British Cardiovascular Society

'Promoting excellence in cardiovascular care'

Coronary physiology: the next step for interventional cardiology

Gautam Sen

Background

Invasive coronary angiography is currently the gold standard for the treatment of atherosclerotic coronary luminal obstruction.[1] There is however a complex and interesting relationship between the anatomical severity of coronary arterial narrowing and the presence of myocardial ischemia. As a result coronary angiography alone is limited in its ability to differentiate whether a luminal stenosis causes ischaemia or indeed symptoms of angina.[2] The last few decades have witnessed a rise in technological advances particularly with regard to physiological lesion assessment; here we review one such development, the fractional flow reserve (FFR).

Take Home Messages

- FFR and IFR are well established in guiding coronary intervention
- It is felt that coronary physiology is likely to be more important than coronary anatomy in successfully identifying the best candidates for revascularisation
- Having the combination of both a physiological and anatomical assessment at the same time and without the need for an invasive procedure is very exciting
- It is likely that in the near future a non-invasive strategy combining CTCA and CT-FFR could become the gold standard to delineate anatomy and identify functionally significant lesions

Fractional Flow Reserve

The FFR is a ratio of the maximal achievable blood flow in the myocardium in the presence of a stenosis, divided by the maximum expected flow if the stenosis were absent. This physiological measurement has been increasingly used in the treatment of atherosclerotic lesions. The validation of FFR as a potentially useful determinant of ischaemia has led to a series of important trials that have since altered the practice of interventional cardiology.

DEFER (Deferral versus performance of PTCA based on coronary pressure derived fractional flow reserve) was one of the first trials to establish the safety of deferring intervention based on the FFR value.[3] DEFER was a multi-centre trial in which angiography and FFR were performed on 325 patients. If the FFR was less than 0.75 patients underwent percutaneous coronary intervention (PCI). If the FFR was greater than 0.75, patients were randomised to deferral of intervention or to PCI. The results showed that in patients with an FFR greater than 0.75, there was no difference in event-free survival at 24 months, at 5 years and more recently at 15 years if PCI was performed or deferred. These findings suggest that PCI can safely be deferred regardless of the anatomical (angiographic) severity of a stenosis and that physiological assessment is potentially more important.[3-5]

Following the DEFER trial findings, attention subsequently turned to the potential role of FFR in guiding PCI rather than deferring it. FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) was an international multi-centre study which compared FFR guided coronary revascularisation to angiographic guided methods in patients with multi-vessel coronary artery disease.[6] Patients who were randomised to the FFR-guided arm underwent PCI only if the FFR was 0.80 or less. The trial included 1005 patients across 20 centers worldwide and demonstrated that at one year patients in the FFR arm were less likely to suffer death, less likely to have heart attacks and less likely to have repeat revascularisation. Overall, the FAME study demonstrated FFR guided PCI reduced adverse cardiovascular events by 30%.[6]

Subsequent to the FAME study, an additional FAME 2 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2) trial showed that in patients with stable coronary artery disease and functionally significant stenoses (FFR of 0.8 or less), FFR-guided PCI plus optimal medical therapy, compared with optimal medical therapy alone, decreased the need for urgent revascularisation. The study also highlighted the benefit of not intervening on FFR negative lesions, where favorable outcomes were seen with optimal medical therapy alone irrespective of angiographic appearance favoring physiological over anatomical assessment.[7-8]

Following on from this, a sub-study of FAME 2 also yielded fascinating results. This study looked at the subset of patients from FAME 2 who did not have revascularisation.[9] In the trial 607 patients were separated into 4 groups based upon the angiographic findings (diameter stenosis, DS) and FFR-based characteristics of their coronary lesions: positive concordance (FFR≤0.80; DS≥50%), negative concordance (FFR>0.80; DS<50%), positive mismatch (FFR≤0.80; DS<50%) and negative mismatch (FFR>0.80; DS≥50%). The four groups were compared with respect to a composite end point of cardiac death, vessel related myocardial infarction, and vessel-related revascularisation. The authors hypothesised positive concordance to be associated with the worst outcomes, negative concordance to be associated with the best outcomes and the positive mismatch group to have poorer outcomes than the negative mismatch group. Intriguingly however they found that there was no difference between the positive concordance (FFR≤0.80; DS≥50%) and positive mismatch (FFR≤0.80; DS<50%) groups, and no difference between the negative mismatch (FFR>0.80; DS≥50%) and negative concordance (FFR>0.80; DS<50%) groups. The authors therefore concluded that in patients with stable coronary disease, physiology is a more important determinant of the natural history of coronary stenoses than the anatomy of the lesion.[9]

Limitations of FFR

Despite such strong evidence and the European Society of Cardiology's (ESC) recommendation for the use of FFR in stable coronary artery disease, the overall rate of FFR use remains low.[10-11] Several possible explanations for this have been put forward, with one of the most frequently quoted being the fact that FFR uses adenosine in order to achieve maximal hyperaemia. This adds an additional level of complexity to the overall procedure, as well as exposing patients to adverse side effects including chest pain and shortness of breath. [12-13] In addition the ischaemic threshold for FFR has varied

in previous studies from 0.75 to 0.80, and this zone has been defined as the grey zone; limiting its use in this particular area.

Instantaneous wave-free ratio

In this way the somewhat limited use of FFR has meant further opportunities to try other techniques and instantaneous wave-free ratio (iFR) is one such example. A number of studies have demonstrated correlations between the FFR and iFR with regard to diagnostic accuracy.[14-15]

In 2017, two landmark papers were published comparing iFR and FFR. DEFINE-FLAIR was a randomised trial which compared iFR-guided or FFR-guided coronary revascularization.[16] At 1 year iFR-guided revascularisation was found to be non-inferior to FFR and patients in the iFR reported fewer symptoms in the procedural period due to the omission of adenosine.

The second study, iFR SWEDEHEART was performed in 2037 patients with stable angina or an acute coronary syndrome.[17] They were randomised to undergo iFR or FFR guided revascularisation. At 1-year iFR was again shown to be non-inferior to FFR and a higher proportion of patients in the FFR group reported chest pain during the procedure, related to adenosine infusion. A more recent meta-analysis reported iFR to have similar diagnostic performance to FFR.[18] These encouraging results have led to increased uptake of iFR by interventional cardiologists, and gives them an option to use FFR or iFR as their tool for assessing the coronary physiology. In fact the ESC guidelines have mentioned that both FFR and iFR are validated tests and the choice is left to the interventionist to decide.

CT Coronary angiogram (CTCA) FFR

Often considered one of the greatest challenges associated with calculating the FFR or iFR, is their invasive nature requiring an angiogram to facilitate use. The arrival of CT-FFR is therefore promising and introduces a non-invasive method of combining both anatomical and physiological assessment. Several studies have been undertaken comparing CT-FFR with invasive FFR to establish the accuracy of the technique.

DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) compared CT-FFR with invasive FFR in patients who were due to have invasive coronary angiography and found the accuracy to be 73% with sensitivity of 90%.[19]

The NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) trial also looked at CT-FFR and using high quality CT images, the diagnostic accuracy improved to 81% with sensitivity of 86%, specificity of 79%.[20]

Another large CT-FFR trial is the Platform trial (Prospective Longitudinal Trial of FFRCT: Outcome and Resource Impacts) with a total of 585 patients, which compared CTCA

plus CT-FFR versus the standard of care.[21] The end point of the study was reduction of invasive angiograms that showed no obstructive CAD. The trial concluded that in patients with stable chest pain planned for invasive coronary angiography, the use of a combined CTCA and CT-FFR strategy compared with usual care was associated with a significantly lower rate of invasive coronary angiogram showing no obstructive CAD. In addition, follow-up at one year demonstrated lower health care costs for those who were in the CT-FFR arm. [21] With such positive results the question has now evolved as to whether or not CT-FFR should be used as a gatekeeper to invasive procedures and revascularisation.

Conclusion

The field of coronary intervention is at a very exciting stage, as demonstrated by the plethora of large trials reported over the last five years. FFR and iFR are well established in guiding coronary intervention and now more than ever it is understood that coronary physiology is likely to be more important than coronary anatomy in successfully identifying the best candidates for revascularisation.

In contrast to the subjective nature of angiographic interpretation, physiology based coronary artery assessment allows interventional cardiologists to make decisions based on objective findings. This approach has now been incorporated into evidence based treatment algorithms, such as those from the ESC. However having the combination of both a physiological and anatomical assessment at the same time and without the need for an invasive procedure is very exciting.

In that regard, it is likely that in the near future a non-invasive strategy combining CTCA and CT-FFR could become the gold standard to delineate anatomy and identify functionally significant lesions, helping to distinguish between patients who can safely avoid angiography and those patients who require revascularisation.

References

1. Patel MR et al. Low diagnostic yield of elective coronary angiography. N. Engl. J. Med. **2010**, 362, 886–895

2. Stone GW et al. A prospective natural-history study of coronary atherosclerosis. N. Engl. J. Med. **2011**, 364, 226–235

3. Bech GJ et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: A randomized trial. Circulation **2001**, 103, 2928–2934

4. Pijls NH et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J. Am. Coll. Cardiol. **2007**, 49, 2105–2111

5. Zimmermann FM, Ferrara A, Johnson NP, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. Eur Heart J **2015**; 36:3182-8

6. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med **2009**; 360:213-24

7. De Bruyne B et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N. Engl. J. Med. **2012**, 367, 991–1001

8. Fearon WF et al, FAME 2 Trial Investigators. Clinical Outcomes and Cost-Effectiveness of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Patients with Stable Coronary Artery Disease: Three-Year Follow-Up of the FAME 2 Trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). Circulation. **2018**, 137, 480–487

9. Ciccarelli G, Barbato E, Toth G, et al. Angiography Versus Hemodynamics to Predict the Natural History of Coronary Stenoses: Fractional Flow Reserve Versus Angiography in Multivessel Evaluation 2 Substudy. Circulation. **2018**; 137:1475–1485.

10. Franz-Josef Neumann et al. 2018 ESC/EACTS Guidelines on myocardial revascularization, *European Heart Journal*, Volume 40, Issue 2, 07 January **2019**, Pages 87–165

11. Pothineni NV et al. Trends in Inpatient Utilization of Fractional Flow Reserve and Percutaneous Coronary Intervention. J. Am. Coll. Cardiol. **2016**, 67, 732–733.

12. Shah Samit & Pfau E, Steven. Coronary Physiology in the Cardiac Catheterization Laboratory. Journal of Clinical Medicine. **2019**. 8. 255.

13. Jeremias A, Kirtane AJ, Stone GW. A Test in Context: Fractional Flow Reserve: Accuracy, Prognostic Implications, and Limitations. J. Am. Coll. Cardiol. **2017**, 69, 2748–2758.

14. Escaned J, Echavarría-Pinto M, Garcia-Garcia HM. Prospective Assessment of the Diagnostic Accuracy of Instantaneous Wave-Free Ratio to Assess Coronary Stenosis Relevance: Results of ADVISE II International, Multicenter Study (ADenosine Vasodilator Independent Stenosis Evaluation II). JACC Cardiovasc Interv. **2015** May;8(6):824-833

15. Park JJ, Petraco R, Nam CW. Clinical validation of the resting pressure parameters in the assessment of functionally significant coronary stenosis; results of an independent, blinded comparison with fractional flow reserve. Int J Cardiol. **2013** Oct 9;168(4):4070-5

16. Davies et al. Use of the InstantaneousWave-free Ratio or Fractional Flow Reserve in PCI. N. Engl. J. Med. **2017**, 376, 1824–1834.

17. Gotberg M et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. N. Engl. J. Med. **2017**, 376, 1813–1823.

18. De Rosa S, Polimeni A, Petraco R, Davies JE, Indolfi C. Diagnostic Performance of the Instantaneous Wave-Free Ratio: Comparison With Fractional Flow Reserve. Circ. Cardiovasc. Interv. **2018**, 11

19. Min JK, Leipsic J, Pencina MJ et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA. 2012 308(12), 1237-1245

20. Nørgaard BL, Leipsic J, Gaur S et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol. **2014** 63(12), 1145-1155

21. Douglas PS et al. 1-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease: The PLATFORM Study. J Am Coll Cardiol. **2016** Aug 2;68(5):435-445