“Resistance in the cath lab”: the utility of hyperemic stenosis resistance in the functional assessment of coronary artery disease

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Abstract
Percutaneous coronary intervention (PCI) guided by functional assessment of coronary stenoses, either non-invasively or invasively, by selective treatment of ischemia-inducing stenoses confers improved cardiovascular outcomes. We present the case of a 56-year-old man with multivessel coronary artery disease, who underwent PCI guided by invasive physiological assessment using both single modality pressure derived, fractional flow reserve and also simultaneous dual pressure and flow assessment of epicardial coronary artery disease, with hyperemic stenosis resistance and hyperemic microvascular resistance. We describe the importance of appreciating the severity of microvascular dysfunction in the context of functional assessment of coronary artery disease, highlighting the potential advantages of using simultaneous pressure-flow technology in stenosis assessment in the presence of increased microvascular resistance.

Keywords: Fractional flow reserve; functional assessment; hyperemic stenosis resistance; microvascular resistance.

Introduction
A 56-year-old man, with a background of hypertension and type 2 diabetes mellitus, had a 6-month history of increasing anginal symptoms (Canadian Cardiovascular Society class 3), despite being on optimal medical therapy. He was admitted to St Thomas’ Hospital, London, UK, for assessment and further management of his angina. He underwent cardiovascular magnetic resonance (CMR) perfusion imaging and coronary angiography sequentially in the hybrid X-ray and magnetic resonance imaging (MRI) laboratory, to assess the presence and severity of ischemia and the underlying coronary anatomy, respectively. The X-ray and MRI laboratory consists of a Philips Healthcare (Best, The Netherlands) 3 Tesla Achieva MRI scanner and an Allura Xper single plane X-ray catheter system (Figure 1), with a floating tabletop allowing direct transfer of patients between the X-ray and MRI components of the laboratory without requiring the patient to move.
The CMR examination was performed with a 32-channel cardiac phased-array receiver coil. Perfusion imaging consisted of three short axis slices acquired with a k-t accelerated (k-t factor 5) ultrafast gradient echo sequence, shortest echo and repetition time, 20° flip angle, 90° prepulse, 120 ms prepulse delay and acquired resolution 1.3 x 1.3 x 10 mm; 0.075 mmol/kg of gadobutrol (Gadovist, Schering, Germany) contrast agent was delivered by a power injector at 4 ml/s. For stress perfusion, adenosine was administered intravenously at a rate of 140 mcg/kg/min for 4 min. Imaging was commenced 3 min into the infusion and continued for 1 min. The perfusion CMR study confirmed the presence of a perfusion defect in the anterior wall, extending from the apex to the mid ventricle (Figure 2).

Following the CMR, the patient was transferred to the X-ray compartment of the suite, where a 6 Fr sheath was inserted into the right femoral artery. Coronary angiography was performed using a standard Judkins technique. The angiogram confirmed the presence of an ostial lesion (80–90% diameter stenosis) in the left anterior descending artery (LAD) and proximal disease (70–80% diameter stenosis) in the first obtuse marginal branch of the circumflex artery, with an angiographically unobstructed, dominant right coronary artery (Figure 3).

Invasive functional assessment of the diseased coronary vessels was performed using a 0.014-inch intracoronary dual pressure Doppler sensor-tipped guide wire (Volcano Therapeutics, San Diego, California, USA), with intracoronary boluses of adenosine given to achieve maximal hyperemia. The resistances exerted by both the epicardial stenosis and the microcirculation were determined through two indices, hyperemic stenosis resistance (HSR) and hyperemic microvascular resistance (HMR), respectively. HSR is defined as the ratio of the pressure gradient and the peak velocity of flow across a coronary lesion, and is derived from the difference in mean aortic and distal coronary pressure (P_a – P_d) divided by the peak velocity during hyperemia (averaged over three to five cardiac cycles; average peak velocity; APV). HSR values in excess of 0.80 mmHg/cm/sec have been shown to correlate with ischemia on noninvasive testing [1]. HMR is defined as the ratio of the pressure gradient across the microvascular bed and the flow in the given microvascular territory, derived as the difference between distal coronary and venous pressure (P_d – P_v) divided by APV in the distal coronary artery (in most instances P_v is assumed to be zero, such that HMR is simplified to P_d/ APV). HMR is thought to be independent of epicardial coronary disease and values in excess of 2.0 mmHg/cm/sec are considered abnormal, although there is significant heterogeneity even in individuals with similar clinical characteristics. We also calculated two single modality indices, the myocardial fractional flow reserve (FFR) and coronary flow reserve (CFR) for each coronary lesion. FFR is the most widely used physiological index in clinical interventional cardiology and is a pressure-based index, defined as the ratio of distal coronary pressure to aortic pressure (P_d/P_a), measured during hyperemia; values below 0.75 have been shown to correlate with ischemia on noninvasive testing [2], and it has been shown that coronary disease associated with a FFR greater than 0.80 can be safely managed with medical therapy rather than revascularisation [3]. CFR is a flow-based index, defined as APV at hyperemia divided by APV at rest, and is an integrated measure of epicardial coronary disease and microvascular function; CFR less than 2 is considered abnormal.

HSR of the LAD lesion was calculated to be 2.91 mmHg/cm/sec, suggesting an unequivocally functionally significant stenosis. HMR in the LAD territory was 2.3 mmHg/cm/sec, suggesting modestly increased microvascular resistance (Figure 4). FFR in this vessel was 0.37 (Figure 4), suggesting that the lesion is capable of producing demand ischemia, concordant with the HSR information. The CFR was reduced at 0.9, showing that the combination of epicardial and microvascular disease in the LAD subtended myocardium cumulatively provides a substrate for ischemia.

The first obtuse marginal branch of the circumflex artery was similarly interrogated during intracoronary bolus injection of adenosine. The values of the four indices were as follows: HSR 0.55, FFR 0.79, CFR 1.94 and HMR 2.1 (Figure 5).

All of the hemodynamic parameters measured in the LAD confirmed that the stenosis was functionally significant, with both dual and single modality markers.
of epicardial stenosis severity, HSR and FFR, respectively, being congruent. Percutaneous coronary intervention (PCI) was therefore performed, with balloon pre-dilatation of the vessel and subsequent deployment of a drug-eluting stent (4.0 × 24 mm) from the distal left main coronary artery to the proximal LAD.

The hemodynamic markers calculated in the circumflex vessel were conflicting, with the single modality (pressure and velocity-based) markers, FFR and CFR, both suggesting the stenosis was likely to be hemodynamically significant. The FFR value was in the “grey zone” between 0.75 and 0.80, which is perceived to categorize stenosis severity inconsistently, although recent clinical trial data use the upper level of 0.80 as the threshold for treatment of a stenosis [4]. However, HSR classified the stenosis as physiologically non flow limiting, with a value clearly below the cutoff of 0.80 mmHg/cm/sec. The invasive measure of microvascular resistance, HMR, was observed to be mildly elevated, suggesting that the microcirculation in this region

![Fig. 2 Adenosine stress perfusion cardiovascular magnetic resonance. (a) Apical slice – anterior perfusion defect. (b) Mid ventricular slice – anterior perfusion defect. (c) Basal slice – no perfusion defect, susceptibility artifact present in the inferior septum.](image1)

![Fig. 3 Coronary angiogram. (a) LAO (Left anterior oblique) – caudal view of severe proximal left anterior descending artery stenosis. (b) PA (posterior-anterior) – caudal view of the moderate to severe proximal stenosis in the first obtuse marginal branch. (c) Normal, unobstructed right coronary artery.](image2)

![Fig. 4 Pressure flow measurement from the left anterior descending vessel. APV = average peak velocity; CFR = coronary flow reserve; FFR = fractional flow reserve; HMR = hyperemic microvascular resistance; HSR = hyperemic stenosis resistance; Pa = aortic coronary pressure; Pd = distal coronary pressure.](image3)
was impaired. A lack of microvascular compliance would consequently result in submaximal pharmaco-logically induced vasodilatation and an inadequate hyperemic response, potentially resulting in an overestima-tion of the stenosis significance by both single modality measures, CFR and FFR. As HSR accounts for coronary flow velocity in conjunction with the simulta-neously obtained distal coronary pressure, it is therefore less dependent on the presence of a maximal hyperemic state. The measured HSR (0.55 mmHg/cm/sec) correlated with the perfusion CMR, which had not shown any significant perfusion abnormality in the myo-cardium subtended by the circumflex and obtuse marginal arteries. Subsequently, no revascularization was performed to this vessel.

The patient underwent a further adenosine stress perfusion CMR immediately following PCI, confirming resolution of the anterior wall defect identified in the pre-PCI scan (Figure 6) and reconfirming the absence of a lateral wall perfusion abnormality. The patient was dis-charged the following day and remains angina free 6 months post procedure.

**Discussion**

PCI guided by functional assessment of coronary stenoses, either noninvasively or invasively, by selec-tive treatment of ischemia-inducing stenoses confers improved cardiovascular outcomes [4, 5]. The use of sensor-equipped guidewires for the invasive assessment of functional coronary lesion severity has emerged as a standard diagnostic modality, providing objective evidence of myocardial ischemia during cardiac catheterization [6, 7]. The current era has been dominated by pressure-derived indices of stenosis assessment, such as FFR, although flow-only-based parameters such as CFR are also utilized. Both of these parameters have been shown to have excellent correlation with noninvasive stress testing [8, 9]. However, an important limitation of using either single-modality technique is the limited differentiation they of-fer between hemodynamic influences exerted by epicardial stenosis and the microcirculation [10]. In certain cases, the presence of an increased microvascular resistance may result in conflicting pressure and flow observations, which could cause ambi-
guty regarding the true severity of a stenosis, as observed in this case. While both FFR and CFR are based on assumptions relating to the presence of maximal hyperemia, HSR incorporates both pressure and flow velocity, and is inherently less dependent on the presence of a hyperemic state, and has been shown to improve diagnostic accuracy [1].

**Advantages of simultaneous pressure flow assessment of stenosis**

FFR remains the most widely used invasive adjunct in the assessment of stenosis severity, and has important, and clinically relevant, advantages over the pressure flow-derived indices. These include the ability accurately to measure phasic pressure with a low degree of variability, along with the ability to measure sequential stenoses or diffuse coronary disease with the “pullback” of the pressure wire. However, the combined pressure-flow velocity assessment offers the most direct physiological measure of stenosis severity, using phasic pressure and velocity signals enables individual assessment of epicardial stenoses (HSR) and microvascular resistance (HMR). HSR is stenosis specific, less dependent on the presence of maximal vasodilatation, the concurrent hemodynamic conditions, and is also independent of baseline flow. While FFR remains a suitable measure of stenosis significance in the vast majority of clinical scenarios, theoretical assumptions regarding FFR are not valid in situations that alter microvascular resistance, such as in patients with impaired left ventricular function, left ventricular hypertrophy, valve disease and recent acute coronary syndromes. In these situations HSR is likely to offer a more robust assessment and characterisation of epicardial and microvascular function.

Furthermore, while HSR was initially validated during pharmacologically induced maximal hyperemia, it has recently been assessed during basal resting conditions in comparison with FFR and myocardial perfusion scintigraphy [11]. Van de Hoef et al [11] observed that this vasodilator-free mode of assessment (basal stenosis resistance) was equivalent to standard hyperemic FFR assessment, in the identification of functionally significant stenoses. Inferring that the absence of hyperemia did not significantly diminish or impair the accuracy of the pressure-flow derived index and may provide, if required, a method of vasodilator-free stenosis assessment.

**Conclusions**

This case demonstrates how simultaneous measurement of phasic flow and pressure provides increased understanding about the pathophysiology of the human coronary circulation, and remains the reference standard for the evaluation of coronary hemodynamics, particularly when assessing the functional significance of a coronary stenosis in the presence of an impaired microcirculation.

**REFERENCES**