Pak Heart J

INSTANTANEOUS WAVE-FREE RATIO (IFR)-AN EMERGING TECHNIQUE

Wahaj Aman[1] , **Mohammad Hafizullah**[2]

[1] Houston Methodist DeBakey Heart & Vascular Center Houston - USA

[2] Department of Cardiology, Lady Reading Hospital, Peshawar -Pakistan

Address for Correspondence:

Prof Mohammad Hafizullah
Department of Cardiology, Lady Reading Hospital, Peshawar -Pakistan

E-mail: mhu5555@gmail.com

This editorial may be cited as: Hafizullah M, Aman W. Instantaneous wave-free ratio (IFR)-an emerging technique. Pak Heart J 2017;50(03): 135-8.

The advent of fractional flow reserve (FFR)changed the landscape of viewing and interpreting coronary artery lesions, particularly intermediate ones.[1] FFR is defined as ratio of the pressure distal to a stenosis (Pd) relative to the pressure proximal to the stenosis (Pa).[2] For FFR to be accurate intra-coronary resistance must be constant and minimal so that the change in pressure across a lesion is proportional to change in blood flow, this requires hyperemia induced by a vasodilating agent typically adenosine. The use of coronary physiology to guide revascularization has been found to improve patient outcomes and defer stenting of nonischemic lesions compared with angio-graphic assessment.[2,3]

A small but impactful study opened doors for FFR to be evaluated in larger trials. This study in population of 45 patients, revealed that when FFR <0.75, ischemia was present in at least one of the following tests; exercise testing, dobutamine stress echocardiography, and exercise thallium scintigraphy.[4]The 3 large trials on FFR were DEFER, FAME and FAME 2.[5-7] DEFER was the first randomized, multicenter study to evaluate FFR. The primary goal was to show that deferring PCI when FFR $\geqslant 0.75$ was safe for intermediate lesions and did not portent to worsening survival. A total of 325 patients underwent FFR assessment, of which those with FFR $\geqslant 0.75$ were split into PCI versus deferral. The initial study followed patients up to 2 years,then followed for 5 years and did not show significant difference in event free survival.[4] FAME sought to show benefits of the modality in guiding PCI. The primary endpoint of major adverse cardiac events (MACE) defined as a composite of death, myocardial infarction, and any repeat revascularization in 1 year occurred in 18.3% ($n=91$) in angiography-guided PCI patients versus 13.2% ($n= 67$) of FFR-guided PCI patients ($p < 0.02$). These results led to a Class IA for FFR guided PCI when objective evidence of ischemia is lacking in the European and ACC guidelines in the setting of stable angina and later in acute coronary syndrome. [8-10]

To understand FAME 2, one must look at COURAGE [11]. The COURAGE trial revealed that for patients with stable angina and intermediate lesions, PCI in additional to optimal medical therapy did not change MACE compared to optimal medical therapy alone. FAME 2 sought to compare FFR guided PCI to optimal medical therapy. This trial focused on patients with high ischemic burden, patients with FFR >0.80 were not included in the randomized portion of the study and were treated medically. The result at 2 year follow up showed a significant reduction in primary end point of composite of death, MI and urgent

revascularization in the FFR guided PCI group compared to medical therapy:4.3% versus 12.7% ($p<0.001$). It must be noted that the difference was primarily driven by urgent revascularization PCI: 1.6% versus medical therapy 11.1% ($p<0.001$).[11]

The aforementioned trials unequivocally established FFR as safe and beneficial, however according to an analysis from the National Cardiovascular Data Registry (NCDR), FFR evaluation across US was being performed in only 6% of intermediate lesions. The lack of utilization primarily stems from the cost and administration of adenosine. Adenosine is contraindicated in patients with asthma, severe COPD, bradycardia and hypotension. Additionally, it may require central venous access.[12]

The instantenous wave-free ratio (iFR) is an improvement on to FFR. It is a physiological assessment as iFR determines effects of a stenosis on limiting blood flow in coronary arteries. Like FFR, iFR is performed with high fidelity pressure wires that are passed distal to the coronary stenosis. iFR utilizes a specific period in diastole known as the wave-free period. During this time, competing forces (waves) that affect coronary flow are quiescent, and pressure and flow distal and proximal to lesion are linearly related. This obviates the need for vasodilators. The wave free period starts after approximately 112 ms from the onset of diastole (25%) and ends 5 ms before the end. The mean duration is around 350ms.If a stenosis is flow limiting, Pd and Pa pressures over the wave-free period diverge, with iFR values below 0.9 suggesting flow restriction, normal value is 1.0. During this wave-free period, intra luminal resistance is constant and minimal, imitating a state of hyperemia typically achieved by adenosine. Though it can be calculated using a single heartbeat, but is typically averaged over five beats for normalization.[13,14]

iFR offers increased diagnostic flexibility without the need for adenosine. In FFR the need for adenosine, is time-consuming and costly,more so for cath labs that use it infrequently and it is contraindicated in some patients. iFR enhances the utility of technique expanding the frontiers by determining pullbacks in different areas that can be done quickly and easily. iFR measurements can be performed from vessel to vessel, and from distal to mid and mid to proximal with ease within those vessels without needing repeated infusions of Adenosine.[15,16]

iFR has been extensively studied to establish its accuracy compared to FFR. ADVISE was the first trial to introduce iFR as an adenosine independent pressure index to evaluate intermediate lesions.The study was divided into two parts, the first focusing on identifying the wave free period and the second to validate it against FFR measurements. With 118 lesions undergoing both FFR and iFR measurements, the specificity, sensitivity, negative and positive predictive values of iFR were 91%, 85%, 85%, and 91% compared to FFR respectively.[17] ADVISE II introduced the idea of hybrid FFR-iFR approach. It revealed that iFR of 0.89 matched best with an FFR of 0.80 with a specificity of 88% and sensitivity of 73%. However when the value was broadened to 0.85-0.94 it correlated to a specificity of 90.7% and sensitivity of 96.2%.[18]

In DEFINE-FLAIR, researchers enrolled 2,492 patients at 49 centers in 17 countries. Half of the patients received iFR and half received FFR. It showed a substantial reduction in symptoms of both patient-reported and physician reported procedure-related adverse events, which occurred in 3 percent of iFR patients and 30.8 percent of FFR patients overall. In this study, FFR was associated with a significantly higher rate of shortness of breath (1% iFR vs 20 % FFR); chest pain (1.5 % in iFR and 7.2 % in FFR); heart rhythm disturbances (0.2 % iFR vs 4.8 % FFR); abnormally low blood pressure (0.3 % iFR vs 1% FFR); and serious adverse events, which included severe shortness of breath or requiring cardioversion to restore normal heart rhythm (0.1% iFR vs 0.6 % FFR). In this study, stents were used in 46 % in iFR and 50 % in FFR. It revealed that the use of iFR significantly reduced the overall length of the procedure, from an average of 45 minutes for FFR to 40.5 minutes for iFR.[19]

In IFR-SWEDEHEART, 2,037 patients were enrolled at 15 centers in Sweden, Denmark and Iceland. A total of 2,019 patients in this study were treated according to protocol, with 1,012 patients receiving iFR and 1,007 receiving FFR. This documented a substantial reduction in patient discomfort, with just 3 % of iFR reporting discomfort compared to 68 % of FFR. A primary end-point event occurred in 68 patients (6.7%) in iFR group and in 61 patients (6.1%) in FFR group (95% confidence interval [CI], −1.5 to 2.8; $p=0.007$ for noninferiority; hazard ratio, 1.12; 95% CI, 0.79 to 1.58; $p=0.53$). The rates of myocardial infarction, target-lesion revascularization, restenosis, and stent thrombosis did not differ significantly between the two groups. A significantly higher proportion of patients in the FFR group than in the iFR group reported chest discomfort during the procedure. Significant lesions were found in 29.2 percent of patients undergoing iFR and 36.8 percent undergoing FFR.[20]

With a combined population of over four thousand patients, both trials showed non-inferiority at 1 year compared to FFR. Adverse procedural symptoms were significantly lower in the iFR group in both trials. Both trials used iFR cutoff of $\leqslant 0.89$.Both studies revealed no significant differences in separate analyses of all-cause mortality, subsequent heart attack or revascularization. Both studies documented a substantial reduction in the number of significant lesions found using iFR versus FFR. [19,20]

Recent advances in radiology technology have been able to superimpose information from iFR on angiographically obtained pictures. This has made it possible to generate a fully-integrated physiological map of any coronary vessel acquired with manual iFR pullback that is integrated with the angiogram in real time. This emerging technology, amalgam of real-time

coregistered iFR pressure mapping with virtual percutaneous coronary intervention (PCI) capability may usher a new era for functional lesion assessment, where physiology is used to both justify and guide optimal coronary intervention.[21,22]

iFR has improved the patient experience and operators can now limit the use of vasodilators, reducing the incidence of chest discomfort, dyspnea, bronchospasm, arrhythmias. With iFR, these are avoided and patient experiences improve. Patients with contraindications to adenosine can also benefit with iFR.This promises increased diagnostic flexibility, as measuring pullbacks in different areas to assess can be accomplished quickly and easily. iFR measurements can be done from vessel to vessel, and from distal to mid and mid to proximal within those vessels. That kind of capability is valuable.[23] Emerging data suggest that iFR may be a superior prognostic tool in comparison with FFR for deferring nonculprit lesions in patients with acute coronary syndrome.[23]

To conclude, if there is a significant lesion that strongly correlates with stress tests, then one should go ahead and revascularize the indicated lesion. However, if the lesion is not absolutely correlating, then one should opt for iFR/FFR evaluation. With reduced procedure length, requirement of fewer stents and elimination of need for a vasodilator drug should translate into significant cost savings iFR appears to be more promising technology.

REFERENCES

1. Pijls NHJ, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334(26):1703-8.
2. Pijls NH, Sels JW. Functional measurement of coronary stenosis. J Am Coll Cardiol 2012;59(12):1045-57.
3. Fearon WF. Percutaneous coronary intervention should be guided by fractional flow reserve measurement. Circulation 2014;129(18):1860-70.
4. Pijls NH, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, et al. Fractional flow reserve: a useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation 1995;92(11):3183-93.
5. Pijls NHJ, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous coronary intervention of functionally non-significant stenoses: 5-year follow-up of the DEFER study. J Am Coll Cardiol 2007;49(21):2105-11.
6. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, , et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360(3):3:213-24.
7. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367(11):991-1001.
8. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS /AHA/ASE /ASNC/SCAI/ SCCT/STS 2017 Appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2017;69(17):2212-41.
9. Kolh P, Windecker S, Alfonso F, Collet JP, Cremer J, Falk V, 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 J Cardiothorac Surg* 2014;46(4):517-92.
10. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/ SCCT/STS 2016 Appropriate use criteria for coronary revascularization in patients with acute coronary syndromes: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2017;69(5):570-91.
11. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary artery disease. N Engl J Med 2007;356(15):1503-16.

12. Dattilo PB, Prasad A, Honeycutt E, Wang TY, Messenger JC. Contemporary patterns of fractional flow reserve and intravascular ultrasound use among patients undergoing percutaneous coronary intervention in the United States: insights from the National Cardiovascular Data Registry. J Am Coll Cardiol 2012;60(22):2337-9.

13. Johnson NP, Kirkeeide RL, Asrress KN, Fearon WF, Lockie T, Marques KM, et al. Does the instantaneous wave-free ratio approximate the fractional flow reserve? J Am Coll Cardiol 2013;61(13):1428-35.

14. Petraco R, Sen S, Nijjer S, Escaned J, Davies JE. Baseline coronary pressures, instant wave-free ratio (iFR) and Pd/Pa: making the most of available information. EuroIntervention 2013;9(1):170-23.

15. Berry C, van't Veer M, Witt N, Kala P, Bocek O, Pyxaras SA, et al. VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): a multicenter study in consecutive patients. J Am Coll Cardiol 2013;61(13):1421-7.

16. Sen S, Asrress KN, Nijjer S, Petraco R, Malik IS, Foale RA, et al. 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(13):1409-20.

17. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, *et al.* Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (A Denosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol 2012;59(15):1392-402.

18. Escaned J, Echavarría-Pinto M, GarciaGarcia HM, van de Hoef TP, de Vries T, Kaul P, et al. Prospective assessment of the diagnostic accuracy of instantaneous wave-free ratio to assess coronary stenosis relevance: results of ADVISE II international, multicenter study (ADenosine Vasodilator Independent Stenosis Evaluation II). JACC Cardiovasc Interv 2015;8(6):824-33.

19. Götberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. N Engl J Med 2017;376(19):1813-23.

20. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. N Engl J Med 2017;376(19):1824-34.

21. Nijjer SS, Sen S, Petraco R, Escaned J, Echavarria-Pinto M, Broyd C, et al. Pre-angioplasty instantaneous wave-free ratio pullback provides virtual intervention and predicts hemodynamic outcome for serial lesions and diffuse coronary artery disease. JACC Cardiovasc Interv 2014;7(12):1386-96.

22. Nijjer SS, Sen S, Petraco R, Mayet J, Francis DP, Davies JE. The Instantaneous wave-Free Ratio (iFR) pullback: a novel innovation using baseline physiology to optimise coronary angioplasty in tandem lesions. Cardiovasc Revasc Med 2015;16(3):167-71.

23. Götberg M, Cook CM, Sen S, Nijjer S, Escaned J, Davies JE. The evolving future of instantaneous wave-free ratio and fractional flow reserve. J Am Coll Cardiol 2017;70(11):1379-402.