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Editorial

Fractional flow reserve for guidance in intervention of multiple sequential lesions

Fractional flow reserve (FFR) is a well-established index for determining the significance of stenosis, and provides useful information in decision-making for the indication of revascularization. FFR-guided percutaneous coronary intervention (PCI) has been recently upgraded to an IA classification for multivessel disease in the Guidelines on Coronary Revascularization of the European Society of Cardiology [1]. FFR can be useful not only for the indication of intervention but also for decision-making at the end of PCI procedures, especially in diffuse and multiple lesions. In this issue of the *Journal of Cardiology Cases*, Kurisu et al. [2] report a case in which FFR was applied to the PCI procedure in multiple sequential stenoses, and transient stenosis by myocardial bridging was assessed; these two points are discussed here.

The concept of FFR was first introduced by Pijls as an index for the functional significance of coronary artery stenosis [3]. FFR is defined as the ratio of maximum blood flow in a stenotic artery relative to maximum blood flow if that same artery were to be normal. In other words, FFR represents the degree by which maximum blood flow is limited in the presence of a stenosis. For example, if FFR is 0.75, it means that maximum blood flow reaches only 75% of its normal value. FFR can be calculated as the ratio of distal pressure over aortic pressure obtained during maximum hyperemia. FFR indicates the significance of the lesion in every vessel [4,5], during the entire PCI procedure [6]. In patients with multivessel disease, FFR allows us to grade the functional severity of the patient and to predict the outcome after PCI. The use of FFR has aided decision-making, achieving a favorable revascularization outcome [7–9].

In the coronary blood stream from aorta to coronary vein, FFR reflects the total amount of resistance to coronary blood flow. Thus, when several stenoses are present in the same artery, distal coronary flow is regulated by the sum of the resistance in each stenosis. In the case of diffuse-long stenosis, distal coronary flow is regulated by the sum of the resistance in the entire length of the vessel. For clinical practice, a pull-back recording of coronary pressure at maximum hyperemia provides important information. Pull-back recording reveals the most critical stenosis in the artery; however, hemodynamic severity of the individual stenosis is always underestimated. The existence of multiple stenoses can cause a decrease in blood flow at each stenosis, and then the pressure gradient at each stenosis can be lower than that at the stenosis if it were a single lesion in a vessel. The severity of the individual stenosis could theoretically be predicted by calculation from coronary pressure and coronary wedge pressure [10,11]. The equation for determining the FFR of individual stenosis in multiple sequential stenoses is as follows:

$$\mathrm{FFR(A)_{pred}} = \frac{P_d - (P_m/P_a)P_w}{P_a - P_m + P_d - P_w}$$

$$\mathrm{FFR(B)_{pred}} = 1 - \frac{(P_a - P_w)(P_m - P_d)}{P_a(P_m - P_w)}$$

P_a, P_m, P_d, and P_w indicate mean hyperemic aortic pressure, mean hyperemic coronary pressure between both lesions, mean hyperemic distal coronary pressure distal to the most distal lesion, and coronary wedge pressure, respectively. The proximal lesion is called stenosis A, the distal stenosis is B, and the FFR associated with each lesion is indicated by FFR(A) and FFR(B), respectively. $\mathrm{FFR_{pred}}$ indicates the value of FFR predicted from the pressure measurements before PCI.

In this equation, measurement of P_w is mandatory, which means that balloon dilatation of at least one lesion should be performed. Thus, $\mathrm{FFR_{pred}}$ cannot be evaluated before PCI. In daily clinical practice, we have to decide the PCI strategy based on functional information by pull-back recording of coronary pressure and anatomical information such as lesion length and the status of the branches. To understand the true hemodynamic significance of residual stenosis, we should re-evaluate the FFR after stenting for one lesion. We should be aware that the true severity of the second stenosis will be unmasked by the increased maximum flow after the elimination of the first stenosis.

Notably, this strategy and equation assume that all stenoses are fixed, although it is not uncommon for transient stenosis by myocardial bridging to be concomitant with fixed stenosis. In the case reported by Kurisu et al., FFR of the left anterior descending artery (LAD) with both fixed stenosis and myocardial bridging was 0.71, indicating that the myocardial ischemia was positive in the LAD territory. Even if there were several stenoses in one vessel, the decrease in FFR suggests reversible ischemia at least distally to the measured vessel territory. This finding supports the indication of PCI. However, it is unclear whether sufficient improvement in FFR can be gained by stenting alone for the most severe lesion. They implanted one stent for fixed stenosis, and then FFR was re-evaluated. FFR improved to 0.82 after stenting, and pull-back recording showed a small pressure gradient remaining at the site of myocardial bridging.

Myocardial bridging is commonly found in routine angiography and is accepted as a harmless variant; however, it has been associated with myocardial ischemia, infarction, and sudden death

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[12,13]. Although surgical treatment and coronary stenting were performed for myocardial bridging, the long-term results remain unclear. Thus, we should avoid unnecessary interventions, and rather assess the physiological significance of myocardial bridging. The mechanisms of ischemia in myocardial bridging include systolic compression and failure of diastolic vascular relaxation, and it is difficult to determine the significance by coronary angiography alone. FFR is widely used for determining the physiological significance of myocardial bridging as in fixed stenosis. Moreover, diastolic FFR has a higher sensitivity compared to conventional FFR for detection of ischemia in patients with myocardial bridging [14]. Dobutamine infusion leads to a diastolic pressure gradient owing to increased contractility of muscle fibers overlying the arterial segment. Consequently, diastolic FFR after dobutamine infusion can better identify its significance compared to conventional FFR [15].

In the case reported by Kurisu et al., the pressure gradient remained at the site of myocardial bridging even after stenting for fixed stenosis. As the FFR value was >0.80, they decided to defer the additional stent implantation. However, if they used inotropic stimulation by dobutamine infusion during FFR measurements, the pressure gradient could have been greater. FFR after dobutamine infusion for the assessment of physiological significance of myocardial bridging may have different clinical significance than conventional FFR, although we do not know yet which would be more predictable of prognosis. The significance of myocardial bridging and the risk of the patient should be investigated.

References

[1] Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, et al. Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501–55.
[2] Kurisu S, Iwasaki T, Ishibashi K, Mitsuba N, Dohi Y, Nishioka K, Kihara Y. Measurement of fractional flow reserve in a patient with combined myocardial bridging and coronary fixed stenosis. J Cardiol Cases 2012;6:e163–5.
[3] Pijls NHJ, De Bruyne B, Peels K, van der Voort PH, Bonnier HJRM, Bartunek J, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary artery stenoses. N Engl J Med 1996;334:1703–8.
[4] 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;66:1105–9.
[5] Tanaka H, Chikamori T, Tanaka N, Hida S, Shindo N, Igarashi Y, Yamashina A. A flow-limiting stenosis is the major determinant of exercise-induced myocardial stunning in patients with coronary artery disease. J Cardiol 2010;55:337–44.
[6] Tanaka N, Takazawa K, Shindo N, Kobayashi K, Teramoto T, Yamashita J, Yamashina A. Decrease of fractional flow reserve shortly after percutaneous coronary intervention. Circ J 2006;70:1327–31.
[7] Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van't Veer M, Klauss V, Manoharan G, Engstrøm 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;360:213–24.
[8] Kobori Y, Tanaka N, Takazawa K, Yamashina A. Usefulness of fractional flow reserve in determining the indication of target lesion revascularization. Catheter Cardiovasc Interv 2005;65:355–60.
[9] Amaya K, Takazawa K, Tanaka N, Yamashina A. Prediction of in-stent restenosis by measurement of fractional flow reserve and the influence of diabetes mellitus. J Cardiol 2002;39:293–8 [in Japanese].
[10] De Bruyne B, Pijls NHJ, Heyndrickx GR, Hodeige D, Kirkeeide R, Gould KL. Pressure-derived fractional flow reserve to assess serial epicardial stenoses: theoretical model and animal validation. Circulation 2000;101:1840–7.
[11] Pijls NHJ, De Bruyne B, Bech GJW, Liistro F, Heyndrickx GR, Bonnier HJRM, Koolen JJ. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. Circulation 2000;102:2371–7.
[12] Bourassa MG, Butnaru A, Lesperance J, Tardif JC. Symptomatic myocardial bridges: overview of ischemic mechanisms and current diagnostic and treatment strategies. J Am Coll Cardiol 2003;41:351–9.
[13] Alegria JR, Herrmann J, Holmes DR, Lerman A, Rihal CS. Myocardial bridging. Eur Heart J 2005;26:1159–68.
[14] Abe M, Tomiyama H, Yoshida H, Doba N. Diastolic fractional flow reserve to assess the functional severity of moderate coronary stenoses. Comparison with fractional flow reserve and coronary flow velocity reserve. Circulation 2000;102:2365–70.
[15] Escaned J, Cortes J, Flores A, Goicolea J, Alfonso F, Hernandez R, Fernandez-Ortiz A, Sabate M, Banuelos C, Macaya C. Importance of diastolic fractional flow reserve and dobutamine challenge in physiologic assessment of myocardial bridging. J Am Coll Cardiol 2003;42:226–33.

Nobuhiro Tanaka (MD PhD FJCC)*
Tokyo Medical University, Department of Cardiology, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

* Tel.: +81 3 3342 6111; fax: +81 3 5381 6652.
E-mail address: n-tanaka@tokyo-med.ac.jp

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