The use of adenosine in the assessment of stable coronary heart disease

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Coronary heart disease (CHD) is a leading global health problem resulting in 7.2 million annual worldwide deaths.[1] A variety of investigations and diagnostic pathways may be used to diagnose CHD and determine the need for revascularisation. In the UK alone 260,000 invasive coronary catheterisation procedures per annum are performed, with 38% of these undergoing revascularisation with percutaneous coronary intervention (PCI).[2] It is well recognised that the concordance between the visual assessment of the severity of the coronary stenosis observed at coronary angiography and demonstrable ischaemia is poor.[3] Current guidelines, therefore, recommend that ischaemia should be demonstrated in those with stable angina before PCI is performed.[4,5]

Myocardial fractional flow reserve (FFR) is a lesion-specific index of the functional significance of an epicardial coronary stenosis. It is defined as the ratio of maximal blood flow in a stenotic artery to normal maximal flow. Maximal flow (hyperaemia) is typically induced by intravenous infusion of adenosine, or with an intracoronary bolus of adenosine. The ratio of the pressure distal to (i.e. guidewire pressure) and proximal to (i.e. the aortic pressure) stenotic lesions at maximal flow is the FFR. An FFR value of 1.0 is considered normal, whereas a ratio of ≤0.80 is an evidence-based physiological threshold that correlates with the presence of inducible ischaemia.[6,7]

In addition, intravenous adenosine may also be administered for the assessment of the microvascular coronary circulation.[8] Under normal physiological conditions, myocardial perfusion is autoregulated by arterioles within the myocardium and prearterioles in the epicardium. Owing to their small calibre (≤300 μm in diameter) the microcirculation is not directly visualised during invasive coronary angiography. These small blood vessels, however, contribute the majority of coronary resistance. Pathological changes, including perivascular fibrosis, occur in those with hypertension,[9] coronary artery disease[10] and after cardiac transplantation. Following the induction of maximal hyperaemia with adenosine the index of microcirculatory resistance can be quantified using pressure and temperature sensitive coronary guidewires.[11] Since resistance is a property of microvascular tone, this provides a direct assessment of microvascular function and is independent of coronary stenosis severity. This is helpful in the assessment of microvascular angina and there is increasing evidence of the prognostic value of microcirculatory resistance following revascularisation for ST-elevation myocardial infarction.[12]

Noninvasive cardiovascular imaging

Evidence from large populations of patients undergoing invasive angiography have demonstrated that only around 40% will undergo revascularisation.[2,13] Thus, over the last decade there has been a rapid expansion in the use of noninvasive cardiovascular imaging with the development of new technologies, such as CT coronary angiography and cardiovascular magnetic resonance (CMR). Noninvasive imaging has become the first-line investigation in national and international guidelines for the investigation of stable coronary artery disease.[5,14] Vasodilating agents, such as

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adenosine, can be used to induce stress in CMR, myocardial perfusion scintigraphy (MPS) and stress echocardiography. MPS with vasodilator stress has for decades been used as an investigation and risk-stratification tool in those presenting with stable angina.[15] Furthermore, there is recent clear demonstrable evidence that using noninvasive imaging in those with stable CHD can safely reduce the inappropriate use of invasive coronary angiography (which may result in potential cost savings and risk reduction).[16] Stress perfusion CMR with adenosine stress has recently been demonstrated to result in fewer revascularisations with no difference in major adverse cardiovascular events.[17]

Adenosine

Adenosine exerts its biological effect on four receptor subtypes (A1, A2A, A2B and A3AR).[18] Adenosine has a very short half-life (<10 s) and, therefore, is administered intravenously or via the intracoronary route. Potential complications of adenosine not only include the risk of acute bronchospasm but also other serious arrhythmias, including ventricular fibrillation in those with an accessory conduction pathway. In this issue of *JRCPE* Morrow et al.[19] demonstrate the very rare incidence of bronchospasm following the administration of adenosine. There is overwhelming evidence for its beneficial use in the functional assessment of CHD (either invasively in the catheterisation laboratory or with noninvasive cardiovascular imaging) or of the microvascular physiology. These data, therefore, add support to the argument for the safety of adenosine and the continued use for the functional assessment of cardiovascular conditions. It ought to be recognised that adenosine is not the only agent to be used for the assessment of functional coronary disease. Other options include regadenoson, dipyridamole, dobutamine, electrical stress and physiological (treadmill or bicycle) exercise.

The future

As an alternative to FFR, instantaneous wave free ratio provides a similar validated method for assessing epicardial coronary disease without the need for administration of adenosine. In addition, CT-FFR has recently been approved by the US Food and Drug Administration. The technology combines anatomical and functional assessment demonstrating coronary physiology simulation using proprietary software. This is able to assess the functional significance of an epicardial stenosis without inducing stress. CT-FFR has been demonstrated to modify treatment recommendation, and reduce rates of invasive coronary angiography and revascularisation without any expense of major adverse cardiovascular events.[20]

Whilst adenosine plays a fundamental role in the current invasive and noninvasive assessment of stable coronary disease and has an excellent safety profile, administration may be uncomfortable for patients and in rare cases have serious side effects. The changing landscape of available technology may allow us to move towards different techniques to evaluate coronary stenosis.

References

1 World Health Organisation. Types of cardiovascular disease. https://www.who.int/cardiovascular_diseases/resources/atlas/en/ (accessed 27/07/19).
2 British Cardiovascular Intervention Society. BCIS Audit Report for 2016. https://www.bcis.org.uk/resources/audit-results/ (accessed 27/07/19).
3 Fischer JJ, Samady H, McPherson JA et al. Comparison between visual assessment and quantitative angiography versus fractional flow reserve for native coronary narrowings of moderate severity. *Am J Cardiol* 2002; 90: 210–5.
4 Windecker S, Kolh P, Alfonso F et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014; 35: 2541–619.
5 Montalescot G, Sechtem U, Achenbach S et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013; 34: 2949–3003.
6 Pijls NH, De Bruyne B, Peels K et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996; 334: 1703–8.
7 Watkins S, McGeoch R, Lyne J et al. Validation of magnetic resonance myocardial perfusion imaging with fractional flow reserve for the detection of significant coronary heart disease. *Circulation* 2009; 120: 2207–13.
8 Corcoran D, Young R, Adlam D et al. Coronary microvascular dysfunction in patients with stable coronary artery disease: the CE-MARC 2 coronary physiology sub-study. *Int J Cardiol* 2018; 266: 7–14.
9 Mundhenke M, Schwartzkopff B, Strauer BE. Structural analysis of arteriolar and myocardial remodelling in the subendocardial region of patients with hypertensive heart disease and hypertrophic cardiomyopathy. *Virchows Archiv* 1997; 431: 265–73.
10 Campbell DJ, Somaratne JB, Jenkins AJ et al. Differences in myocardial structure and coronary microvasculature between men and women with coronary artery disease. *Hypertension* 2011; 57: 186–92.
11 Fearon WF, Balsam LB, Farouque HM et al. Novel index for invasively assessing the coronary microcirculation. *Circulation* 2003; 107: 3129–32.

12 Fearon WF, Low AF, Yong AS et al. Prognostic value of the index of microcirculatory resistance measured after primary percutaneous coronary intervention. *Circulation* 2013; 127: 2436–41.
13 Patel MR, Dai D, Hernandez AF et al. Prevalence and predictors of nonobstructive coronary artery disease identified with coronary angiography in contemporary clinical practice. *Am Heart J* 2014; 167: 846–52.e2.
14 *Chest Pain of Recent Onset: Assessment and Diagnosis (CG95).* London: National Institute for Health and Care Excellence; 2010 (Updated 2016).
15 Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging: a diagnostic tool comes of age. *Circulation* 1991; 83: 363–81.
16 Greenwood JP, Ripley DP, Berry C et al. Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE Guidelines on subsequent unnecessary angiography rates: the CE-MARC 2 randomized clinical trial. *JAMA* 2016; 316: 1051–60.
17 Nagel E, Greenwood JP, McCann GP et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. *N Engl J Med* 2019; 380: 2418–28.
18 Sheth S, Brito R, Mukherjea D et al. Adenosine receptors: expression, function and regulation. *Int J Mol Sci* 2014; 15: 2024–52.
19 Morrow A, Ford TJ, Brogan R. Incidence of acute bronchospasm during systemic adenosine administration for coronary angiography. *J R Coll Physicians Edinb* 2019; 49: 204–6.
20 Fairbairn TA, Nieman K, Akasaka T et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE Registry. *Eur Heart J* 2018; 39: 3701–11.