

Fractional Flow Reserve in Angiographically Insignificant Stenoses: Unmasking the Lesion or Creating Disease?

Christopher M. Cook, MD; Justin E. Davies, MD, PhD

From earliest days of coronary angiography, we have been seeking hemodynamic confirmation of what our eyes tell us in the laboratory. Even before the clinical outcomes for patients undergoing percutaneous transluminal coronary angioplasty were barely known (and certainly before the manufacture of dedicated pressure-sensor guidewires), Grüntzig made efforts to measure the transstenotic pressure gradient,¹ aware of the limitations of a 2-dimensional image to completely describe the coronary flow dynamics in a diseased vessel.

In intermediate coronary lesions, it can still feel uncomfortable when our eyes “get it wrong.” With randomized trial data supporting that, in such circumstances, fractional flow reserve (FFR) is the better judge of outcomes,^{2–6} we can at least feel justified in quelling that uncomfortable feeling. But what about situations in which our eyes always get it wrong? Is it plausible that the oculostenotic reflex is so poorly calibrated that it can never be trusted, or are other factors at play that call into question the validity of positive FFR values in the absence of a significant lesion?

FFR: A surrogate measure of coronary flow

In the pre-FFR era, physiological indexes focused on direct measurements of coronary flow to determine the hemodynamic impact of a coronary stenosis.⁷ However, because of difficulties in obtaining reproducible, high-quality flow signals and the need for post hoc computation and analysis, the use of flow-based or combined pressure- and flow-based indices

failed to translate into mainstream clinical practice. In 1993, FFR was uniquely proposed as a pressure-only surrogate measure of flow.⁸ The rationale was that during maximal pharmacological hyperemia, microvascular resistance was stabilized, and transstenotic changes in pressure became linearly related to changes in flow.

During hyperemia, coronary flow increases. In the presence of a stenosis, the relationship between pressure loss due to a stenosis (shown as ΔP) and flow velocity (shown as V) is related by the equation $\Delta P = FV + SV^2$, where F is the coefficient of pressure loss due to viscous friction in the stenotic segment and S is the coefficient of pressure loss due to flow separation at the diverging end of the stenosis.⁹ Consequently, even in the presence of an angiographically insignificant stenosis, if coronary flow velocity increases by a large amount in response to adenosine (a sign of both a healthy microcirculation and, by definition, a non-flow-limiting stenosis), the transstenotic pressure gradient (ΔP) will also increase, and the resultant FFR value will be low (Figure).

This situation reveals an important limitation of the pressure-based FFR technique to provide a complete and accurate surrogate measure of coronary flow. With FFR, the paradox exists in which patients with the mildest stenoses, the healthiest microcirculations, and the greatest increments in coronary flow can still generate low FFR values. Furthermore, because the greatest increments in transstenotic flow occur in vessel locations with the largest amounts of downstream myocardium, these situations occur most frequently in proximal left anterior descending artery or left main stem stenoses.^{10,11} Such positive FFR values are similar to a young patient with mild aortic stenosis on echocardiographic assessment developing severe aortic stenosis in the same setting with increased flow during exercise. We do not perform aortic valve replacement in such circumstances because we know this measurement is an anomaly caused by a huge increase in flow. So, in the presence of an angiographically insignificant stenosis, does FFR really unmask the lesion or simply create disease? To answer this, we must see past the FFR value and determine whether ischemia itself is truly present. The problem for us as interventionalists is that we have become accustomed to thinking about ischemia in terms of hyperemic transstenotic

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Imperial College London, London, United Kingdom.

Correspondence to: Justin E. Davies, MD, PhD, NHLI – Cardiovascular Science, The Hammersmith Hospital, Imperial College London, B block South, 2nd floor, Du Cane Road, London W12 0NN, United Kingdom. E-mail: justin.davies@imperial.ac.uk

J Am Heart Assoc. 2017;6:e007085. DOI: 10.1161/JAHA.117.007085.

© 2017 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

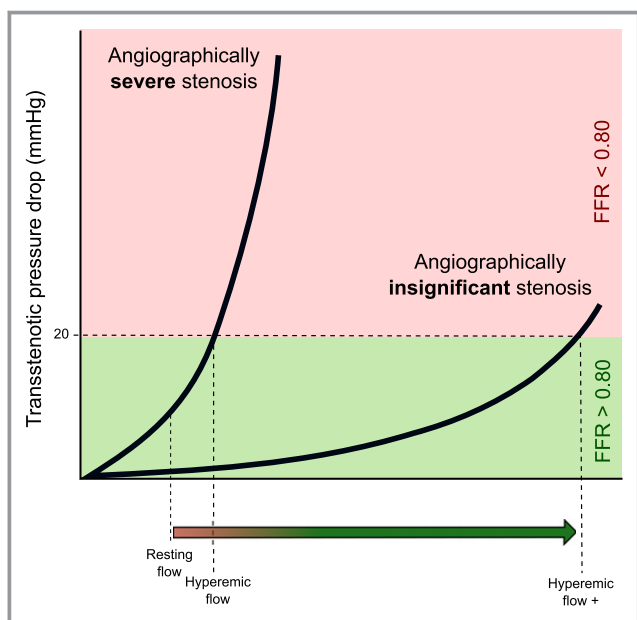


Figure. The relationship between pressure loss due to a stenosis and coronary flow velocity. Schematic representation of how low fractional flow reserve (FFR) values can be generated by both angiographically severe (small hyperemic flow increase) and angiographically insignificant (large hyperemic flow increase) coronary stenoses.

pressure ratios; however, even quick revision of supply-demand mechanics reminds us that the ischemia results from a reduction in coronary flow, not simply a reduction in coronary pressure. This notion is supported by numerous studies in the literature that proved ischemia detection with FFR fallible to demonstrably high coronary flow situations.^{12–17}

Vulnerable Plaque or Vulnerable End Point?

In this issue of *JAHA*, a subgroup analysis from the 3-Vessel Fractional Flow Reserve for the Assessment of Total Stenosis Burden and its Clinical Impact in Patients With Coronary Artery Disease (3-Vessel FFR-FRIENDS) study provides novel insight into patient outcome data for low-FFR but angiographically insignificant lesions.¹⁸ The majority of the findings by Lee et al are consistent with much of what we already know about FFR, namely, that low-FFR values can be generated in even mild stenoses and that these situations arise most frequently in left main stem and proximal left anterior descending artery lesions. In this patient population, however, in which a low-FFR value may have previously been rationalized away as an indirect sign of high flow and a healthy microcirculation, the (comparatively) unfavorable major adverse cardiac event (MACE) outcomes reported by Lee et al potentially imply an altogether different prognosis. The finding that, at 2-year follow-up, deferred angiographically

insignificant stenosis with low FFR showed significantly higher event rates than those with high FFR (3.3% versus 1.2%; hazard ratio: 3.371; 95% confidence interval, 1.346–8.442; $P=0.009$) is very interesting, not least because it appears at odds with the oculostenotic reflex, the physiological mechanisms outlined above, and previous studies.^{12–17}

Before proceeding to interpret the meaning of the findings on MACE, a number of observations should be highlighted. First, the authors are correct to stress that the study design does not reflect current guideline practice for the physiological assessment of coronary stenoses. The 3-Vessel FFR-FRIENDS study, from which this data set is drawn, mandated FFR measurement in all major epicardial coronary arteries regardless of angiographic severity. Second, the overall MACE rate in this cohort is low. To put it into context, the 1-year MACE rate for deferred FFR lesions in angiographically intermediate stenoses was 4.1% for the combined DEFINE-FLAIR⁵ and iFR-SWEDEHEART⁶ studies and 8.0% from DEFER.⁴ Indeed, in the present study, MACE attributable to hard clinical end points (cardiac death and vessel-related myocardial infarction) occurred in just 1.1% of the low-FFR group and 0.7% of the high-FFR group.

With these considerations in mind, how do we explain the higher MACE in low-FFR angiographically insignificant lesions? Two potential explanations exist. The first explanation is that in quantifying the transstenotic pressure ratio during pharmacological hyperemia, FFR is somehow also capable of identifying vulnerable plaque. Were this to be true, this synergistic feature of FFR would go far beyond the hopes of even the most optimistic proponents of the coronary physiological technique. The second explanation is that the MACE findings are attributable not to the identification of vulnerable plaque but rather to the inclusion of a vulnerable end point.

The overall MACE rate in this study was driven primarily by so-called ischemia-driven revascularization. Because the definition of ischemia-driven revascularization included “a positive invasive physiologic test” result, this major contributing factor to the overall MACE rate was a de facto foregone conclusion. Compounded by the lack of blinding to the knowledge of previously low FFR value, bias may have occurred, leading to ischemia-driven revascularization events.

FFR in Angiographically Insignificant Stenoses: Just Because We Can Does Not Mean We Should

As the authors of the study suggest, does the angiographic threshold for FFR measurements need to be lowered? Certainly, the possibility that FFR may identify vulnerable plaque in otherwise unobstructed coronary vessels should be

investigated; however, perhaps this is best explored with noninvasive FFR modalities. Wiring vessels that you might otherwise potentially have left alone is not a benign process. In the Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction (COMPARE ACUTE) trial, complications (including vessel dissection resulting in death) attributed to FFR measurement in non-infarct-related arteries occurred in 0.2% of the study population.¹⁹ Furthermore, FFR computed tomography may provide additive information beyond what the invasive coronary angiogram can offer, given the ability of FFR computed tomography to characterize the plaque itself and not just the lumen. Nevertheless, it is likely any such study would still require an invasive FFR measurement for comparison, given that the accuracy of FFR computed tomography compared with invasive FFR values has recently been called into question.²⁰

Otherwise, we do not support the notion that the angiographic threshold for FFR measurements should be lowered. As already suggested, the findings of the post hoc analysis by Lee et al are difficult to rationalize physiologically. Furthermore, they may reflect nothing more than clinician bias and a vulnerable trial end point. Although it may not be en vogue to say so, it appears that in a small number of situations in the catheter laboratory, we must question FFR and remember the importance of flow, which underpins it.

Sources of Funding

Dr Cook (MR/M018369/1) is a Medical Research Council fellow.

Disclosures

Dr Davies holds patents pertaining to the instantaneous wave-free ratio technology, which is under license to Philips Volcano. Dr Davies is a consultant for and has received significant research funding from Philips Volcano. Dr Cook has conducted teaching sessions supported by Philips Volcano.

References

- Grüntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med*. 1979;301:61–68.
- Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van't Veer M, Klauss V, Manoharan G, Engström T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213–224.
- De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991–1001.
- Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, Stella PR, Boersma E, Bartunek J, Koolen JJ, Wijns W. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation*. 2001;103:2928–2934.
- Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, Bhandi R, Lehman SJ, Walters D, Sapontis J, Janssens L, Vrints CJ, Khashaba A, Laine M, Van Belle E, Krackhardt F, Bojara W, Going O, Härle T, Indolfi C, Niccoli G, Ribichini F, Tanaka N, Yokoi H, Takashima H, Kikuta Y, Erglis A, Vinhas H, Canas Silva P, Baptista SB, Alghamdi A, Hellig F, Koo BK, Nam CW, Shin ES, Doh JH, Brugaletta S, Alegria-Barrero E, Meuwissen M, Piek JJ, van Royen N, Sezer M, Di Mario C, Gerber RT, Malik IS, Sharp ASP, Talwar S, Tang K, Samady H, Altman J, Seto AH, Singh J, Jeremias A, Matsuo H, Kharbanda RK, Patel MR, Serruys P, Escaned J. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med*. 2017;19:1824–1834.
- Götberg M, Christiansen EH, Gudmundsdottir JJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Ohagen P, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Tödt T, Venetsanos D, James SK, Käregren A, Nilsson M, Carlsson J, Hauer D, Jensen J, Karlsson AC, Panayi G, Erlinge D, Fröbert O; iFR-SWEDEHEART Investigators. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med*. 2017;376:1813–1823.
- Serruys PW, Di Mario C, Meneveau N, de Jaegere P, Strikwerda S, de Feyter PJ, Emanuelsson H. Intracoronary pressure and flow velocity with sensor-tip guidewires: a new methodologic approach for assessment of coronary hemodynamics before and after coronary interventions. *Am J Cardiol*. 1993;71:D41–D53.
- Pijls NH, van Son JA, Kirkeeide RL, Bruyne BD, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation*. 1993;87:1354–1367.
- Young DF, Cholvin NR, Kirkeeide RL, Roth AC. Hemodynamics of arterial stenoses at elevated flow rates. *Circ Res*. 1977;41:99–107.
- Kobayashi Y, Johnson NP, Berry C, De Bruyne B, Gould KL, Jeremias A, Oldroyd KG, Pijls NHJ, Fearon WF; CONTRAST Study Investigators. The influence of lesion location on the diagnostic accuracy of adenosine-free coronary pressure wire measurements. *JACC Cardiovasc Interv*. 2016;9:2390–2399.
- Cook CM, Jeremias A, Ahmad Y, Shun-Shin M, Nijjer S, de Waard G, Sen S, van de Hoef T, Echavarría Pinto M, van Lavieren M, Petraco R, Al-Lamee R, Meuwissen M, Danad I, Knaapen P, Maehara A, Koo BK, Mintz G, Escaned J, Stone G, Piek J, van Royen N, Davies JE. TCT-513 discordance in stenosis classification by pressure-only indices of stenosis severity is related to differences in coronary flow reserve: the RESOLVING DISCORD study. *J Am Coll Cardiol*. 2016;68:B206–B207.
- Sen S, Asrress KN, Nijjer S, Petraco R, Malik IS, Foale RA, Mikhail GW, Foin N, Broyd C, Hadjiloizou N, Sethi A, Al-Bustami M, Hackett D, Khan MA, Khawaja MZ, Baker CS, Bellamy M, Parker KH, Hughes AD, Francis DP, Mayet J, Di Mario C, Escaned J, Redwood S, Davies JE. Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration. Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study). *J Am Coll Cardiol*. 2013;61:1409–1420.
- Yanagisawa H, Chikamori T, Tanaka N, Hatano T, Morishima T, Hida S, Iino H, Amaya K, Takazawa K, Yamashina A. Correlation between thallium-201 myocardial perfusion defects and the functional severity of coronary artery stenosis as assessed by pressure-derived myocardial fractional flow reserve. *Circ J*. 2002;66:1105–1109.
- de Waard G, Danad I, Petraco R, Teunissen P, van de Hoef T, Rajmakers P, Lammertsma A, Davies J, Knaapen P, Van Royen N. Hyperemic FFR and baseline IFR have an equivalent diagnostic accuracy when compared to myocardial blood flow quantified by H2150 PET perfusion imaging. *J Am Coll Cardiol*. 2014;63:A1692. Abstract. DOI: 10.1016/S0735-1097(14)61695-8. Accessed June 3, 2015.
- van de Hoef TP, Meuwissen M, Escaned J, Sen S, Petraco R, van Lavieren MA, Echavarría-Pinto M, Nolte F, Nijjer S, Chamuleau SA, Voskuil M, van Eck-Smit BL, Verberne HJ, Henriques JP, Koch KT, de Winter RJ, Spaan JA, Siebes M, Tijssen JG, Davies JE, Piek JJ. Head-to-head comparison of basal stenosis resistance index, instantaneous wave-free ratio, and fractional flow reserve: diagnostic accuracy for stenosis-specific myocardial ischaemia. *EuroIntervention*. 2015;11:914–925.
- Petraco R, van de Hoef TP, Nijjer S, Sen S, van Lavieren MA, Foale RA, Meuwissen M, Broyd C, Echavarría-Pinto M, Foin N, Malik IS, Mikhail GW, Hughes AD, Francis DP, Mayet J, Di Mario C, Escaned J, Piek JJ, Davies JE. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity—Coronary Flow Reserve). *Circ Cardiovasc Interv*. 2014;7:492–502.

17. Hwang D, Jeon KH, Lee JM, Park J, Kim CH, Tong Y, Zhang J, Bang JI, Suh M, Paeng JC, Na SH, Cheon GJ, Cook CM, Davies JE, Koo BK. Diagnostic performance of resting and hyperemic invasive physiological indices to define myocardial ischemia: validation with ¹³N-ammonia positron emission tomography. *JACC Cardiovasc Interv*. 2017;10:751–760.
18. Lee JM, Koo BK, Shin E-S, Nam C-W, Doh J-H, Hu X, Ye F, Chen S, Yang J, Chen J, Tanaka N, Yokoi H, Matsuo H, Takashima H, Shiono Y, Hwang D, Park Y, Kim K-J, Akasaka T, Wang J. Clinical outcomes of deferred lesions with angiographically insignificant stenosis but low fractional flow reserve. *J Am Heart Assoc*. 2017;6:e006071. DOI: 10.1161/JAHA.117.006071.
19. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Włodarczak A, Ong PJ, Hambrecht R, Angerås O, Richardt G, Omerovic E; Compare-Acute Investigators. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med*. 2017;376:1234–1244.
20. Cook CM, Petraco R, Shun-Shin MJ, Ahmad Y, Nijjer S, Al-Lamee R, Kikuta Y, Shiono Y, Mayet J, Francis DP, Sen S, Davies JE. Diagnostic accuracy of computed tomography-derived fractional flow reserve: a systematic review. *JAMA Cardiol*. 2017;2:803–810.

Key Words: Editorials • coronary flow • coronary physiology • fractional flow reserve



Fractional Flow Reserve in Angiographically Insignificant Stenoses: Unmasking the Lesion or Creating Disease?

Christopher M. Cook and Justin E. Davies

J Am Heart Assoc. 2017;6:e007085; originally published August 22, 2017;

doi: 10.1161/JAHA.117.007085

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://jaha.ahajournals.org/content/6/8/e007085>