The Present and Future of Fractional Flow Reserve
Bon-Kwon Koo, MD, PhD

Revascularization of coronary artery stenosis should be based on objective evidence of ischemia. Fractional flow reserve (FFR) is an invasive physiologic index that can be easily measured in the cardiac catheterization laboratory to assess the functional significance of coronary stenosis. FFR-guided revascularization strategy has been proven to be better than angiography-guided strategy in patients with coronary artery disease. Recent development of more convenient ways to induce hyperemia will reduce the barrier to measuring FFR and further expand its clinical applicability. Invasive physiologic indices without hyperemia are also under active investigation. Moreover, a novel noninvasive FFR measurement based on coronary CT angiography and computational fluid dynamics has been developed and will soon be incorporated into clinical practice. Given the rapid adoption of invasive and noninvasive physiologic indices in daily practice, a review of the current status of FFR and future perspectives is presented. (Circ J 2014; 78: 1048–1054)

Key Words: Computational fluid dynamics; Coronary artery disease; Coronary computed tomographic angiography; Fractional flow reserve; Ischemia

The presence of myocardial ischemia is associated with future cardiovascular events, and revascularization of these ischemia-causing stenoses can improve the patient’s symptoms and outcomes. Therefore, the decision to revascularize in patients with coronary artery disease (CAD) should be guided by the evidence of myocardial ischemia. The limitation of coronary angiography in the determination of ischemia-causing stenosis, especially in patients with intermediate or ambiguous lesions, is well known. This uncertainty may cause unnecessary revascularization of insignificant lesions or failure to revascularize the clinically significant ones. Therefore, additional invasive imaging and physiologic tools are commonly used in the cardiac catheterization laboratory.

Fractional flow reserve (FFR) is a reliable physiologic index for determining the functional significance of a coronary stenosis. FFR is the fraction of the maximal achievable myocardial flow that can be maintained in the presence of epicardial coronary stenosis. FFR represents the extent to which maximal myocardial blood flow is limited by the presence of epicardial stenosis and can be easily measured by the ratio of distal coronary pressure to aortic pressure during maximal hyperemia in the cardiac catheterization laboratory.

**FFR: The Present**

**Clinical Application and Evidence**

Since the concept of myocardial FFR was developed and introduced by Pijs and De Bruyne in the early 1990s, the clinical benefit of a FFR-guided revascularization strategy has been proven in several studies with different lesion subsets from simple intermediate lesions to complex left main or bifurcation lesions (Figure 1). As the cutoff value of FFR for clinical decision making, many clinicians now use FFR ≤0.80 as a guide to performing revascularization because of the small zone of uncertainty (FFR 0.75–0.80) and the results of the FAME study. Clinical studies, including DEFER, FAME and FAME II, have proved the safety of deferral according to FFR and the danger of medical treatment for functionally significant stenoses. After 5 years’ follow-up of the DEFER study, the composite rate of death and acute myocardial infarction (MI) in the defer group was only 3.3% in 5 years. In the FAME study, investigators hypothesized that FFR-guided percutaneous coronary intervention (PCI) with drug-eluting stents would be superior to conventional angiography-guided PCI in patients with multivessel CAD. At 1-year follow-up, the FFR group had fewer total clinical events (13.2% vs. 18.4%, P=0.02) and less combined death or MI (7.3% vs. 11%, P=0.04) compared with the angiography-guided PCI group, even with fewer stents per patient (1.9±1.3 vs. 2.7±1.2, P<0.001). Further analysis showed that a FFR-guided strategy is not only cost-effective but also cost-saving compared with an angiography-guided strategy. The FAME II study randomized patients with stable CAD to FFR-guided revascularization or medical therapy alone and found that FFR-guided revascularization decreased the need for urgent revascularization (1.6% vs. 11.1%; hazard ratio, 0.13; 95% confidence interval [CI] 0.06–0.30; P<0.001) which were mainly derived by less frequent MI or ECG-documented ischemia.

Recently, 3 large registries again confirmed the clinical benefit of FFR in daily practice. A French registry revealed that the use of FFR during angiography was associated with revasc-
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Although FFR has become the gold-standard assessment for detecting the ischemia-related lesion, it is an invasive procedure, requires expensive devices and pharmacologic intervention to induce maximal hyperemia. Therefore, to expand the clinical applications of FFR, further development is still needed.

Novel Hyperemic Stimuli

Continuous infusion of adenosine through the femoral vein has been considered as the gold-standard method of inducing hyperemia for FFR measurement. However, it requires large doses of adenosine, resulting in high cost, an additional procedure for femoral vein access and is not feasible during transradial procedures. Furthermore, the adenosine administration itself is associated with systemic adverse effects for the patient such as AV conduction block, dyspnea and chest discomfort.

Seo et al investigated the hyperemic efficacy of continuous intravenous (IV) infusion of adenosine through the forearm vein, which is the most commonly used access in the catheterization laboratory. They found that the hyperemic efficacy of forearm vein infusion was not inferior to that of femoral vein infusion (FFR: 0.80±0.11 vs. 0.80±0.10, P for non-inferiority=0.01). Therefore, a forearm vein can be used as an access for adenosine infusion during transradial procedures or when femoral vein access is not feasible. However, a large needle (18G) should be used and access around and distal to the wrist should be avoided.

To facilitate the use of FFR during daily practice, novel hyperemic agents have been also introduced. Regadenoson is a selective A2A receptor antagonist and a single IV bolus injection of this drug is reported to induce maximal hyperemia within 30s. Nair et al compared the hyperemic efficacy of regadenoson
Novel Physiologic Index Without Hyperemia

Recently, physiologic indices that do not require hyperemia have been introduced and have drawn attention because they can reduce procedural time and cost as well as patients’ discomfort.22,23

The instantaneous wave-free ratio (iFR) was developed from an investigation of coronary flow, velocity and resistance. There is a certain period in the cardiac cycle during which the resistance at rest is stable (wave-free period) such that the ratio of the proximal and distal pressures can be proportional to that of coronary flow (Figure 3).23 In the first-in-human ADVISE study, the distal-to-proximal pressure ratio during this period (iFR) had a good correlation with FFR (r=0.9, P<0.001) and showed excellent diagnostic performance.23 The best cutoff value of iFR to predict FFR ≤0.8 was 0.83 and the overall diagnostic accuracy to define FFR ≤0.8 was 88%.

Since then, there has been a big debate over the background and clinical relevance of this index.7,24,25 Park et al performed an independent, blinded comparison between iFR and FFR in 238 consecutive lesions in which FFR was measured with both intravenous and intracoronary adenosine administration. There was a good correlation between iFR and FFR (r=0.77, 95% CI 0.71–0.82) and the best cutoff value of iFR for FFR ≤0.8 was 0.9. Although the resting Pd/Pa showed almost the same diagnostic performance as the iFR, the latter had better discriminatory power than the resting Pd/Pa. In a large multicenter core laboratory comparison of iFR and FFR (n=1,593), overall sensitivity, specificity, positive predictive and negative predictive values of iFR ≤0.90 (for FFR ≤0.80) were 78.9%, 82.4%, 85.2%, and 81.4%, respectively.
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Figure 3. Concept of instantaneous wave-free ratio (courtesy of Justin Davies, MD).

Figure 4. Process for the computation of CT-derived computed fractional flow reserve (FFR_{CT}). CTA, computed tomography angiography.
technology that enables determination of the functional significance of lesions, noninvasively, from computational fluid dynamics (CFD) applied to coronary computed tomography angiography (cCTA). The scientific principles that underlie this technology are well summarized in previous review papers. Briefly, a 3-dimensional patient-specific anatomic model is first constructed from the cCTA data (Figure 4). For assigning the boundary conditions of the CFD domain, the basal coronary outlet resistances at rest are determined from the principles of an allometric scaling law that allows estimation of total coronary flow from myocardial mass and a morphometry law that relates the resistance of a downstream vessel to the vessel size at each outlet. These novel concepts, especially, iFR, have great appeal as they may be able to provide faster and easier invasive physiologic assessments of CAD. However, studies still lack clinical outcome data and await further validation. It will be interesting to see the results of the ongoing FLAIR study, which compares the outcomes of FFR-guided vs. iFR-guided revascularization.

Noninvasive CT-Derived Computed FFR

Noninvasive CT-derived computed FFR (FFR_{CT}) is a novel technology that enables determination of the functional significance of lesions, noninvasively, from computational fluid dynamics (CFD) applied to coronary computed tomography angiography (cCTA). The scientific principles that underlie this technology are well summarized in previous review papers. Briefly, a 3-dimensional patient-specific anatomic model is first constructed from the cCTA data (Figure 4). For assigning the boundary conditions of the CFD domain, the basal coronary outlet resistances at rest are determined from the principles of an allometric scaling law that allows estimation of total coronary flow from myocardial mass and a morphometry law that relates the resistance of a downstream vessel to the vessel size at each outlet. This method is based on the fundamental “form-function” relationship that modulates the size of organs according to metabolic demand. A mathematical model of hyperemic conditions is derived from the effect of adenosine on reducing the resistance of the coronary microcirculation. Lastly, on the basis of a discretized model of patient-specific geometry and boundary conditions, CFD analysis is performed to numerically solve the governing equations of fluid dynamics (ie, Navier Stokes equations) as a Newtonian fluid. The numerical solutions of coronary flow and pressure fields are used to compute a com-

Table. Diagnostic Performance of CT-Derived Computed Fractional Flow Reserve (FFR_{CT}) and Coronary CT Angiography (cCTA) in 3 Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>DISCOVER-FLOW$^{31}$ (n=103)</th>
<th>DeFACTO$^{32}$ (n=252)</th>
<th>NXT$^{33}$ (n=254)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>FFR_{CT} cCTA</td>
<td>FFR_{CT} cCTA</td>
<td>FFR_{CT} cCTA</td>
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<tr>
<td>Accuracy</td>
<td>84% 61%</td>
<td>73% 64%</td>
<td>81% 53%</td>
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<tr>
<td>Sensitivity</td>
<td>93% 94%</td>
<td>90% 84%</td>
<td>86% 94%</td>
</tr>
<tr>
<td>Specificity</td>
<td>82% 25%</td>
<td>54% 42%</td>
<td>79% 34%</td>
</tr>
<tr>
<td>PPV</td>
<td>85% 58%</td>
<td>67% 61%</td>
<td>65% 40%</td>
</tr>
<tr>
<td>NPV</td>
<td>91% 80%</td>
<td>84% 72%</td>
<td>93% 92%</td>
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<td></td>
<td>PPV, positive predictive value; NPV, negative predictive value.</td>
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Another resting index is the basal stenosis resistance index (bSR), which can be calculated by the ratio of pressure gradient to distal flow velocity under resting conditions. In a study by van de Hoef et al, the diagnostic performance of bSR (area under the curve 0.77; 95% CI 0.73–0.83) was comparable to that of FFR (area under the curve 0.77; 95% CI 0.73–0.83) for the detection of myocardial ischemia assessed by myocardial perfusion scintigraphy. However, this index requires a dedicated wire equipped with both pressure- and velocity-monitoring sensors and reliable measurement is technically difficult.

These novel concepts, especially, iFR, have great appeal as they may be able to provide faster and easier invasive physiologic assessments of CAD. However, studies still lack clinical outcome data and await further validation. It will be interesting to see the results of the ongoing FLAIR study, which compares the outcomes of FFR-guided vs. iFR-guided revascularization.

Figure 5. Example of virtual stenting and post-stenting CT-derived computed fractional flow reserve (FFR_{CT}). (A) Two consecutive intermediate stenoses (white arrows) can be seen in the left anterior descending coronary artery and FFR_{CT} is 0.72. (B) After stenting the proximal lesion, the FFR_{CT} is 0.76, which suggests insufficient hemodynamic improvement after stenting. (C) Post-virtual stenting FFR_{CT} is 0.86 after stenting both lesions.
Conclusions

FFR has become the gold standard for defining the functional significance of coronary stenosis. Routine use of FFR in daily clinical practice will reduce unnecessary intervention and improve the outcomes of patients with CAD. Novel hyperemic stimuli and novel physiologic indices without hyperemia will reduce the current procedural barriers and expand the clinical application of physiologic assessment in the cardiac catheterization laboratory. Furthermore, noninvasive assessment of the functional significance of coronary stenosis such as FFR CT can be helpful in predicting the functional significance of coronary lesions and in planning the treatment strategy before the invasive procedures actually take place. Future developments in this technological realm will continue to improve clinical outcomes for patients with CAD.

Disclosures

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