IJC Heart & Vasculature 18 (2018) 39–45

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vasculature

Invasive physiological indices to determine the functional significance of coronary stenosis

Firas R. AL-Obaidi [a,b], William F. Fearon [c], Andy S.C. Yong [a,d,*]

[a] Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia
[b] College of Medicine, University of Thi Qar, Iraq
[c] Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA, USA
[d] ANZAC Research Institute, Concord Hospital, Sydney, Australia

ARTICLE INFO

Article history:
Received 17 November 2017
Accepted 13 February 2018
Available online xxxx

Keywords:
Coronary physiology
Fractional flow reserve
Resting physiological indices
Coronary flow reserve

ABSTRACT

Physiological measurements are now commonly used to assess coronary lesions in the cardiac catheterisation laboratory, and this practice is evidence-based and supported by clinical guidelines. Fractional flow reserve is currently the gold standard method to determine whether coronary lesions are functionally significant, and is used to guide revascularization. There are however several other physiological measurements that have been proposed as alternatives to the fractional flow reserve. This review aims to comprehensively discuss physiological indices that can be used in the cardiac catheterisation laboratory to determine the functional significance of coronary lesions. We will focus on their advantages and disadvantages, and the current evidence supporting their use.

1. Introduction

Physiological measurements are being increasingly used in the cardiac catheterization laboratory to evaluate the functional significance of coronary stenoses. The fractional flow reserve (FFR) is used to assess whether coronary lesions should be revascularized. However, a multitude of physiological indices have been proposed for similar clinical application. The aim of this review is to provide a comprehensive discussion of the most common invasive physiological indices to assess coronary lesions, including their advantages, disadvantages and the evidence that supports their use.

1.1. Fractional Flow Reserve (FFR)

FFR is currently considered the gold standard for the physiological assessment of coronary artery stenosis in the catheterization laboratory. The FFR is derived from the ratio between the mean coronary blood pressure distal to a stenosed segment (P_d) and the mean proximal coronary pressure (P_a) during maximum coronary blood flow and a state of minimum microvascular resistance [1]. Essentially, FFR = P_d/P_a during induced hyperemia. FFR is meant to represent the ratio of maximal myocardial blood flow in the territory supplied by the coronary stenosis being interrogated to the maximal myocardial blood flow in the same territory if the coronary artery in question was normal and without stenosis.

Measurement of FFR is performed by using a pressure-sensor wire or microcatheter to record pressure distal to the target lesion while simultaneously recording proximal coronary pressure via the guiding catheter. FFR is measured after administration of intracoronary nitroglycerin (100–200 μg) to dilate the vessel, followed by adenosine to induce maximum hyperemia and minimum microvascular resistance [2]. Other vasodilators such as regadenoson, nicorandil, nitroprusside and dobutamine have been proposed for use as substitute vasodilators to induce hyperemia, but adenosine remains the gold standard for FFR measurement [2].

The results of the FAME-1 (**F**ractional Flow Reserve Versus **A**ngiography for **M**ultivessel **E**valuation) and FAME-2 trials which demonstrate clinical benefit in using FFR to guide revascularization decisions have led to the adoption of FFR use in clinical practice [3–5]. The role of FFR to guide revascularization has been adopted by international guidelines. The American College of Cardiology guidelines provides a class IIa recommendation for the use of FFR to evaluate intermediate lesions (30–70% stenosis) in patients with stable ischaemic heart disease [6]. The European society of cardiology 2014 revascularization guidelines provides a class 1A recommendation for the use of FFR to guide revascularization in patients with stable ischaemic heart disease or silent angina [7].

Abbreviations: FFR, fractional flow reserve; P_a, proximal (aortic) pressure; P_d, distal coronary pressure; iFR, instantaneous wave-free reserve; cFFR, contrast Fractional Flow Reserve; CFR, coronary Flow Reserve; HSR, hyperaemic stenosis resistance; BSR, basal stenosis resistance.

* Corresponding author at: Faculty of Medicine and Health Sciences, Suite 17, Level 1, 75 Talavera Road, Macquarie University, NSW 2109, Australia.
E-mail address: andy.yong@sydney.edu.au (A.S.C. Yong).

https://doi.org/10.1016/j.ijcha.2018.02.003

FFR use to guide revascularization was found to be cost-effective by reducing the number of unnecessary interventions [8], which can potentially lead to cost-savings of $1200–$5000 per patient [9]. FFR use was found to be more cost-effective than a nuclear imaging guided revascularization strategy [10].

Despite the fact that FFR use to guide revascularization is backed by a substantial body of evidence, and is cost-effective, it remains underutilised. This is likely due to a combination of factors including added procedural time, operator unfamiliarity, side effects and cost of adenosine, and lack of reimbursement for the procedure [11]. Consequently, there have been several attempts at developing alternative physiological approaches to detect ischemia in the cardiac catheterisation laboratory.

1.2. The instantaneous wave-free ratio (iFR)

The principle of iFR is based on the concept that coronary microvascular resistance is constant during the diastolic wave-free period, defined as beginning from 25% into diastole to 5 ms before the end of diastole, and that P_d/P_a measured during this period is a surrogate of coronary flow during maximal hyperaemia. Measurement of iFR requires the use of a pressure wire but obviates the need for adenosine. It therefore avoids the side-effects and symptoms associated with adenosine infusion and incurs less cost.

The ADVISE (**AD**enosine **V**asodilator **I**ndependent **S**tenosis **E**valuation) study was the first to validate iFR in the clinical setting. A total of 131 patients with 157 stenoses were enrolled. iFR had good correlation with FFR ($r = 0.90$, $p < 0.001$). The area under the curve was 0.93 for iFR cutoff 0.83 to predict FFR <0.80 with 85% sensitivity and 91% specificity [12].

Several comparative studies to validate iFR in patients with intermediate coronary artery stenoses followed. The VERIFY (**VER**ification of **I**nstantaneous Wave-Free Ratio and **F**ractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in Everyda**Y** Practice) study, which was performed by a different group of investigators reported AUC 0.87 with high specificity of 96% but low sensitivity of 54% for iFR ≤0.83 to predict FFR ≤0.80. In addition, these investigators found that adenosine infusion resulted in the iFR dropping from 0.82 to 0.64 ($p < 0.0001$), and this demonstrated that microvascular resistance is not minimal during the diastolic wave-free period [13].

In response, proponents of the iFR conducted the CLARIFY study (**Cl**assification **A**ccuracy of Pressure-Only **R**atios Against **I**ndices Using **F**low stud**y**). This demonstrated that vasodilators only affected the numerical value of iFR and not its diagnostic performance. When comparing iFR with iFRa (iFR measured with hyperemia) using the hyperemic stenosis resistance (HSR) index as the gold standard, the area under the curve of iFR was 0.93, iFRa was 0.94 and FFR was 0.96, $p = 0.48$ [14]. However, the use of HSR as a reference is debatable as it has not been validated in any large scale studies.

iFR can also be used by way of a hybrid approach whereby iFR <0.86 is considered functionally significant and iFR >0.93 is considered not functionally significant, and if iFR falls within the grey zone of between 0.86 and 0.93, then the operator should perform FFR. The hybrid iFR approach can correctly classify patients into functionally significant or non-significant FFR 95% of the time, and obviated the need for adenosine 57% of the time [15,16]. Using this approach in the ADVISE II study, which involved 598 patients, resulted in 94.2% agreement between iFR and FFR, and eliminated the need for adenosine in 69.1% of the time [17].

Recently, two large randomised control trials tested the validity of using iFR to guide revascularization. Both studies demonstrated that using an iFR cut off of ≤0.89 was not inferior to FFR in guiding revascularization for the primary outcome of one year composite risk of major adverse cardiac events including death, nonfatal myocardial infarction and unplanned revascularization. The DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) trial [18], which involved 2492 patients, showed that the rate of major adverse cardiac events was 6.8% in the iFR group and 7.0% in the FFR group with hazard ratio of 0.95 (95% CI 0.68 to 1.33; $p = 0.78$) and $p < 0.001$ for non-inferiority. The iFR-SWEDEHEART (Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome) trial [19], which involved 2037 patients, showed that the rate of major adverse cardiac events at one year was 6.7% for the iFR group and 6.1% for the FFR group with $p = 0.007$ for non-inferiority. The use of iFR in these trials resulted in shorter procedure time and less patient discomfort when compared to FFR as adenosine infusion was not required for iFR measurement.

In both studies, the FFR arm had a greater number of revascularization procedures, resulting in a higher number of stents deployed (number of significant lesions detected in iFR group vs FFR group: 451 vs. 557, $p = 0.004$ in the DEFINE-FLAIR trial and 457 vs. 528, in the iFR-SWEDEHEART trial, $p < 0.001$). There are two ways to interpret this data. The first is to assume that there was a larger number of patients with significant lesions in the FFR arm in both trials. This assumption would suggest that the FFR cohorts should theoretically have worse outcome results, and this could have confounded the results of the studies. The second way to interpret this data is to assume that iFR is less sensitive in assessing stenosis severity when compared to FFR. It is our opinion that the second explanation is true, as this phenomenon was found independently in both studies, and encountering iFR negative but FFR positive is a common occurrence in the cardiac catheterisation laboratory.

The two major trials did not address the issue of discordance between iFR and FFR, which can affect up to 20% of patients, especially those with left main and LAD lesions [20]. It has been suggested that patients with high iFR and low FFR have preserved coronary flow (CFR) and higher myocardial blood flow compared to patients with low iFR and low FFR [21]. These patients tend to have less complex coronary disease and less comorbidities [22]. It remains unclear whether lesions with low FFR but normal iFR should be revascularized. In addition, a meta-analysis combining both these studies showed that use of iFR resulted in a numerically higher rate of subsequent death or myocardial infarction (relative risk 1.3, $p = 0.09$) [20].

In patients with serial stenoses, FFR measurement of a specific lesion can be affected by upstream or downstream disease [23]. iFR has been proposed as a useful measurement in these situations. Theoretically, pressure gradients during resting conditions may be less susceptible to effects of inter-lesional dependence, and the use of iFR pullback with automated iFR-angiography co-registration provides an attractive tool to guide revascularization in this setting [24,25]. However, the use of iFR in this setting has only been validated in a small study involving 29 patients [24].

The accumulated data for iFR therefore suggests that it is a reasonable alternative to performing FFR in the cardiac catheterisation laboratory, with the advantage of obviating the need for adenosine administration. However, there is a need to determine the long-term outcome of unrevascularized patients who are iFR negative but FFR positive. A summary of studies comparing iFR to FFR is shown in Table 1, and a summary of clinical outcome studies involving FFR and iFR is shown in Table 2.

1.3. Resting P_d/P_a

In an effort to further simplify FFR, investigators have studied the use of baseline mean P_d/P_a over the entire cardiac cycle without hyperaemia. An initial single centre retrospective study showed a significant linear correlation between resting P_d/P_a and FFR $r = 0.74$, and area under the curve was 0.86 for resting P_d/P_a to predict FFR ≤0.8 [26]. Subsequent prospective studies demonstrated AUC of 0.88–0.89, specificity of 91.7–92%, and sensitivity of 60–68.9% for $P_d/P_a \leq 0.91$ to predict FFR ≤0.8 [27,28].