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ORIGINAL ARTICLE

The Utility of Contrast Medium Fractional Flow Reserve in Functional Assessment Of Coronary Disease in Daily Practice

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Background Adenosine induced hyperaemic fractional flow reserve (aFFR) is a validated predictor of clinical outcome and part of routine interventional practice. Protocol issues associated with the adenosine infusion limit the use of aFFR in clinical practice. Contrast medium induced hyperaemic FFR (cFFR) is a simpler procedure from a practical standpoint. We compared the two in a real world setting.

Methods We analysed 76 patients that had both cFFR and aFFR assessment of 100 angiographically indeterminate coronary stenosis. cFFR was performed with intracoronary contrast medium injections (10 ml for left coronary lesions and 8 ml for right coronary lesions). The diagnostic performance of cFFR was analysed and compared to the gold standard aFFR.

Results Mean cFFR was 0.87 (±0.07) and mean aFFR was 0.84 (±0.08). Bland-Altman analysis revealed a close agreement between cFFR and aFFR (0.035 ± 0.032; 95% CI: −0.028 to 0.098) and good linear correlation ($r = 0.92$, $r^2 = 0.86$; $p < 0.0001$). Using cFFR cut-off values of ≤0.83 in predicting an aFFR value of ≤0.80 or a cFFR value ≥0.88, predicting an aFFR value of >0.80 yielded a sensitivity of 100%, specificity of 96.1%, positive predictive value of 92.3%, negative predictive value of 100% and diagnostic accuracy of 96%. Only 24% of cFFR values were in the 0.84 to 0.87 range.

Conclusion Contrast medium induced hyperaemic FFR as an initial assessment may limit the need for adenosine to when cFFR falls in the 0.84 to 0.87 range. The use of adenosine infusion potentially could have been avoided in the majority of patients in this study.

Keywords Contrast Fractional Flow Reserve

Abbreviations: FFR, Fractional flow reserve; aFFR, Adenosine fractional flow reserve; cFFR, Contrast fractional flow reserve; ml, Millilitre; PCI, Percutaneous coronary intervention; ETT, Exercise treadmill test; DSE, Dobutamine stress echocardiography; MPI, Myocardial perfusion imaging; CTCA, Coronary artery computed tomography; QCA, Quantitative coronary angiography; IC, Intracoronary; IV, Intravenous; mcg, Micgrograms; kg, Kilogram; min, Minute; ROC, Receiver operating characteristic; CI, Confidence interval; AUC, Area under ROC curve; LAD, Left anterior descending artery; iFR, Instantaneous wave-free ratio; CABG, Coronary artery bypass surgery; MI, Myocardial infarction

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Introduction

The importance of physiological assessment of coronary artery disease and percutaneous coronary intervention (PCI) was recognised by Andreus Gruentzig when he first described coronary angioplasty. He stressed the need for translesional pressure gradient measurement before and after angioplasty to guide procedural success [1]. Physiological significance can now be assessed with the development of fractional flow reserve (FFR) that was first described by Pijls and co-workers and De Bruyne and colleagues in 1993 and 1994 respectively [2,3]. Fractional flow reserve was first validated in 1996 by Pijls, De Bruyne, and colleagues [4]. With advances in pressure wire technology and several randomised control trials that showed superior clinical outcomes when PCI is guided by physiological assessment, FFR has now become an important component of PCI in routine clinical practice [5–7].

Accurate FFR assessment requires hyperaemia in order to achieve a linear relationship between coronary flow and pressure. Agents known to induce hyperaemia include adenosine, papaverine, regadenoson and nicorandil [8–11,18]. Although it could be administered via intra-coronary bolus, intravenous adenosine infusion is considered the gold standard for hyperaemic FFR assessment, further referred to as aFFR. However adenosine administration can cause chest discomfort, bronchial hyperreactivity, atrioventicular (AV) conduction delay, it adds to the cost of the procedure, may be burdensome and is certainly time consuming especially when done via the intravenous infusion route. Although major side effects from adenosine are rare, the administration of adenosine in many cases leads to transient discomfort for the patient. Therefore, a more convenient and safe method that is more tolerable to the patient may facilitate the wider use of FFR measurement in the day-to-day cardiac catheterisation laboratory [12].

Radiographic contrast media has also been shown to induce reproducible hyperaemia, albeit at sub-maximal levels [13,14]. The mechanism of vasodilatory and hyperaemic effect of contrast media is poorly understood, however, it has been shown to be independent of nitric oxide (NO) activity in animal studies [15]. Other animal studies suggest that the hyperaemic effect of contrast media relates to its hyperosmolar effect triggering opening of K^+ (ATP) channels in the vascular endothelium resulting in vasodilatation [13].

Contrast induced hyperaemic FFR (cFFR) may therefore be useful as an easy diagnostic screening tool for physiological evaluation of indeterminate coronary stenosis. The utility of cFFR has been evaluated in prospective pilot studies and suggested that aFFR may only be required if the cFFR value falls within an indeterminate range [16,17,22].

The aim of our study was to evaluate the real world diagnostic accuracy of cFFR relative to aFFR and test the hypothesis that a cFFR value of $\leq$0.83 accurately predicts an aFFR value of $\leq$0.80 and a cFFR value of $\geq$0.88 accurately predicts an aFFR value of $\geq$0.81.

Methods

We prospectively performed cFFR on consecutive patients that had aFFR assessment of indeterminate coronary stenosis (visual diameter stenosis of 30%–80%) at a tertiary referral hospital. Since February 2015, cFFR has also been performed as a screening tool for the physiological significance of indeterminate coronary stenosis. We analysed all patients that had both cFFR and aFFR assessments. Following request of ethical approval, a formal New Zealand Health and Disability Ethics committee review was deemed not necessary, on the basis that this study incorporated only an additional haemodynamic as explained in the methods below.

Patient demographics and risk factors were recorded as well as the indication for coronary angiography. Prior cardiac stress testing (exercise treadmill test (ETT), dobutamine stress echocardiography (DSE) and myocardial perfusion imaging (MPI)) or coronary artery computed tomography (CTCA) results were obtained. Retrospective quantitative coronary angiography (QCA) was used to provide an objective evaluation of angiographic stenosis severity.

All FFR assessments were performed after administration of 80–100 IU/kg heparin prior to passing a 0.014 inch pressure monitoring guidewire (Aeris Pressure wire®, St Judes Medical, Minnesota USA) into the coronary artery requiring FFR assessment. Pressure wire equalisation to the guide catheter was performed with the pressure wire sensor just distal to the guide catheter tip. Contrast was not flushed from the guide catheters so as to ensure that the proximal pressure obtained from the guide catheter at the time of pressure equalisation would be comparable to the proximal pressure obtained during cFFR as well as aFFR. Following pressure equalisation the pressure wire was advanced across and distal to the stenotic lesion in question.

Contrast medium induced hyperaemic FFR was performed prior to aFFR. The standard practice at our centre has been to perform a contrast injection to illustrate the pressure wire position. cFFR was obtained during this wire position image by injecting 8–10 ml (8 ml at a flow rate of 2.5 ml/second and a pressure of 300 psi for assessing right coronary artery stenosis and 10 ml at a flow rate of 3.0 ml/second and a pressure of 300 psi for assessment of left coronary stenosis) of non-ionic radiographic contrast medium (Visipaque 320®, GE Healthcare). Effectively, no additional contrast injection was made to obtain cFFR as compared to our usual practice, however the volume of contrast used for this injection to obtain a cFFR value would be two to three millilitres more than a standard wire positioning injection. Immediately after contrast injection and normalisation of the pressure wave pattern cFFR values recorded was the lowest distal to proximal pressure ratio (Pd/Pa) achieved. If two or more measurements were performed, the lowest value was used for this study analysis. Following cFFR measurement, the Pd/Pa ratio was allowed to return to initial resting ratio prior to performing aFFR.

Adenosine induced hyperaemic fractional flow reserve was performed with administering adenosine either via

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