

EDITORIAL COMMENT

“Just Puff”

The Continued Quest to Simplify Physiological Lesion Assessment*



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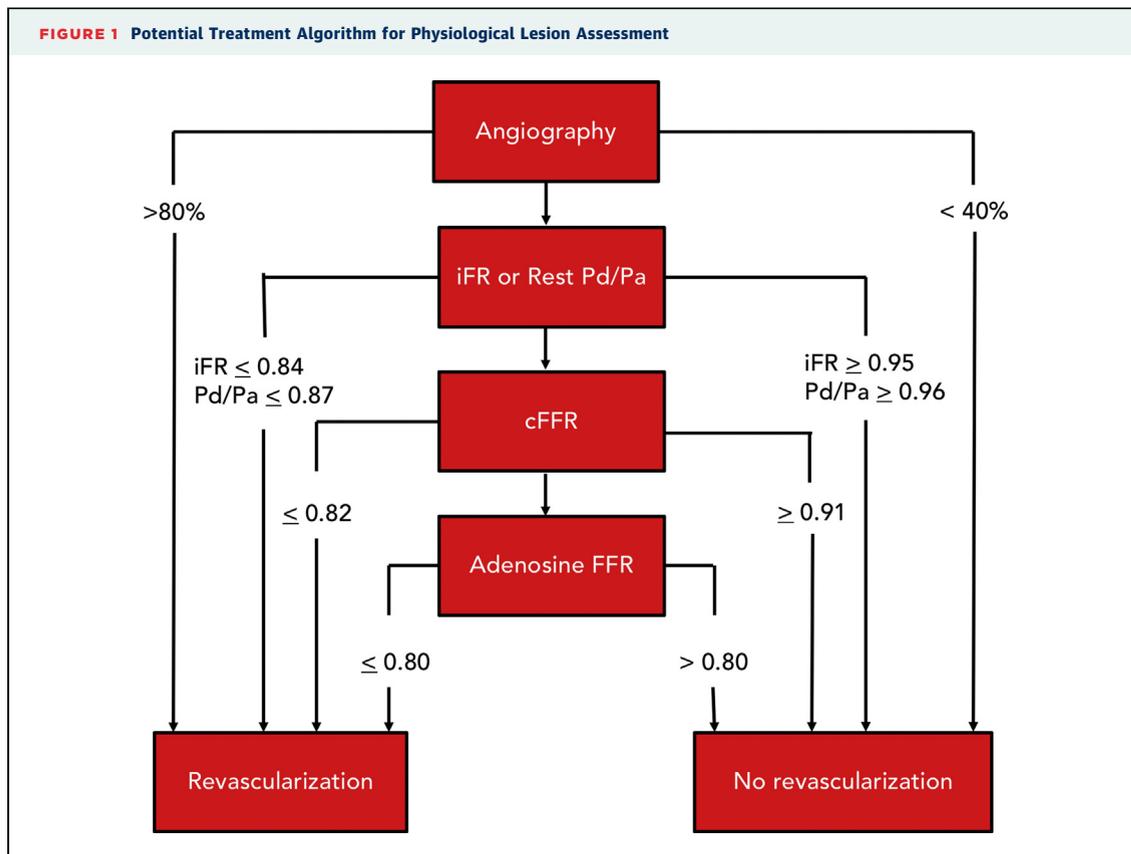
In the 30% of percutaneous coronary interventions (PCIs) being performed to treat symptoms of stable coronary artery disease (CAD), an ischemia-guided approach to revascularization is advocated over an anatomically guided approach. Consequently, the appropriate use criteria for coronary revascularization emphasizes the presence of ischemic symptoms refractory to medical therapy and documentation of ischemia as justification of appropriate revascularization. To date, documentation of ischemia is largely performed by noninvasive imaging. However, noninvasive imaging has limited diagnostic accuracy due to its variable image quality, attenuation artifacts, and its inherent limitation in identifying relative, not absolute, myocardial flow. This latter principle results in underestimation of the ischemic burden, particularly in patients with left main and multivessel CAD in whom the stakes are highest. It is not surprising, therefore, that although many interventional cardiologists value noninvasive imaging as a “gatekeeper” to the catheterization laboratory, they often witness its lack of accuracy in localizing vessel- or lesion- specific ischemia that is required for decision making regarding revascularization.

Invasive physiological assessment was first recognized as the resting pressure gradient by Andreas Gruentzig (1) and further refined and reintroduced as fractional flow reserve (FFR) by Pijls and

De Bruyne (2,3). FFR is defined as stenotic myocardial flow divided by normal myocardial flow within a vessel, and because flow is difficult to measure, pressure is used as a surrogate for flow. FFR has a clear normal value of 1 and is lesion specific (although there may be interaction between stenoses in serial lesions). It is important to remember that vasodilation during FFR measurement is performed to maximally reduce myocardial resistance so that coronary pressure becomes proportional to coronary flow. The diagnostic accuracy of FFR to detect ischemia compared with composite noninvasive ischemia testing has been shown to be 93% (3), and FFR has been validated against a multitude of noninvasive modalities in different myocardial disease states. Its use, in conjunction with coronary angiography, has been demonstrated to be superior to angiography alone for directing revascularization in single-vessel, multivessel, and left main disease (4,5). In fact, FFR-directed PCI, but not angiographically guided PCI, has been shown to be superior to medical therapy in reducing the composite endpoint of death, myocardial infarction, and urgent revascularization (6,7). This extensive validation literature and demonstrated cost-effectiveness of FFR make it valuable in directing revascularization in the cath lab in a clinical setting of absent, equivocal, or conflicting noninvasive testing. However, a recent survey revealed that physiological CAD assessment is used in less than one-third of coronary angiograms and is never used by ~15% of operators (8). This leaves considerable room to increase the use of FFR, potentially improving patient outcomes and health care resource utilization. Some have argued that simplifying invasive physiological assessment of CAD would result in its greater use. Elimination of the need for pharmacological induction of maximal hyperemia needed for traditional FFR is 1 step in this

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direction. Arguments for elimination of adenosine (Astellas Pharma US, Northbrook, Illinois) use during FFR measurement include its cost, side-effects profile, additional set-up of equipment, and the time required to administer. Intravenous (IV) adenosine costs \$50 to \$200, and the incidence of side effects in patients undergoing adenosine stress perfusion imaging is ~81%, although this incidence is likely lower in the sedated patients receiving IV or intracoronary adenosine (9). Although most side effects of IV adenosine are minor and self-limited, a 7.6% incidence of atrioventricular block can occur (9). In addition, measurement of FFR using IV adenosine can add an additional 2 to 5 min in procedural time. In a survey of FFR use, 24% of responding operators said they did not use it because it “takes too much time to set up and perform the test” (8). Other vasodilators such as sodium nitroprusside (10), nicorandil (11), and selective adenosine receptor agonists (12) have also been proposed, although these are also costly and/or have less optimal diagnostic accuracy.

In recent years, resting physiological indexes, including distal pressure divided by aortic pressure over the entire cardiac cycle (Pd/Pa), Pd/Pa during the diastolic wave-free period or instantaneous wave-free ratio (iFR), and basal stenosis resistance,

have been proposed in an effort to streamline invasive physiological testing. The diagnostic accuracy of Pd/Pa and iFR compared with FFR and other physiological indexes has been extensively investigated and has been found to be in the range of 80% to 85%. Another approach to address potential downsides of adenosine for FFR measurement is to investigate the diagnostic accuracy of radiographic contrast, the most commonly used vasodilator in the cath lab. Indeed, whether a limited dose of contrast during FFR measurement can effectively reduce myocardial resistance to make coronary pressure proportional to flow and allow a rapid contrast FFR (cFFR) assessment to be performed has not been definitively determined.

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In this issue of *JACC: Cardiovascular Interventions*, Johnson et al. (13) compare Pd/Pa, iFR, and cFFR with adenosine FFR as well as with each other. In the largest multicenter comparison to date, 763 patients with single-vessel disease were analyzed in a blinded core laboratory. The authors found the following: 1) cFFR and FFR had the least variance on repeated measures (although the average variance of <0.005 for all metrics is clinically insignificant); and 2) a

single optimal cFFR cut point of ≤ 0.83 was 86% accurate in predicting an FFR ≤ 0.80 , more accurate than the optimal Pd/Pa cut point of < 0.92 (78.5%) and the iFR cut point of < 0.90 (79.9%). The authors further identified that a hybrid strategy of initially measuring cFFR with conversion to adenosine FFR in $\sim 37\%$ of patients when cFFR measurements fell into an intermediate FFR “gray zone” of 0.83 to 0.90 increased its diagnostic accuracy of predicting an FFR ≤ 0.80 to 95%. This accuracy was superior to that of hybrid strategies using Pd/Pa or iFR with FFR, with these latter strategies also requiring greater rates of patients needing adenosine infusion compared with the hybrid cFFR strategy (50% vs. 37%). In short, this and other previous studies demonstrate that simpler nonadenosine-based Pd/Pa measurements can be used to predict FFR ≤ 0.80 with a reasonable degree of accuracy and could be part of a comprehensive hybrid angiographic physiological assessment of CAD (Figure 1) (14,15).

Depending on the specific clinical situation, less-than-perfect diagnostic accuracy of an index may be adequate for clinical decision making and can spare the patient and operators the expense, time, and side effects of IV adenosine. A quicker diagnostic test such as cFFR and iFR can streamline care, increase adoption of physiology, and is likely better than angiographically guided revascularization. This compromise may be even more palatable if one acknowledges that revascularization in stable CAD is primarily for symptomatic

and not prognostic benefit and that our gold standard of FFR also has some degree of variability. This variability may relate to different degrees of microvascular disease; variations in dose, location, and rate of adenosine delivery; and the spectrum of adenosine response related to interaction with caffeine and other drugs. Nevertheless, in clinical instances when the stakes are highest (e.g., left main or proximal large-vessel disease), optimal accuracy is warranted, and currently one might insist on using adenosine FFR.

In summary, although adoption of the simpler resting indexes has coincided with wider penetration of coronary physiology, FFR has the best evidence base supporting its clinical utility. Until results of outcome-based trials investigating Pd/Pa and iFR (and possible future outcome trials using contrast FFR) are available, straying from the FFR standard depends on the perceived balance between the price of adenosine administration (cost, time, side effects) and the value of evidence-based revascularization decision making.

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