Editorial

FFR-Guided CABG

Will Simpler and Better Be Enough to Change Practice?

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The remarkable success of coronary artery bypass graft surgery (CABG) in reducing angina, death, and myocardial infarction (MI) is attributed mostly to complete rather than incomplete revascularization. The concept of complete revascularization is at the crux of CABG decision-making, but it is anatomically based, bypassing all angiographic stenoses >50% diameter narrowing with the assumption that such lesions were always indicative of flow limitation (ie, ischemia) to the supplied region. Because visual assessment of a stenosis has a ±20% variance, even milder lesions are sometimes bypassed with the rationale that if coronary disease progressed, the bypass graft would be protective. This concept has been a source of significant controversy[1] and refuted in several studies demonstrating that bypassing functionally insignificant lesions results in early graft failure and acceleration of native artery disease, potentially exacerbating the consequences of late graft failure.[2,3] It has been reported[4] that up to 25% of bypass grafts to vessels that are not physiologically stenosed actually provide no measurable perfusion to the territory.

See Article by Fournier et al

After 2 decades of studies, most coronary interventionalists have incorporated fractional flow reserve (FFR), an invasively-measured translesional pressure ratio during hyperemia, and an important marker of lesion-specific ischemia, into their practice. FFR has repeatedly demonstrated that angiography is often unreliable, failing to correctly identify ischemic lesions, especially for intermediately severe (40%–70%) stenoses. Even intravascular ultrasound imaging of a stenosis has only a modest correlation to its physiology.[5] Myocardial mass and flow, microvascular disease, and lesion morphology are just a few of the factors contributing to the deceptive visual-functional mismatch, obscuring an accurate clinical assessment of a stenosis. Applied to practice, FFR-guided revascularization provides improved outcomes at lower cost to the healthcare system.[6]

Multiple studies support the applicability of FFR to patients planned to undergo CABG,[7] including the functional SYNTAX score[8] in which the angiographic complexity score is coupled to the FFR, which changes the ischemic burden and number of vessels in need of bypass. However, the message that angiographic stenosis severity does not always correlate to functional severity has not reduced the surgeon's reliance on anatomy alone as their standard of care. Years ago, Botman et al[3] demonstrated that the less severe anatomic (% diameter angiographic narrowing) and higher FFR stenoses were associated with reduced graft patency at 1 year; stenoses with an FFR >0.80 had graft occlusion rates >20%. In 2013, Toth et al[9] reported that FFR-guided CABG reduced the number of graft anastomoses and the on-pump surgery rate. Bypass graft patency at 3 years was higher with FFR-guided compared with only angiographic-guided CABG. However, despite a reduction in angina, FFR-guided CABG did not reduce mortality or MI over the 3-year follow-up of that original report.

The time-dependent, natural history of CABG conduits adds complexity to outcome studies as the potential benefits of surgical technique, number of arterial and vein grafts used, and lesion selection may not appear in the short term. With this in mind, in this issue of *Circulation: Cardiovascular Interventions*, Fournier et al[10] now report the extended 6-year results of their initial study[9] in which arteries were grafted based on either the angiographic severity or an FFR ≤0.80. Outcomes in 627 consecutive patients between 2006 and 2010 were analyzed by group; 198 having an FFR-guided approach on at least 1 artery and 429 having the standard angiographic-guided approach. The primary end points were overall death and MI and major adverse cardiovascular events including target vessel revascularization. At a mean of 87-month follow-up, Fournier et al[10] found that both the rate of composite death or MI as well as death alone was significantly lower in the FFR-guided CABG group than in the angiographic-guided group. By Cox multivariate regression analysis, FFR-guidance was an independent predictor of reduced death or MI (P=0.008). Of note, the Kaplan–Meier event rates only begin to diverge after 3 years to favor the FFR-guided CABG group. Last, to address several clinical differences between groups, a propensity-matched cohort also showed significantly fewer events in the FFR-guided group compared with the angiographic-guided group (16% versus 25%, P<0.02). This study is in concert with the large body of work supporting the application of physiologically-guided revascularization. Concerns that ungrafted lesions with nonischemic FFR values might progress and produce adverse events should be allayed by these reassuring results.

As shown in the DEFER trial (Deferral vs Performance of Percutaneous Coronary Intervention of Functionally

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Non-Significant Coronary Stenosis) and FAME study (Fractional Flow Reserve Versus Angiography for Guiding Percutaneous Coronary Intervention),[11,12] Fournier et al[10] demonstrated that revascularization of ischemic lesions while deferring bypass on those without ischemia produces superior clinical results. Although surgeons and interventional cardiologists alike are predisposed to think that their revascularization procedures are purely beneficial or protective, the evidence suggests otherwise. What accounts for the increased event rates in those patients having revascularization either by stenting or bypass grafting when the treated lesion was not flow-limiting (ie, the FFR is nonischemic)? In the DEFER study, FFR-negative stented patients had an increased major cardiovascular event rate presumed to be related to the adverse consequences of the initial implant and later because of late stent-associated events (in-stent restenosis or thrombosis, ie, stent disease). The increased event rates in the CABG patients having one or more bypass grafts on non-flow limiting stenoses may be related to a delayed effect of local vascular trauma and later to unappreciated graft closure and acceleration of coronary artery disease.[13] Closure of bypass grafts on vessels with preserved native flow, while often clinically silent in the short-term, likely has a significant negative clinical impact in the long term. The precise mechanisms of adverse events are certainly multifactorial and at this time remain speculative.

Limitations

The Fournier et al[10] study was retrospective and observational, and as such, there is a potential for bias in patient selection and underreporting of events. As a single center study, its site-specific protocols may not be completely generalizable. The surgeons were not tracked by technique or outcomes and hence the variance among surgical technique, judgment and expertise might be quite large. A higher repeat revascularization rate observed in the FFR-guided group during first 3 years may be related to the unblinded awareness of ungrafted stenoses. Outcomes of isolated intermediate left main stenoses were not separately reported. Moreover, the cause of death was not specifically known and thus includes both cardiac and noncardiac causes regardless of the revascularization approach.

A low rate of repeat coronary angiography in this study (36% of FFR-guided; 23% in the angiographic-guided groups) provides only a glimpse of the true graft patency rate, which was significantly higher in the FFR-guided group. It is noteworthy that there was a linear increase in the rate of death or MI with an increasing number of venous bypass grafts only in the angiographic-guided group. Some clinical differences in the FFR-guided group (eg, slightly younger, more often male, less often diabetic) were addressed by propensity matching but may have partly contributed to the lower overall incidence of death or MI in the FFR-guided group (16% versus 25%, P=0.02).

Going Forward

Now for the hard part. Though the present study required only that at least one artery be assessed by FFR before surgery, ideally all coronary arteries that are candidates for a bypass graft would have physiological assessment, not only those that have intermediately severe narrowings. Operators performing routine coronary angiography are often reluctant to assess all lesions before referring patients for CABG. In practice, FFR is easier said than done. Resting distal/proximal pressure ratios without hyperemia (eg, iFR, Pd/Pa, dPR) would simplify multivessel assessment but outcome data using resting nonhyperemic pressure ratios are currently limited. The acceptance of ischemia-guided CABG is not intuitive for the surgeon who must redefine the paradigm of his/her procedure. Even after the completion of large prospective, multicenter randomized FFR-guided CABG studies (eg, FAME 3, GRAFFITTI, FARGO) will the results be enough to change practice?

Critically important to accepting then changing CABG practice is the reality that interventional cardiologists must also accept it and help their surgical colleagues appreciate the value of ischemia-directed revascularization. New technologies such as FFR-computed tomography or angiographically-derived FFR will likely make this task considerably easier than an invasive pressure wire measurement. Will a CABG procedure needing fewer graft anastomoses, associated with higher graft patency and reduced late death and MI move the approach from traditional complete angiographic revascularization to complete functional revascularization? Given the current data, it would seem that simpler will be better.

Disclosures

Dr Kern is a consultant and speaker for Abbott/St. Jude, Philips/Volcano, Acist Medical Inc, Opsens Inc, and Heartflow Inc. Dr Seto is a speaker for Acist Medical and Philips/Volcano.

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