Fractional flow reserve in the assessment of coronary artery lesions

Fractional flow reserve is a vital tool for assessing the functional significance of a coronary stenosis, with higher sensitivity and specificity relative to non-invasive techniques. This article reviews the basic principles and applications of fractional flow reserve measurement, potential pitfalls and areas of controversy.

Diagnostic coronary angiography remains the gold standard and most accurate anatomical assessment of the lumen of epicardial coronary arteries. Despite high topographical precision, diagnostic coronary angiography correlates poorly with the functional significance of a coronary stenosis, especially in the context of angiographically moderate disease.

It is the functional significance of a coronary stenosis with regard to the ischaemia it produces that affects prognosis in patients with documented coronary artery disease. The DEFER study suggests that the annual rate of death and myocardial infarction is only 1% in patients with angiographic coronary stenosis found not to be functionally significant (Pijls et al, 2007).

In everyday practice, when lesions of intermediate severity are found, patients infrequently undergo non-invasive testing to document ischaemic burden. Even when ischaemia is identified in one particular territory of the heart, it can often remain unclear which particular lesion represents the anatomical substrate. Therefore, the ideal test for the interventional cardiologist would combine specific anatomical assessment of a lesion in combination with the functional assessment of the ischaemia induced. Use of the coronary pressure wire and measurement of fractional flow reserve offers both this anatomical and physiological assessment, and this article reviews the basic principles and current practices relating to its applications.

Definition

Fractional flow reserve is the ratio of maximal myocardial blood flow in a diseased artery relative to maximal myocardial blood flow if that same artery were to be disease free (Pijls et al, 1993). It represents the extent to which maximal myocardial blood flow is limited by the presence of an epicardial stenosis, and is calculated as the ratio of two pressures, distal coronary pressure (Pd) and aortic pressure (Pa), during maximal hyperaemia (*Figure 1*).

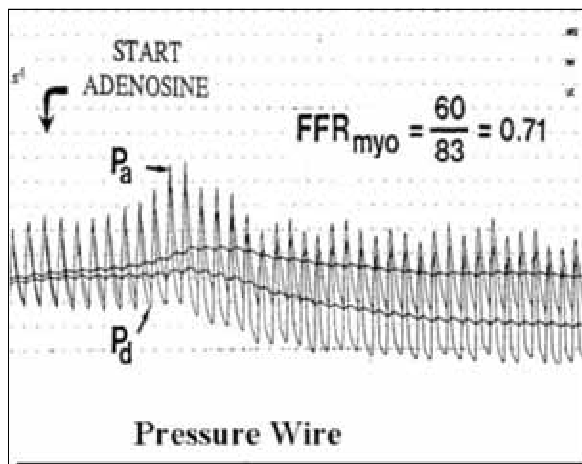
The reproducibility of fractional flow reserve is excellent, and it is largely unaffected by haemodynamic parameters such as blood pressure and heart rate (De Bruyne et al, 1996). It also takes into consideration the contribution of collaterals to myocardial perfusion during hyperaemia (Pijls et al, 1993).

In large studies, a fractional flow reserve of 0.75–0.80 or less has been found to be predictive of functional significance and hence represents the threshold at which revascularization should be considered.

Its greatest strength is its unequalled spatial resolution. Non-invasive stress testing at best can localize ischaemia to an epicardial coronary territory, whereas the pressure wire and measurement of fractional flow reserve can localize ischaemia to a particular lesion with millimetre precision.

It is therefore encouraging to see an increase in the number of percutaneous coronary intervention cases using the pressure wire to guide interventional practice in the UK, with an average increase of 4% year on year (Ludman, 2009) (*Figure 2*).

Figure 1. Fractional flow reserve (FFR) is the ratio of two pressures, distal coronary pressure (Pd) and aortic pressure (Pa) during maximal hyperaemia.



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Practical aspects for accurate fractional flow reserve measurement

Catheter choice

Despite being technically feasible to perform a pressure wire study via a diagnostic catheter, guiding catheters are generally used. 6F or 7F are recommended as they allow the operator to perform ad-hoc percutaneous coronary intervention if the fractional flow reserve is less than 0.80, or in the rare event of vessel dissection or perforation caused by pressure wire manipulation.

Wires

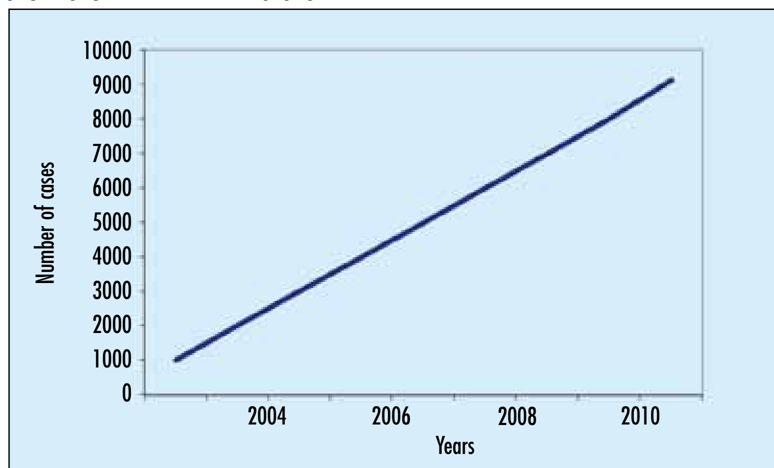
Measurement of intracoronary blood flow requires a pressure sensor mounted 3 cm from the end of a 0.014 inch angioplasty wire. Currently there are two commercially available systems, PressureWire (RadiMedical Systems Inc, Uppsala, Sweden) and Volcano Wave Wire (Volcano Inc, Rancho Cordova, California, USA). The wire needs to be flushed with normal saline and zeroed before being introduced, and anticoagulation given to maintain an activated coagulation time of >250 s. The wire should then be equalized with the manometer at the mouth of the guide before passage down the artery. If the pressure wire is to be used to interrogate a left main stem lesion, then this equalization should be performed in the aortic root, and the wire then reintroduced into the artery.

Achieving maximal hyperaemia

Key to achieving an accurate fractional flow reserve measurement is inducing maximal hyperaemia in both the epicardial conductance arteries and the microvasculature resistance vessels. Sub-maximal hyperaemia will reduce any gradient produced by a lesion and falsely elevate the fractional flow reserve result.

Use of a bolus of intracoronary nitrate abolishes any form of epicardial resistance and should be given after guide catheter intubation.

Figure 2. Increased use of the pressure wire to guide percutaneous coronary intervention. From British Cardiovascular Intervention Society data 2004–10 (www.bcis.org.uk/pages/page_box_contents.asp?pageid=697&navcatid=11 accessed 22 November 2012).



Microvascular vasodilatation is achieved using adenosine, either by a constant intravenous infusion via a large calibre vein or by intracoronary bolus injection. Intravenous adenosine at a dose of 140 μg/kg/min is considered the gold standard dose to achieve maximal hyperaemia, as higher doses do not have any further vasodilatory effect (De Bruyne et al, 2003).

With regard to intracoronary bolus dosing, 15–20 μg has been suggested for the right coronary artery and 18–24 μg for the left coronary system (Lopez-Palop et al, 2004). Intracoronary bolus dosing has been criticized as it may only offer a brief period of maximal vasodilatation because of the short half life of adenosine, relative to constant intravenous infusion, and does not allow for pull-back measurements. It is also unsuitable when there is possible disease at the ostium of the artery being assessed.

Fractional flow reserve in different coronary lesion subtypes

Fractional flow reserve and angiographically moderate or intermediate stenosis

It is very important when undertaking percutaneous coronary intervention to target ischaemia.

Irrespective of this, evidence suggests that up to 71% of percutaneous coronary intervention cases are performed in the absence of any functional evaluation (Topol et al, 1993). This is important as angiographic intermediate lesions may not induce significant ischaemia. As a consequence, patients undergoing percutaneous coronary intervention for angiographically moderate disease may not derive symptomatic or prognostic benefit and may be put at risk. Moreover, the DEFER study suggests that the annual rate of death or myocardial infarction is only 1% in patients with angiographic coronary stenosis found to be functionally insignificant (Pijls et al, 2007). Hence, the commonest indication for fractional flow reserve remains the precise evaluation of coronary lesions where the functional significance is otherwise uncertain.

Two examples of angiographically intermediate stenoses where the fractional flow reserve results have determined subsequent management can be seen in *Figures 3a* and *b*.

Fractional flow reserve and serial stenoses

If several discrete lesions are present in the same coronary artery then each of these will influence hyperaemic blood flow and therefore the pressure gradient across each one. Distal lesions will have more significant effect on fractional flow reserve measurement of proximal disease. The evidence suggests that although it is theoretically feasible to calculate the fractional flow reserve for each stenosis individually, this is not easy or practical (De Bruyne et al, 2000).

In this situation where there are either serial stenoses or diffuse disease, the pressure wire should be placed in the distal vessel and a slow pull-back of the manometer

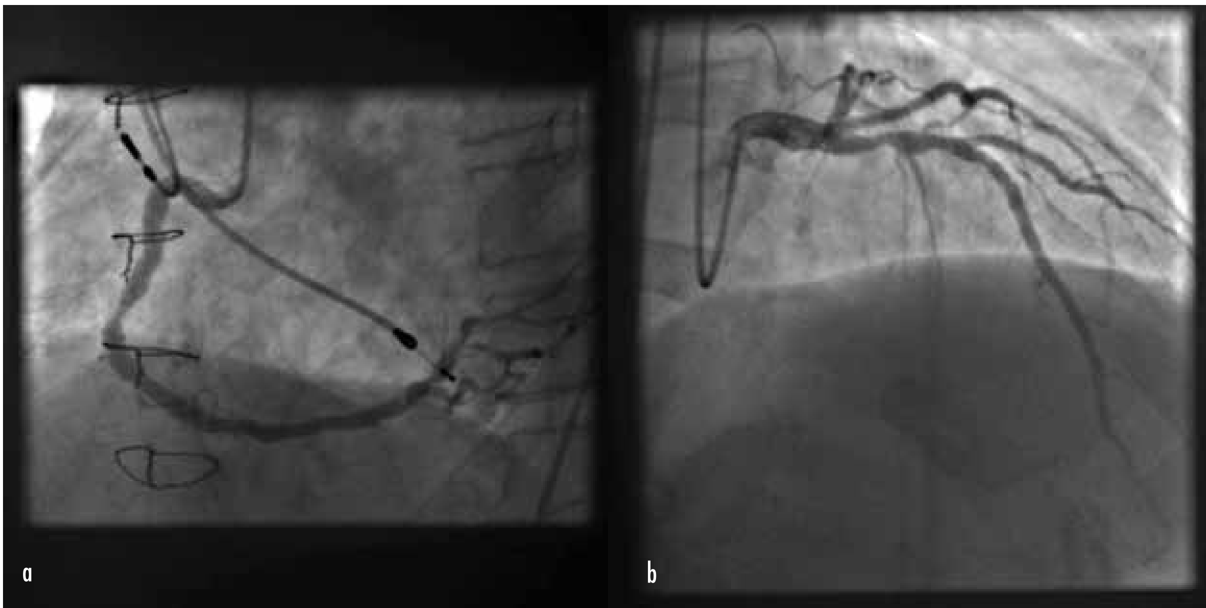


Figure 3. Fractional flow reserve and angiographically moderate or intermediate stenosis. a. Fractional flow reserve 0.76 – proceeded to percutaneous coronary intervention. b. Fractional flow reserve 0.84 – no percutaneous coronary intervention, for optimal medical therapy.

made under maximal hyperaemia, looking for a step up in the fractional flow reserve value, which suggests the location of the significant stenosis, and allows every lesion to be interrogated in conjunction with the angiographic morphological findings.

Fractional flow reserve in multi-vessel disease

Accurate assessment of ischaemia in multi-vessel coronary disease is important as it can have a major impact on the revascularization strategy appropriate for the patient. Many studies have shown that non-invasive stress imaging in this cohort of patients is difficult to interpret as, despite showing global ischaemic burden, this rarely localizes which lesion is responsible for the ischaemia (Lima et al, 2003; Ragosta et al, 2007). However, the pressure wire can accurately determine this. The FAME study compared angiographically guided percutaneous coronary intervention with fractional flow reserve-guided percutaneous coronary intervention in a multi-centred study of over 1000 patients with multi-vessel coronary artery disease. Fractional flow reserve-guided percutaneous coronary intervention significantly reduced the primary end point of death, myocardial infarction and revascularization at 1 year, and also used lower number of stents, less contrast, and did not prolong the procedure therefore reducing overall procedural costs (Tonino et al, 2009).

Fractional flow reserve in left main stem disease

Significant coronary disease involving the left main stem is of prognostic importance. It is also one of the more difficult segments of the coronary circulation to assess with angiography alone (Lindstaedt et al, 2007), hence precise functional testing is crucial in achieving optimal outcomes. Non-invasive testing has poor specificity for left main stem disease (De Bruyne and Sarma, 2008). Bech et al (2001) found that a fractional flow reserve of 0.75 remains applicable to isolated left main stem disease to guide revascularization strategies. Issues arise when left main stem disease occurs in the presence of additional distal stenoses. As discussed previously, a stenosis in the left anterior descending or circumflex arteries will tend to increase the fractional flow reserve measured across the left main stem stenosis, potentially underestimating its functional significance.

Fractional flow reserve in bifurcation disease

Fractional flow reserve can play a crucial role in bifurcation stenting strategies. In patients with significant bifurcation disease the default strategy is the provisional T procedure. This involves stenting the main vessel and only intervening on the side branch if there is significant pinching at the ostium or dissection involving the side branch vessel. Koo (2005) very elegantly showed that stenoses at the ostium of a side branch are often overestimated angiographically. In his series, fractional flow reserve measurements were made in ostial side branch lesions with angiographic diameters of <75%, and none were found to have a fractional flow reserve below 0.75 suggesting significant ischaemia.

He also reported that if treatment was required at the ostium of a side branch (fractional flow reserve <0.75) and kissing balloon dilatations (simultaneous balloon dilatation in the main vessel and side branch) were made to optimize vessel and stent patency, then the fractional flow reserve at 6 months was >0.75 in 95% of cases (Koo, 2005).

Fractional flow reserve in vein grafts

To date there are limited data in this patient group whereby decisions regarding revascularization have been made on the basis of the fractional flow reserve. Aqel et al (2008) showed that a cut off of 0.75 had acceptable specificity and negative predictive value when compared to stress myocardial perfusion scanning, but this was only in a series of 10 patients so further studies are required.

Fractional flow reserve after ST elevation myocardial infarction in bystander lesions

One area of considerable debate in the setting of acute myocardial infarction has been the possible significance of angiographically intermediate disease in bystander coronary artery territories and whether these lesions could be assessed accurately immediately after restoration of blood flow in the infarct vessel.

There is good evidence to suggest that, despite restoration of epicardial artery patency, in the setting of acute myocardial infarction microvascular abnormalities persist, often recognized as persistent ST elevation on the electrocardiogram. Microvascular resistance increases, which would decrease any trans-lesional gradient. Moreover these abnormalities of microvascular function extend to all arterial territories (Kyriakides et al, 1998), therefore any measurement of fractional flow reserve performed in non-infarct arteries may well be underestimated and therefore inaccurate. Consequently the default strategy has been to postpone the assessment of stenoses in the 'non-culprit' arteries to a later stage. However, another small case series has suggested that hyperaemic resistance may be normal in remote territories after acute myocardial infarction, suggesting that fractional flow reserve may well be accurate (De Bruyne et al, 2001). Further studies are required.

Fractional flow reserve after unstable angina and non-ST elevation myocardial infarction

As with fractional flow reserve assessment of a non-culprit stenosis following acute myocardial infarction, there remains considerable controversy about the reproducibility of fractional flow reserve in the setting of unstable angina and non-ST elevation myocardial infarction. Again this relates to whether or not microvascular function during unstable angina or non-ST elevation myocardial infarction is abnormal in remote myocardial areas.

Unlike acute myocardial infarction, where there is usually complete occlusion of an epicardial coronary artery, in unstable angina or non-ST elevation myocardial infarction the vessel remains patent or is only temporarily occluded in the presence of a significant stenosis.

It may be that the pro-thrombotic and pro-inflamamtory conditions known to increase microvascular resistance occur transiently, rather than persisting, making any effects to reduce any translesional gradient less marked.

Additionally, any effects on microvascular resistance may have resolved by the time fractional flow reserve is performed, as diagnostic coronary angiography in the presence of unstable angina or non-ST elevation myocardial infarction is often carried out within 72 hours of presentation rather than immediately as in the case of ST elevation myocardial infarction.

In one study including 101 patients with acute coronary syndrome and 26 patients with non-ST elevation myocardial infarction, the fractional flow reserve was measured in the non-culprit stenoses immediately after percutaneous coronary intervention of the culprit stenosis and again at day 35 (Ntalianis and Sels, 2010). The fractional flow reserve value of the non-culprit stenoses did not change between the acute and follow-up period (0.77±0.13 *vs* 0.77±0.13 respectively, *P*=NS). In only two patients, the fractional flow reserve value was higher than 0.8 at the acute phase and lower than 0.75 at follow up. This suggests that during the acute phase of acute coronary syndromes, the severity of non-culprit coronary artery stenoses can reliably be assessed by fractional flow reserve.

Potential cofounding factors when measuring fractional flow reserve

Right atrial pressure

It has always been considered that when measuring fractional flow reserve, right atrial pressure can be assumed to be zero. However, Perera et al (2004) found that in 63 patients with angiographically intermediate disease, 14% of lesions were misclassified as insignificant on the basis of ignoring right atrial pressure, as an elevated right atrial pressure tended to result in an underestimate of fractional flow reserve and a low right atrial pressure in an overestimated fractional flow reserve measurement. Right atrial pressure can be measured simply through a femoral venous sheath, which also offers an ideal route for central venous adenosine administration.

Left ventricular hypertrophy

In left ventricular hypertrophy, a lower ischaemic threshold is seen as there is reduced capillary supply relative to muscle mass (Krams et al, 1998). It is therefore feasible that, in patients with left ventricular hypertrophy, ischaemia may be present with a lesser degree of epicardial obstruction, and therefore the fractional flow reserve cut off of 0.75 may be too low. For this reason the threshold for significance has been extended to 0.75–0.8 to mitigate this potential confounding factor.

Endothelial dysfunction

Endothelial dysfunction is the precursor of atherosclerosis and has been postulated to cause paradoxical vasoconstriction. As most patients undergoing fractional flow reserve therefore have a degree of endothelial dysfunction, it is crucial that fractional flow reserve be measured after administration of intracoronary nitrate to maximize endothelial independent vasodilatation.

Future techniques

The novel technique of instantaneous wave free ratio is currently under investigation to determine whether an angiographically intermediate coronary stenosis is significant or not. This technique has the advantage that it does not require adenosine to induce maximal hyperaemia, and therefore could reduce time, cost and patient discomfort. The ADVISE study found, in 157 patients, that this technique produced similar results to traditional fractional flow reserve. The technique uses wave intensity analysis to identify a period during the normal cardiac rhythm cycle when intracoronary resistance is similar in variability and magnitude to those during fractional flow reserve. In the study, the resisting ratio of the distal to proximal pressure during this period, instantaneous wave free ratio, correlated closely with fractional flow reserve ($r=0.9$, $P=0.001$), with excellent diagnostic efficacy (receiver operating characteristic area under curve of 93% at fractional flow reserve <0.80). It also had high specificity and sensitivity and negative and positive predictive values (91%, 85%, 85% and 91% respectively) (Sen et al, 2012).

Further research is needed, but it may be in due course that instantaneous wave free ratio replaces fractional flow reserve as the gold standard to determine if an anatomical coronary obstruction is functionally significant or not.

Conclusions

Use of the coronary pressure wire and measurement of fractional flow reserve in conjunction with angiography offers both an anatomical and physiological assessment of epicardial coronary disease, offering an ischaemic-driven approach to revascularization on an individual patient basis.

Provided that maximal hyperaemia is achieved and that potential confounding factors are taken into account, fractional flow reserve is a theoretically robust and simple technique to perform that can enhance patient outcomes during coronary revascularization. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Fractional flow reserve is simple to perform.
- The key to successful fractional flow reserve measurement is achieving maximal hyperaemia.
- Fractional flow reserve-guided percutaneous coronary intervention offers an ischaemic driven approach to revascularization.