Fractional Flow Guided Coronary Artery Bypass Grafting:

A Word of Caution

Running title: Lazar; Fractional flow and coronary surgery

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The traditional basis for all forms of coronary artery revascularization has been the percent stenosis due to 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 which takes into account the physiology of that stenosis.

FFR is defined as the ratio of maximal blood flow across a stenotic lesion compared to normal maximal flow. It is measured using a coronary pressure guidewire and is compared to 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%. The FFR technique requires some extra manipulation during the cath and a central line may be necessary if IV 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 co-workers 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 FAME (Fractional Flow Reserve vs. Angiography in Multivessel Evaluation) I trial used FFR to determine the need for stent deployment in 1005 patients with two or more diseased coronary arteries vs. decisions based on angiography alone. The primary endpoint, a combination of death, MI, and the need for repeat revascularization occurred in 18.3% of patients in the angiography group vs. 13.2% in the FFR group (p = 0.02). There was no statistical difference in all cause mortality or the incidence of MIs but the need for repeat revascularization was decreased (9.5% angio vs. 6.5% 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 two-year follow-up analysis of the FAME patients, the incidence of mortality or MI was significantly lower in the FFR group. In those lesions which were deferred based on FFR > 0.80; the incidence of an MI 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 vs. medical therapy alone, significantly decreased the need for urgent revascularization. In those patients with a 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 angiographical equivocal left main stenosis to decide whether a revascularization procedure was necessary. These trials helped to support the premise that PCI should be guided more by physiological considerations and not solely by anatomical factors.

In this edition of Circulation, Barbato and co-workers sought to determine the effects of FFR on coronary artery bypass graft surgery (CABG) and compare the outcomes of FFR-guided grafts with that of grafting guided by angiography. In the angio-guided group, 429 patients underwent grafting based solely on contrast angiography. In the FFR group, the decision to bypass a vessel in 198 patients was determined if the FFR was < 0.80 or deferred it if was > 0.80. In the FFR group, the incidence of multivessel disease was significantly downgraded and was associated with a decreased number of grafts. Following three years, there was no difference in the incidence of MACE (overall death, MI, or need for target revascularization) between the groups. However, FFR-guided patients has a lower incidence of Class II-IV angina (31% vs. 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 in this study which limit the conclusions that
can be drawn regarding the role of FFR-guided CABG surgery. The sample size was relatively
small and was derived from a retrospective, non-randomized, single center study. The type of
surgical technique used, on vs. off pump, and the decision to use FFR was left to the discretion
of the operator. Important factors which affect graft patency are not reported. There is no
mention of the specific types of conduits that were used, the use of antiplatelet agents, the use of
statins and whether target LDL levels were achieved or the size of the distal vessels that were
grafted. Angio-guided patients were more likely to have had diabetes - 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 only performed in 25% of patients. Of the 234 grafts studied, 174
were in the angio-guided group and only 60 in the FFR group. Furthermore, no mention is made
as to how many FFR guided > 0.80 vessels, in whom 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 co-workers who prospectively studied the patency of bypass grafts in 164 patients one year
after randomization to FFR vs. angiography-guided grafting. A significant graft occlusion was
found in 8.9% of the FFR-guided vs. 21.4% of the angiography-guided patients (p < 0.01). There
were significantly less occlusions in FFR-guided vessels for both arterial (13.7% vs. 21.9%; 9 <
0.2) and venous grafts (5.9% vs. 20.0%; p < 0.03). Graft patency was significantly higher in
vessels > 2.0 mm. In those patients with a 50-70% stenosis based on angiography, the graft patency was higher if the FFR was < 0.75. However, these findings were of no clinical significance since patients with occluded grafts on non-critical lesions had no significant increase in angina or a need for repeat revascularization. Further evidence to support the concept that an anatomical stenosis may not be physiological in CABG patients was provided by Ferguson and co-workers who used near-red fluorescence (NIRF) 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 and 22% of vein rafts showed no change in regional perfusion response to bypass grafting. In 165 left internal mammary to left anterior descending artery (LAD) grafts with at least a 70% proximal LAD 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 regarding angina or graft patency was provided. However, these results suggest that angiographic-guided grafts may not alter perfusion to regions of the myocardium based on visual stenosis alone.

Based on these studies, should FFR also become the gold standard for determining which vessels to graft during CABG surgery? The FFR technique has several limitations which may have a greater impact in surgical grafting vs. PCI stenting. FFR is based on models which 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 or diffuse coronary atherosclerosis where 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 PCI. The value of FFR may also be limited to detect 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 is yet to be determined since 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 will be necessary to determine its accuracy in bifurcation lesions, 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 due to 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 (14, 15). FFR may help to avoid grafts which result in competitive flow and in smaller vessels with noncritical stenosis.

One of the reasons patients are referred for surgical revascularization rather than PCI 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 re-
revascularization procedures\textsuperscript{17,18}. Nevertheless, FFR-guided grafting may have an important role in determining whether angiographic lesions with a 50-70\% 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 will be needed to better understand the role of this technology.

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**References:**


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