

EDITORIAL COMMENT

The Crux of Maximum Hyperemia

The Last Remaining Barrier for Routine Use of Fractional Flow Reserve*

Nico H. J. Pijls, MD, PhD,
Pim A. L. Tonino, MD, PhD

Eindhoven, the Netherlands

In the decision-making process of revascularization of coronary artery stenoses by percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), the presence and extent of reversible ischemia associated with such particular stenoses is of paramount importance (1–3). A stenosis associated with reversible ischemia (also called functionally significant or hemodynamically significant stenosis) causes symptoms of angina pectoris and has a negative influence on outcome (1,2). Therefore, the general feeling is that such lesions should be revascularized if technically feasible. On the contrary, functionally nonsignificant stenoses do not cause symptoms by definition and have an excellent outcome with medical therapy (3–5). Therefore, revascularization of such lesions is generally not indicated.

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In the ideal case, reversible ischemia should be documented before PCI or bypass surgery in a noninvasive way. However, in most patients, such documentation is not present, insufficient, or unreliable. The most important reason for the lack of such data is that all known noninvasive tests have a limited accuracy. Especially in the presence of multivessel coronary artery disease, noninvasive tests are rarely accurate enough to assess separately the ischemic potential of an individual stenosis (6).

Fractional flow reserve (FFR), on the contrary, is a stenosis-specific measure of ischemia and is considered as the gold standard method to investigate whether any par-

ticular stenosis is responsible for inducible ischemia. FFR-guided PCI has been shown to result in favorable outcomes compared with angiography-guided PCI (3,4). Consequently, in Europe, FFR currently enjoys class IA recommendation for assessment of stable coronary stenosis ahead of revascularization when other functional information is lacking (7).

The technique of FFR measurement became available in the catheterization laboratory in the late nineties but a number of technical and practical shortcomings had to be overcome before the technique could be applied as a routine treatment in the catheterization laboratory (8–10).

Presently, the last remaining barrier of generalizing FFR as a first-line catheterization laboratory tool is the issue of achieving maximum coronary and myocardial hyperemia (11).

The principal of FFR is based upon the presence of true maximum hyperemia. That is paramount. If full maximum hyperemia is not present, FFR is overestimated and stenosis severity underestimated (8–11).

At this point, the studies by Nair et al. (12) and by De Luca et al. (13), published in this issue of *JACC: Cardiovascular Interventions*, come into perspective.

Presently, central intravenous administration of adenosine at a rate of 140 $\mu\text{g}/\text{kg}/\text{min}$ is the gold standard of maximum coronary hyperemia (11,14). Not only does this create a reproducible and maximum arteriolar vasodilatation, but it also enables a hyperemic state lasting long enough to make a reliable pullback recording along a diseased artery. If adenosine is not administered by a central venous line but by peripheral infusion, sometimes its action may be less reliable because adenosine is rapidly inactivated in blood, and a maximum hyperemic status is not always achieved. Some operators have increased this peripheral venous dosage to 180 $\mu\text{g}/\text{kg}/\text{min}$, others were prone to increase the ischemic threshold of FFR in such a case, but we should admit such actions mean covering one mistake by another.

Despite the fact that central venous infusion of adenosine is the gold standard, and insertion of a femoral sheath is very easy in a catheterization laboratory, it does entail a small additional risk and, in the case of radial procedures, is inconvenient.

The alternative is intracoronary administration of adenosine, which does not require central venous cannulation but only creates very short-lasting hyperemia that is insufficient to make a pressure pullback recording (11,14). In patients with a single stenosis in an otherwise rather normal coronary artery, that is not a true problem. But unfortunately, most of our patients have multivessel disease, multiple abnormalities along a coronary artery, or focal lesions superimposed upon diffused disease. Therefore, when using intracoronary adenosine, only the total FFR is obtained, without information about the pressure decline along the coronary artery. So, part of the essential information is lacking, and it is difficult

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From the Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands; and Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, the Netherlands. Dr. Pijls received institutional research grants from St. Jude Medical, Abbott, and Maquet; and is a consultant for St. Jude Medical. Dr. Tonino has received lecture fees from St. Jude Medical.

to judge whether it makes sense to stent (in case of focal pressure drops) or not (in case of a gradual decline of pressure) (15).

Furthermore, reliable intracoronary administration of adenosine requires a stable guiding catheter position to avoid spillage into the aorta. However, a guiding catheter too deeply engaged might partly prevent true maximum hyperemia. This makes intracoronary adenosine a much more complicated hyperemic stimulus than often believed, producing ambiguity with respect to the necessary dosage (as shown by De Luca et al. [13]), along with difficulties in interpretation, and is often much more time-consuming compared with centrally administered intravenous adenosine.

Furthermore, the use of intracoronary adenosine is complicated by the very short half-life without a steady-state. In the study by De Luca et al. (13), the good news is that the absolute differences in FFR between the lowest and highest doses of adenosine were very small (decreasing from 0.79 to 0.77) and most likely none, or very few, of their patients moved from above the currently accepted upper limit of the gray zone of FFR (0.76 to 0.80) to below the lower limit.

Intracoronary papaverine, in a dosage of 8 to 12 mg in the right coronary artery and 12 to 20 mg in the left coronary artery, is an alternative method creating sufficiently long hyperemia (30 to 60 s) to make a pullback recording, with some dislodging of the guiding catheter if indicated, but is less used in the United States and Western Europe because of a small risk of polymorphous ventricular tachycardia (11,14).

The ideal hyperemic stimulus should be easy to administer (e.g., in a peripheral venous infusion or intracoronarily), have a short onset until maximum hyperemia is achieved, have a duration long enough to enable pressure pullback recordings (a few minutes), have few side effects, and be eliminated within a few minutes.

In the paper by Nair et al. (12), such a stimulus is proposed, i.e., regadenoson in a dosage of 400 μ g as a single injection in a peripheral infusion. If a central vein is present, it might be assumed that it will act in a similar way. The study by Nair et al. (12) was carefully performed and encouraging because the rate of hyperemia was almost exactly identical to intravenous adenosine without misclassifying any stenosis when the FFR threshold of 0.80 was used (16). The hemodynamic effects (a slight decrease in blood pressure and increase in heart rate) were comparable between both stimuli, whereas only minimal subjective side effects were observed.

However, before accepting regadenoson as a sufficient (and maybe ideal) hyperemic stimulus for FFR measurement, some more work has to be done, and a number of limitations should be critically assessed. First, the study by Nair et al. (12) was performed in a small group of patients with intermediate stenoses in single-vessel disease only and under favorable clinical conditions. In those patients, a

marvelous correlation was found between both intravenous adenosine as a gold standard and regadenoson as the proposed alternative. Furthermore, the assessment of side effects was somewhat clouded by the fact that the patients in this study were sedated, which is not routine in patients undergoing PCI in a catheterization laboratory. Validation in many more patients over a larger range of stenoses and a larger variety of clinical conditions should be performed.

Furthermore, in creating maximum hyperemia in a coronary artery for FFR measurement, 2 aspects are important: induction of truly maximum hyperemia to calculate FFR and maintaining maximum hyperemia for a period long enough to perform a pressure pullback recording to analyze a decline of pressure along the artery. From the data by Nair et al. (12), it seems that regadenoson is sufficient, but in their study, no exact time intervals were measured with respect to the duration of action of regadenoson.

In addition, the measurements were not performed in duplicate, and before accepting regadenoson as the gold standard, reproducibility should be tested.

Next, measurements and validation versus intravenous adenosine should also be performed over a wider spectrum of stenosis severity with FFR values over the complete range (in stable patients between 0.35 and 1.00).

The study by Nair et al. (12) was performed meticulously, using state-of-the-art FFR measurements. The authors equalized pressures before entering the coronary artery, careful attention was paid to avoid arterial pressure damping (1 of the reasons why FFR can be measured artificially too high), and the pressure differences were assessed on a beat-to-beat basis and not from a mean pressure tracing which can lead to overestimation of FFR, especially when intracoronary adenosine is used.

Also and importantly, the authors took the responsibility and consequences of their actions by strictly adhering to treating patients with FFR <0.80 and deferring PCI or CABG in patients with FFR >0.80.

As mentioned, the side effects of both drugs seemed to be favorable although this group of patients is very small. The authors are careful to say that regadenoson maybe safely used with mild or moderate reactive airway disease and chronic obstructive pulmonary disease. It should be emphasized that adenosine is also safe in these patients and that only in cases of severe asthma, might intravenous adenosine cause problems.

In the practice of the authors of this editorial in more than 10,000 patients in whom intravenous adenosine was administered for FFR measurement, severe asthma attacks were only observed 3 times. More often, the subjective and harmless feeling of dyspnea experienced by patients receiving adenosine-like drugs (also regadenoson) is sometimes confused with asthma. Safety of intravenous adenosine is beyond doubt, and it might be anticipated that the same holds true for regadenoson.

Obtaining a reliable FFR measurement depends on induction of maximum coronary hyperemia. Failure to induce maximum hyperemia will result in overestimation of FFR and undertreatment of the patient. Therefore, the endeavors to find easier hyperemic stimuli are important and the authors of the papers in this issue of *JACC: Cardiovascular Interventions*, should be commended for their contribution.

Nevertheless, further studies in a larger group of patients with a large variety of stenosis severity and clinical conditions, and further investigation of the time intervals of action, are mandatory before large-scale use of regadenoson for FFR measurement can be recommended. In the mean time, it is likely that operators experienced in fractional flow reserve, will already build up experience on a compassionate-use basis.

Reprint requests and correspondence: Dr. Nico H. J. Pijls, Catharina Hospital, P.O. Box 1350, 5602 ZA Eindhoven, the Netherlands. E-mail: nico.pijls@inter.nl.net.

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