IJC Heart & Vasculature 47 (2023) 101225

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Editorial

Hyperemic and non-hyperemic indexes in coronary physiology. Causes and implications of discordant results

ARTICLE INFO

keywords
Coronary physiology
Fractional flow reserve
Angiography
Ischemic heart disease
Acute myocardial infarction

The introduction of fractional flow reserve (FFR) represented a major paradigm shift in the study of coronary lesions boosting the use of coronary physiology to guide revascularization decisions [1,2]. FFR requires measuring the intralesional pressure gradient under maximal hyperemia. In normal conditions epicardial arteries are merely conductance vessels and coronary flow is largely modulated by the changes in microvascular resistance. However, in the presence of a coronary artery stenosis the microvascular resistance is reduced -to a variable extent- to maintain an adequate coronary flow [1,2]. Accordingly, maximal vasodilation of the microvascular bed is required to fully understand the implications of the flow resistance caused by the epicardial lesion. Importantly, however, 2 large randomized clinical trials demonstrated that revascularization decisions guided by iFR (a non-hyperemic pressure ratio [NHPR]), was not inferior to those using FFR with regard to long-term clinical outcomes [3,4]. As the use of adenosine or other vasodilators of the microvascular bed remains cumbersome and may cause side-effects, different NHPRs have recently flourished to facilitate a wider use of coronary physiology in every day clinical practice [2–3]. Notably, the correlation among the different NHPR indexes has been found to be excellent. Currently, both FFR and NHPRs can be readily obtained during routine cardiac catheterization [5–15]. In some cases, however, results of these diagnostic strategies are discordant and thus complicate rather than facilitate the decision-making process [5–15]. In that situation, considering all technical issues have been properly implemented, FFR is usually considered as the gold standard. Major factors associated with discordant results between FFR and different NHPR indexes have been previously studied (Table 1) [5–15] but controversy still exists regarding underlying causes and potential implications.

1. Present study

In this issue of the Journal Scoccia et al. [16] sought to assess predictors of discordance between FFR and the diastolic pressure ratio (dPR) (a NHPR). PREDICT is a retrospective, single center (Erasmus University Medical Center), investigator-initiated study including 813 patients (1092 vessels) who underwent FFR assessment of intermediate coronary lesions (angiographic 30 %–80 % diameter stenosis on visual assessment). FFR was measured using intraveneous adenosine (140 µg/Kg/min). Conversely, dPR was calculated off-line and post hoc using individual pressure waveforms and a dedicated software with an algorithm able to detect the wave-free period with low and stable resistances. Hemodynamically significant lesions, as defined by

Table 1
Factors associated with discordant FFR and NHPR indexes.

1- Clinical and Anatomic Variables*
Age, gender, body surface area
Diabetes mellitus, hypertension, chronic kidney disease (and hemodialysis)
Atrial fibrillation, high heart rate, use of betablockers
Heart failure, high BNP levels, anemia
LAD lesion location, large amount of subtended myocardium
Stenosis severity, lesion length and physiological pattern (focal vs diffuse)
Impaired LVEF and LVEDP
Severe aortic stenosis
Arterial stiffness/peripheral vascular disease
2- Physiological issues
Microvascular dysfunction
Resting and hyperemic flow/velocity
Inadequate hyperemia (microvascular vasodilation) (insufficient adenosine)
FFR/NHPR indexes close to the dichotomic clinical cut-off.

* Inducing changes in NHPR indexes considering FFR as the gold standard. Most factors are interrelated and influence microvascular function or resting or hyperemic coronary flow (references 5–15). LAD = left anterior descending coronary artery. BNP = brain natriuretic peptide. LVEF = Left ventricular ejection fraction. LVED = Left ventricular end-diastolic pressure FFR = fractional flow reserve. NHPR = non-hyperemic pressure ratio.

https://doi.org/10.1016/j.ijcha.2023.101225
Received 9 May 2023; Accepted 12 May 2023
Available online 7 June 2023

FFR ≤ 0.80, and dPR ≤ 0.89, were identified in 29.6 % and 30.3 % of cases, respectively. The area under the curve of dPR+ to predict a FFR+ was 0.88. Overall, FFR and dPR values were discordant in 22.1 % patients (17.4 % of vessels). Discordance was related to FFR+/dPR− and FFR−/dPR+ in 11.8 % and 10.3 % of patients, respectively. In case of FFR/dPR discordance, a higher prevalence of left anterior descending coronary artery (LAD) lesions was observed and mean values of both FFR and dPR were significantly lower as compared to vessels showing concordance. Following multivariable adjustment, dPR "delta" (defined as the absolute difference between the measured dPR and its cut-off value of 0.89) was identified as the only independent predictor of discordance (OR = 0.74, 95 %CI 0.68–0.79, $p < 0.001$).

Discordance between FFR and NHPR indexes represents a clinical problem potentially affecting revascularization decisions. In this study FFR/dPR discordance occurred in one-fifth of patients and absolute dPR delta emerged as the only independent predictor of discordance. This large study, from a respected group of investigators, is the first to ascertain discordances between FFR and dPR (rather than other NHPR indexes) and provides interesting insights on the prevalence, associated factors and potential clinical implications of FFR/dPR discordance. Therefore, discussing some methodological issues would be of interest.

First, dPR was defined as the ratio of mean distal coronary artery pressure to mean aortic pressure in the resting state (Pd/Pa) over the diastolic period and was calculated from individual pressure waveforms using a recently validated software [5,16]. However, as this is a retrospective study it is important to emphasize the careful protocol systematically followed in this experienced center before considering that the results may be extrapolated to other cardiac catheterization environments. In this regard, paying meticulous attention to technical details remains crucial to obtain reliable physiologic data. In this study exclusion criteria included pressure waveforms tracings with dampening or with drift larger than >0.03. The number of patients eventually excluded for these reasons was very low (only 8 patients) and this should be also considered before generalizing these findings to other settings.

Second, one-third of included patients presented with an acute coronary syndrome, although only non-culprit vessels were analyzed. Interestingly, no significant differences in baseline characteristics were observed between patients with and without FFR/dPR discordance. Moreover, the consistent results of the sensitivity analysis performed after excluding patients presenting with an acute myocardial infarction, are reassuring. However, in unstable patients both indexes may be affected, even in non-culprit vessels and, therefore, the presence of concordance does not necessarily mean that results are accurate or reliable to inform treatment decisions [1,2].

Third, hemodynamically significant lesions, defined by FFR ≤ 0.80, and dPR ≤ 0.89, were only identified in 29.6 %, and 30.3 % of cases, respectively. This suggests that relatively mild lesions were also included. Results might have been different if the study population would have included more lesions with physiological significance. In this regard, it would have been of additional interest to assess whether the use of quantitative coronary angiography (rather than eyeballing assessment of lesion severity) could provide additional information, regarding the correlation with FFR and dPR.

Fourth, in case of FFR/dPR discordance, a higher prevalence of LAD lesions was observed. Importantly, almost 58 % of lesions in the LAD-group were FFR negative, as compared to 90 % of lesions in the non-LAD group. The high number of non-LAD FFR- lesions is also of concern as a larger sample of severe non-LAD lesions would have provided a more robust dataset.

Fifth, discordance of patients with values near the cut-off of each technique is well expected and reproducibility issues may be also involved in this challenging zone. One can only speculate on the clinical implications of this finding. Therapeutic decisions are dichotomic in nature, but it is well established that ischemia severity is indeed a continuous variable that has clear influence not only on symptoms but also on clinical outcomes [1–4].

Sixth, in this study FFR−/dPR+ and FFR+/dPR- discordances were lumped together although they may result from different underlying pathophysiological mechanisms. The differences found between the 2 discordant groups were attributed to different prevalence of microvascular dysfunction (FFR+/dPR−) but this remains largely speculative and should only be considered hypothesis generating.

Finally, the present study lacks clinical follow up, which might be of particular interest in patients with discordant FFR/dPR values.

2. Final remarks

FFR and NHPR indexes provide distinct physiological information and it is of paramount importance to understand their differential characteristics, limitations and implications in every individual patient. This large study by Scoccia et al. [16] advances our understanding of factors accounting for the discrepancies between both diagnostic strategies. Further studies are required to refine the causes of these discrepancies to better inform revascularization decisions and, eventually, improve clinical outcomes.

References:

[1] N.H. Pijls, B. De Bruyne, K. Peels, P.H. Van Der Voort, H.J. Bonnier, J. Bartunek, J. J. Koolen, Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses, N. Engl. J. Med. 334 (26) (1996) 1703–1708.

[2] F. Alfonso, F. Rivero, Value of different physiological indexes to defer coronary revascularization, J. Am. Coll. Cardiol. Intv. 11 (15) (2018) 1450–1453.

[3] J.E. Davies, S. Sen, H.M. Dehbi, R. Al-Lamee, R. Petraco, S.S. Nijjer, R. Bhindi, S. J. Lehman, D. Walters, J. Sapontis, L. Janssens, C.J. Vrints, A. Khashaba, M. Laine, E. Van Belle, F. Krackhardt, W. Bojara, O. Going, T. Härle, C. Indolfi, G. Niccoli, F. Ribichini, N. Tanaka, H. Yokoi, H. Takashima, Y. Kikuta, A. Erglis, H. Vinhas, P. Canas Silva, S.B. Baptista, A. Alghamdi, F. Hellig, B.K. Koo, C.W. Nam, E.S. Shin, J.H. Doh, S. Brugaletta, E. Alegria-Barrero, M. Meuwissen, J.J. Piek, N. van Royen, M. Sezer, C. Di Mario, R.T. Gerber, I.S. Malik, A.S.P. Sharp, S. Talwar, K. Tang, H. Samady, J. Altman, A.H. Seto, J. Singh, A. Jeremias, H. Matsuo, R.K. Kharbanda, M.R. Patel, P. Serruys, J. Escaned, Use of the instantaneous wave-free ratio or fractional flow reserve in PCI, N. Engl. J. Med. 376 (19) (2017) 1824–1834.

[4] M. Götberg, E.H. Christiansen, I.J. Gudmundsdottir, L. Sandhall, M. Danielewicz, L. Jakobsen, S.E. Olsson, P. Öhagen, H. Olsson, E. Omerovic, F. Calais, P. Lindroos, M. Maeng, T. Tödt, D. Venetsanos, S.K. James, A. Kåregren, M. Nilsson, J. Carlsson, D. Hauer, J. Jensen, A.C. Karlsson, G. Panayi, D. Erlinge, O. Fröbert, iFR-SWEDEHEART investigators. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI, N. Engl. J. Med. 376 (19) (2017) 1813–1823.

[5] J. Ligthart, K. Masdjedi, K. Witberg, F. Mastik, L. van Zandvoort, M.E. Lemmert, et al., Validation of resting diastolic pressure ratio calculated by a novel algorithm and its correlation with distal coronary artery pressure to aortic pressure, instantaneous wave-free ratio, and fractional flow reserve, Circ. Cardiovasc. Interv. 11 (12) (2018) e006911.

[6] Y. Kobayashi, N.P. Johnson, C. Berry, B. De Bruyne, K.L. Gould, A. Jeremias, K. G. Oldroyd, N.H.J. Pijls, W.F. Fearon, CONTRAST study investigators. The influence of lesion location on the diagnostic accuracy of adenosine-free coronary pressure wire measurements, J. Am. Coll. Cardiol. Intv. 9 (23) (2016) 2390–2399.

[7] F. Rivero, J. Cuesta, T. Bastante, A. Benedicto, M. García-Guimaraes, M. Fuentes-Ferrer, T. Alvarado, F. Alfonso, Diagnostic accuracy of a hybrid approach of instantaneous wave-free ratio and fractional flow reserve using high-dose intracoronary adenosine to characterize intermediate coronary lesions: Results of the PALS (Practical Assessment of Lesion Severity) prospective study, Catheter. Cardiovasc. Interv. 90 (7) (2017) 1070–1076.

[8] C.M. Cook, A. Jeremias, R. Petraco, S. Sen, S. Nijjer, M.J. Shun-Shin, Y. Ahmad, G. de Waard, T. van de Hoef, M. Echavarria-Pinto, M. van Lavieren, R. Al Lamee, Y. Kikuta, Y. Shiono, A. Buch, M. Meuwissen, I. Danad, P. Knaapen, A. Maehara, B. K. Koo, G.S. Mintz, J. Escaned, G.W. Stone, D.P. Francis, J. Mayet, J.J. Piek, N. van Royen, J.E. Davies, fractional flow reserve/instantaneous wave-free ratio discordance in angiographically intermediate coronary stenoses: An analysis using doppler-derived coronary flow measurements, J. Am. Coll. Cardiol. Intv. 10 (24) (2017) 2514–2524.

[9] T. Warisawa, C.M. Cook, J.P. Howard, Y. Ahmad, S. Doi, M. Nakayama, S. Goto, Y. Yakuta, K. Karube, M.J. Shun-Shin, R. Petraco, S. Sen, S. Nijjer, R. Al Lamee, Y. Ishibashi, H. Matsuda, J. Escaned, C. di Mario, D.P. Francis, Y.J. Akashi, J. E. Davies, physiological pattern of disease assessed by pressure-wire pullback has an influence on fractional flow reserve/instantaneous wave-free ratio discordance, Circ. Cardiovasc. Interv. 12 (5) (2019) e007494.

[10] F. Dérimay, N.P. Johnson, F.M. Zimmermann, J. Adjedj, N. Witt, B. Hennigan, B. K. Koo, E. Barbato, G. Esposito, B. Trimarco, G. Rioufol, S.J. Park, S.B. Baptista, G. S. Chrysant, A.M. Leone, A. Jeremias, C. Berry, B. De Bruyne, K.G. Oldroyd, N.H. J. Pijls, W.F. Fearon, Predictive factors of discordance between the instantaneous wave-free ratio and fractional flow reserve, Catheter. Cardiovasc. Interv. 94 (3) (2019) 356–363.

[11] S.H. Lee, K.H. Choi, J.M. Lee, D. Hwang, T.M. Rhee, J. Park, H.K. Kim, Y.K. Cho, H. J. Yoon, J. Park, Y.B. Song, J.Y. Hahn, J.H. Doh, C.W. Nam, E.S. Shin, S.H. Hur, B. K. Koo, Physiologic characteristics and clinical outcomes of patients with discordance between FFR and iFR, J. Am. Coll. Cardiol. Intv. 12 (20) (2019) 2018–2031.

[12] R. Goto, H. Takashima, H. Ohashi, H. Ando, A. Suzuki, S. Sakurai, Y. Nakano, H. Sawada, M. Fujimoto, Y. Suzuki, K. Waseda, W. Ohashi, T. Amano, Independent predictors of discordance between the resting full-cycle ratio and fractional flow reserve, Heart Vess. 36 (6) (2021) 790–798.

[13] T. Yonetsu, M. Hoshino, T. Lee, T. Murai, Y. Sumino, M. Hada, M. Yamaguchi, Y. Kanaji, T. Sugiyama, T. Niida, J. Matsuda, Y. Hatano, T. Umemoto, T. Sasano, T. Kakuta, Impact of sex difference on the discordance of revascularization decision making between fractional flow reserve and diastolic pressure ratio during the wave-free period, J. Am. Heart Assoc. 9 (5) (2020) e014790.

[14] T. Yamazaki, Y. Saito, T. Kobayashi, H. Kitahara, Y. Kobayashi, Factors associated with discordance between fractional flow reserve and resting full-cycle ratio, J. Cardiol. 80 (1) (2022) 9–13.

[15] H. Matsumoto, S. Higuchi, H. Tanaka, R. Masaki, S. Kondo, H. Tsujita, T. Shinke, Insufficient adenosine-induced hyperemia is a major determinant of discordance between non-hyperemic pressure ratio and fractional flow reserve, Sci. Rep. 13 (1) (2023) 729.

[16] A. Scoccia, T. Neleman, A.C. Ziedes, et al. Predictors of discordance between fractional flow reserve (FFR) and diastolic pressure ratio (dPR) in intermediate coronary lesions. IJC Heart and Vasculature 2023 (Cross reference).

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