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EDITORIAL COMMENT

Is it Time to Measure Fractional Flow Reserve in All Patients?*

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The shortcomings of angiography to assess the physiologic significance of coronary atherosclerosis are well known (1,2). Particularly in patients with diffuse disease or unstable coronary syndromes, the angiogram is of little help to ascertain the potential of an individual stenosis to cause reversible myocardial ischemia. Waiting for noninvasive testing such as nuclear stress perfusion scintigraphy (SPS) in patients admitted for acute chest pain, whether or not true angina, is often time consuming and prolongs hospital stay. If signs of reversible ischemia are found at stress testing, angiography will be performed anyway, and even then uncertainty quite often persists, especially in the setting of multivessel disease (3,4). Therefore, the need for a reliable lesion-specific invasive index to indicate whether a particular stenosis is responsible for transient ischemia, and consequently should be treated, is indisputable.

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Fractional flow reserve (FFR) is such an index. Fractional flow reserve is defined as the ratio of maximum blood flow in a stenotic artery to normal maximum flow in the same vessel (5,6). Stated another way, maximum flow in the presence of the stenosis is expressed as a fraction of maximum flow in the hypothetical case that the epicardial artery is completely normal. In contrast to most other invasive indexes, fractional flow reserve has a direct clinical relevance: for example, FFR of 0.60 means that the maximum amount of blood (and oxygen) supplying that particular myocardial distribution only reaches 60% of what it would be if the respective artery were completely normal. An increase to 0.90 after coronary intervention indicates that maximum blood supply has increased now by 50% (5–8).

The characteristics of FFR have been extensively described and validated over recent years. Fractional flow reserve can be calculated by taking the ratio of mean distal coronary pressure to aortic pressure during maximum coronary hyperemia. The latter can be achieved by intracoronary adenosine or papaverine administration or by intravenous infusion of adenosine (5–8). Fractional flow reserve has a uniform normal value of 1 for every patient and every coronary artery (7–9). In contrast to other invasive indexes, it is not dependent on changes in heart rate, blood pressure, or contractility (10); it accounts for the presence of collaterals (5,11), and has a sharp threshold value to indicate inducible ischemia: FFR <0.75 always indicates inducible ischemia; FFR >0.80 excludes ischemia in 90% of the cases (6,7,12–14). The "gray zone" is very limited, which is important for clinical decision making in an individual patient.

In contrast to some years ago, when wires to measure coronary pressure were more difficult to handle and had technical shortcomings, the present pressure wires have handling characteristics similar to normal guide wires. Intracoronary pressure measurements are very easy now and do not significantly prolong the procedure, even when multiple vessels are interrogated. As shown in several large studies published recently, FFR can be measured successfully in 99% of the arteries, and the measurements are extremely reproducible (4,15,16). More recently, the prognostic value of FFR measurement post-stenting has been demonstrated in a large multicenter study in 750 patients. Normalization of FFR after stent placement (thereby restoring normal conductance of the artery) was accompanied by a restenosis rate of $<5\%$ at six-month follow-up, with a strong inverse correlation between post-stent FFR and event rate (16).

FFR in unstable coronary syndromes. The usefulness of FFR in unstable coronary syndromes has been less well documented to date. In the early phase after myocardial infarction, severe microvascular impairment (no reflow, stunning, inflammation) may be present but often improves over time. The impact of a "residual" epicardial stenosis may therefore be underestimated in the first days after infarction (17–19). A low FFR still indicates hemodynamic significance of the residual stenosis, but high FFR does not necessarily exclude this. Yet, it has been shown recently that, much as in patients with stable coronary artery disease, the classical 0.75 to 0.80 threshold value could be used from five days after acute myocardial infarction (19,20).

In patients admitted for unstable angina or non–ST-segment elevation myocardial infarction (NSTEMI), no data were available. In this issue of the *Journal*, Leesar et al. (21) publish an interesting study to fill this gap. Patients admitted for unstable angina pectoris, stabilized with medical treatment, were randomly assigned to either invasive evaluation, including coronary pressure measurement, or noninvasive evaluation by SPS. The invasive approach with FFR not only proved to be equally effective in terms of preventing adverse events after one year and resulted in less angina at follow-up, but was also associated with a shorter hospital stay and significant decrease in total costs of treatment.

It should be emphasized that this study applies only to those patients with unstable angina/NSTEMI who could be initially stabilized by medical treatment. It is clear that in

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case of failure of clinical stabilization, urgent angiography is generally warranted and that in such cases no pressure measurement or other additional information is necessary to justify percutaneous coronary intervention (PCI) of the culprit lesion. Even in those cases, after treatment of the culprit lesion, FFR analysis of other stenoses (when present) can be helpful and indicate the need for additional treatment, preventing repeated invasive procedures later on and thereby reducing costs even more, as will be outlined.

The way in which Leesar et al. (21) performed their cost-efficiency analysis is straightforward and understandable. Rather than assuming complex models with multiple theoretical assumptions and extrapolations, the true costs of the hospital stay and investigations were calculated (21).

More complex and extensive coronary disease. The study by Leesar et al. (21) was restricted by design to patients with single-vessel disease. Thus, the only question to be solved was if the residual stenosis was still responsible for inducible ischemia and should be treated. Yet, this approach of invasive functional assessment is even more useful (and probably even more cost-efficient) in patients with unstable angina and multivessel disease. In such patients (unfortunately more common in today's catheterization laboratory), other stenoses can be evaluated as well and treated consequently. In the case of diffuse coronary atherosclerosis or multivessel disease, it is often impossible both by nuclear stress testing and by angiography to indicate which of several stenoses may be culprit (4). Systematic segmental analysis of the coronary arteries by pressure pull-back recording has shown that the real culprit spots or segments are often different from those expected by angiography (9,16,22). Treatment based upon the angiogram alone is often incomplete or performed at the wrong location, necessitating further interventions in the short term. Ironically, these early reinterventions are often attributed to restenosis, rapid progression of disease, or bad luck, whereas they may actually relate to a hemodynamically significant stenosis that remained undetected at initial angiography.

To make a pressure pull-back recording, the sensor-tipped guide wire is placed in the distal coronary artery, steady-state maximum hyperemia is induced, and the sensor is pulled back slowly under fluoroscopy while the pressure recording is watched. The spatial resolution of this method is unsurpassed by any other invasive or noninvasive methodology. A correct selection of segments to be stented is obtained in minutes and delayed discharge from the hospital because of additional noninvasive testing or expensive repeated hospitalization later on can be avoided. The savings demonstrated in the study by Leesar et al. (21) in patients with single-vessel disease are likely to be even larger in such patients with more complex disease.

With the introduction of drug-eluting stents, many more patients with complex coronary disease will probably present in our cathlabs in the next years (23). This underscores the importance of a simple, swift, and safe method to determine the hemodynamics of each individual stenosis in the catheterization laboratory.

Consequences for health care. More important than the savings demonstrated by Leesar et al are the implications for patient care. It is not acceptable to treat patients in a suboptimum way simply because we do not understand physiology or just do not want to spend a few more minutes to acquire fundamental information. In an era of major breakthroughs in diagnosis (24–26) and treatment of coronary artery disease (23), it can be anticipated that patients with even more complex forms of coronary artherosclerosis will be considered for PCI. A more refined and individualized understanding of their disease and a more appropriate selection of the epicardial lesions to be treated will be paramount not only for patient care but also to keep health care affordable (27–29). Therefore, a simple, reliable, and relatively cheap technology such as coronary pressure measurement, although not indicated in all patients, should become standard in at least the majority.

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