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The Instantaneous wave-Free Ratio (iFR) pullback: a novel innovation using baseline physiology to optimise coronary angioplasty in tandem lesions

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ABSTRACT

Coronary intervention is increasingly performed in complex disease with tandem and diffuse disease. Pressure wires enable detailed assessment of the physiological significance of a stenosis but in the presence of tandem disease, predicting the impact of a stenting a given stenosis can be difficult and is impeded by flow interaction between stenoses under hyperemia. In this review, we consider the physiological difficulties posed by flow interaction under hyperemia and consider alternative approaches such as assessment under baseline conditions. Specifically we consider the potential value of the iFR-Pullback approach and its capacity to enable Virtual-PCI, which may assist in planning intervention.

Pressure wire technology has revolutionised our treatment of coronary disease, by identifying clinically important stenoses. Physiology provides an objective marker to support intervention by identifying haemodynamically significant lesions [1,2]. However, currently used physiological indices have limited ability to isolate individual lesion significance in vessels with multiple lesions. The prevalence of such diffuse coronary disease is increasing and accurate assessment to guide appropriate therapy is paramount.

Current physiological assessment in such vessels does not automatically indicate the haemodynamic improvement that would be expected post stenting. The clinical utility of an index would be enhanced if it could inform the clinician of the likely effect of any intervention. A tool that can inform the clinician of the haemodynamic benefit of inserting a stent at a particular point in the vessel, over a specific length would help clinicians rationalise their revascularisation procedure. However, predicting the haemodynamic response to stenting has been difficult and up to now complex and time consuming. Overcoming these barriers, and amalgamating pressure wire and imaging technology to aid in decision making is the next frontier for an interventional cardiology community that is being confronted by an increasing prevalence of diffuse coronary artery disease. This review article will discuss some of the physiological aspects of tandem lesion assessment, the limitations of current invasive modalities and the potential for new indices that utilise the vast improvement in pressure wire technology.

1. Assessment of individual stenoses in tandem lesions or diffusely diseased vessels – an unmet clinical need

In unobstructed vessels, flow during hyperemia can be many fold higher than that observed during rest. In the presence of a single stenosis, resting flow is typically maintained while hyperemic flow diminishes for any stenosis >40–50% in anatomical severity (Fig. 1, upper panel) [3]. It was this finding in animals that lead to the concept that stenoses >50% are haemodynamically important. Since for practical reasons we are typically reliant upon pressure measurements rather than flow measurements, then understanding pressure-flow relationships is essential.

The degree of pressure drop across a stenosis is dependent upon the (1) stenosis severity and (2) the amount flow across it. Using flow velocity as a surrogate for volumetric flow, this relationship between stenosis pressure gradient and flow can be measured to yield a specific fingerprint of the stenosis; with each single stenosis having a specific haemodynamic signature as originally described by Gould [3,4].

In the situation of a vessel with two tandem lesions, hyperemic flow across the proximal lesion is a function not only of the stenosis geometry but also the effect of the second, distal lesion. Similarly hyperemic flow across the second lesion is a function of its specific geometry and its inlet flow, which is influenced by the proximal stenosis (Fig. 2). As a result, a pressure assessment in the distal vessel under 'maximal hyperaemia' will not be specific to either stenosis, rather it informs us

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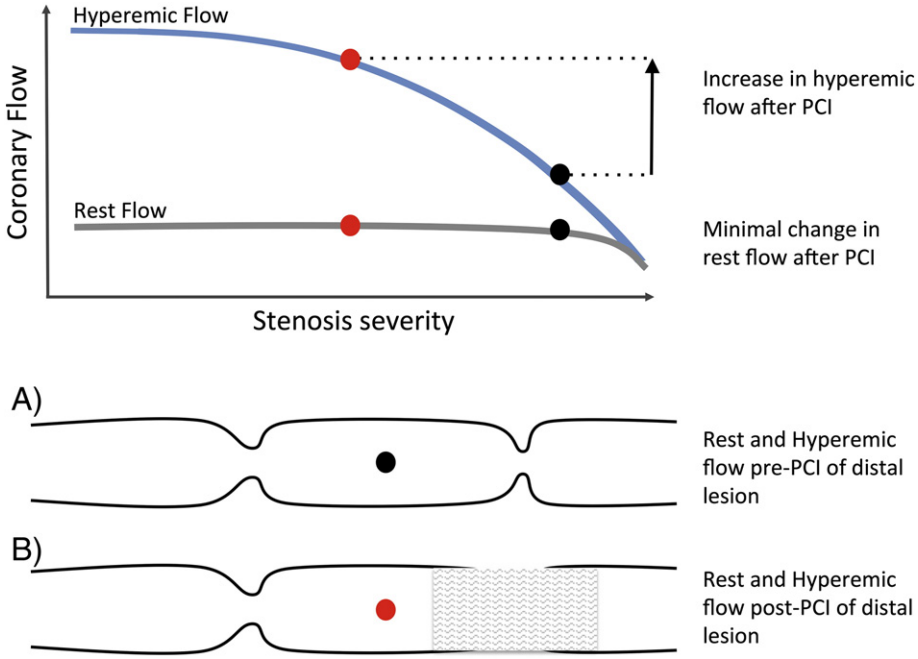

Fig. 1. The expected behaviour of hyperemic and resting flow after removal of stenosis. Upper panel. Pioneering studies demonstrated that resting flow is preserved until stenoses are critical or subtotally occluded. Hyperemic flow falls in the presence of any stenosis but does so significantly as stenoses exceed 40-50%. Lower panel. In Tandem stenoses (A), a measurement of flow at the black marker (•) will elicit a flow value as denoted by the black dot on the upper panel. In (B), the distal stenosis has been stented. Under hyperemic conditions, flow will have increased significantly (red dot); however, under resting conditions, there is minimal change expected.

of the haemodynamic impact of all the disease in the entire vessel. If surgical revascularisation is being considered, where a graft is positioned distally, then this may be helpful information. However, it is not possible to determine an accurate FFR for each individual stenosis. Due to the sensitivity of hyperaemic flow to the presence of proximal or distal disease, a measurement of FFR between two tandem stenoses will differ from that measured after one of the stenoses is treated. Therefore, placing the pressure wire between tandem stenoses to attempt to understand the flow limitation caused by the proximal stenosis can be misleading [5]. This is because the presence of the distal stenosis means the increase in flow caused by the hyperaemic agent is not transmitted uniformly though the vessel; as a result the measured pressure distal to the proximal stenosis may be higher than may actually be the case, causing the severity of the proximal stenosis to be underestimated. The removal of the distal stenosis by intervention will increase hyperaemic flow and thereby change the pressure ratio

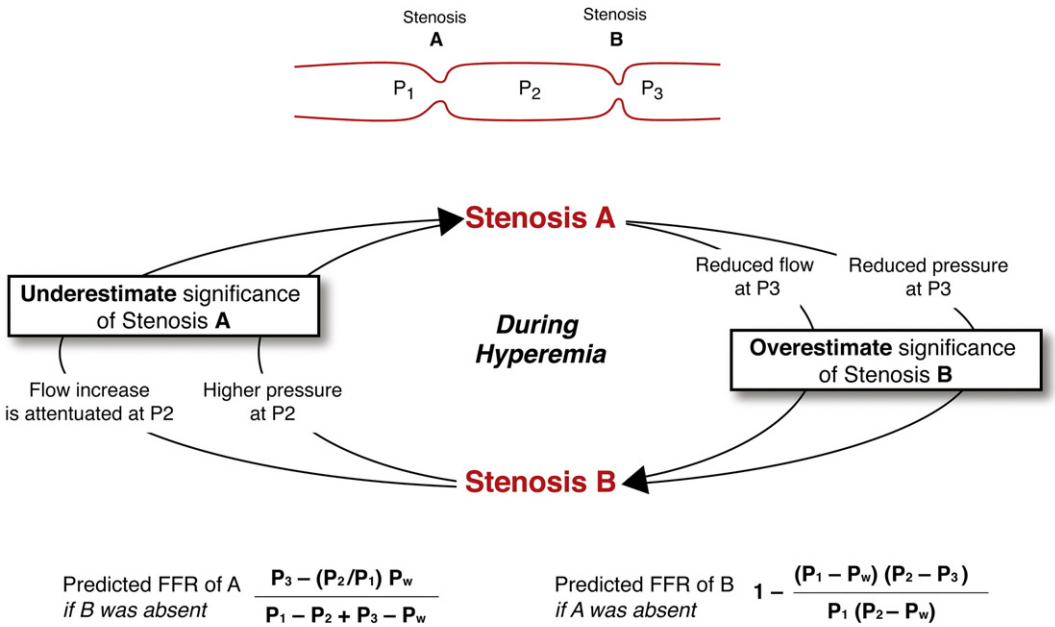

Fig. 2. Tandem stenoses cause flow interaction under hyperemic conditions. The presence of two or more stenoses creates complex interaction of flow and thereby impacts upon pressure measurements. Formulae are available to estimate the FFR of a given stenosis without the impact of another but requires balloon occlusion of the stenosis in question (Pw).

across the residual stenoses (Fig. 1). To overcome this haemodynamic interaction between stenoses and determine an accurate FFR for the residual stenosis, the second lesion must be treated and physiological assessment must then be repeated.

Complex formulae have been derived in an attempt to try and overcome these difficulties but are difficult to apply in the catheter laboratory (Fig. 2) [6,7]. They require a commitment to ballooning one of the stenoses for determination of wedge pressure and when there is uncertainty over stenoses, an interventionalist would prefer to avoid vessel trauma. A more practical solution to circumvent this limitation is the process of performing multiple hyperaemic measurements whist pulling the pressure wire back along the length of the artery. This aims to demonstrate where in the vessel the greatest steps in pressure gradient are present. It does not overcome the issue of stenosis interaction but can be used to help a cardiologist decide which lesion is likely to be causing most of the pressure loss. Such an approach only offers a crude estimate of the severity of each stenosis and the issue remains that, after stenting, the pattern of flow in the vessel will change, rendering the initial assessment of any residual stenosis inaccurate. Therefore such gradients cannot not predict coronary haemodynamics post-PCI [5].

These difficulties imposed by hyperemia has hindered the development of predictive systems that can model the physiological result of stenting in the presence of multiple lesions [6,7]. As a result this is currently not possible in clinical practice. A modality that can facilitate stenosis specific assessment would add significant value in the management of these patients. Potentially it may permit tailoring of the stenting strategy to optimise physiological outcome.

2. Baseline physiology provides a potential solution to tandem lesion assessment

A potential solution for the assessment of tandem lesions is to use the unique characteristics of baseline physiology. Auto-regulatory mechanisms ensure resting flow is stable and changes little regardless of stenosis severity [3,8]. The distal microcirculatory bed, a key governor of coronary flow, dilates under resting conditions to maintain resting flow even when severe epicardial artery narrowings are present [9]. Whilst flow is maintained, this is at the expense of resting distal coronary pressure. The dilation of the microcirculation causes distal pressure to fall, generating a pressure gradient that is essential to maintain coronary flow. It is this pressure gradient that is detected by modern high fidelity pressure wires, permitting stenosis assessment under basal conditions [9–11].

Whilst baseline flow is maintained constant [8] until almost subtotal occlusion of the vessel, hyperaemic flow changes dramatically according to the presence or absence of distal and proximal disease (Fig. 2). This means that the basal state is uniquely suited to the assessment of vessels with diffuse or tandem lesions; because basal flow across the lesion of interest is expected to be negligibly affected by other lesions in the vessel (Fig. 1) provided they are not critical or subtotal occlusions. Even if there is some interaction under resting conditions at a given point, the interaction is expected to be very small and much less than that seen under hyperemia.

This minimal interaction between the stenoses means that a given trans-stenotic pressure ratio measured at a particular point in a vessel is less likely to be affected by other stenoses within the vessel. Similarly, the haemodynamic assessment of the stenosis would not be affected when another stenosis in the vessel is treated by stenting, since the nature of resting flow suggests that there would be minimal change in resting flow after stenting typical stenoses. This allows several assessments of the coronary artery that are clinically useful, such as:

1. Evaluation of the stenosis burden of the complete vessel; providing a cumulative assessment of all stenoses in that territory. This is also currently possible with hyperaemic measures.
2. Quantification of the impact of individual stenoses within a diffusely diseased vessel or a vessel with tandem stenoses; permitting the differentiation of stenoses according to their magnitude of contribution to the overall disease burden of the vessel – impossible with current hyperaemic measures.
3. Prediction of the physiological effect of treating a particular stenosis within the vessel; permitting intervention according to the likely physiological gain. This is not possible with current hyperaemic measures but is particularly advantageous for diffusely diseased vessels as it may prevent the clinician from embarking on a revascularisation strategy that may improve the appearance of the vessel but not improve the blood flow to the subtended territory.

Resting flow therefore offers unique properties that may overcome the difficulties seen during hyperaemia. A pressure wire pullback under basal conditions may therefore offer an innovation to improve physiological assessment in vessels with diffuse or tandem coronary disease by providing stenosis specific information. For such an innovation to be readily applicable to day-to-day practice, the approach must be simple, glean the most information from the basal haemodynamics, easy to perform and be done using routinely available pressure wires.

3. Instantaneous wave-free ratio (iFR) utilises basal physiology to isolate the haemodynamic impact of individual stenoses in diffusely diseased vessels

iFR is a resting index of stenosis severity that is measured without a vasodilator. It is the ratio of distal and proximal pressures over the wave-free period, a specific part of diastole during which coronary flow velocity is naturally at its highest [10]. This higher flow velocity allows iFR to assess higher pressure gradients across stenoses than possible by using the complete cardiac cycle whilst also preserving the key characteristic of constant flow [9]. As a result iFR has a greater ability to identify small gradients pertinent to the assessment of a diffusely diseased vessel [9,12].

We have evaluated the instantaneous wave-free ratio (iFR) for the assessment of diffuse disease to ascertain the potential clinical utility of iFR in this domain. If measured continuously during a pressure wire pullback a haemodynamic map of the coronary artery can be created [13]. Importantly, the higher flow velocity during the iFR window when compared to resting whole cycle window provides greater pressure-spatial resolution.

With the advent of modern computer processing, it is possible to integrate the pressure wire data to plot the change in iFR over a given length of vessel, and thereby calculate the change in iFR per millimetre of vessel, a marker of pressure-loss intensity (iFR intensity $=\Delta$iFR/distance, Fig. 3) [13].

The value of mapping the iFR intensity in diffusely diseased vessels enables identification of any focal areas of disease that may cause the predominant pressure loss (Fig. 3), and therefore be targeted for percutaneous intervention. The percentage contribution of pressure loss can be displayed to assist decision-making. The mapping can be displayed in a number of different ways (Fig. 3). With co-registration, the pressure wire pullback can become integrated with the angiographic findings to enhance the ease of understanding of the data. 'Dots' representing units of pressure loss can help identify which stenoses are most haemodynamically important. In addition, iFR intensity plotted as a function of distance can give additional information regarding the length over which the pressure drop occurs (Fig. 3). This may assist in identifying which lesions in the vessel contribute most to pressure loss and allow operators to estimate the physiological length of a stenosis to help decide between different revascularisation strategies (PCI/CABG) (Fig. 4).

This approach also allows the operator to predict the haemodynamic effect of their intervention by modelling the expected improvement in coronary physiology for a given stenting approach [13]. Since length has been integrated into the information, a haemodynamic map can

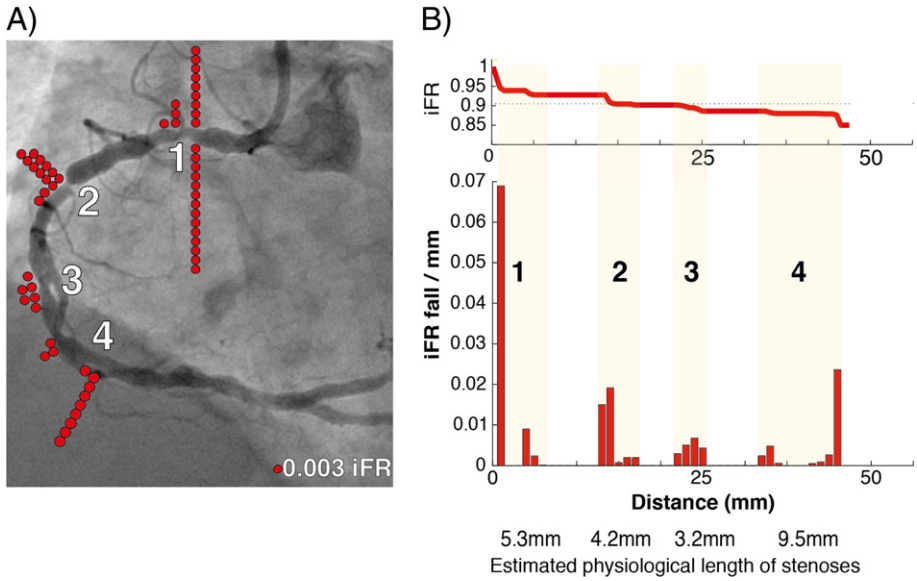

Fig. 3. iFR Pullback can display iFR-intensity and integrate onto angiography. A. Right coronary artery with 4 discrete stenoses. A pressure wire is pulled back at rest from the distal vessel the proximal vessel at 0.5 mm/sec using a motorised device. The red-dots correspond to the iFR-intensity plot shown in B lower panel. The numbers correspond to the four discrete physiological lesions identified on iFR-pullback. B. Upper panel: The red line shows the iFR-Pullback. Focal lesions are visualised as sudden steps while diffuse disease is a gradual slope. Distance is used as the x-axis since the distance of the wire-movement is known enabling estimation of the physiological length of the lesion. Lower panel: The iFR-intensity (ΔiFR/mm) can be plotted as bar chart to identify where the greatest pressure loss in the vessel.

be overlaid the coronary anatomy and stenting strategies modelled to predict physiological improvement from stenting prior to PCI (Fig. 4). In simple disease, this could be used to predict the post-intervention iFR result. In more complex disease, such technology permits the clinician to simulate multiple different stenting approaches to identify the most appropriate for the most favourable haemodynamic outcome (Fig. 3). In the iFR-Pullback study, complex tandem stenoses and diffuse disease was assessed in patients undergoing coronary intervention [13]. Using iFR-Pullback it was possible to predict an expected iFR value for the treatment of a selected stenosis. When compared to the real-world observed iFR value achieved after stenting, there was a close relationship between the predicted delta and a close relationship on Bland-Altman analysis [13]. There was no significant bias in the prediction and overall, it was possible to predict the post-PCI iFR result within 5% error even in complex disease [13].

iFR-Pullback measurements can be made using manual pullback of pressure wires. Performed over 20 to 30 seconds, physiological data can be processed 'live' and display the resting iFR gradients throughout the vessel.

The concepts of producing a physiological map of the vessel, to aid planning and virtual PCI represent a change in the application of physiological measurements. Previously, there may have been temptation to use physiology as a binary value, with a 'stent everything' and 'stent nothing' approach. However, pullback assessment of complex and diffuse disease exposes physiological assessment as a continuous variable along the length of the vessel. This objective physiological approach

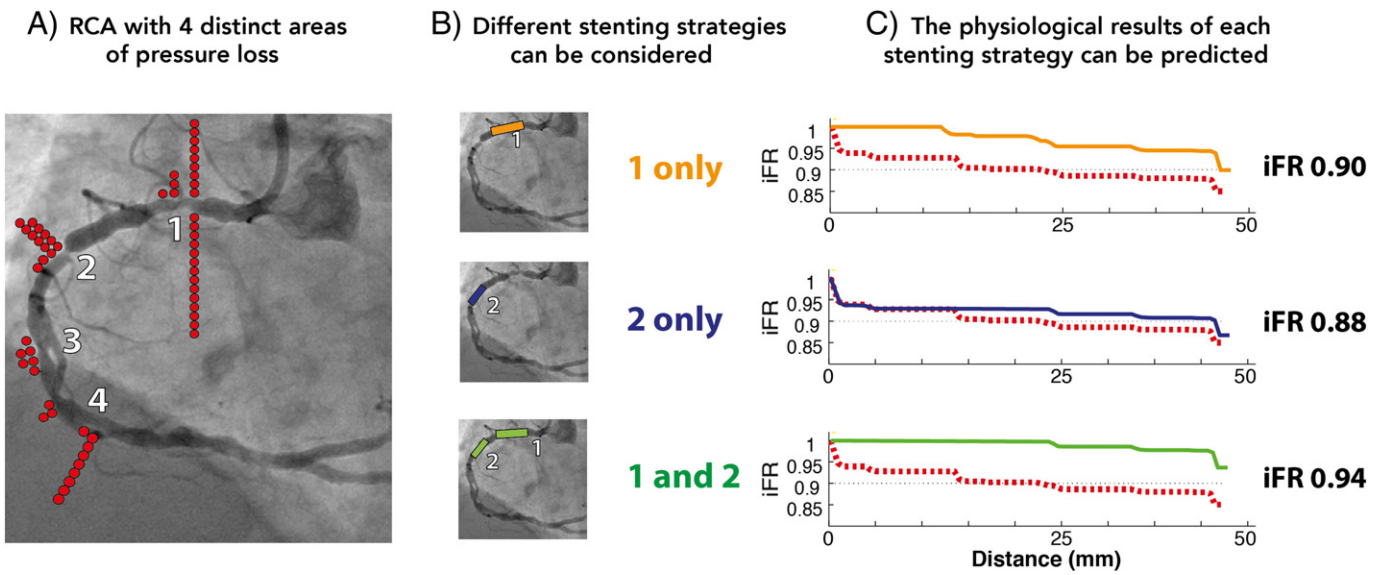

Fig. 4. Virtual PCI can be performed on iFR-Pullback to calculate the effect of removing a stenosis. A. A resting iFR-Pullback is performed on a RCA with significant disease. iFR-intensity is displayed as small red dots representing pressure loss and is integrated onto the angiogram. B. Different stenting strategies can be considered. C. On the iFR-pullback trace, a stenosis can be selected for removal, and computer algorithms will model the impact upon the rest of the vessel. Removing stenosis 1 or 2 alone will not give the vessel an iFR well above the threshold for treatment; both stenoses are required for an optimal result.

has the potential to offer an important adjunct to the armamentarium of the interventional cardiologist.

One area of potential change may be that focal areas causing pressure loss within a vessel could be specifically targeted for intervention. Presently, coronary intervention is typically performed from normal-to-normal segments with a view to avoid geographical miss, which has been associated with higher rates of target vessel revascularisation, myocardial infarction; imaging studies with IVUS have suggested stent edge plaque burden and geographical miss are associated with early stent thrombosis and restenosis [14,15]. However, it is also known that excessive stent length is associated with increased lumen loss, which may itself have further implications [16]. Achieving an optimal physiological result without total coverage of all possible atheroma may be a compromise. With the advent of physiological mapping there is now an opportunity to assess this in detail. In an hypothesis generating analysis from the iFR-Pullback study, it was noted that physiological lesion length was significantly shorter than anatomical length and the total stent length deployed [13]. Furthermore, virtual-PCI analysis suggested optimal physiological results could be achieved with significantly less stent length. At present these concepts are nascent, and there is no outcome data for either approach of physiologically focused stenting versus stenting covering larger lengths. Detailed future studies will be required before such an approach can be advocated.

4. Conclusion

Physiological assessment has already demonstrated great value in the management of coronary disease. iFR pullback is an innovation that refines this technology to aid clinical decision making in diffuse coronary artery disease and vessels with tandem lesions.

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