attributed to Albert Einstein, the saying, “Everything should be made as simple as possible, but not simpler,” embodies a concept that certainly applies to our understanding and interpretation of fractional flow reserve (FFR) across the most clinically important stenosis interventionalists encounter, the left main (LM) stenosis. Remarkable technical advances supported by multicenter, long-term outcome studies have validated FFR for daily use in the cardiac catheterization laboratory. FFR, the ratio of coronary pressure beyond a stenosis to the aortic pressure (representing the normal coronary pressure in the absence of a stenosis), measured during maximal hyperemia (ie, minimal myocardial bed resistance) identifies the ischemic potential of the lesion. In practice, FFR guidance for multivessel percutaneous coronary intervention compared with angiographic guidance alone produces better clinical and economic outcomes.1,2

Now for the not-so simple part, interpreting LM FFR in the more complicated angiographic scenario where there is downstream stenoses (ie, LM/LAD), the combination of LM/LAD stenoses requires understanding FFR and the interplay of 2 new conditions: (1) lesions acting in series and (2) potential reduction of the maximal LM blood flow (and myocardial bed size), as a function of the degree of obstruction of the downstream lesion.

For serial lesions, an accurate FFR requires that maximal hyperemia be achieved across a target lesion. Each of the serial lesions blunts the hyperemia of the other, and thus simple pressure ratios (without using a distal coronary balloon occlusion pressure)4,5 cannot produce accurate individual FFR values. In clinical practice, the summed FFR across both lesions (LM+LAD=FFRepicardial) determines the need to treat; and a pressure pullback recording tells us which lesion to treat. The lesion with the largest pressure (ΔP, not FFR) is treated first, and then FFR across the remaining lesion determines the next treatment decision. Such a method can be used to assess serial LM with LAD disease, but this approach engenders a downside: accepting stenting of the unprotected LM, if after treating the LAD the LM FFR becomes abnormal.

### Table. Factors Confounding the Interpretation of FFR

<table>
<thead>
<tr>
<th>Category</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Equipment factors</td>
<td>Erroneous zero</td>
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<tr>
<td></td>
<td>Incomplete pressure transmission (tubing/connector leaks)</td>
</tr>
<tr>
<td></td>
<td>Faulty electric wire connection</td>
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<tr>
<td></td>
<td>Pressure signal drift</td>
</tr>
<tr>
<td></td>
<td>Hemodynamic recorder miscalibration</td>
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<tr>
<td>2. Procedural factors</td>
<td>Guide catheter damping</td>
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<td></td>
<td>Incorrect placement pressure sensor</td>
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<td></td>
<td>Inadequate hyperemia</td>
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<td>3. Physiological factors</td>
<td>Serial lesion</td>
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<tr>
<td></td>
<td>Reduced myocardial bed</td>
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<tr>
<td></td>
<td>Acute myocardial infarction</td>
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<tr>
<td></td>
<td>Theoretical conditions that might influence FFR</td>
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<tr>
<td></td>
<td>Severe left ventricular hypertrophy</td>
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<tr>
<td></td>
<td>Exuberant collateral supply</td>
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<tr>
<td></td>
<td>Adenosine insensitivity</td>
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</tbody>
</table>

FFR indicates fractional flow reserve.
For the role of the myocardial bed, fundamental theory states that myocardial blood flow is related to ventricular mass (i.e., the size of the myocardial bed). The LM myocardial bed is large, comprising the LAD and CFX beds. However, an LAD lesion downstream from the LM narrowing makes assessment problematic with the unknown amount of bed flow beyond an LAD obstruction. Convincing demonstrations of the influence of myocardial bed size on FFR have been provided by Iqbal et al.\(^6\) and Sachdeva and Uretsky,\(^7\) showing that LAD FFR can increase after right coronary artery recanalization of previously collateral supplied right coronary artery territory (Figure).

Because coronary artery disease is a diffuse process, there is always some disease in branches beyond a narrowed LM. Although this situation seems complex enough to invalidate FFR for the LM/LAD anatomy, in this issue of *Circulation: Cardiovascular Interventions*, Yong et al.\(^9\) demonstrate that only a severe and proximal LAD will artificially influence the LM FFR. Extending the prior research of Daniels et al.\(^10\) from a bench model to experimental animals, Yong et al.\(^9\) answered the question, “How severe does an LAD stenosis need to be to affect the FFR across a LM stenosis?” Using pressure sensor wires in the LAD and CFX, balloon catheters were used to create variable stenoses in the LM and LAD. After establishing an LM stenosis, followed by increasing LAD stenoses, the investigators found that the difference between the FFR in the LM with no LAD stenosis (FFR\(_{\text{true}}\)) and the LM FFR with an LAD stenosis (FFR\(_{\text{apparent}}\)) correlated directly with increasing LAD stenosis severity. For the whole cohort of measurements, the mean difference (FFR\(_{\text{true}}\)−FFR\(_{\text{apparent}}\)) was 0.035 U and was only >0.05 U when the FFR\(_{\text{epicardial}}\) was <0.50. Worth noting is that the proximal compared with mid-LAD stenosis had greater effect on FFR\(_{\text{apparent}}\) and there were no cases of FFR\(_{\text{true}}\) <0.75 when the FFR\(_{\text{apparent}}\) >0.80 appeared with FFR\(_{\text{epicardial}}\) was >0.5, findings that mean only a severe and proximal LAD stenosis significantly influenced the LM FFR\(_{\text{true}}\).

Yong et al.\(^9\) are to be congratulated for translating the clinical problem to the research bench\(^10\) and back to the animal model, providing some direction for the clinician in the human laboratory. We should keep several limitations of this study in mind. The measurements of reversing the bed stenosis, that is producing a CFX stenosis and measuring beyond the LM in the LAD, were not performed. There is no reason to think that in the same model, the same results could not be obtained from the reverse situation with LM/CFX disease. Of relevance to this issue is that unlike in sheep, patients usually have a larger LAD than CFX myocardial bed. Another scenario that remains to be investigated is the LM FFR with both LAD and CFX (LM/LAD/CFX) stenoses. This problem moves the clinical decision into consideration of the patient with multivessel, complex coronary artery disease where coronary bypass graft surgery may be a more practical and better therapeutic option.

Another minor methodologic concern was the difficulty in creating acutely a stable stenosis in compliant sheep arteries and the potential of rapidly forming collaterals, both of which may explain some of the variance of the FFR\(_{\text{apparent}}\) > FFR\(_{\text{true}}\). Differences of >0.025 U can be seen at all FFR\(_{\text{epicardial}}\) values, with the largest difference occurring at FFR\(_{\text{epicardial}}\) <0.60. FFR\(_{\text{apparent}}\) < FFR\(_{\text{true}}\) by >0.025 U, however, is rare. It was also gratifying to know that FFR\(_{\text{apparent}}\) >0.80 was unaffected by FFR\(_{\text{epicardial}}\) when >0.5, a valuable observation that will need validation before widespread clinical application. For the moment and based on these results, the principal finding

**Figure.** The influence of myocardial bed size on left main fractional flow reserve (FFR). A, left main artery with stenosis has an FFR\(_{\text{true}}\) of 0.78. The myocardial perfusion bed of the left main is the sum of the left anterior descending (LAD) and circumflex (CFX) artery beds (blue circles and summed bed is yellow oval). B, an LAD stenosis is now present. The FFR\(_{\text{apparent}}\) increases to 0.82 because the left main (LM) perfusion bed (yellow oval) is reduced by the LAD stenosis. The concept of stenting the LAD and then finding the FFR\(_{\text{true}}\) is 0.78 presents a difficult decision regarding further treatment of the unprotected LM stenosis. C, in a different scenario, the left main stenosis FFR is 0.78 but the RCA is 100% occluded and filled by left to right collaterals (red arrow). The LM myocardial bed is now much larger with the sum of the LAD/CFX/RCA regions (blue circles, summed bed in yellow oval). D, on restoration of RCA flow after stenting (cylinder in RCA), FFR\(_{\text{true}}\) becomes 0.84 because myocardial bed is reduced to normal LM bed. Adapted from Kern\(^8\) with permission of John Wiley & Sons, Inc.
that an $\text{FFR}_{\text{epicardial}} > 0.5$ has a limited effect on our ability to correctly interpret $\text{FFR}_{\text{lumbar}}$ for the LM/LAD lesion should be accepted.

However, there will be some uncertainty about the LM/LAD complex when the $\text{FFR}_{\text{epicardial}} < 0.5$. What should we do in lieu of definitive clinical, human data on the LM/LAD scenario? Although personally not a strong advocate of intravascular ultrasound for LM lesion assessment, we should consider the work of Puri et al\textsuperscript{11} recommending the use of FFR for the assessment of the simple, isolated ostial or midshaft LM coronary stenoses. In those patients with the not-so-simple lesions, for example, distal LM bifurcation or LM/LAD±CFX coronary arterial disease, the liberal use of intravascular ultrasound is suggested. Because this recommendation appeared before the current study of Yong et al\textsuperscript{9}, a cautionary note regarding intravascular ultrasound is in order. Although a minimal luminal area of >6 mm\textsuperscript{2} is an oft-quoted threshold,\textsuperscript{12} it is but a conservative approximation of true physiology, best indicating a lack of functional significance rather than an minimal luminal area <6 mm\textsuperscript{2} being an indication to treat.

Although incompletely studied at this time in patients having the scenario tested by Yong et al,\textsuperscript{9} it is highly likely that the FFR will be proved to be as useful and efficacious for the LM/LAD lesion assessment as it has in other simple and complex lesions subsets. For patient care, FFR is just simple enough, providing objective information for excellent clinical decisions in the catheterization laboratory.

Disclosures

Dr Kern is a speaker for St. Jude Medical Inc, and Volcano Therapeutics Corp, manufacturers of the pressure wires.

References


Key Words: Editorials ■ coronary artery disease ■ coronary angiography ■ coronary physiology ■ fractional flow reserve
When Does a Left Anterior Descending Stenosis Alter Flow Across a Left Main Segment?: Interpreting Left Main Fractional Flow Reserve With Downstream Obstruction

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