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Fractional flow reserve in acute coronary syndromes: A review

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ABSTRACT

Fractional flow reserve (FFR) assessment provides anatomical and physiological information that is often used to tailor treatment strategies in coronary artery disease. Whilst robust data validates FFR use in stable ischaemic heart disease, its use in acute coronary syndromes (ACS) is less well investigated. We critically review the current data surrounding FFR use across the spectrum of ACS including culprit and non-culprit artery analysis. With adenosine being conventionally used to induce maximal hyperaemia during FFR assessment, co-existent clinical conditions may preclude its use during acute myocardial infarction. Therefore, we include a current review of instantaneous wave free ratio as a novel vasodilator independent method of assessing lesion severity as an alternative strategy to guide revascularisation in ACS.

1. Fractional flow reserve assessment in acute coronary syndromes

Acute coronary syndromes (ACS) are the only clinical condition in which there is a proven mortality benefit with percutaneous coronary intervention (PCI) [1]. In the case of ST-elevation and acute coronary occlusion, the culprit vessel is usually identifiable. However, bystander coronary artery disease or multi-vessel disease occurs in approximately one half of ACS presentations, where diagnosing the culprit lesion can be less straight-forward with an associated poorer prognosis [2–4]. Whilst in stable coronary artery disease, physiological assessment using techniques such as fractional flow reserve (FFR) assessment is often used to aid operators in deciding which lesion to treat [5–8], its use in ACS is less well investigated. (See Table 1.)

Identification of the culprit artery in ST elevation MI is usually straight-forward by utilising information from the surface electrocardiogram and coronary angiography. It is recognised that FFR values in the culprit vessel are higher during acute episodes when compared to measurements made after the microcirculation has had some time to recover [9,10]. It is postulated that this is due to a reduction in the level of attainable hyperaemia in the culprit vessel due to embolisation of thrombus and plaque, ischaemic microvascular dysfunction and myocardial stunning [11]. These states are perhaps most marked in acute ST elevation myocardial infarction. Therefore, the physiological community remain cautious about the application of FFR in culprit artery disease [12]. The use of FFR in assessing the haemodynamic significance of non-culprit lesions in AMI and unstable angina has only been assessed in small studies with differing conclusions. Some studies suggest that transitory microvascular damage in myocardial territories remote from the culprit lesion and the dynamic nature of the injuries limit the reliability of measured indices. Whilst others suggest that FFR can be reliably measured to guide management in this population [13,14].

By demonstrating territories of inducible ischaemia in the context of stable coronary artery disease, lesion selection for coronary intervention can be made easier particularly in multi-vessel disease [15]. Physiological assessment offers an invasive pressure based index of the haemodynamic significance of coronary stenoses and its use has been validated in several clinical trials to guide appropriateness of PCI in stable coronary disease [5–7].

Data suggests that complete revascularisation of patients with significant multi-vessel disease within a month of primary PCI is associated with an improved survival benefit [2,3]. More recent data from the randomised PRAMI (Preventative Angioplasty in Acute Myocardial Infarction) trial showed that immediate preventative revascularisation of non-culprit arteries with an angiographically significant stenosis at the time of primary PCI for an ST segment elevation myocardial infarction may have prognostic advantages over culprit PCI alone [4,16]. It is important to note, however, that the PRAMI trial compared non-culprit PCI to abstinence from further PCI even where significant or high-grade stenosis was left untreated. This meant that physiologically significant lesions would have been treated in the same manner as intermediate and mild lesions (>50% stenosis). By deferring high grade stenosis, PRAMI deviated significantly from routine practice where high grade stenoses are known to be

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Table 1
Summarising results from studies using FFR in ACS.

Study/Ref.	N	Exclusions	Study outline	Significant results
De Bruyne et al. [24] Circulation 2001	57	Myocardial akinesia, LVSD in non-culprit territories, diameter of target vessel < 2.5 mm	FFR[a] vs SPECT > 6 days post ACS	Sensitivity/specificity: 82%/87% p < 0.001)
Samady et al. [25] J Am Coll Cardiol 2006	48	CTO, ongoing ischaemia, haemodynamic instability, prior MI in index territory, LMS disease, three vessel disease	FFR[a] vs SPECT and contrast echo < 6 days post ACS	Sensitivity/specificities: SPECT: 83%/93% Contrast echo: 90%/100% (p < 0.001)
Ntalianis et al. [27] JACC Cardiovasc Interv. 2010	101	Haemodynamic instability	FFR measured acutely and 35 +/− 4 days in non-culprit arteries post ACS	Acute and follow-up FFR: both 0.77 +/− 0.13 (p = NS)
Sels et al. [28] JACC Cardiovasc Interv. 2011	328	LMS disease, previous CABG, STEMI < 5 days prior	Outcomes of using FFR to guide revascularisation in FAME population with ACS vs stable angina (SA)	Absolute risk reduction of ACS vs SA :5.1% vs 3.7% (p = 0.92)
Lopez-Palop et al. [29] Rev Esp Cardiol 2012	107	ISR, patients pre-scheduled for angiography	Outcomes of using FFR[a] to guide revascularisation in non-culprit arteries in ACS	MACE of non-treated vs treated group: 7.4% vs 7.7% (p = 0.52)

MACE — major adverse cardiovascular events (cardiovascular related death, non-fatal MI, urgent revascularisation), CTO — chronic total occlusion, LMS — left main stem, ISR — in-stent re-stenosis, LVSD — left ventricular systolic dysfunction, CABG — coronary artery bypass graft.
[a] FFR cut off value used <0.75.

associated with high event rates [7]. However, treating all patients with a greater than 50% stenosis means that a significant number of patients will receive stents which may be considered physiologically inappropriate. This strategy of deferral of all lesions greater than 50% stenosis with physiologically negative lesions to conservative management in the control arm may also explain why a staged approach to complete revascularisation of significant stenoses confers a prognostic advantage to immediate PCI of non-culprit vessels [17,18]. It is now recognised from the French Registry, earlier studies and the RIPCORD study that angiography guided revascularisation can be misleading when compared to a physiological guided strategy [19,20].

2. Myocardial infarction and micro-vascular disease

There are various theories describing the pathophysiological mechanisms underlying micro-vascular dysfunction in the peri-infarct period. It is hypothesised that endothelial cell integrity is jeopardised in ischaemic reperfusion injury, with a subsequent reduction in endothelial derived vasodilators such as nitric oxide and an increase in potent vasoconstrictors such as endothelin and oxygen free radicals. This culminates in an overall reduction in myocardial flow. Endovascular injury results in a pro-coagulant and pro-inflammatory state caused by a cascade of activated platelets, neutrophils and adhesion molecules known to mediate myocardial damage [21] (See Fig. 1).

When accompanied by interstitial oedema and cell contraction, this can result in micro-capillary occlusion. Oxidative stress by the generation of oxygen free-radicals can directly cause further myocardial injury to an ischaemic focus. The release of increased intracellular calcium can alter sarcolemmal calcium regulation which can promote myofibrillar damage in addition to generating a pro-arrhythmic state [22].

Micro-vascular dysfunction in AMI patients is accepted as occurring in territories supplied by culprit arteries and forms the mechanism behind the 'no re-flow' phenomenon post intervention. Although regional micro-vascular dysfunction in territories remote from an acutely infarcted area has been described [23], small studies have attempted to address whether this would impact on FFR measurements of non-culprit lesions [12]. This can also aid in the identification of culprit lesions in multi-vessel disease.

3. FFR assessment in AMI

FFR is described as the ratio of maximal hyperaemic myocardial blood flow in the presence of a coronary stenosis to the normal hyperaemic blood flow in the same vessel if it were normal. In other words, the extent to which maximal myocardial blood flow is impeded by an epicardial stenosis. In order to achieve maximal myocardial flow and to minimise intracoronary resistance which is essential in the determination of the FFR, both the epicardial and microvasculature are vasodilated. The commonest agent used to ensure vasodilatation is adenosine [12]. Based on large clinical outcome trials ESC/AHA/ACC guidelines recommend a cut-off value of less than or equal to 0.80 as a guide to perform revascularisation [8].

It has been hypothesised that microvascular congestion may attenuate hyperaemic blood flow, following AMI, leading to a reduced transstenotic pressure gradient. The resulting effect could theoretically lead to an underestimation of lesion severity producing an artificially high FFR reading. Tamita et al. reported that post-interventional FFR was higher in AMI patients than in the stable angina patients following PCI with no significant differences in IVUS parameters (mean luminal areas) [9]. Tani et al. described an exploratory finding in patients post AMI who had related wall ischaemia on myocardial perfusion single-photon emission computed tomography (SPECT), but had non-physiologically significant FFR measurements of 0.87 and 0.89 in the left anterior descending and right coronary arteries respectively. The mismatch between the diagnostic modalities led the authors to suggest applying caution when interpreting FFR in culprit lesions post MI [10]. It is important to note, however, that both of these small studies measured FFR in the peri-infarct period in culprit arteries only and no assessments were performed in non-culprit bystander lesions.

De Bruyne et al. examined 57 patients at least six days post AMI, the sensitivity and specificity of FFR with a cut-off level of less than 0.75 to detect a perfusion defect on SPECT was 82% and 87%, respectively. When only true positive and negative SPECT imaging was considered, the corresponding values were 87% and 100% (p < 0.001) [24]. Accordingly, the authors concluded that when measured greater than six days post AMI, FFR accurately reflects the haemodynamic lesion severity and its impact on myocardial perfusion despite the damaged infarct zone microvasculature.

Samady et al. went on to study 48 patients earlier post AMI (3.7 +/− 1.3 days) than De Bruyne et al. and compared the relationship of FFR with SPECT and myocardial contrast echo. To identify true reversibility, follow-up SPECT was performed 11 weeks after PCI. The sensitivity, specificity, and concordance of FFR ≤ 0.75 for detecting true reversibility on SPECT were 88%, 93%, and 91% (chi-square p < 0.001) and for detecting reversibility on myocardial contrast echo were 90%, 100%, and 93% (chi-square p < 0.001), respectively. The optimal FFR value for discriminating inducible ischaemia on non-invasive imaging was demonstrated as 0.78, similar to findings from De Bruyne et al. Thus FFR of the infarct related artery accurately identified reversibility on non-invasive imaging, supporting its use early post AMI.

Whilst these studies evolved the physiological field towards a growing population of unstable patients, many of these studies were