

WHAT WOULD YOU DO?

Diagnosing Gray Zone Coronary Physiology

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CASE PRESENTATION

A 50-year-old man with hypertension, dyslipidemia, and a family history of premature coronary disease presents to the catheterization laboratory with a 2-month history of exertional angina. His primary care physician ordered an exercise nuclear perfusion scan, during which the patient achieved 10 METs (metabolic equivalents of task) of exercise and 100% of his maximum predicted heart rate, with a normal blood pressure response. At peak exercise, he had recurrence of his angina and 1 mm of downsloping inferior ST-segment depression. Compared with his resting images, the stress images showed apical hypoperfusion involving 5% to 10% of the myocardium.

Based on his history, risk factors, and stress imaging study results, he is referred for elective coronary angiography. The patient has been taking aspirin, a statin, and an angiotensin-converting enzyme (ACE) inhibitor. His referring physician added a prescription of sublingual nitroglycerin to be used as necessary for chest pain. Coronary angiography is performed, identifying a 50% lesion in the midportion of a large posterior descending branch of the right coronary artery (RCA) and a 50% lesion in the proximal left anterior descending (LAD) artery. The remaining coronary vessels are free of disease and the patient has normal left ventricular (LV) function.



What is your initial approach to this patient and why?

- **Complete revascularization with percutaneous coronary intervention (PCI) of the LAD and posterior descending artery (PDA)**
- **Stop the procedure and optimize medical therapy**
- **Perform further invasive testing**

Dr. Kern: This middle-aged man with a recent onset of typical angina on medications for hypertension and hyperlipidemia has a small ischemic area by nuclear perfusion imaging. Coronary angiography shows two intermediate lesions in the PDA and LAD. Although he is not on a β -blocker, which would represent optimal antianginal medical therapy, I favor having the most accurate assessment of the significance of the two lesions given the marginal stress ischemia result (despite 10 METs as a good workload) at the time of diagnostic angiography. I would perform fractional flow reserve (FFR) of both the LAD and PDA. If both are negative, I would continue medical therapy and add a β -blocker in any case.

Dr. Johnson: Given his risk factor burden and now proven atherosclerosis (likely coronary calcium would also have been seen prior to invasive angiography), the aspirin, statin, and blood pressure control remain the most essential treatments to improve outcomes. Although the patient clearly has typical symptoms, he has not received dedicated antianginal therapy, only as-needed nitroglycerin. Many cardiologists would have appropriately escalated medical therapy to try and make him feel better.

In my own practice, stable patients like him rarely reach invasive coronary angiography without previous cardiac positron emission tomographic imaging and absolute blood flow quantification to address physiologic severity and amount of affected myocardium. However, now that a decision has been made for invasive catheterization, the causal relationship between the observed lesions and symptoms remains unclear. Is it the LAD? PDA? Or both? Or neither?

Dr. Hodgson: The patient's Duke treadmill score is likely around 0 (assumed 9-minute exercise time on a

Bruce protocol). He has an intermediate-risk myocardial perfusion imaging (MPI) scan and therefore meets the 2012 appropriate use criteria (AUC) for diagnostic catheterization (scenario 16 [intermediate-risk findings, 5%–10% ischemic myocardium on stress single-photon emission CT MPI or stress positron emission tomography, stress-induced wall motion abnormality in a single segment on stress echo, or stress cardiac MR]).¹

With respect to proceeding to PCI (assuming his angina was Canadian Cardiovascular Society II), the 2017 AUC would suggest that with a proximal LAD lesion and two-vessel coronary artery disease (CAD), PCI would be indicated (scenario 11 [two vessel disease: proximal LAD involvement and no diabetes present]).² Going strictly by the guidelines, one could justify proceeding to complete revascularization. However, the patient's perfusion defect could be due to either the LAD or the RCA lesions, and he is not on any antianginal therapy.

Personally, I would not proceed to PCI immediately. Without more information, one cannot be certain that both lesions need intervention. This is a great case for determining the physiology of both lesions before committing to PCI. Based on the subtended myocardium, it is likely that the PDA lesion will not significantly impair peak flow, although the proximal LAD lesion certainly could. Once the physiology is known, the exact lesion morphology must also be taken into account, especially for the proximal LAD where risk of injury to the left main or circumflex could be possible. Taking the patient off the table and initiating antianginal therapy could also be justified given the moderate nature of the lesions; however, this approach is rarely favored in the United States.



You elect to perform further invasive testing. Which approach do you use and why?

- Intravascular ultrasound (IVUS)
- Optical coherence tomography (OCT)
- FFR
- A nonhyperemic diastolic ratio (eg, instantaneous wave-free ratio [iFR])
- Contrast FFR

Dr. Johnson: Of the options for invasive testing, only FFR assessment has been demonstrated to improve clinical outcomes compared with an angiography-guided strategy. IVUS lacks outcomes trials and yields only a modest correlation with FFR at a population level, yet involves similar equipment cost and procedural risk.

In some patients, a large pressure gradient exists at rest or after documenting pressure wire position using a brief injection of contrast, which also produces mild, transient hyperemia. For these cases that occur in 10% to 30% of

lesions, a positive resting Pd/Pa or contrast FFR implies that FFR would only be more positive (lower FFR value or larger gradient). For a markedly abnormal resting Pd/Pa or contrast FFR, I sometimes avoid full hyperemia depending on clinical and angiographic circumstances.

Dr. Hodgson: In cases where the lesion is well identified (as it is here), a physiologic measure is the optimal choice for determining the need for revascularization. Both FFR and iFR have been shown in large trials to predict ischemia by noninvasive testing, and both have been shown effective for determining whether stenting should be performed or deferred. I routinely use intracoronary adenosine bolus dosing for FFR studies (unless the left main or RCA ostium is involved). This approach is fast, free of significant patient discomfort, and can easily be repeated in multiple lesions. My practice is to measure both iFR and FFR, typically relying on the FFR for a treatment decision and the iFR pullback for localizing the exact treatment zone. In some cases, such as this younger patient with no previous myocardial damage, flow may greatly increase after adenosine and result in an mildly depressed FFR, but with a normal iFR at rest. In these infrequent cases, the treatment decision can be difficult and I rely on the patient's symptoms, previous treatment response, and stress findings.

Dr. Kern: As previously noted, I favor FFR for lesion assessment, although many would be satisfied with a nonhyperemic pressure ratio (eg, iFR) because of the straightforward nature of the two mild LAD/PDA lesions. Contrast FFR is always part of FFR and perhaps has a closer relationship to the true FFR with maximal hyperemia using adenosine than resting pressure ratios. If the resting Pd/Pa or contrast FFR are below the ischemic threshold, a full FFR with adenosine is unnecessary as the lesion is deemed flow limiting. If nonhyperemic ratios are negative, I confirm with FFR.

As reported many times, imaging with IVUS or OCT has poor correlation to the physiologic ischemic indices (especially FFR) and should not be used in place of FFR when deciding whether to place a stent.



iFR is measured across the PDA lesion and is found to be 0.95. It is then measured across the LAD lesion and found to be 0.90. What do you do and why?

Dr. Hodgson: The iFR value in the PDA is expected given the small territory subtended and the LAD value is very much in the "gray zone." Although recent population studies suggest a dichotomous cutpoint at 0.89,^{3,4} I never act on a single value alone. As mentioned earlier,

this could easily be a patient who has a high coronary flow reserve. One way to assess this would be to perform FFR. If the distal pressure significantly drops (FFR would be lower), then a significant increase in flow can be inferred. Alternatively, coronary flow velocity could be measured and flow reserve calculated. If flow reserve were above 2.0, a good prognosis can be expected. Of course, one has to manage the patient's symptoms, so this additional physiologic information would be helpful in making the important decision to stent the proximal LAD.

Dr. Kern: In this case, iFR across the PDA is nearly normal, and I have confidence that the PDA lesion is not flow limiting. For the LAD, the iFR is slightly above the ischemic threshold (> 0.89 from the DEFINE-FLAIR and iFR-SWEDE-HEART studies^{3,4}), but because of the large myocardial mass, abnormal perfusion images, and importance of the LAD in this patient's course, I would confirm the satisfactory nature of the physiology with FFR. Little is lost to confirm the meaning of resting pressure information before a final decision is made to stent or continue with medical therapy.

Dr. Johnson: This patient has no symptoms at rest. Therefore, the negative resting iFR value for both lesions provides no information regarding the reduction in pressure and flow that occurs with exercise when he experiences his angina, electrocardiography changes, and perfusion defect.

Approximately 10% to 20% of patients will have a negative iFR but a positive FFR. Although it can happen in any epicardial vessel, such discordance exists more commonly in the left main and proximal LAD. As a result, I routinely administer hyperemic medications when the resting physiology is negative. Having already opened a pressure wire and instrumented the vessel, the relative extra time and cost for hyperemia adds little but could completely change the diagnosis and treatment. If we sent the patient for a stress test outside the cath lab, then why skip a stress test inside the cath lab?



FFR is then measured across the LAD lesion and found to be 0.77. What do you do and why?

Dr. Johnson: The invasive stress test with a reduced FFR matches his classic angina, treadmill-induced ST-segment depression, and imaged perfusion defect. As a result, we can expect that much or perhaps all of his angina can be improved by revascularization. Therefore, I would most likely proceed with PCI of the LAD, although in rare situations, coronary artery bypass grafting (CABG) could also be considered depending on the FFR of the PDA, angiographic characteristics, ability to tolerate dual antiplatelet

therapy, upcoming noncardiac surgical procedures, and patient preference.

In this case, the FFR value of 0.77 falls into the gray zone between 0.75 and 0.80, where clinical circumstances remain especially important. The concordance among the clinical symptoms, noninvasive and invasive stress testing, and angiographic appearance make PCI a compelling option in this particular case. Emerging data also suggest a reduction in spontaneous myocardial infarction (MI) by FFR-guided PCI compared with medical therapy alone. As a result, we can simultaneously improve his prognosis and symptoms with FFR-guided coronary revascularization.

Dr. Kern: For the LAD, the FFR value < 0.80 is the cutoff for the FAME trials.⁵ It can be an indicator of ischemia and be used to justify stenting. The continuum of FFR parallels the ischemic risk with the lower values representing worse ischemic burden. An FFR value of 0.77 is close to the ischemic threshold. With this relatively high but still abnormal FFR value, one can safely consider a further trial of maximal medical therapy, adding β -blockers to his regimen (in accordance with guideline-directed goals). Afterward, if the patient is still symptomatic, one can proceed to stenting. Alternatively, an FFR of 0.77 would justify stenting for ischemia at the time of diagnostic angiography and would provide a level of reassurance to both the patient and treating physician; therefore, an ischemia-producing lesion would be completely removed from the clinical scenario going forward.

Practically speaking, many would proceed to ad hoc stenting during this diagnostic angiographic procedure, provided of course that they have previously addressed the potential risks and benefits of stenting during an ad hoc intervention with consent obtained. This approach is reasonable for simple lesions but not suitable for complex CAD where full discussions about CABG versus PCI options and maximal medical therapy are addressed before undertaking revascularization, preferably at a second procedure.

Dr. Hodgson: As anticipated, this patient likely has a good coronary flow reserve resulting in a fall in distal pressure across the lesion with high velocity. We must also remember that prior to the FAME trial, the cutpoint for FFR "significance" was < 0.75 , not < 0.80 . Based on current studies, however, the iFR would suggest deferral and the FFR would suggest PCI.^{1,2,5}

Personally, I would defer. Proximal LAD stenting is not without potential serious complications both acutely and chronically. Some of these are life threatening. The patient is not currently on antianginal therapy, he can exercise for 10 METs, his LV function is normal, and he has just been started on a statin. A trial of medical therapy, aggressive

lowering of low-density lipoprotein levels, and lifestyle modification could be very effective. PCI can always be done in the future if symptoms progress or become lifestyle limiting. *Primum non nocere!*

APPROACH OF THE MODERATOR

A substudy from the CONTRAST trial found that iFR and FFR are discordant approximately 20% of the time and that this rate increases to 27% when interrogating lesions involving the left main coronary or proximal LAD. Given the wealth of clinical data supporting both deferral of lesions with FFR > 0.80 and treatment of lesions with FFR ≤ 0.80 in a variety of randomized studies and registries from around the world, I believe FFR remains the reference standard. The 3-year economic and clinical outcome analysis of the FAME 2 trial, which compared medical therapy with PCI in patients with stable coronary disease and at least one lesion with an FFR ≤ 0.80, found that patients treated with PCI had significantly lower rates of urgent revascularization, less angina, better quality of life, required fewer medications, and by 3 years, showed no difference in cost between the two strategies.⁶

Most recently, the 5-year data from the FAME 2 trial continued to show significantly lower rates of the composite endpoint of death, MI, and hospitalization requiring urgent revascularization. Interestingly, the rate of spontaneous MI was lower in the PCI arm compared with the medical therapy arm, despite the fact that > 50% of the medical therapy group crossed over to PCI.⁷

Given the large size of the FAME 2 trial, the long-term follow-up, and the fact that PCI was guided by FFR, and despite the lack of a sham treatment arm, I believe that PCI improves outcomes in this setting. For these reasons, this patient underwent PCI of his LAD at the time of the initial angiography. His angina resolved and he remains symptom free at 3-year follow-up. He is still on an aspirin regimen, a statin, and an ACE inhibitor; clopidogrel was stopped after 1 year because of complaints about bruising. ■

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