

Predicting functional significance of each stenosis in serial coronary artery stenoses: Where there is a will, there is a way

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The presence of multiple or serial stenoses in one coronary artery is common, and understanding the functional significance of *each* coronary lesion is important for the selection of an appropriate treatment strategy. Although fractional flow reserve (FFR) is a reliable index for defining the presence of per-vessel level ischemia, a single FFR measurement has limitations in predicting the true functional significance of each lesion in serial coronary artery stenoses. For example, in a case involving two stenoses in one coronary artery, the presence of one lesion decreases the hyperemic flow across the other lesion, thereby causing an underestimation of the true pressure difference across the lesion. Therefore, current practice is to perform a pullback pressure tracing under stable hyperemia and revascularize the lesion that causes a higher change in coronary pressure or FFR across the lesion, and then measure FFR again to define the functional significance of the other lesion [1]. Kim et al. [2] reported FFR measurement with repetitive pullback pressure recordings is safe and useful in determining the proper target lesions for revascularization and can reduce unnecessary intervention in patients with serial stenoses. How-



ever, this method requires repeated FFR measurements, which is not risk-free, and the functional significance of residual lesion cannot be assessed prior to treatment of the first lesion. To overcome these limitations, Pijls et al. [3] proposed a rather complex formula to pre-

dict the FFR of one lesion in serial stenoses which requires a coronary wedge pressure (Pw) measurement. Since then, several investigators have proposed equations to predict true FFR in cases with serial stenoses (Table 1) [3–6].

In this issue of “Cardiology Journal”, Gutiérrez-Chico et al. [6] report the performance of a simplified formula to estimate FFR of each lesion in serial coronary stenoses that *does not* require balloon inflation to measure coronary wedge pressure. This multicenter, prospective pilot study investigated 36 patients with two serial lesions with $\geq 50\%$ diameter stenosis and $\text{FFR} \leq 0.8$. The authors assumed that Pw could be negligible in the original Pijls formula [3] and it was substituted with constant value of 12 mmHg. To compare the performance of their formula with Pijls et al. [3], the investigators measured wedge pressure (Pw) in all patients. This novel and simple formula showed excellent correlation with the original formula ($R^2 = 0.997$ for the proximal lesion, $R^2 = 0.999$ for

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Table 1. Formulas for predicting fractional flow reserve of each lesion in serial coronary artery stenoses.

Studies	Subject number	Predicted FFR after treatment of one lesion	Predicted vs. measured FFR
Pijls et al. [3]	32	$\frac{Pd - (Pm/Pa) \times Pw}{(Pa - Pm) + (Pd - Pw)}$ or $1 - \frac{(Pm - Pd) \times (Pa - Pw)}{Pa \times (Pm - Pw)}$	R ² = 0.92
Saito et al. [4]	30	$\frac{Pd - Pw}{Pa - \Delta P - Pw} + \frac{Pw (Pa - \Delta P - Pd)}{Pa (Pa - \Delta P - Pw)}$	R ² = 0.97
Kweon et al. [5]	50	FFRp - $\frac{\Delta FFRp}{1 - 1.33k \times \Delta FFRd}$ or FFRp - $\frac{\Delta FFRd}{1 - 1.33 \times \Delta FFRp}$	R ² = 0.92
Gutiérrez-Chico et al. [6]	36	$\frac{Pd - (Pm/Pa) \times 12}{(Pa - Pm) + (Pd - 12)}$ or $1 - \frac{(Pm - Pd) \times (Pa - 12)}{Pa \times (Pm - 12)}$	R ² = 0.72 For Pijls et al.'s formula R ² = 0.997 for the proximal lesion R ² = 0.999 for the distal lesion

FFR — fractional flow reserve; Pa — mean aortic pressure; Pm — mean hyperemic coronary pressure between both lesions; Pd — mean hyperemic coronary distal pressure; Pw — coronary wedge pressure; ΔP — pressure gradient across on lesion; ΔFFRd — FFR gradient across distal lesion; ΔFFRp — FFR gradient across proximal lesion; k — flow fraction of the distal main branch at the bifurcation point

the distal lesion) and good agreement between predicted and measured FFR (R² = 0.717). This novel formula is simple and easy to apply in daily practice, and the investigators should be commended for their efforts to develop and validate the concept of a simple formula. However, this method still needs to be validated in various coronary anatomies considering the relatively small number of cases in this pilot study. It should be pointed out that this formula is based on the assumption of a uniform flow rate across stenoses, and may be inaccurate in cases with large side branches between stenoses. In addition, this formula cannot be applied in cases with high Pw.

Recently, novel methods based on new concepts and technologies were introduced to define the functional significance of each lesion in serial coronary stenoses. An interesting concept is using the pressure difference during a resting condition. As resting coronary flow is stable across most ranges of stenoses, measurements of resting pressure gradient, such as instantaneous pressure ratio (iFR) across the lesion, can present the hemodynamic significance of each stenosis, even in cases of serial stenoses. In addition, the operators can easily recognize the local hemodynamic changes in each lesion when pressure pullback data are combined with angiographic co-registration technology [7]. Moreover, technological advancements have enabled applying the concept of virtual stenting using invasive coronary angiography or coronary computed tomography (CT) angiography in daily practice [8–10]. With a combination of coronary imaging and computational fluid dynam-

ics technologies, measurement of CT-derived or angiography-derived FFR after virtual stenting for one lesion can provide functional significance of residual stenosis. Considering the economic and operational benefits over other invasive coronary physiology indexes, these CT- or angiography-derived physiology assessments have the potential for greater adoption in real-world practice. However, these concepts need further validation in terms of accuracy and precision of CT-derived and angiography-derived FFR after virtual stenting.

In the field of coronary physiology, remarkable theoretical and technological breakthroughs have been achieved over the last 40 years since the first coronary angioplasty. The same holds true for evaluating the functional significance of serial coronary lesions in selecting the appropriate treatment strategy. Although some obstacles still remain, the quest to refine assessment methodologies of coronary artery disease continues.

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References

1. Park SJ, Ahn JM, Pijls NHJ, et al. Validation of functional state of coronary tandem lesions using computational flow dynamics. *Am J Cardiol.* 2012; 110(11): 1578–1584, doi: [10.1016/j.amjcard.2012.07.023](https://doi.org/10.1016/j.amjcard.2012.07.023), indexed in Pubmed: 22921996.
2. Kim HL, Koo BK, Nam CW, et al. Clinical and physiological outcomes of fractional flow reserve-guided percutaneous coronary intervention in patients with serial stenoses within one coro-

- nary artery. *JACC Cardiovasc Interv.* 2012; 5(10): 1013–1018, doi: [10.1016/j.jcin.2012.06.017](https://doi.org/10.1016/j.jcin.2012.06.017), indexed in Pubmed: [23078728](https://pubmed.ncbi.nlm.nih.gov/23078728/).
3. Pijls NH, De Bruyne B, Bech GJ, et al. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. *Circulation.* 2000; 102(19): 2371–2377, doi: [10.1161/01.cir.102.19.2371](https://doi.org/10.1161/01.cir.102.19.2371), indexed in Pubmed: [11067791](https://pubmed.ncbi.nlm.nih.gov/11067791/).
 4. Saito N, Matsuo H, Kawase Y, et al. In vitro assessment of mathematically-derived fractional flow reserve in coronary lesions with more than two sequential stenoses. *J Invasive Cardiol.* 2013; 25(12): 642–649, indexed in Pubmed: [24296384](https://pubmed.ncbi.nlm.nih.gov/24296384/).
 5. Kweon J, Kim YH, Yang DH, et al. In vivo validation of mathematically derived fractional flow reserve for assessing haemodynamics of coronary tandem lesions. *EuroIntervention.* 2016; 12(11): e1375–e1384, doi: [10.4244/EIJ-D-15-00469](https://doi.org/10.4244/EIJ-D-15-00469), indexed in Pubmed: [27934610](https://pubmed.ncbi.nlm.nih.gov/27934610/).
 6. Gutiérrez-Chico JL, Cortés C, Jaguszewski M, et al. A simplified formula to calculate fractional flow reserve in sequential lesions circumventing the measurement of coronary wedge pressure: The APIS-S pilot study. *Cardiol J.* 2019; 26(4): 310–321, doi: [10.5603/CJ.a2019.0067](https://doi.org/10.5603/CJ.a2019.0067), indexed in Pubmed: [31257567](https://pubmed.ncbi.nlm.nih.gov/31257567/).
 7. Kikuta Y, Cook CM, Sharp ASP, et al. Pre-Angioplasty instantaneous wave-free ratio pullback predicts hemodynamic outcome in humans with coronary artery disease: primary results of the international multicenter iFR GRADIENT Registry. *JACC Cardiovasc Interv.* 2018; 11(8): 757–767, doi: [10.1016/j.jcin.2018.03.005](https://doi.org/10.1016/j.jcin.2018.03.005), indexed in Pubmed: [29673507](https://pubmed.ncbi.nlm.nih.gov/29673507/).
 8. Kim KH, Doh JH, Koo BK, et al. A novel noninvasive technology for treatment planning using virtual coronary stenting and computed tomography-derived computed fractional flow reserve. *JACC Cardiovasc Interv.* 2014; 7(1): 72–78, doi: [10.1016/j.jcin.2013.05.024](https://doi.org/10.1016/j.jcin.2013.05.024), indexed in Pubmed: [24332418](https://pubmed.ncbi.nlm.nih.gov/24332418/).
 9. Modi BN, Sankaran S, Kim HJ, et al. Predicting the physiological effect of revascularization in serially diseased coronary arteries. *Circ Cardiovasc Interv.* 2019; 12(2): e007577, doi: [10.1161/CIRCINTERVENTIONS.118.007577](https://doi.org/10.1161/CIRCINTERVENTIONS.118.007577), indexed in Pubmed: [30722688](https://pubmed.ncbi.nlm.nih.gov/30722688/).
 10. Morris PD, van de Vosse FN, Lawford PV, et al. „Virtual” (Computed) Fractional Flow Reserve: Current Challenges and Limitations. *JACC Cardiovasc Interv.* 2015; 8(8): 1009–1017, doi: [10.1016/j.jcin.2015.04.006](https://doi.org/10.1016/j.jcin.2015.04.006), indexed in Pubmed: [26117471](https://pubmed.ncbi.nlm.nih.gov/26117471/).