Editorial Commentary

Can routine quantitative flow ratio guide coronary artery bypass grafting?

Joseph M. O'Brien[1,2], Dennis T. L. Wong[1,2], Adam J. Nelson[2,3,4]^

[1]Victorian Heart Hospital, Monash Health, Melbourne, Australia; [2]Victorian Heart Institute, Monash University, Melbourne, Australia; [3]Department of Cardiology, Royal Adelaide Hospital, Adelaide, Australia; [4]Adelaide Medical School, University of Adelaide, Adelaide, Australia

Correspondence to: Adam J. Nelson, MBBS, MBA, MPH, PhD. Department of Cardiology, Royal Adelaide Hospital, Port Road, Adelaide, South Australia 5000, Australia; Victorian Heart Institute, Monash University, Melbourne, Australia; Adelaide Medical school, University of Adelaide, Adelaide, Australia. Email: Adam.Nelson@adelaide.edu.au.

Comment on: Tian M, Xu B, Chen L, *et al.* Quantitative flow ratio and graft outcomes of coronary artery bypass grafting surgery: A retrospective study. J Thorac Cardiovasc Surg 2023;S0022-5223(23)00335-5.

Keywords: Quantitative flow ratio (QFR); coronary artery bypass graft surgery; graft occlusion; coronary artery disease (CAD); machine learning

Submitted Jan 24, 2024. Accepted for publication Apr 30, 2024. Published online Jun 25, 2024.
doi: 10.21037/jtd-24-145
View this article at: https://dx.doi.org/10.21037/jtd-24-145

Coronary artery bypass grafting (CABG) has been shown to reduce angina, death, and myocardial infarction (MI), and accordingly carries a Class I recommendation for management of complex, multivessel coronary artery disease (CAD) (1). Underlying this benefit is the ability for CABG to achieve complete revascularisation whereby lesions reaching >50% diameter narrowing are bypassed on the presumption of being flow-limiting. Some leniency in this threshold is often exercised with milder lesions also receiving bypasses, given that visual assessment is fallible and in the event that disease progresses, a bypass will conceptually provide protection to the distal arterial bed. Despite being well-intentioned, bypassing lesions that are not flow-limiting may result in premature graft failure and accelerate native vessel atherosclerotic disease (2). Thus, as the practice of percutaneous revascularisation has moved towards more objective methods for quantifying lesion severity with the goal of increasing the yield of stenting, there is great interest in applying these techniques for CABG (3).

One such approach is using fractional flow reserve (FFR) to guide bypass grafting. FFR is a hyperaemic index that determines the pressure ratio proximal and distal to a diseased segment of coronary vessel, with a ratio of ≤0.80 associated with myocardial ischaemia (4,5). Functional assessment of CAD with FFR performed pre-operatively has been demonstrated to result in improved anginal symptom scores at three years (6), reduced rate of death and MI at six years (7), and increased long-term graft patency (4). A significant disadvantage to the use of FFR is the requirement for invasive pressure wires, the procedural aspect of which carries the risk of coronary perforation, dissection, or occlusion, and inaccurate data acquisition if performed incorrectly (8). Vessels which are highly tortuous or otherwise anatomically challenging are also at increased risk of complication and may not be feasible or safe to perform FFR. From a non-procedural perspective, performing routine FFR on all lesions increases the radiation and duration of the procedure in addition to cost without evidence of proven health-economic benefit. Thus, a hybrid approach to FFR assessment of native coronary vessels is typically used pre-operatively, with severe stenoses >70% left unwired and physiological assessment performed only on arteries exhibiting angiographically intermediate (50–70%) lesions.

While a number of studies advocate for the use of FFR in the percutaneous coronary intervention (PCI) setting, data evaluating its role in CABG is limited to three randomized studies. The FARGO (Fractional Flow Reserve Versus

^ ORCID: 0000-0003-0990-2548.

Angiography Randomization for Graft Optimization) trial published in 2018 compared the outcomes of 100 participants randomized to either angiographically-determined revascularization or physiology-guided grafting of only the angiographically severe lesions with an FFR ≤0.80. There were no differences between the arms with regards to graft failure (16% *vs.* 12%) or clinical events at 6 months follow-up. The study had multiple limitations including premature termination, short duration of follow-up, missing data for the primary endpoint in 25% of participants, and a lack of fidelity to treatment allocation. Similarly, the GRAFFITI (GRAft patency after FFR-guided versus angiography-guided CABG) published in 2019 which randomized 172 participants with stable coronary disease to angiography or FFR-guided CABG only after the surgical plan had been made using the angiogram alone. As with FARGO, the GRAFFITI trial was terminated prematurely due to slow enrolment (83% of sample size) with statistical power further hampered by almost 1/3 of the cohort not returning for follow-up angiography. Nonetheless, overall patency was similar between arms with no difference in clinical outcomes. In contrast, the IMPAG (Impact of Preoperative FFR on Arterial Bypass Graft Functionality) trial published in 2019 required all 67 participants (and 199 lesions) to undergo FFR in addition to coronary angiography, but mandated all participants undergo total arterial CABG. FFR values were made available to the surgeons, however grafting strategy was left to the operator's discretion. At six months, FFR was associated with the primary endpoint of graft patency while angiographic stenosis severity was not (9). Thus, the current limited (and conflicting) evidence suggests FFR use shortens the CABG procedure through reducing the number of grafts required, and may help determine appropriate conduit use with physiologically non-significant lesions associated with arterial graft failure. However, these studies have been challenging to execute and ultimately underpowered for clinical outcomes; thus, more physiologically-guided CABG data are needed.

Quantitative flow ratio (QFR) is an angiographic-based technique that utilises computational flow dynamics and contrast velocity estimates to digitally recreate the three-dimensional lumen of a coronary artery to help guide PCI. Originally established as a non-hyperaemic adjunct to FFR, its role in determining haemodynamic significance of lesions has continued to expand from initial use in stable CAD, to MI, to predictive modelling pre-operatively in bypass surgery (5,10,11). Employing a simplified form of machine learning, the software which powers QFR continues to improve as the quantity of data put through the application increases. Similar to FFR, thorough assessment with QFR used to guide PCI has been shown to reduce the risk of 12-month major adverse cardiovascular and cerebral events (MACCE) compared with visual angiography alone (12). QFR is a complementary rather than competitive tool to FFR—its greatest utility is in cases where FFR may be complicated, such as tortuosity or otherwise challenging-to-wire anatomy, and with a strong negative predictive value can prevent the need for invasive pressure wiring saving both time and money (13).

Recent work by Tian *et al.* explores the novel use of QFR as a predictive tool in CABG outcomes (14). Prior work in this area with small patient cohorts using QFR in patients with left main coronary artery (LMCA) disease has demonstrated QFR may predict long-term graft patency (15). Tian *et al.* (14) further hypothesised that there would be a relationship between the pre-operative QFR value determined at the time of invasive coronary angiography, and the primary outcome of graft occlusion as assessed at 12 months by computed tomography (CT) angiography. In order to evaluate this hypothesis, Tian *et al.* performed a post hoc analysis of the PATENCY trial which originally compared no-touch with conventional vein harvesting techniques among participants undergoing CABG (16). The overall results showed that among arterial grafts, the incidence of graft occlusion was significantly higher in the QFR >0.80 group than in the QFR ≤0.80 group (7.1% *vs.* 2.6%; P<0.001) while there was no significant difference in these groups for vein grafts (4.6% *vs.* 4.3%; P=0.67). In multivariable modelling a QFR >0.80 remained associated with the primary outcome in arterial grafts but not for vein grafts. There was no discernible impact of graft occlusion in QFR >0.80 vessels, although the study was underpowered.

This study offers promising preliminary data supporting the use of QFR in pre-operative angiography and has a number of strengths, most notably its large sample size of over 7,000 grafts from 1,875 participants. Furthermore, the authors used the standard diagnostic cut-off for a functionally significant QFR value (i.e., >0.80) (17) which is consistent with the current clinical application of the software (14). The participants appear to have received high quality CABG, with very few (<7%) grafts described as poor quality and low reported rates of adverse events, likely owing to the operator's requirement to reach a volume threshold for participation in PATENCY. Additionally, the care was contemporary with all patients

requiring dual antiplatelet therapy for at least three months post-operatively. The use of a blinded core lab to assess QFR in an experienced and independent manner is a strength of the data.

Some limitations to this analysis need to be considered. As the authors point out, a total of 614 participants (23.1%) had to be excluded due to at least one target vessel being unavailable for analysis, which raises questions of generalisability. While this could affect the fitness-for-use of the technology in a retrospective manner, use of purposely acquired, prospective imaging for QFR results in <3% of lesions being non-evaluable. The authors also do not elaborate on angiographic imaging parameters and specifically, frame rate. QFR has been shown to be non-inferior to FFR when the evaluated angiographic images are shot at a frame rate of ≥15 frames/sec (11). However, to minimise the radiation dosage to patients and staff some centres acquire images at 10 frames/sec with little appreciable drop in image quality (18,19). The acquisition frame rate for PATENCY is not published, and thus it is unclear if this impacted the QFR values and their relationship to outcomes. The statistical approach is overall sound with robust sensitivity analyses and interaction testing and the sequential multivariable modelling approach allows for an interpretation of residual confounding. However, it is unclear whether the authors prespecified an evaluation of the primary outcome in arterial and venous grafts separately as it is unlikely the primary endpoint would have been significant if evaluated together. While this represents the largest QFR and CABG experience, follow-up of only twelve months still means the long-term clinical implications of pre-operative QFR analysis remain largely uncharacterised. The observed association between QFR and outcomes using arterial but not with venous conduit in Tian *et al.* (14) deserves further comment. A similar result was observed in another observational analysis in which invasive FFR related to bypass graft patency only in arterial grafts but not in venous grafts (4). Furthermore, the lesion location was predominantly within the left anterior descending (LAD) artery. It is rare for patients to be referred for surgical revascularisation in the absence of LAD disease. This will have led to a significantly larger volume of patients who have had severe LAD disease being included in this study, limiting its clinical applications in non-LAD disease. It is unclear if the cut-off of a QFR >0.80 would carry the same predictive value in the left circumflex or right coronary arteries.

The clinical implications of Tian *et al.* (14) remain to be seen however perhaps the most important outcome is that its findings encourage the field to perform adequately powered prospective, randomized and double-blinded QFR strategy trials. The open label RIPCORD 2 trial demonstrated no incremental benefit of routine FFR to guide revascularisation but most importantly there was a price to pay with procedural duration, radiation and cost (20). Thus, QFR is ideally placed to enable larger studies whereby there is little-to-no additional risk to a patient and the information can be generated quickly. These elements have been leveraged in the multi-center FAVOR trials which remain in longer-term follow-up but have shown promising early results in guiding PCI (21,22). The ease of performing QFR also lends itself to strategy trials such as DECISION-QFR which is evaluating the agreement of a Heart Team discussion using QFR-based information compared with FFR-based information (23). Further studies could trial a precision-based strategy to conduit choice—for example, vessels with a QFR ≤0.80 would receive arterial conduit and those with QFR >0.80 would receive venous conduit—compared with standard of care. Such a trial's feasibility would be significantly increased by using QFR *vs.* FFR which would reduce the risk of wire-based complications and facilitate easier masking of this information to the precision-strategy group only.

So, is QFR ready to guide clinical CABG decision making? No, and it remains unlikely to be until FFR (upon which the QFR technology is entirely based) has a demonstrable benefit in guiding long-term outcomes among those undergoing CABG. The totality of invasive (and now non-invasive) data suggests functional significance predicts graft patency, at least among arterial conduits. QFR has its proven role elsewhere in coronary physiology, particularly in its ability to confirm non-significant lesions with an appreciably high negative predictive value and sensitivity to guide decision making in PCI. However, the benefits of a bypass graft across an area of large plaque burden that is not functionally significant perhaps underlies the contrasting and underwhelming results from prospective large trials of FFR-guided CABG (7,24,25). More prospective data that accommodates nuance in aligning graft conduit choice with vessel or lesion characteristics is needed. Perhaps QFR provides an important mechanism to address some of these unanswered questions—it is simple and non-invasive nature could be leveraged to run trials that are cheaper, faster, and carry greater feasibility at scale.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article has undergone external peer review.

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-145/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-145/coif). J.M.O.B. declares a PhD scholarship (107718) from the National Heart Foundation of Australia. D.T.L.W. declares research grant funding from Medis and a Future Leaders scholarship from the National Heart Foundation of Australia. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Byrne RA, Fremes S, Capodanno D, et al. 2022 Joint ESC/EACTS review of the 2018 guideline recommendations on the revascularization of left main coronary artery disease in patients at low surgical risk and anatomy suitable for PCI or CABG. Eur Heart J 2023;44:4310-20.
2. Harskamp RE, Alexander JH, Ferguson TB Jr, et al. Frequency and Predictors of Internal Mammary Artery Graft Failure and Subsequent Clinical Outcomes: Insights From the Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT) IV Trial. Circulation 2016;133:131-8.
3. Pellicano M, De Bruyne B, Toth GG, et al. Fractional flow reserve to guide and to assess coronary artery bypass grafting. Eur Heart J 2017;38:1959-68.
4. Fournier S, Toth GG, Colaiori I, et al. Long-Term Patency of Coronary Artery Bypass Grafts After Fractional Flow Reserve-Guided Implantation. Circ Cardiovasc Interv 2019;12:e007712.
5. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334:1703-8.
6. Smits PC, Abdel-Wahab M, Neumann FJ, et al. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. N Engl J Med 2017;376:1234-44.
7. Fournier S, Toth GG, De Bruyne B, et al. Six-Year Follow-Up of Fractional Flow Reserve-Guided Versus Angiography-Guided Coronary Artery Bypass Graft Surgery. Circ Cardiovasc Interv 2018;11:e006368.
8. Altstidl JM, Gaede L, Troebs M, et al. Side effects and major adverse cardiac events caused by fractional flow reserve measurement: a systematic review and meta-analysis of 12,215 patients. Eur Heart J 2022. doi: 10.1093/eurheartj/ehac544.2022.
9. Glineur D, Grau JB, Etienne PY, et al. Impact of preoperative fractional flow reserve on arterial bypass graft anastomotic function: the IMPAG trial. Eur Heart J 2019;40:2421-8.
10. Wong DT, Narayan O, Ko BS, et al. A novel coronary angiography index (DILEMMA score) for prediction of functionally significant coronary artery stenoses assessed by fractional flow reserve: A novel coronary angiography index. Am Heart J 2015;169:564-71.e4.
11. Westra J, Tu S, Winther S, et al. Evaluation of Coronary Artery Stenosis by Quantitative Flow Ratio During Invasive Coronary Angiography. Circ Cardiovasc Imaging 2018;11:e007107.
12. Jin Z, Xu B, Yang X, et al. Coronary Intervention Guided by Quantitative Flow Ratio vs Angiography in Patients With or Without Diabetes. J Am Coll Cardiol 2022;80:1254-64.
13. Mehta OH, Hay M, Lim RY, et al. Comparison of diagnostic performance between quantitative flow ratio, non-hyperemic pressure indices and fractional flow reserve. Cardiovasc Diagn Ther 2020;10:442-52.
14. Tian M, Xu B, Chen L, et al. Quantitative flow ratio and graft outcomes of coronary artery bypass grafting surgery: A retrospective study. J Thorac Cardiovasc Surg

2023;S0022-5223(23)00335-5.
15. Dowling C, Nelson AJ, Lim RY, et al. Quantitative flow ratio to predict long-term coronary artery bypass graft patency in patients with left main coronary artery disease. Int J Cardiovasc Imaging 2022;38:2811-8.
16. Tian M, Wang X, Sun H, et al. No-Touch Versus Conventional Vein Harvesting Techniques at 12 Months After Coronary Artery Bypass Grafting Surgery: Multicenter Randomized, Controlled Trial. Circulation 2021;144:1120-9.
17. Ties D, van Dijk R, Pundziute G, et al. Computational quantitative flow ratio to assess functional severity of coronary artery stenosis. Int J Cardiol 2018;271:36-41.
18. Badawy MK, Scott M, Farouque O, et al. Feasibility of using ultra-low pulse rate fluoroscopy during routine diagnostic coronary angiography. J Med Radiat Sci 2018;65:252-8.
19. Badawy MK, Clark T, Carrion D, et al. Radiation Dose Optimization in Interventional Cardiology: A Teaching Hospital Experience. Cardiol Res Pract 2018;2018:6912841.
20. Stables RH, Mullen LJ, Elguindy M, et al. Routine Pressure Wire Assessment Versus Conventional Angiography in the Management of Patients With Coronary Artery Disease: The RIPCORD 2 Trial. Circulation 2022;146:687-98.
21. Westra J, Andersen BK, Campo G, et al. Diagnostic Performance of In-Procedure Angiography-Derived Quantitative Flow Reserve Compared to Pressure-Derived Fractional Flow Reserve: The FAVOR II Europe-Japan Study. J Am Heart Assoc 2018;7:e009603.
22. Xu B, Tu S, Song L, et al. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. Lancet 2021;398:2149-59.
23. Miyata K, Asano T, Saito A, et al. Heart Team risk assessment with angiography-derived fractional flow reserve determining the optimal revascularization strategy in patients with multivessel disease: Trial design and rationale for the DECISION QFR randomized trial. Clin Cardiol 2022;45:605-13.
24. Toth GG, De Bruyne B, Kala P, et al. Graft patency after FFR-guided versus angiography-guided coronary artery bypass grafting: the GRAFFITI trial. EuroIntervention 2019;15:e999-e1005.
25. Thuesen AL, Riber LP, Veien KT, et al. Fractional Flow Reserve Versus Angiographically-Guided Coronary Artery Bypass Grafting. J Am Coll Cardiol 2018;72:2732-43.

Cite this article as: O'Brien JM, Wong DTL, Nelson AJ. Can routine quantitative flow ratio guide coronary artery bypass grafting? J Thorac Dis 2024;16(6):4064-4068. doi: 10.21037/jtd-24-145