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>RTMCE–</td>
<td>1</td>
<td>21</td>
</tr>
</tbody>
</table>

FFR indicates fractional flow reserve and RTMCE, real-time myocardial contrast echocardiography.
of abnormal FFR during adenosine MRI by examining for a visually evident transmural perfusion gradient, but this also included vessels with high grade stenoses or total occlusions. Despite adding these severely stenosed vessels, the positive predictive value of a visually evident subendocardial perfusion defect was still <80%. It is also important to emphasize that perfusion defects observed with RTMCE during demand stress reflect myocardial blood flow changes, whereas those seen with vasodilator stress MRI or Technesium-based radionuclide imaging reflect myocardial blood volume changes. Myocardial blood flow reductions are observed before myocardial blood volume changes in significant CAD, and this difference in sensitivity may explain why FFR correlates slightly better with vasodilator stress MRI or Technesium-based vasodilator stress perfusion techniques.

Study Limitations
Our results represent a single-center retrospective study involving 58 patients having RTMCE before the catheterization procedure. If we treat the summary statistics in Figure 3 as population parameters for designing a new prospective study which starts with the basic conclusions from the current study, then a power calculation for the sample size of the current study using a 1-sided exact Fisher exact test would be over 0.90. However, with retrospective studies, selection bias may affect results, and therefore prospective studies are needed to test both the correlation of CBF with FFR in intermediate stenoses, and what impact an abnormal CBF finding during demand stress with normal FFR has on patient outcome.

The time period over which these studies were performed was long because of the slow increase in the use of FFR to examine intermediate stenosis at our institution. During this time period the use of FFR was primarily in those with no prior stress echocardiography data before their diagnostic angiogram. However, the purpose of the study was to determine the frequency with which an abnormal demand CBF study correlates with FFR measurements of physiological relevance in vessels with a 50% to 80% diameter stenosis, not to publish data on overall sensitivity and specificity of RTMCE in this setting. In this context, it is important to note that FFR was only measured in vessels which had an intermediate range of stenosis severity. Other studies comparing FFR with angiographic measurements have found that FFR correlates better with angiographic measurements of intermediate stenosis than with those from severe stenoses.
with perfusion imaging techniques have included vessels with minimal or no disease in the vascular territory, as vessels with more severe stenoses including coronary occlusions. This would naturally improve the agreement between techniques, but would not help us understand whether important clinically relevant disagreement exists in the evaluation of an intermediate stenosis.

Our study was performed to simulate real-world practice, where FFR is currently being utilized to evaluate and guide management in intermediate level stenoses. However, we did have a higher prevalence of diabetics and smokers when compared with other clinical trials, and these risk factors may increase the likelihood of stress-induced microvascular abnormalities. It is in this setting where equipoise is needed to consider the potential role of capillary contributions to coronary blood flow abnormalities when FFR is found to be >0.8.

Finally, although patients were held without food or water for 12 hours before the procedure, no specific policies were in place to restrict caffeine use for 24 hours before FFR measurements. It is possible that this led to higher FFR values.

Conclusions
Our findings confirm that abnormal CBF with RTMCE has high sensitivity for detecting an abnormal FFR of an intermediate stenosed vessel subtending the abnormal myocardial territory. A normal FFR value, however, has a low sensitivity in predicting normal CBF by RTMCE. This might reflect microvascular abnormalities which are a significant pathophysiological mechanism by which myocardial ischemia is produced in patients with moderate epicardial stenoses.

An FFR-based strategy has been shown to be preferable to an invasive anatomic approach in deciding when lesions should be revascularized. By revascularizing only those atherosclerotic coronary arteries with FFR<0.8, a significant number of atherosclerotic lesions in the 50% to 80% diameter range have not been intervened on. Our study demonstrates that relying on FFR alone in evaluating these intermediate level stenoses may require further consideration if the territories they subtend exhibit inducible ischemia or CBF abnormalities during demand stress.

Acknowledgments
We thank Carol Gould for her administrative assistance with the preparation of the manuscript, and Robin High, PhD, for his statistical comments regarding the power calculation.

Sources of Funding
This project was supported in part by the Theodore F. Hubbard Foundation, Omaha, NE.

Disclosures
Dr. Porter has received research support from Lantheus Medical Imaging and Astellas Pharma, Inc. He has received instrument and equipment loan and research support from Philips Research North America and General Electric Global Research. The other authors have no conflicts of interest to disclose.

References


13. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography’s Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440–1463. doi: 10.1016/j.echo.2005.10.005.


Comparison of Fractional Flow Reserve Assessment With Demand Stress Myocardial Contrast Echocardiography in Angiographically Intermediate Coronary Stenoses
Juefei Wu, David Barton, Feng Xie, Edward O'Leary, John Steuter, Gregory Pavlides and Thomas R. Porter

Circ Cardiovasc Imaging. 2016;9:
doi: 10.1161/CIRCIMAGING.116.004129
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/9/8/e004129

Data Supplement (unedited) at:
http://circimaging.ahajournals.org/content/suppl/2016/08/10/CIRCIMAGING.116.004129.DC1.html

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/
Movie Legends

Movie Legend 1. Example of an inducible inferior perfusion defect and wall thickening abnormality in a patient with a right coronary stenosis that had an FFR value of 0.94.

Movie Legend 2. Example of an inducible apical perfusion defect in a patient with a left anterior descending stenosis that had an FFR value of 0.84.