

New Mathematical Correction Model in Pursuit of Optimal Hemodynamic Assessment of Serial Coronary Artery Disease: Overcoming Hyperemic Cross Talk Between Coronary Stenoses in Series?

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There is growing evidence suggesting that ischemia-guided revascularization using invasive physiological indexes confers clinical and prognostic benefit in the management of patients with coronary artery disease. Consistently, the new guidelines have provided the class IA recommendation for physiological indexes for the objective assessment of the ischemic potential of a given coronary lesion. In humans, however, coronary atherosclerosis is a diffuse disease, and coronary angiograms frequently demonstrate serial stenoses along the same epicardial artery, the severities of which need to be determined individually. This is especially critical while deciding the most appropriate stenosis to be dilated in patients with several intermediate stenoses in the same vessel when composite fractional flow reserve (FFR) indicates ischemia and/or in those who have diffuse disease in conjunction with several segmental stenoses. However, currently used physiological indexes show limited ability to isolate individual lesion significance in vessels with serial lesions.

In tandem disease, mutual fluid dynamic interaction between the stenoses during maximal hyperemia alters their relative severity and complicates determination of FFR for each stenosis in isolation. Furthermore, the extent of such interplay between stenoses is not appreciable from pressure measurements before revascularization. This is because calculation of FFR requires maximal hyperemic transstenotic flow, which is impeded by the additional resistance induced by a secondary

stenosis. In serial stenoses, maximal transstenotic flow through the proximal stenosis is hindered by distal stenosis and vice versa. Because of this flow impediment during maximal hyperemia caused by secondary stenosis, lower pressure decrease (ΔP) across the stenosis in question occurs, leading to an artificial overestimation of the FFR or underestimation of lesion severity. In particular, this overestimation of FFR is more pronounced for the proximal lesions than for the distal lesion. Removal of distal resistance by intervention results in a large increase in hyperemic flow and, therefore, in ΔP across the remaining proximal stenosis, unmasking the true hemodynamic significance of the lesion in question. Moreover, the distance between the lesions may also influence the dynamic interaction between serial stenoses. In general, hemodynamic interaction of serial stenoses increases as the distance between them decreases because of the greater potential for flow turbulence.¹ On the other hand, as the distance between serial stenoses increases, the hemodynamic interaction between them decreases, which results in the increase of peak pressure gradient across the stenoses¹ (lesser underestimation of the stenosis severity). When the distance between 2 lesions is >6 times the vessel diameter, the stenoses generally behave independently, and the overall pressure gradient is the sum of the individual pressure losses at any given flow rate.² Besides these factors, hyperemic microvascular resistance can also decrease after stenting, which will alter hyperemic flow velocity and ΔP further.³ Hence, because of this dynamic interaction between serial stenoses, FFR of a proximal stenosis is inevitably influenced by the presence or removal of a distal stenosis and vice versa.

To overcome this obstacle, a method to compute an individual FFR for each lesion in series has been described.⁴ However, it is mathematically complicated, requires the input of coronary occlusive pressure (coronary wedge pressure [Pw]) measured between stenoses, and can only be applied to serial stenoses without an intervening side branch. In particular, the necessity to measure Pw, which represents the contribution of collateral flow to total hyperemic myocardial perfusion, is considered the main obstacle to the clinical

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use of this prediction model. Measuring Pw requires temporary balloon occlusion, which may cause vessel trauma. Especially, when there is uncertainty over stenosis, interventionalists would avoid any attempt that may cause vascular endothelial injury. Therefore, although equations have been formulated to circumvent the issue of hyperemic interaction between serial stenoses,^{4–6} FFR-based predictors of post-percutaneous coronary intervention physiological features remain underused.

On the other hand, 3 validated, practical, and clinically applicable methods have been suggested to be most accurate in assessing the hemodynamic significance of individual lesions in serial disease. These are manual pullback with treatment of the greatest pressure gradient (ΔP),⁷ manual pullback with the treatment of the greatest FFR gradient (ΔFFR),⁸ and the use of a large disease-free side branch to isolate the significance of a proximal lesion in the context of serial disease involving the left main (LM) coronary artery.^{9,10} On the basis of this approach, treatment for an individual stenosis within non-LM coronary tandem lesions could be prioritized by ΔFFR or ΔP , such as first treating the lesion with large ΔP ⁷ or ΔFFR ⁸ and subsequently reassessing the FFR for the remaining lesion. Indeed, theoretically, ΔP across the stenosis and ΔFFR have the same hemodynamic meaning, assuming a fixed aortic pressure during pullback. This practical approach, which does not require the measurement of Pw and has been shown to be associated with good clinical outcome,^{7,8} is clinically applicable to tandem lesions without an intervening major side branch when the composite FFR is <0.80 . However, this method does not overcome the issue of stenosis interaction but can be used to help decide which lesion is likely to be responsible for most of the ΔP along the length of the artery. Therefore, such an approach offers an estimate of the severity of each stenosis; the issue remains that, after stenting, the pattern of flow in the vessel will change, rendering the initial assessment of any residual stenosis inaccurate. LM disease with concomitant left anterior descending or left circumflex artery stenoses represents a special case of sequential lesions, because there is a major side branch in these cases. Although in theory, downstream epicardial disease affects the FFR assessment of intermediate LM lesions with the pressure wire in the nondiseased vessel, in practice, this effect was shown to be clinically irrelevant unless the downstream stenosis is very proximal and severe.^{9,10} Considering both feasibility and reliability, hemodynamic assessment of LM stenosis using FFR in the presence of an accompanying lesion in the left circumflex or left anterior descending artery seems to be safely performed with a pressure wire in the uninvolved vessel in most cases.

All these difficulties seem to arise mainly because of relative hemodynamic interdependence of serial stenoses under the condition of hyperemia. Because hyperemic flow

declines significantly whenever any 50% reduction in lumen diameter is observed¹¹ and, therefore, causes stenosis interplay in cases of serial stenoses, then even mild secondary lesions can affect hyperemic pressure-only indexes. Moreover, the physiological gain of revascularization of the individual stenosis cannot be estimated by FFR beforehand because the change in transstenotic flow after revascularization of either stenosis is unpredictable. On the other hand, under resting conditions, in contrast to hyperemic flow, basal flow is maintained at a constant level, even in the presence of a severe stenosis up to 90%^{12,13} via autoregulatory mechanisms. Therefore, every stenosis within a vessel is exposed to a stable and similar flow velocity at rest at the expense of decrease in resting distal pressure attributable to compensatory dilation of microcirculation. This may mean that the resting condition can be particularly suited to the assessment of vessels with tandem lesions because basal flow across the lesion of interest is expected to be negligibly affected by presence or removal of other lesions in the same vessel, if they are not causing severe stenosis ($>90\%$). Hence, instantaneous wave-free ratio (iFR), using basal physiological features, may isolate the hemodynamic impact of individual lesions within a diffusely diseased vessel with multiple stenoses. Accordingly, in 2 recent studies on tandem disease, iFR pullback during resting conditions was shown to provide a physiological mapping of the entire vessel and seemed to allow both isolation of stenosis severity and prediction of hemodynamic consequences of stenting specific stenoses.^{14,15} In these studies, the mean difference between predicted iFR and observed iFR was 0.01 ± 0.004 ¹⁴ and 0.016 ± 0.004 ,¹⁵ and the difference between the predicted and observed iFR after percutaneous coronary intervention was reported to be as low as $<5\%$.¹⁵ On the basis of these rationales and observations, in tandem disease, iFR pullback seems to be a favorable tool in quantifying hemodynamic impact of specific lesions individually and in predicting post-percutaneous coronary intervention hemodynamic improvement.

With this background in mind, in this issue of the *Journal of the American Heart Association (JAHA)*, Modi et al¹⁶ report an alternative mathematical correction model to improve prediction of the FFR_{true} of individual stenoses in serial coronary artery disease without the need for Pw measurement. The authors developed an in vitro model on the basis of the 3-dimensional printed serial disease phantoms, in which physiological assessments were first performed by pressure-wire pullback (ΔFFR_{app}) and then compared with physiological findings obtained from phantoms with the stenosis in isolation (ΔFFR_{true}). The extent of serial stenosis interplay was assessed by examining the magnitude of difference between ΔFFR_{app} and ΔFFR_{true} , and the potential impact of several factors on this difference was assessed. Mathematical solutions to predict FFR_{true} were derived from the results

within a derivation cohort of the in vitro study and then tested within a clinical cohort of patients with tandem coronary artery disease.

They reported that in the presence of an additional lesion, the true contribution of a given lesion was underestimated in 88% of phantoms, with underestimation proportional to total FFR. The overall difference between FFR_{app} and FFR_{true} , which was 17.1% in the in vitro model, improved substantially to 0.6% when the proposed theoretical correction equation, based on knowledge of pressure distal to the stenoses and ΔP across the stenosis, was applied. In addition, factors such as lesion length, distance between lesions, and physiological length were shown not to be correlated with the extent of serial stenosis underestimation. However, in the clinical cohort, relative discrepancy between FFR_{app} and FFR_{true} was 38.5%, which improved to 15.4% (absolute difference, 0.02 ± 0.03) after mathematical correction.

Modi et al¹⁶ are to be congratulated for this thorough and both hypothetically and technically challenging study, the results of which provide a validated, simple mathematical correction model to minimize error while assessing individual physiological significance of a stenosis in tandem disease. The authors should also be commended for effectively bringing together an in vitro and a clinical trial.

It should be kept in mind that the presented formula was derived from data obtained through motorized pullback of a pressure wire in an in vitro model developed on the basis of 3-dimensional printed configurations of tandem disease. Obviously, such an approach is limited practically by the requisite of a mechanical pressure wire pullback device and theoretically by idealized lesion features in phantom models. Notably, compared with the in vitro cohort, residual error in estimating true physiological significance of a stenosis was substantially greater in the clinical cohort (0.6% versus 15.4%, respectively). In the serial disease phantoms, many factors that can readily affect ΔP across the stenosis in the clinical setting, such as vessel wall compliance and remodeling, functional and structural status of the subtended microcirculation, lesion shape, surface properties, and plaque composition, may not be considered. In particular, although lesion length was found not to be as important in influencing serial stenosis underestimation in the presented study, it appears to be strongly correlated with FFR in intermediate stenoses in clinical studies,^{17,18} despite being a weaker determinant of ΔP across the stenosis compared with minimal luminal area in Poiseuille's formula. This brings to mind that, beyond anatomical lesion length in millimeters, factors may exert their effect along the length of the lesion, causing irregularities and roughness on the lesion's surface that induce greater resistance to hyperemic flow and resulting in greater frictional energy loss and, therefore, further ΔP .

Thus, the substantial difference observed between in vitro and clinical cohorts can at least partly be attributable to the lesion characteristics and status of subtended microcirculation that could not be readily generated in phantom models of serial disease but that otherwise contribute to ΔP across the stenosis in a clinical setting.

Using the mathematical correction model provided in the present report, the mean absolute difference between predicted and true FFR values was 0.02 ± 0.03 , which compares favorably with coronary occlusive FFR models that report a mean difference of 0.03 ± 0.04 ⁶ and the iFR pullback model that reports a mean difference of 0.016 ± 0.004 .¹⁵ However, a relative difference of 15.4% reported between predicted and true FFR in this study is much higher than the relative difference reported in coronary occlusive ($4 \pm 0\%$)⁴ and iFR ($<5\%$) pullback models.¹⁴

At last, the mathematical correction model provided in the present study seems to be applicable only to serial lesions within the same coronary artery without a major intervening side branch, where there is a uniform flow rate across the stenoses; therefore, results cannot be extrapolated to the tandem lesions involving LM, because there is a major side branch.

Notwithstanding the inherent limitations of the method used, the present report is of high interest, and Modi et al¹⁶ should be commended for their contribution to this challenging and mostly confusing area of interventional cardiology. Accurate assessment of hemodynamic significance of each individual stenosis in series and prediction of post-percutaneous coronary intervention physiology could result in more precise, safe, and effective procedures that treat only lesions with hemodynamic significance with the fewest stents possible. The simple mathematical correction model provided in the present study may enable preprocedural planning, allowing operators to treat the lesions most likely to have hemodynamic significance and defer those of lesser importance in the presence of multiple lesions. Therefore, this approach may also produce better clinical outcome in patients with multiple stenoses along the same coronary artery in long-term follow-up.

Disclosures

None.

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