Coronary Physiology – the current state of play

Background

The concept of using the trans-stenotic pressure gradient in a diseased coronary artery as a measure to guide percutaneous coronary intervention (PCI) has been with us since the 1980s. In a seminal paper, Andreas Gruentzig's group reported that the magnitude of pressure gradient reduction could be used to judge the success of angioplasty [1]. Subsequently, and in recognition of the fact that identifying haemodynamically significant stenoses based upon angiography alone can be difficult, fractional flow reserve (FFR) was developed as a technique to enable physiological assessment of coronary lesions.

FFR expresses the maximum achievable blood flow to the myocardium supplied by a stenotic artery as a fraction of normal maximum flow. Its initial utility was to identify angiographic lesions in which PCI was not required. The DEFER (Deferral versus performance of PTCA based on coronary pressure derived fractional flow reserve) study demonstrated the short and long-term safety of deferring PCI for coronary stenoses with an FFR ≥0.75 [2, 3]. Attention then turned to using FFR in order to guide rather than defer PCI; the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial showed that FFR-guided PCI in patients with multivessel coronary disease results in lower 1-year adverse events and reduced costs [4]. The follow-up FAME 2 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2) trial went on to highlight the superiority of FFR-guided PCI plus medical therapy compared to medical therapy alone for lesions with an FFR ≤0.80 [5]. The study once again also highlighted the benefit of not intervening on FFR-negative lesions, where excellent outcomes were seen with medical therapy alone irrespective of angiographic appearance.

Based upon this body of evidence, use of FFR is advocated in both the current European Society of Cardiology (ESC) and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for myocardial revascularisation [6, 7].

Growing evidence for FFR

In the last 12 months, there have been 2 published sub-studies from FAME-2 which provide increasingly robust evidence for the use of FFR. The first paper, which provides the 3-year follow up data, highlights 2 key findings; major adverse cardiac events (MACE, defined as death, MI, and urgent revascularization) were lower in the PCI group, and the initial higher cost associated with PCI compared to medical therapy equalised over the course of the follow-up period [8]. The second paper was perhaps even more interesting, and focussed on

the subset of patients from FAME-2 in whom no revascularisation was undertaken [9]. These 607 patients were separated into 4 groups based upon the angiographic (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 groups were compared with respect to a composite end point of cardiac death, vessel related myocardial infarction, and vessel-related revascularization. Predictably, the study found 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. More interesting however, was the findings of 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. These results substantiate the concept that the physiological impact of lesions is a more important determinant of outcome than the angiographic appearance.

The remaining grey area

The use of FFR to guide intervention in the context of stable coronary artery disease (CAD) is now well established. However, its utility in the context of acute coronary syndromes (ACS) remains contentious. Patients presenting with ACS often display multi-vessel disease, and the use of FFR to assess non-culprit lesions has obvious theoretical appeal. However, use of FFR is dependent upon achieving maximal hyperaemia in the vascular bed distal to the coronary lesion being measured, thereby producing a near-linear relationship between pressure and flow. One of the concerns regarding the use of FFR in ACS patients is that the process of plaque rupture and thrombosis formation creates a milieu of vasoactive factors which may preclude an adequate hyperaemic response during the test. Nevertheless, there have been recent studies which suggest that use of FFR may be viable in this setting. The DANAMI-3-PRIMULTI (The Third Danish Study of Optimal Acute Treatment of Patients With STEMI: Primary PCI in Multivessel Disease) trial demonstrated that FFR-guided staged complete revascularization during the index admission led to a reduction in the primary composite end-point compared to culprit-lesion only treatment [10]. Similarly, the Compare-Acute (Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction) trial reported that FFR-guided revascularization at the time of primary PCI was associated with a lower rate of a composite cardiovascular events at 1 year [11].

Whilst these results are ostensibly encouraging, it must be borne in mind that in both cases the positive findings were driven by a reduction in future revascularisation rather than

mortality or myocardial infarction. As such, the evidence base for the use of FFR in the context of ACS remains a work in progress rather than providing a compelling indication.

iFR – a game-changer?

Despite the ever-increasing evidence base for the use of FFR in stable CAD, its usage remains disappointingly low [12]. One of the barriers associated with its use is the requirement for an infusion of adenosine in order to achieve maximal hyperaemia. This adds time and complexity to the procedure, as well as exposing patients to adverse side-effects including chest pain, shortness of breath and flushing. In recent years, the development of instantaneous wave-free ratio (iFR) has been seen as a breakthrough in the field of coronary intervention. The technique is centred around the concept that at a specific point in diastole, referred to as the wave-free period, flow and pressure within the coronary arteries are linearly related. Therefore, measurement of a pressure gradient across a stenosis during the wave-free period obviates that need to generate hyperaemia, and thus the need for adenosine. A number of studies have demonstrated correlation between FFR and iFR with regard to diagnostic accuracy [13-15]. In 2017, two landmark papers were published which highlighted iFR-guided PCI to be non-inferior to FFR-guided PCI with regard to major adverse cardiac events at 1 year [16, 17]. These encouraging results have led to increased uptake of iFR by interventional cardiologists, and it is possible that it could replace FFR as the default physiological measure of coronary lesions in years to come.

Conclusion

It is now becoming accepted that the physiological impact of coronary stenoses is more important than their angiographic severity. With new techniques such as iFR enabling pressure wire measurements to be made without use of adenosine, the traditional barriers that existed to the widespread use of FFR can now be circumvented. The question is, will this lead to a tangible change in practice, or are we still beholden to the ‘occulo-stenotic reflex’?

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