Fractional Flow–Guided Coronary Artery Bypass Grafting
A Word of Caution

Harold L. Lazar, MD

The traditional basis for all forms of coronary artery revascularization has been the percent stenosis resulting from an atherosclerotic plaque or thrombotic occlusion based on coronary angiography. With the introduction of fractional flow reserve (FFR) technology, a new gold standard has been developed to assess the severity of a coronary artery stenosis that takes into account the physiology of that stenosis.

FFR is defined as the ratio of maximal blood flow across a stenotic lesion compared with normal maximal flow. It is measured with a coronary pressure guidewire and is compared with the aortic pressure measured simultaneously with the guide catheter during maximum hyperemia. An FFR value of <0.80 is predictive of a coronary stenosis responsible for ischemia with an accuracy >90%.1 The FFR technique requires some extra manipulation during the catheterization, and a central line may be necessary if intravenous adenosine is used to elicit the maximal hyperemic response. Although there is potential for trauma to the coronary vessel, this complication is rarely reported.

Initially, FFR was used to determine the applicability of stenting for patients with single-vessel disease. In a study involving 67 patients with multivessel disease, Melikian and coworkers2 showed that FFR measurements were not influenced by either the presence or absence of stenosis in other adjacent vessels and could be used to assess coronary stenosis in patients with multivessel disease. The Fractional Flow Reserve Versus Angiography in Multivessel Evaluation (FAME) I trial used FFR to determine the need for stent deployment in 1005 patients with ≥2 diseased coronary arteries compared with decisions based on angiography alone.3 The primary end point, a combination of death, myocardial infarction, and the need for repeat revascularization, occurred in 18.3% of patients in the angiography group compared with 13.2% in the FFR group (P=0.02). There was no statistical difference in all-cause mortality or the incidence of myocardial infarctions, but the need for repeat revascularization was decreased (9.5% for angiography versus 6.5% for FFR; P=0.08) in the FFR group. FFR reduced the number of stents and the amount of contrast used. The procedure-related costs were also significantly lower with FFR. In a 2-year follow-up analysis of the FAME patients, the incidence of mortality or myocardial infarction was significantly lower in the FFR group.4 In those lesions that were deferred on the basis of an FFR >0.80, the incidence of a myocardial infarction was 1.8% and the rate of revascularization was 3.2%. In the FAME II trial, the combination of PCI plus optimal medical therapy for coronary lesions with an FFR <0.80 compared with medical therapy alone significantly decreased the need for urgent revascularization.5 In those patients with stenosis with an FFR >0.80, medical therapy alone resulted in excellent outcomes, regardless of the angiographic appearance of the stenosis. FFR was also helpful in determining the significance of angiographic equivocal left main stenosis to decide whether a revascularization procedure was necessary.6 These trials helped to support the premise that PCI should be guided more by physiological considerations and not solely by anatomic factors.

In this edition of Circulation, Toth et al7 sought to determine the effects of FFR on coronary artery bypass graft surgery (CABG) and to compare the outcomes of FFR-guided grafts with those of grafting guided by angiography. In the angiography-guided group, 429 patients underwent grafting on the basis of contrast angiography only. In the FFR group, the decision to bypass a vessel in 198 patients was made if the FFR was <0.80 or deferred it if it was >0.80. In the FFR group, the incidence of multivessel disease was significantly downgraded and was associated with a decreased number of grafts. After 3 years, there was no difference in the incidence of major adverse cardiac events (overall death, myocardial infarction, or need for target revascularization) between the groups. However, FFR-guided patients has a lower incidence of class II through IV angina (31% versus 4%; P<0.001). The number of venous anastomoses was significantly lower in the FFR group. In a subgroup of 155 patients (25%) who underwent recatheterization, freedom from graft occlusion was higher in the FFR patients. The incidence of arterial graft occlusion was equivalent in both groups. The authors concluded that FFR-guided CABG did not result in a higher incidence of adverse clinical events and was associated with a lower incidence of recurrent angina.

There were, however, numerous limitations of this study that limit the conclusions that can be drawn on the role of FFR-guided CABG surgery. The sample size was relatively small and was derived from a retrospective, nonrandomized, single-center study. The type of surgical technique used, on versus off pump, and the decision to use FFR were left to the discretion of the operator. Important factors that affect graft patency are not reported. There is no mention of the specific types of conduits used, the use of antiplatelet agents, the use of statins,
whether target low-density lipoprotein levels were achieved, or the size of the distal vessels that were grafted. Angiography-guided patients were more likely to have had diabetes mellitus, a group of patients known to have decreased graft patency. FFR patients were also more likely to have received an arterial conduit, which could also have explained the higher freedom from graft reocclusion in this group. Angiographic follow-up was performed in only 25% of patients. Of the 234 grafts studied, 174 were in the angiography-guided group and only 60 were in the FFR group. Furthermore, no mention is made of how many FFR-guided vessels with FFR values >0.80, in which grafting was deferred, now had progression of native disease and required intervention.

Further insight into the potential role of FFR in CABG patients was provided by Botman and coworkers, who prospectively studied the patency of bypass grafts in 164 patients 1 year after randomization to FFR compared with angiography-guided grafting. A significant graft occlusion was found in 8.9% of the FFR-guided versus 21.4% of the angiography-guided patients (P<0.01). There were significantly fewer occlusions in FFR-guided vessels for both arterial (13.7% versus 21.9%; P<0.2) and venous (5.9% versus 20.0%; P<0.03) grafts. Graft patency was significantly higher in vessels >2.0 mm. In those patients with 50% to 70% stenosis as indicated by angiography, the graft patency was higher if the FFR was <0.75. However, these findings were of no clinical significance because patients with occluded grafts on noncritical lesions had no significant increase in angina or need for repeat revascularization. Further evidence to support the concept that an anatomic stenosis may not be physiologic in CABG patients was provided by Ferguson and coworkers, who used near-red fluorescence angiography to detect coronary blood flow in bypass grafts during CABG surgery. In this technique, indocyanine green dye is administered as a bolus injection. A change in fluorescence intensity is proportional to myocardial tissue perfusion. A total of 359 grafts were imaged in 160 patients. All grafts were patent; however, 24% of arterial grafts and 22% of vein grafts showed no change in regional perfusion response to bypass grafting. In 165 left internal mammary to left anterior descending artery grafts at least 70% proximal, 40 grafts showed no change in regional myocardial perfusion response to bypass grafting. In 165 left internal mammary to left anterior descending artery grafts with at least 70% proximal left anterior descending artery stenosis, 40 had no change in regional myocardial perfusion, and 32 of those 40 grafts had evidence of competitive flow. No long-term follow-up on angina or graft patency was provided. However, these results suggest that angiography-guided grafts may not alter perfusion to regions of the myocardium based on visual stenosis alone.

On the basis of these studies, should FFR also become the gold standard for determining which vessels to graft during CABG surgery? The FFR technique has several limitations that may have a greater impact in surgical grafting compared with percutaneous coronary intervention stenting. FFR is based on models that assume a normal distal microcirculation. However, this may not be true in the presence of distal small vessel disease such as in patients with diabetes mellitus or diffuse coronary atherosclerosis in whom FFR may not accurately reflect flow beyond the tip of the pressure-measuring device. This patient population is more likely to be referred for CABG surgery than for percutaneous coronary intervention. The value of FFR may also be limited for detecting distal disease in patients with left ventricular hypertrophy because of the poor response that these patients have to coronary vasodilators. The accuracy of FFR in bifurcation lesions has yet to be determined because no randomized studies have demonstrated the efficacy of this technique for these lesions. Finally, the cutoff of FFR <0.080 was determined in a select group of patients, most of whom had normal left ventricular function. Further trials are necessary to determine its accuracy in bifurcation lesions, in small diffuse vessel disease, and in myocardium with significantly reduced regional wall motion.

The goal of all surgical revascularization is to provide optimal graft patency. The majority of grafts fail because of technical factors and progression of graft and native vessel disease. However, competitive flow may lead to decreased graft patency in both single and sequential arterial grafts. Furthermore, patency of all conduits is reduced in smaller vessels (≤1 mm), especially in arterial conduits used to anastomose vessels with <80% stenosis. FFR may help to avoid grafts that result in competitive flow and in smaller vessels with noncritical stenosis.

One of the reasons patients are referred for surgical revascularization rather than percutaneous coronary intervention is the concept that CABG offers the patient more complete revascularization. Previous studies have shown that incomplete revascularization is associated with reduced long-term survival. Before embracing the FFR-guided approach to surgical revascularization, we must keep in mind the current limitations of FFR and understand that most studies involving FFR-guided CABG have only short-term follow-up (1–3 years) and include only a small number of patients. We still do not know what the long-term effects of not grafting angiographic stenotic lesions will be on the distal myocardium. The experience with off-pump CABG surgery strongly suggests that patients referred for CABG who leave the operating room with an incomplete revascularization based on angiography alone have decreased long-term survival and a higher incidence of revascularization procedures. Nevertheless, FFR-guided grafting may have an important role in determining whether angiographic lesions with a 50% to 70% stenosis should be bypassed and the role of physiology of the distal myocardium in determining graft patency. However, before changes are made in determining what vessels should be grafted during CABG based on FFR, larger prospective, randomized trials with longer follow-up are needed to better understand the role of this technology.

Disclosures
None.

References
3. Tonino PA, DeBruyne B, Pijls NH, Siebert V, Ikeo F, van’t Veen M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG; Ver Lee PN; MacCarthy PA,


Fractional Flow–Guided Coronary Artery Bypass Grafting: A Word of Caution

Harold L. Lazar

_Circulation_. 2013;128:1393-1395; originally published online August 28, 2013;
doi: 10.1161/CIRCULATIONAHA.113.005397

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/128/13/1393

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/