Fractional flow reserve guided coronary artery bypass grafting - new developments and future perspectives

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Abstract

The potential role of fractional flow reserve (FFR) in coronary artery bypass grafting (CABG) planning and post-CABG patency assessment are currently under intense investigation to determine whether the favourable outcomes reported with FFR-guided percutaneous coronary intervention can be translated to surgical practice. This review provides an overview of the principles that guide FFR measurement, the clinical evolution of FFR in CABG practice, the much anticipated outcomes of recent investigations that compare FFR-guided and angiography guided CABG and outlines the potential of alternative technology that may assist in ensuring ongoing improvement in surgical revascularization outcomes.

Keywords: Coronary artery bypass grafting, percutaneous coronary intervention, fractional flow reserve, outcomes

INTRODUCTION

We are currently witnessing rapid evolution in diagnostic and interventional technology for coronary artery disease (CAD). It is now well recognized that the visual assessment of coronary artery stenosis by angiography[1] or intravascular ultrasound[2,3] do not accurately reflect its physiological impact on myocardial territory. Fractional flow reserve (FFR) emerged as a transcatheter tool to potentially quantify the physiological significance of coronary artery stenosis[4,5] and various reports over the last 2 decades repeatedly confirmed the favorable impact of FFR on percutaneous coronary intervention (PCI) decision-
making and clinical outcomes\textsuperscript{[6-13]}. These studies also suggested that less than 50\% of angiographic significant lesions were functionally significant and that up to 25\% of post-angiography guided-coronary artery bypass grafting (CABG) targets had no impact of physiological myocardial perfusion, potentially risking early graft failure, accelerate native artery disease and late graft failure exacerbation\textsuperscript{[14]}. This review provides an outline of the principles that guide FFR measurement, the clinical evolution of FFR in CABG practice, the outcomes of recent investigations that compare FFR-guided and angiography guided CABG and describe potential alternative technology that may assist in ensuring ongoing improvement in surgical revascularization outcomes.

**FRACTIONAL FLOW RESERVE AS A PHYSIOLOGICAL MEASURE OF CORONARY ARTERY STENOSIS**

FFR measurements usually form part of routine diagnostic radial or femoral access cardiac catheterization under local anaesthesia\textsuperscript{[6-13]}. A pressure transducer within a fluoroscopically visible guide wire record the coronary arterial pressure distal to the identified lesion and once in position, facilitate the administration of a hyperemic stimulus by intracoronary or intravenous vasodilator (usually adenosine) injection. The mean arterial pressures from the pressure wire transducer and from the guide catheter are then used to calculate FFR, which is defined as the ratio of the average distal coronary pressure to average aortic pressure at maximal steady state hyperemia (normal value = 1.0). This equates to expressing the maximum achievable blood flow across an epicardial coronary stenosis to the maximum achievable blood flow in the absence of any stenosis. Various anatomical and clinical scenarios\textsuperscript{[15-24]}, which are outlined in Table 1, potentially influence FFR measurement accuracy that may result in deferral- or over-treatment of physiologically significant culprit lesions (FFR measurement ratio of 0.8 or less).

**THE EVOLUTION OF FFR IN CORONARY ARTERY BYPASS GRAFTING**

The indications and procedural recommendation for CABG, which now include minimally invasive- and hybrid surgical procedures are well described in contemporary guidelines\textsuperscript{[25]}. CABG of target lesions more than 50\% stenosis were historically performed with the intention of restoring distal perfusion and to provide distal protection against native disease progression\textsuperscript{[26]}. Subsets of early FFR-PCI measurement trials identified that up to 25\% of target lesions had no myocardial perfusion improvement post-CABG with early graft failure, accelerate native artery disease and late graft failure exacerbation considered to be unfortunate consequences\textsuperscript{[14]}.

The well-defined benefits of CABG compared with angiography-guided PCI as reported in the ASCERT\textsuperscript{[27]}, SYNTAX\textsuperscript{[28,29]}, FREEDOM\textsuperscript{[30]} and BEST trials\textsuperscript{[31]} became subjected to intense scrutiny following the introduction of FFR and newer generation drug-eluting stent technology. Following the ground-breaking DEFER study\textsuperscript{[6]}, which established the basis for FFR-guided PCI investigation, the FAME\textsuperscript{[7,8]} and FAME II trials\textsuperscript{[9,10]} introduced the concept of physiological revascularization and reinforced the positive impact of FFR in PCI of multi-vessel disease, which included decreased repeat revascularization (4.3\% in the FFR-guided group, 17.2\% in angiography-guided group, \(P < 0.001\)), number of stents (mean 1.9 in FFR-guided group, mean 2.7 in angiography-guided group) and equivalence in 3-year comparative PCI-procedural costs ($16,792 for FFR-guided group, $16,737 for angiography guided group, \(P = 0.94\)). However, after 5 years, the authors reported no statistically significant difference in the incidence of major adverse cardiac events (MACE) between FFR-guided and angiography-guided PCI (31\% in the angiography-guided group, 28\% in the FFR-guided group, \(P = 0.31\)). A functional SYNTAX score of lesions with FFR less than 0.8 reclassified up to 32\% of CABG candidates to lower risk groups treatable with both FFR-guided PCI and CABG as opposed to CABG alone\textsuperscript{[13]}. Whether the favorable impact of FFR on PCI outcomes could be translated to surgical practice, became a subject of intense investigation.
The impact of FFR on CABG graft patency was investigated by Botman and coworkers [33], who reported a statistically significant 1 year graft occlusion incidence of 8.9% in FFR-guided vs. 21.4% of the angiography-guided CABG patients for both arterial (13.7% FFR-guided vs. 21.9% angiography-guided; \( P < 0.2 \)) and venous (5.9% FFR-guided vs. 20.0% angiography-guided; \( P < 0.03 \)) grafts. In those patients with angiographic stenosis of 50% to 70%, the graft patency was higher if the FFR was less than 0.75 and vessels diameter more than 2.0 mm.

A comparative study of angiography-guided- and FFR-guided CABG at the Cardiovascular Centre, Aalst (Belgium) [33] observed that FFR measurement resulted in a significant downgrade of multi-vessel disease functional severity, a subsequent decrease in the number of CABG grafts applied and no difference in the incidence of MACE between the 2 groups after 3-year follow-up. The incidence of severe recurrent angina was significantly lower in the FFR-guided CABG group (31% vs. 4%; \( P < 0.001 \)). In a subgroup of 155 patients (25%) who underwent repeated coronary angiography for clinical indications, freedom from graft occlusion was higher in the FFR-guided group (31% in angiography-guided group, 5% in FFR-guided group, \( P = 0.031 \)). The extended 6-year results were recently reported by Fournier and colleagues [34] and included 627 consecutive patients between 2006 and 2010. Both the rate of composite death or myocardial infarction (16% for FFR-guided group, 25% for angiography-guided group, \( P = 0.020 \)) as well as death alone (11% for FFR-guided group, 18% for angiography-guided group, \( P = 0.013 \)) were significantly lower in the FFR-guided CABG group. By Cox multivariate regression analysis, FFR-guidance was an independent predictor of reduced death or MI (\( P = 0.008 \)). The Kaplan-Meier event rates diverged after 3 years to favour the FFR-guided CABG group. A propensity-matched cohort identified fewer MACE in the FFR-guided group (16% in FFR-guided group, 25% in angiographic-guided group, \( P < 0.02 \)), which implies no increased risk of MACE by deferring FFR insignificant lesions.

The association of preoperative FFR on isolated total arterial CABG functionality 6 months postoperatively in patients with triple vessel disease were recently reported in the interim results of the IMPAG trial [35] as a 2-centre, single-arm, blinded study. The interim results of 63 patients (54 bilateral internal thoracic Y-graft configurations), included the evaluation of 199 arterial anastomoses, of which 135 were sequential anastomoses. Overall, 85% of the left internal thoracic artery (ITA) and 69% of the right ITA were functional and patent, which was statistically significantly associated with preoperative FFR values of 0.78. As arterial grafts are physiologically active and risk atrophy if subjected to competitive flow, the authors suggested that sequential anastomosis that provide continuous antegrade flow to multiple targets

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FFR: fractional flow reserve
may provide graft protection for lesions in which FFR values were greater than 0.78. Antegrade flow in angiographic stenosed target vessels with large diameters, especially the right coronary artery (RCA), may still be adequate to cause significant competitive flow in arterial grafts and it is therefore suggested that the most appropriate FFR value for optimal RCA graft outcome was less than 0.71. The right ITA is often used for non-left anterior descending artery target vessels with poor distal run-off and apart from technical aspects, potentially explain the inferior graft patency.

NEW DEVELOPMENT AND CONCERNS OF ROUTINELY APPLYING FRACTIONAL FLOW RESERVE-GUIDED CORONARY ARTERY BYPASS GRAFTING

The recently published FARGO trial\[36\] evaluated graft patency and clinical outcome of 100 patients referred for CABG by a heart team after randomly being assigned to either FFR- or angiography-guided CABG. In FFR-guided CABG, coronary lesions with FFR > 0.80 were deferred, and a new graft plan was designed accordingly, whereas the surgeon was blinded to the FFR values in patients who underwent angiography-guided CABG. Angiographic follow-up at 6 months were available for 39 and 33 patients in the FFR- and angiography-guided groups respectively. Graft failures of all grafts, death, myocardial infarction, stroke and repeat revascularization were similar in both groups (16% vs. 12%; \(P = 0.97\)). After 6 months, deferred lesions (\(n = 24\)) showed a significant reduction in mean FFR from index to follow-up (0.89 ± 0.05 vs. 0.81 ± 0.11; \(P = 0.002\)). The authors concluded that FFR-guided CABG had similar graft failure rates and clinical outcomes as angiography-guided CABG. However, FFR was reduced significantly after 6 months in deferred lesions and may potentially result in adverse events over longer follow-up.

The GRAFFITI trial\[37\], of which the 12 month outcomes were presented at Euro-PCR in 2018 (Paris, France), was a prospective randomized trial that investigated the potential clinical benefits of FFR-guided vs. angiography-guided CABG in patients with left anterior descending or left mainstem disease and at least one other major coronary artery with angiographic intermediate stenosis (30%-90% diameter stenosis). The study design is described in Figure 1. The intended CABG strategy was based solely on coronary angiography after which patients underwent FFR- or angiography-guided randomization. In the FFR group, the surgical planning was revised according to the functional significance of each coronary stenosis after the FFR values were disclosed to the surgeons. After 12 months follow-up, the rate of graft occlusion (20% and 19% in angiography- and FFR-guided groups respectively, \(P = 0.885, 64.5\%\) complete), rate of death (2% and 3% in angiography- and FFR-guided groups respectively, \(P = 0.65\)), myocardial infarction (2% and 0% in angiography- and FFR-guided groups respectively, \(P = 0.15\)), stroke (0% and 2% in angiography- and FFR-guided groups respectively, \(P = 0.16\)) and repeat revascularization (5% and 2% in angiography- and FFR-guided groups respectively, \(P = 0.35\)) were reported to be similar for both groups. Lesions with FFR measurement less than 0.8 were deferred in 53% and 29% in the angiography-guided and FFR-guided groups respectively, which suggested that FFR-guidance was associated with higher functional appropriateness (69% and 79% in angiography- and FFR-guided groups respectively). CABG was performed on 44% of stenotic lesions with preserved FFR and deferred on 53% of lesions with abnormal FFR, which translated to a significant reduced number of grafts.

Despite the paradigm shift toward physiological revascularization with all the benefits described, the value of complete anatomical revascularization remains relevant. Mulukutla and colleagues\[38\] recently reported a propensity-matched retrospective, observational analysis of patients with multi-vessel CAD who underwent angiography-guided CABG or FFR-PCI with second generation drug eluting stents between 2010 and 2018 and for whom data were available through the National Cardiovascular Data Registry or The Society of Thoracic Surgeons Adult Cardiac Surgery Database. Of the initial 6163 patients identified, the propensity-matched cohort included 844 in each group. The estimated 1-year mortality was 11.5% and 7.2% (\(P < 0.001\)) in the PCI and CABG groups respectively and overall MACE and individual outcomes of
mortality, readmission, and repeat revascularization all favored CABG across all major clinical subgroups. CABG was angiography-guided and suggest that excellent outcomes that outperform PCI are achievable without FFR guidance.

The FUTURE trial, which was presented by Rioufol and colleagues at European Society of Cardiology Congress in Munich (Germany, 2018), was designed to explore the impact of FFR guided treatment strategies in patients with angiographic multi-vessel coronary disease in 31 French centers. In the FFR-guided group, FFR was performed on all target lesions, with FFR less than 0.80 regarded as eligible for PCI or CABG. There planned enrolment of 1,728 patients was halted due to an observed difference in all-cause mortality after 938 patients were randomized. The presenters highlighted three factors that could have played a role in the higher rate of mortality in the FFR-guided group: the lower-than-expected rate of CABG considering that all patients had multi-vessel disease, the higher rate of PCI in severe patients with a SYNTAX score over 32, and the high rate of ad hoc PCI (about 90% in both groups).

**POTENTIAL ALTERNATIVE MODALITIES THAT MAY IMPROVE CORONARY ARTERY BYPASS GRAFTING PLANNING AND DECISION-MAKING**

The rapid development in non-invasive imaging technology offers exciting potential alternatives to conventional invasive coronary angiography. Computerised tomographic coronary angiography (CTCA) is...
a non-invasive, repeatable, safe and efficient primary investigation in stable CAD that reduces the incidence of “negative” invasive angiography where no intervention is indicated or required. Significant progress has been achieved regarding radiation exposure, with the introduction of dose-sparing protocols for ECG synchronization, the widespread use of lower tube voltages, and the development of iterative reconstruction algorithms. It has the major benefit of documented correlation with invasive FFR [Figure 2] and may result in a significant paradigm shift towards non-invasive coronary stenosis assessment and appropriate referral for treatment by CABG or PCI. Nogaard and colleagues reported that 185 (98%) of 189 patients (mean age 59 years, 59% male) that underwent FFR-CTCA had conclusive results, with FFR-CTCA < 0.8 correlating with invasive coronary angiography in 73% of patients and 70% of vessels. In patients with FFR-CTCA lesions > 0.80, invasive coronary angiography was deferred with no adverse cardiac events observed during a median follow-up period of 12 months (range 6 to 18 months). They calculated per-patient sensitivity and specificity (95% CI) to identify myocardial ischemia as 86% and 79% for FFR-CTCA, 94% and 34% for standard CTCA and 64% and 83% for invasive coronary angiography respectively.

Two non-hyperemic, invasive measures of inducing pressure might be useful for assessing the severity of coronary stenosis. The resting distal coronary artery pressure/aortic pressure (Pd/Pa) is the ratio of distal coronary artery pressure to aortic pressure over the entire cardiac cycle. Instantaneous wave-free ratio (iFR) measures coronary pressure during a specific period of diastole when the resting resistance is the lowest. Shiode and colleagues investigated the correlation between FFR-angiography, iFR and resting Pd/Pa by continuously measuring each component in 123 lesions in 103 patients with stable CAD by an intracoronary injection of papaverine. A receiver operator curve analysis revealed that the optimal iFR cut-off value for predicting an angiographic FFR of < 0.80 was 0.89 (sensitivity 84.1%, specificity 80.0%, diagnostic accuracy 81.3%), while the optimal resting Pd/Pa cut-off value was 0.92 (sensitivity 90.9%, specificity 78.5%, diagnostic accuracy 82.9%). Lesions with an iFR value < 0.89 and a Pd/Pa value < 0.92 were defined as double-positive lesions, while the lesions with an iFR value of > 0.89 and a Pd/Pa value of > 0.92 were defined as double-negative lesions. The ADVISE, ADVISE-e and RESOLVE trials also suggested that iFR compares favourably with FFR-angiography, may defer up to 16% of FFR significant lesions, may reduce procedural time, lower procedural cost, improve patient comfort and avoid side effects of adenosine, especially for patients at risk. The clinical application of iFR and Pd/Pa will soon be defined.
CONCLUSION
Various studies now confirm that physiological revascularization by FFR-guided CABG result in fewer target lesions and improved conduit patency in the short term. Even though intermediate follow-up results suggest no significant difference in clinical outcomes compared to angiography-guided CABG, the risk that angiographic significant/FFR insignificant lesions may progress to detrimental clinical events are of greatest concern. Current evidence therefor does not support the routine use of FFR in CABG planning. The current CABG procedure recommendation of complete angiographic- and total arterial revascularization with minimal aorta manipulation should remain the standard until future studies clarify the role of FFR in long term CABG outcomes. Non-invasive CAD diagnostic modalities are rapidly developing and may offer exciting alternatives to FFR in planning CABG target lesions. The diagnostic-, shared decision-making-, informed consent- and therapeutic practices related to CAD treatment are sure to evolve with CABG to remain an invaluable- and excellent option.

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