

Physiologic Assessment for Revascularization Strategy and Multivessel PCI

Fractional flow reserve is a useful supplement to angiography for accurate decision making.

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A 72-year-old man presented to the hospital to have his chest pain evaluated. He underwent CT angiography (CTA) because of multiple risk factors for coronary artery disease (CAD), which revealed multiple calcified plaques. Ischemic stress testing was performed, which revealed a small apical reperfusion abnormality. In the catheterization lab, coronary angiography confirmed multiple coronary narrowings, at least one of which was 60% to 70% in the right coronary artery and two other 50% to 60% stenoses in the left anterior descending and circumflex coronary arteries. What is the best revascularization option for treating this patient? Is the chest pain ischemic, given the stress test result? If so, which of the several lesions is responsible? Should all lesions be stented? And, finally, with multivessel disease, should coronary artery bypass graft (CABG) surgery be the best revascularization modality?

These questions are not trivial and have grave implications for patients and their families. In many centers, the treating physicians would likely elect a simple and straightforward approach—stent the most severe lesion, institute medical therapy, perform a stress test at a later time, and bring the patient back as needed to stent additional lesions. Alternatively, others

would stent all lesions with >50% narrowing, assuming they were clinically significant by angiography. In patients with three-vessel coronary disease and diabetes, CABG might be recommended despite having some apparently mild lesion narrowing (50%–70%).

However, recent information suggests ischemia-directed revascularization may be the best approach.¹

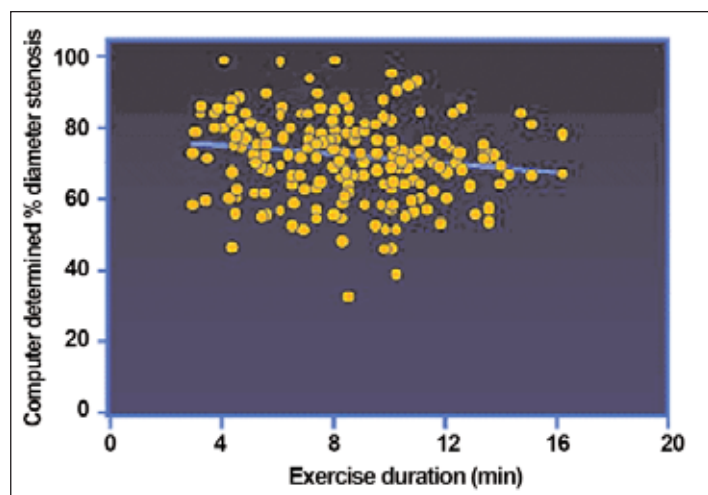


Figure 1. Poor correlation between angiography and functional class of ischemia is demonstrated in the ACME trial comparing medical therapy to coronary angioplasty. The percent diameter stenosis versus exercise duration has a weak correlation. (Adapted from Parisi AF, et al. *N Engl J Med*. 1992;326:10.²)

With optimal medical therapy and then stenting of only the lesions that are ischemia producing and refractory to medical management, 5-year event-free survival is excellent and equivalent to a routine stent-all strategy.¹ Importantly, stenting only lesions that are associated with reduced flow and ischemia, as identified by direct in-lab coronary pressure measurements, is better than stenting at random. Deferring stents in lesions that are not flow limiting with continued medical therapy has also been shown to have a superior 5-year outcome.³ Deferring stenting based on normal coronary physiology is especially important given the concern about the downside of universal stenting, with the potential of subacute thrombosis. Although subacute thrombosis has been exaggerated in the lay press, stenting should be performed with good reason and only in vessels that will benefit.

WHAT IS THE RATIONALE FOR USING PHYSIOLOGIC ASSESSMENT (CORONARY PRESSURE MEASUREMENTS) IN PATIENTS WITH MULTIVESSEL CAD?

In patients referred to the catheterization lab with or without previous noninvasive stress imaging, decision making for complex multivessel coronary anatomy based on angiography alone is known to be highly problematic. The rationale for physiologic lesion assessment is straightforward.

The angiogram cannot be relied upon exclusively to direct coronary revascularization.⁴ Angiography fails because it cannot fully characterize the clinical or hemodynamic significance of many coronary stenoses. This fact is well recognized and documented repeatedly by intravascular ultrasound imaging, CTA, and the ubiquitous necessity for stress testing to clarify the clinical importance of lesions seen on coronary angiography (Figure 1).

It is worth noting that coronary angiography does not visualize CAD, an abnormality of the vessel wall but rather generates a two-dimensional (2D) luminogram (a silhouette

image of the three-dimensional [3D] vascular lumen). It does not truly identify atherosclerosis but merely provides a shadowgram without intraluminal detail sufficient to characterize a plaque. The eccentric shapes of plaques do not permit the observer to determine whether such an opening is limiting coronary blood flow.⁵ The accurate identification of both normal and diseased vessel segments by angiography further complicates the determination of a lesion's significance in the setting of diffuse CAD, which cannot easily be seen on an angiogram (Figure 2A). Angiographic artifacts, including contrast streaming, branch overlap, vessel foreshortening, calcifications, and ostial origins, further make the interpretation of some luminal narrowings unreliable (Figure 2B). Despite numerous attempts to improve angiographic imaging of complex anatomy, the angiographer is still confronted with a visual dilemma in which no single view or multiple views provide an answer. Hence, the use of the physiology to assess the coronary stenosis is required, either out of the catheterization lab by stress testing or in the catheterization lab by coronary pressure measurement.⁶⁻⁸

Resolving this visual dilemma is especially important in patients with multivessel disease who have numerous lesions termed *intermediately severe* (commonly 40%–70% narrowed). Confirmatory stress ischemic testing is often, but not always, useful in such patients to

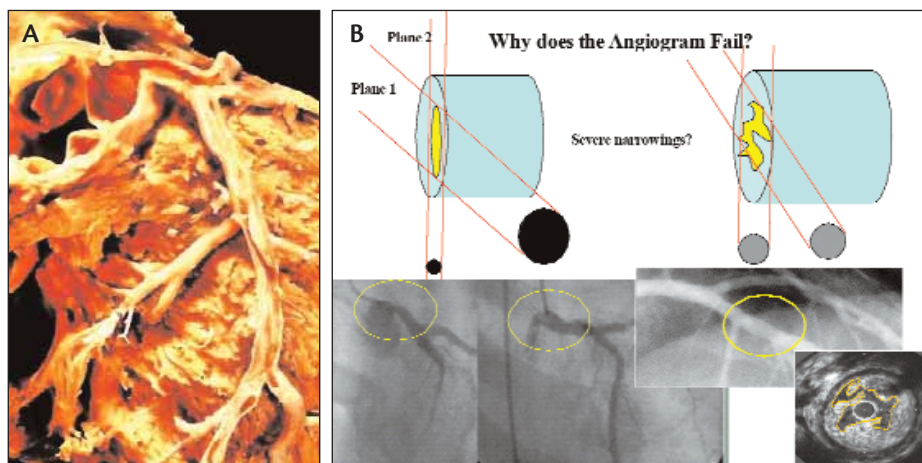


Figure 2. Coronary artery and myocardium. Pathologic specimen showing an opened coronary artery with a focal coronary stenosis and diffuse CAD throughout its distribution. The artery has branches proximal to the stenosis that are less diseased and have lower resistance to flow. Measurements of coronary physiology should be made distal to a stenosis to examine the effect of the stenosis on coronary blood flow (A). The angiogram is a 2D image of 3D structures. Most intermediate lesions are oval-shaped, with a narrowed dimension and a wide dimension. The angiogram cannot reliably indicate which is responsible for flow limitations. Some lesions (lower right) may appear hazy but widely patent, only to be responsible for angina due to plaque rupture, as demonstrated by intravascular ultrasound cross-section (far right corner) (B).

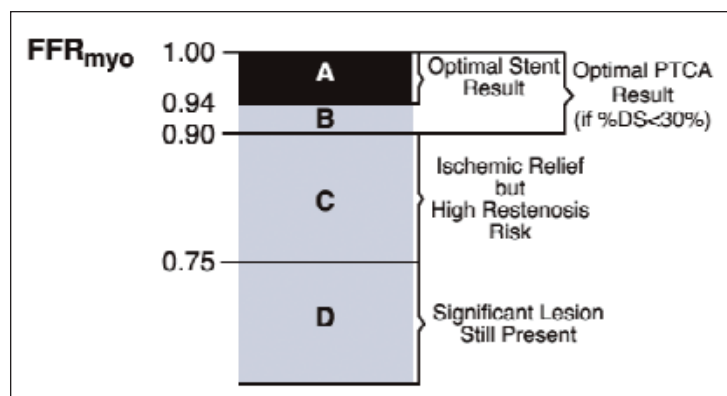


Figure 3. Grading of interventions with FFR based on levels after the procedure.

assist in decision making before performing an intervention. This approach may require an angiogram on one day to be followed by a stress test on another day, followed by subsequent repeat angiography and potential coronary intervention. Similar to stress testing, in-lab measurements of translesional pressure (and flow) provide critical physiologic information, which complements the morphologic appreciation of the lesion and objectively supports the appropriate revascularization approach.

FRACTIONAL FLOW RESERVE

Fractional flow reserve (FFR) values ≤ 0.75 are associated with ischemic stress testing in numerous comparative studies. The converse is true for FFR values > 0.80 , with $> 95\%$ of stress testing having negative ischemic results. There is a small gray zone of uncertainty in the 0.75 to 0.80 range, which demands clinical judgment (Figure 3). A summary of physiologic threshold values for common clinical applications is provided in Table 1. Strong correlations exist between myocardial stress test-

ing and myocardial FFR or coronary flow reserve by Doppler. A myocardial FFR < 0.75 identifies physiologically significant stenoses associated with inducible myocardial ischemia, with high sensitivity (88%), specificity (100%), positive predicted value (100%), and overall accuracy (93%). An abnormal coronary flow reserve (CFR) (< 2) corresponds to reversible myocardial perfusion imaging defects with high sensitivity (86%–92%), specificity (89%–100%), predictive accuracy (89%–96%), and positive and negative predictive values (84%–100% and 77%–95%, respectively) (Table 2).⁹

Studies have shown that the measurement of FFR is highly specific and sensitive for ischemia in single-vessel CAD and that long-term outcomes guided by FFR in patients with multivessel disease and various additional clinical settings are excellent. The usefulness of FFR for the assessment of intermediate lesions in single-vessel disease, multivessel disease, left main disease, ostial lesions, and collateral flow has been reviewed.⁸ FFR supports decisions for stent deployment based on clinical indications. Although not useful for determining the endpoint of stent implantation and apposition to the vessel wall, FFR after stent deployment has prognostic value for major adverse cardiac events within the next several years.^{10–12}

Given the economic and safety concerns regarding the appropriateness of drug-eluting stent (DES) placement, FFR can be used to direct percutaneous coronary interventions (PCI) to only flow-limiting lesions and assist in achieving an optimal revascularization strategy. The American College of Cardiology and the American Heart Association have recently provided a consensus statement and guidelines for the physiologic assessment of CAD in the cardiac catheterization lab.⁹

TABLE 1. PHYSIOLOGIC CRITERIA ASSOCIATED WITH CLINICAL APPLICATIONS

Indication	CFR	rCFR	HSRv*	FFR
Ischemia detection	< 2	< 0.8	> 0.8	< 0.75
Deferred angioplasty	> 2	—	—	> 0.8
Endpoint of angioplasty	> 2 – $2.5^{\dagger}$	—	—	> 0.9
Endpoint of stenting	—	—	—	> 0.9

rCFR, relative CFR; HSRv, hyperemic stenosis resistance index.
 *mm Hg/cm per second.
[†]With $< 35\%$ diameter stenosis.
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MULTIVESSEL DISEASE AND PERFUSION IMAGING

With the increasing use of coronary stents in an ever-more complex patient population, a frequent application of physiologic assessment involves lesion selection in patients with multivessel disease. Accurate lesion selection is important because noninvasive studies have demonstrated that MIBI-SPECT fails to correctly indicate all ischemic areas in 90% of patients.¹³ Moreover, in 35% of patients with multivessel disease, no perfusion defect was present, possibly due to balanced ischemia. One ischemic area was often masked by another more severely underperfused area. Furthermore, when several stenoses or diffuse disease is present within one coronary artery, an abnormal MIBI-SPECT hypoperfusion image cannot discriminate among the different stenoses along the length of that vessel. For clinical practice, these observations highlight the fact that regions that may not appear responsible for ischemia may contain significant angiographic narrowings, whereas other more severe-appearing lesions may not be hemodynamically important. Coronary pressure measurements are particularly useful to localize regions of suspected ischemia in patients with multivessel disease.

Does Angiographic Three-Vessel CAD Equal Physiologic Three-Vessel CAD?

It is notable that some patients, even with angiographic three-vessel CAD, may not need either stenting or CABG. Sant'Anna et al have shown that when physiologic lesion significance is measured and compared with the angiographic diagnosis of diseased vessels, the incidence of significant three-vessel CAD decreased from 27% to 9%, two-vessel CAD decreased from 43% to 17%, and single-vessel disease increased from 30% to 60%, thus making the patient readily treatable by stenting or continued medical therapy (Figure 4).¹⁴

Best medical care indicates that anti-ischemic and risk factor modification therapy should be part of every CAD patient's treatment plan before and after stenting. The COURAGE trial¹ reminded us that PCI was no better than medical therapy for death and myocardial infarction reduction, but PCI still has high value for the majority of patients not enrolled in the trial (90% of those screened were excluded) and provides the benefits of revascularization when appropriately employed. Patients with ischemia did better with PCI.¹⁵

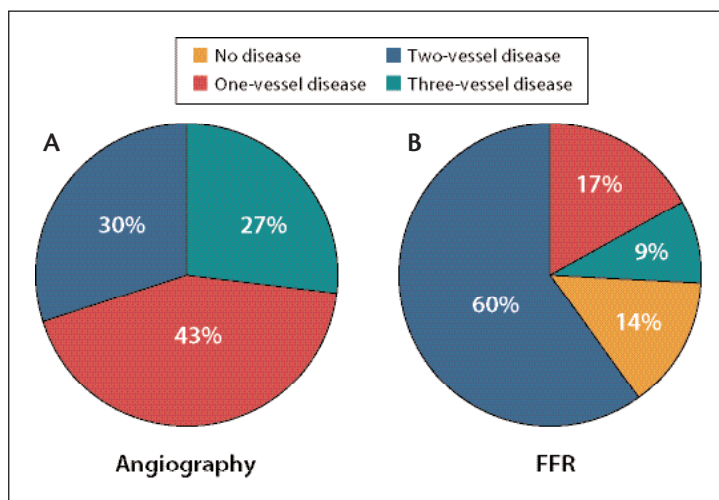


Figure 4. Extent of CAD as assessed by angiography (A) compared with the functional extent of this disease after FFR assessment (B). (Adapted with permission from Sant'Anna FM, et al. *Am J Cardiol*. 2007;99:504-508.)

What Happens to Patients With Intermediate Severe CAD Lesions Who Have Deferred Intervention and Are Followed for 5 Years?

The 5-year follow-up outcome of percutaneous intervention of functionally nonsignificant stenosis was reported by Pijls et al.³ The DEFER study randomized 325 patients scheduled for PCI of an intermediate lesion. FFR was measured before planned intervention. If the FFR was ≥ 0.75 , patients were randomly assigned to the deferral group ($n=91$) or the performance group ($n=90$) of PCI. If the FFR was <0.75 , PCI was performed as planned, and patients were entered into the reference group ($n=144$). There were no differences in baseline clinical characteristics between the groups. Complete follow-up was obtained in 98% of patients. Overall survival was not different between the deferred and performed groups (80% and 73%, respectively; $P=.52$) and was significantly better in the reference group (63%; $P=.03$). The composite rates of cardiac death and acute myocardial infarction in the deferred, performed, and reference groups were 3.3%, 7.9%, and 15.7%, respectively ($P=.21$ for deferred vs performed and $P=.003$ for reference vs both of the deferred and performed groups) (Figure 5). The percentage of patients free from chest pain on follow-up was not different between the deferred and performed groups. The 5-year outcome after deferral PCI of an intermediate lesion with normal FFR is excellent. The risk of cardiac death and infarct related to stenosis was $<1\%$ per year and was not decreased by stenting. The DEFER trial employed bare-metal stents as opposed to DESs. Although events in the DES group compared to the

TABLE 2. FFR AND ISCHEMIC TESTING

FFR Study	n	Ischemic Test	Threshold	Physiologic Sensitivity	Specificity	PV+	PV-	Accuracy
Pijls et al ⁶	45	Four-test standard*	<0.75	88	100	100	88	93
de Bruyne et al ¹⁹	60	Ex ECG	<0.72	100	87	—	—	—
Bartunek et al ²⁰	37	Dobu/Ex echo	<0.68	95	90	—	—	—
Chamuleau et al ²¹	127	Dipy MIBI	<0.75	—	—	—	—	75
Caymaz et al ²²	30	Ex thallium	<0.75	—	—	91	100	—
Fearon et al ¹⁷	10	Ex thallium	<0.75	90	100	—	—	93

Adeno/Dipy MIBI, adenosine or dipyridamole sestamibi scan; Dobu, dobutamine; ECG, electrocardiogram; Echo, echocardiogram; Ex, exercise; PV+/PV–, predictive value positive/negative.

*Four tests were used: ECG, Echo, pacing, and nuclear stress tests.

bare-metal stent group were lower after 1 year, these differences were gone by 5 years. Deferral of intervention still has favorable outcomes with no risk of subacute thrombosis of DES.

What Does This Mean for Patients With Multivessel Disease Undergoing Revascularization for Angina?

CAD is a diffuse disease process. The clinical debility of such disease can only be sporadically treated by stenting lesions that produce ischemic chest pain. Stenting must be directed at lesions that limit blood flow and account for the chest pain. Unfortunately, angiography frequently cannot always identify which lesions are flow limiting. Nonetheless, cardiologists have a long-standing and intuitive bias toward using the angiography as an indicator of CAD and its prognosis. A common dilemma faced by a treating physician is the management of an asymptomatic middle-aged patient with a 75% stenosis with marginally abnormal or even normal stress test results. It is a rare interventionist who can resist the urge to stent this lesion to not only relieve presumed ischemia (silent or symptomatic) but also, and perhaps wishfully, prevent the potentially life-threatening anterior myocardial infarction. The oculostenotic reflex (ie, treating by angiography alone) is so powerful that routine stenting has become ingrained in the current treatment of CAD. If the coronary flow is normal across a given lesion, medical therapy will do as well or better than a stent,

which has its own well-known limitations.

Given the results of COURAGE¹ and DEFER,³ some patients likely did not benefit (nor were they harmed) from stenting. These data remind us that it is possible to perform selective intervention for only those lesions that are truly ischemia producing by in-lab functional testing. FFR-guided intervention produces outcomes equivalent to CABG of all lesions.¹² Such an approach may be the best option for use of PCI in multivessel patients.

Finally, it is important to reflect on the fate of saphenous vein grafts placed on normally perfused arter-

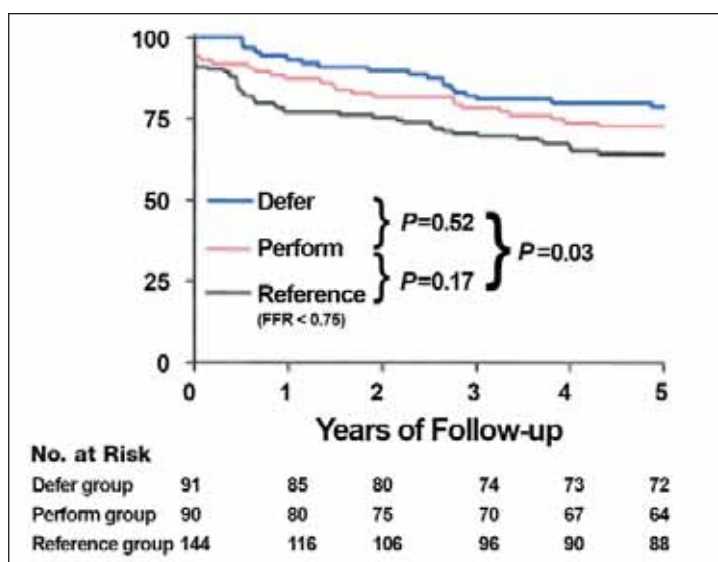


Figure 5. The DEFER Study: 5-year follow-up. (Adapted with permission from Pijls NHJ, et al. J Am Coll Cardiol. 2007;49:2105-2111.)

ies—that is, performing vein graft bypass surgery for nonsignificant lesions. Botman et al reported that 25% of CABG grafts placed on arteries with lesions that had diameters narrowed <50% or with FFR >0.8 were occluded at 1-year follow-up.¹⁵ Normal flow through native arteries favors the path of least resistance and, as such, promotes premature closure of saphenous vein grafts.¹⁶ Assessment of lesions even in patients with three-vessel disease has serious implications for long-term best outcomes and which lesions may benefit from stenting or bypass grafting.

ECONOMICS OF PHYSIOLOGIC-GUIDED INTERVENTIONS

The economics of physiologic lesion assessment indicate that there is a cost savings to the health care system by assessing multivessel disease in the catheterization lab.^{17,18} Current reimbursement provides for a partial recovery of the expenses of performing physiologic measurements in the catheterization lab. Available data suggest significant overall savings to the health care delivery system and a substantial clinical benefit directly provided to the patient for accurate and objective decision making.

CONCLUSION

The decision to employ physiologic assessment to the revascularization strategy in patients with multivessel disease should not be based on coronary angiography alone. Coronary physiology in the form of FFR represents a precise and powerful adjunctive tool in the cardiac catheterization lab to complement angiography and provide objective data about ischemia. FFR is considered one of the standards for functional assessment of CAD, acting as a stress test within the cardiac catheterization lab environment. FFR facilitates accurate decision making for patients with CAD undergoing cardiac catheterization in a manner similar to the use of stress imaging. Physiologic data acquired during the angiographic procedure can support timely and economically sound decision making regarding therapy. By overcoming the limitations of coronary angiography, FFR provides the angiographer with an objective indicator of clinically relevant CAD and provides patients, their family, and the health care system with the best chance of optimal care. ■

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