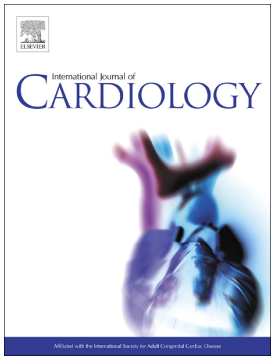
The fallacies of fractional flow reserve



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The Fallacies of Fractional Flow Reserve

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Fractional flow reserve (FFR) is an invasive assessment of coronary physiology, developed to determine the hemodynamic significance of an epicardial stenosis of intermediate severity on coronary angiography. It is calculated by measuring the ratio of distal coronary pressure to proximal coronary pressure during hyperemia induced by adenosine. The development of FFR was stimulated by the recognized shortcomings of coronary angiography in determining the hemodynamic effect of a focal coronary stenosis. However, during its development, FFR was calibrated against stress tests which were, themselves, calibrated against the presence or absence of an obstructive stenosis as defined by coronary angiography [1]. Of concern, despite the circular reasoning that led to its development, FFR is now being used as a "gold standard" for the development of further derivative methods to determine the hemodynamic effects of a coronary stenosis including iFR, QFR and CCTA-FFR. This is despite ongoing uncertainty regarding what value actually defines a normal versus an abnormal FFR. On the basis of the 1996 study by Piljs and colleagues [1], a value of 0.75 was determined to be the optimal cutoff for distinguishing lesions that were and were not associated with ischemia on stress testing. In that study, there were no patients with FFR values between 0.75 and 0.80 who had abnormal stress tests. In fact, using the 0.75 FFR cutoff value, the DEFER trial demonstrated that it was safe to defer PCI in lesions with an FFR of 0.75 or greater [2]. Subsequently, the cutoff value migrated to 0.80, which gave license to performance of PCI on the many lesions that cluster between FFR values of 0.75 and 0.80 despite the DEFER study demonstrating no harm in not performing PCI on those lesions.

The recently released 2019 European Society of Cardiology (ESC) guidelines recommend invasive angiography with FFR if the clinical likelihood of obstructive

coronary artery disease (CAD) is high [3]. This recommendation and the pervasive focus on measuring the isolated hemodynamic effects of individual lesions in a generally diffuse rather than focal disease ignores at least four fundamental fallacies of FFR.

The first fallacy is the foundational premise of FFR that ischemia caused by a focal obstructive epicardial coronary stenosis is on the direct pathway to death or MI and therefore should be a target of revascularization [4]. Although it has been repeatedly demonstrated that moderate to severe myocardial ischemia is associated with myocardial infarction (MI) or death, this association does not prove causation [5]. In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, atherosclerotic burden, but not ischemic burden, was predictive of the composite outcome of death, MI, and non-ST segment elevation acute coronary syndromes [6], suggesting that ischemia is a surrogate for atherosclerotic plaque burden, which is the proximate driver of MI and death. Moreover, in a meta-analysis of five clinical trials with a total enrollment of 5286 patients with stable CAD and myocardial ischemia documented by stress testing or FFR, percutaneous coronary intervention (PCI) in combination with medical therapy resulted in no significant reduction in mortality, non-fatal MI, unplanned revascularization, or angina compared with medical therapy alone [7].

A second fallacy is that the microvasculature is irrelevant in the assessment of coronary physiology and pathophysiology in patients with angina. The coronary circulation includes both the macrocirculation, which is evaluated by FFR, and the microcirculation, which is responsible for most of the resistance to coronary flow [8]. Because FFR measures the pressure gradient induced by a stenosis and distal pressure is

influenced by microvascular resistance, the measured value of FFR becomes greater (more normal) with increasing microvascular resistance [9]. Thus, a patient with a hemodynamically significant epicardial lesion and microvascular dysfunction may be told they are "normal" when in reality they have significant epicardial and microvascular dysfunction, placing them at high risk for future events.

A third fallacy is that FFR-guided PCI improves outcomes through targeted lesion selection as asserted in the Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention (FAME) trial, which found that measurement of FFR in patients undergoing PCI significantly reduced death or nonfatal MI at one year by 34% compared to lesion selection using angiography [10]. FFR was greater than 0.80 in 37% of lesions leading to deferral of PCI on those lesions [10]. However, without a medical treatment control group, it is unknown if the lower event rate in FAME was due to hemodynamic selection of lesions or just due to the placing of 37% fewer stents with the associated avoidance of periprocedural MI.

A fourth fallacy is that FFR-guided PCI improves outcomes compared to optimal medical therapy (OMT). In the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 2 trial, recruitment was halted prematurely because of the significant increased incidence of the primary end point in the OMT group (12.7% versus 4.3% in the PCI group) [11]. There was no significant reduction in death or MI at 213 days, 3 years, or 5 years of follow-up. The difference in the composite event rate was primarily due to the increased rate of urgent revascularization in the OMT arm [11]. However, urgent revascularization events were likely an artifact of the unblinded nature of the study in which patients and their physicians were informed that a significant lesion

was not stented [12]. This phenomenon, termed subtraction anxiety, was likely a potent force in the urgent revascularizations observed in the unblinded FAME 2 trial [12]. In the only sham-controlled trial of PCI in stable CAD ever performed, the Objective Randomized Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA) trial, there was no interaction between FFR and randomized treatment assignment to a sham procedure or PCI for exercise time, angina frequency, freedom from angina, or quality of life [13].

In conclusion, FFR in isolation is of no proven clinical value in the evaluation of patients with suspected ischemia. The ESC guidelines continue to promote an outdated paradigm for the evaluation of suspected ischemia that focuses on the focal epicardial stenosis. Ideally, the entire coronary vasculature should be assessed at initial evaluation for a comprehensive understanding of the pathophysiology and preferred treatment of individual patients.

References

[1] N.H. Pijls, B. De Bruyne, K. Peels, P.H. Van Der Voort, H.J. Bonnier, J.J. Bartunek J Koolen, J.J. Koolen, Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses., N. Engl. J. Med. 334 (1996) 1703–1708. https://doi.org/10.1056/NEJM199606273342604.

[2] G.J. Bech, B. De Bruyne, N.H. Pijls, E.D. de Muinck, J.C. Hoorntje, J. Escaned, P.R. Stella, E. Boersma, J. Bartunek, J.J. Koolen, W. Wijns, Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial., Circulation. 103 (2001) 2928–2934. https://doi.org/10.1161/01.cir.103.24.2928.

[3] J. Knuuti, W. Wijns, A. Saraste, D. Capodanno, E. Barbato, C. Funck-Brentano, E. Prescott, R.F. Storey, C. Deaton, T. Cuisset, S. Agewall, K. Dickstein, T. Edvardsen, J. Escaned, B.J. Gersh, P. Svitil, M. Gilard, D. Hasdai, R. Hatala, F. Mahfoud, J. Masip, C. Muneretto, M. Valgimigli, S. Achenbach, J.J. Bax, 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC), Eur. Heart J. (2019). https://doi.org/10.1093/eurheartj/ehz425.

[4] N.H.J. Pijls, J.-W.E.M. Sels, Functional measurement of coronary stenosis., J. Am. Coll. Cardiol. 59 (2012) 1045–1057. https://doi.org/10.1016/j.jacc.2011.09.077.

[5] R. Hachamovitch, D.S. Berman, L.J. Shaw, H. Kiat, I. Cohen, J.A. Cabico, J. Friedman, G.A. Diamond, Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death:

differential stratification for risk of cardiac death and myocardial infarction., Circulation. 97 (1998) 535–543. https://doi.org/10.1161/01.cir.97.6.535.

[6] G.B.J. Mancini, P.M. Hartigan, L.J. Shaw, D.S. Berman, S.W. Hayes, E.R. Bates, D.J. Maron, K. Teo, S.P. Sedlis, B.R. Chaitman, W.S. Weintraub, J.A. Spertus, W.J. Kostuk, M. Dada, D.C. Booth, W.E. Boden, Predicting outcome in the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation): coronary anatomy versus ischemia., JACC. Cardiovasc. Interv. 7 (2014) 195–201. https://doi.org/10.1016/j.jcin.2013.10.017.

[7] K. Stergiopoulos, W.E. Boden, P. Hartigan, S. Mobius-Winkler, R. Hambrecht, W. Hueb, R.M. Hardison, J.D. Abbott, D.L. Brown, Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials., JAMA Intern. Med. 174 (2014) 232–240. https://doi.org/10.1001/jamainternmed.2013.12855.

[8] B. De Bruyne, K.G. Oldroyd, N.H.J. Pijls, Microvascular (Dys)Function and Clinical Outcome in Stable Coronary Disease., J. Am. Coll. Cardiol. 67 (2016) 1170–1172. https://doi.org/10.1016/j.jacc.2015.11.066.

[9] T.P. van de Hoef, F. Nolte, M. EchavarrIa-Pinto, M.A. van Lavieren, P. Damman, S.A.J. Chamuleau, M. Voskuil, H.J. Verberne, J.P.S. Henriques, B.L.F. van Eck-Smit, K.T. Koch, R.J. de Winter, J.A.E. Spaan, M. Siebes, J.G.P. Tijssen, M. Meuwissen, J.J. Piek, Impact of hyperaemic microvascular resistance on fractional flow reserve measurements in patients with stable coronary artery disease: insights from combined stenosis and microvascular resistance assessment., Heart. 100

(2014) 951–959. https://doi.org/10.1136/heartjnl-2013-305124.

[10] P.A.L. Tonino, B. De Bruyne, N.H.J. Pijls, U. Siebert, F. Ikeno, M. van' t Veer, V. Klauss, G. Manoharan, T. Engstrom, K.G. Oldroyd, P.N. Ver Lee, P.A. MacCarthy, W.F. Fearon, Fractional flow reserve versus angiography for guiding percutaneous coronary intervention., N. Engl. J. Med. 360 (2009) 213–224. https://doi.org/10.1056/NEJMoa0807611.

[11] B. De Bruyne, N.H.J. Pijls, B. Kalesan, E. Barbato, P.A.L. Tonino, Z. Piroth, N. Jagic, S. Mobius-Winkler, G. Rioufol, N. Witt, P. Kala, P. MacCarthy, T. Engstrom, K.G. Oldroyd, K. Mavromatis, G. Manoharan, P. Verlee, O. Frobert, N. Curzen, J.B. Johnson, P. Juni, W.F. Fearon, Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease., N. Engl. J. Med. 367 (2012) 991–1001. https://doi.org/10.1056/NEJMoa1205361.

[12] C.A. Rajkumar, S.S. Nijjer, G.D. Cole, R. Al-Lamee, D.P. Francis, "Faith Healing" and "Subtraction Anxiety" in Unblinded Trials of Procedures: Lessons from DEFER and FAME-2 for End Points in the ISCHEMIA Trial., Circ. Cardiovasc. Qual. Outcomes. 11 (2018) e004665. https://doi.org/10.1161/CIRCOUTCOMES.118.004665.

[13] R. Al-Lamee, J.P. Howard, M.J. Shun-Shin, D. Thompson, H.-M. Dehbi, S. Sen, S. Nijjer, R. Petraco, J. Davies, T. Keeble, K. Tang, I.S. Malik, C. Cook, Y. Ahmad, A.S.P. Sharp, R. Gerber, C. Baker, R. Kaprielian, S. Talwar, R. Assomull, G. Cole, N.G. Keenan, G. Kanaganayagam, J. Sehmi, R. Wensel, F.E. Harrell, J. Mayet, S.A. Thom, J.E. Davies, D.P. Francis, Fractional Flow Reserve and Instantaneous Wave-Free Ratio as Predictors of the Placebo-Controlled Response

to Percutaneous Coronary Intervention in Stable Single-Vessel Coronary Artery Disease., Circulation. 138 (2018) 1780–1792. https://doi.org/10.1161/CIRCULATIONAHA.118.033801.