ISCHEMIC HEART DISEASE (D MUKHERJEE, SECTION EDITOR)

Physiology-Guided Management of Serial/Diffuse Coronary Artery Disease

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Abstract

Purpose of Review Just over four decades ago, the management of coronary artery disease (CAD) witnessed a major breakthrough with the advent of minimally invasive treatment modalities like angioplasty followed by coronary stenting. Dr. Andreas Gruentzig pioneered this field in 1977 by adding a balloon to the Dotter catheter. From its inception, he was cognizant of the need for measuring pressures before and after balloon inflation in the treated coronary artery, device placement in the treated coronary artery. However, for decades subsequently, emphasis was placed primarily on preprocedural non-invasive tests and angiographic assessment of lesions based on percent diameter stenosis to guide therapeutic interventions. We review the progress of these physiologic advancements in management over the last 20 years, as well as the current state and prospects for the future.

Recent Findings More recently, clinical features heavily drive the decision whether or not to stent the diseased segment. A little more than two decades ago, a new approach to facilitate the decision whether or not to intervene on intermediate stenoses began to evolve. It became clear that other features besides angiography are important when considering benefit of mechanical intervention. The emphasis shifted to assessment of the physiological significance of coronary lesions, rather than solely anatomical identification of lesions at angiography. Physiological assessments have served to better discriminate potentially flow-limiting lesions, utilizing cutoff measurements to determine which patients would benefit from intervention in addition to medical therapy.

Summary We have found that there is still need for arrival at a consensus as regards the best practice in the context of physiological assessment of serial stenotic lesions, but that studies do show that techniques currently available are non-inferior to each other, and highly effective.

Keywords Percutaneous coronary intervention · Fractional flow reserve · Instantaneous wave-free ratio · Flow physiology · Revascularization · Serial coronary lesions

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Introduction

Percutaneous coronary intervention (PCI) has had an indelible impact on a tremendous segment of the global populace, as ischemic heart disease has increasingly been contributory to global health expenditures and clinical outcomes. Cardiovascular disease has been increasingly associated with adult deaths and is now the number one killer of adults worldwide. PCI has been a major breakthrough in CAD management and has demonstrated a mortality benefit in patients presenting with acute coronary syndromes, particularly with more high-risk profiles like ST elevation MI (STEMI), especially in the setting of cardiogenic shock. Since Dr. Gruentzig's revolutionary first coronary balloon inflation in a Zurich hospital in 1977, the technique has been criticized for being excessively and at times inappropriately used. Decisions to revascularize were being based on the visualization of the stenotic lesion alone, termed the "oculostenotic reflex." Results of PCI on mortality compared to medical therapy alone were not significantly improved in stable patients with CAD treated with PCI. Subsequently, this attendant scrutiny has resulted in the evolution of a more stringent selection criteria of intravascular lesions warranting intervention. It has been found that coronary stenoses have varying ischemic potential regardless of initial visual appearance, and this ischemic potential must be accurately and reliably assessed. Translesional pressure indices are now a staple in this regard [1]. The use of resting translesional pressure gradients as well as whole cardiac cycle resting Pd/Pa ratios were studied to assess functional significance, and this in turn led to the concept of hyperemic Pd/Pa, which was thought to better define ischemic processes than its resting counterpart. Ultimately, the concept of the fractional flow reserve (FFR) was developed [2, 3]. Currently the most widely used index, this adenosine-induced hyperemic translesional physiologic pressure index serves multiple purposes. It can identify the ischemic potential of a stenosis, as well as eliminate interobserver shortcomings with direct visualization and assessment of lesion severity, and help garner and arrive at the best and most cost-effective approach, when compared to the original, conventional angiographic approach. The physiologic assessment of lesions is well validated, and correlated with clinical outcomes [4].

At present, ischemia-guided revascularization is now integral to the current management of CAD and is now an expected real-time assessment after lesion identification with diagnostic cardiac catheterization. These physiological indices in conjunction with other clinical features guide decision-making and are cited in Appropriate Use Criteria (AUC) [5••]. Studies using hyperemic assessments have shown inaccuracies in determining the physiologic significance of stenoses. This limitation gave rise to a renaissance of diastolic importance, resulting in resting physiologic indices taking center stage, these harnessing the diastolic wave-free Pd/Pa, where microvascular resistance is said to be constant, otherwise known as the instantaneous wave-free pressure ratio (iFR) and this has engendered a further combination of interest and criticism. The RESOLVE study served to validate iFR against FFR with agreement in the vicinity of 80% [4], and iFR was then also found to be non-inferior to FFR in two further studies looking at clinical outcome [6••, 7••]. However, a diagnostic physiological challenge is presented with complex anatomy and or serial stenotic lesions, necessitating the grasp of specific physical considerations between the physiology of hyperemic and resting stenotic physiology.

It should be noted that reduced poststenotic pressure results from loss of flow energy from resistance as the blood passes through narrowed intralesional spaces in the coronary vasculature as a result of stenosis, with induced hyperemic flow increasing the magnitude of the pressure gradient, bearing in mind that increased rate of flow via a stenotic area results in yet a greater loss in pressure [5••]. Except for very severe stenoses, however, that is, greater than 90%, constant resting coronary blood flow is maintained by autoregulation, and for an individual stenosis, the hyperemic pressure gradient represents a true FFR. This changes for diseased vessels containing serial lesions, however, as the presence of interaction of hemodynamics between lesions prevents achievement of the production of maximal hyperemia across individual lesions and this invalidates the abovementioned hyperemic monolesional FFR. Complex equations involving multiple stenoses in a hyperemic state have been developed and validated [2, 3]; these involve the coronary occlusion wedge pressure, but have been found not to be pragmatic and lacking in simplicity for everyday use despite their proven reliability. Ischemia-guided revascularization with FFR or iFR confers clinical and prognostic benefit versus treatment based on angiography alone.

Physiological Approaches to Accurate Multi-lesion Assessment

There are several factors governing pressure changes across a lesion. There are those governed by the principles of the Bernoulli equation and Poiseuille's Law. However, lesion geometry also plays a role; furthermore, lesion length contributes linearly to viscous resistance. This is exceedingly important in long, diffuse segments of disease. Flow conditions also play a role, as eddy currents can form where laminar flow meets the stenosis, resulting in non-laminar flow. Velocity of the flow is also influenced by changes in resistance downstream and this can be another contributing factor [5••].

The use of FFR and iFR has been met with a mixture of criticism and diversity of medical opinion. This lack of consensus has led to a number of perceived best practices in the

physiology-guided assessment of serial lesions which we will individually discuss, namely:

- The Isolation of Lesions with an FFR Between Same
- The Educated Guess Method
- The Manual Pullback Method
- The Adoption of a Large Disease-Free Side Branch [5••]

The Isolation of Lesions with an FFR Between Same

It is a common practice to overlook the possible interaction of serial stenotic lesions in an afferent coronary vessel, with the tendency to assess the intracoronary pressure gradient between and distal to serial lesions, and assign the total FFR as a composite attributable to operator-designated culprit stenoses. This is erroneous as the total vessel resistance is greater with an intermediary stenosis, which can lead to the pressure gradient being underestimated. It should be noted as previously stated that additional lesions also alter flow conditions and intravascular turbulence, which can be contributory to distal flow [5••].

The Educated Guess Method

Another common approach is to visualize and make an educated guess as to which segment of the morbid vessel with an FFR deemed to be less than 0.80 is most likely functionally significant, and then stent that segment. Treatment is then followed by repeating the FFR measurement and stenting additional lesions if it is still < 0.80. Research has shown that post-PCI FFR significantly and reliably predicted a 6-month likelihood of events, with there being a directly proportional correlation between FFR and event rate. This approach has drawbacks because this angiographic judgment relies on the operator and lacks a robust physiological assessment which would analyze individual stenotic contributions and mitigate interlesional interplay [8].

The Manual Pullback Method

This increasingly practiced technique involves pulling back a pressure guidewire from the most distal to the proximal aspect of the diseased vessel, and measuring coronary pressure serially, at intervals, to assess for incremental decrements in coronary pressure. A limitation of this method is that it assumes that the presence of a lesion is solely responsible for changes in pressure gradient. However, this particular approach is buttressed by two observational studies utilizing the principle of

revascularization primarily of the stenotic segment which was demonstrated to have the greatest pressure gradient [9, 10]. There are other drawbacks to this method also, in that there may be errors in estimation of the change in FFR, [2, 3, 9, 10] resulting in unnecessary stenting of vascular segments that may not be physiologically significant based on anatomical obstruction but rather attributable to turbulent flow. Further still, interobserver error may lead to erroneous decisions, due to phenomena such as misinterpretation of artifact. A surgical approach in some instances may be more precise for serial stenoses by more complete revascularization where intralesional interplay would obviate individual suppositions of lesion contributions to limitations in distal coronary flow [11] (Fig. 1a, b).
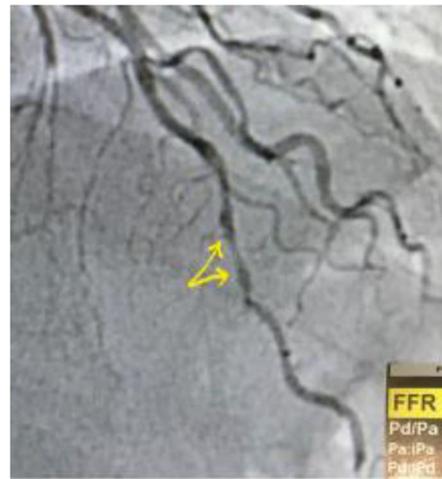
The Adoption of Large Disease-Free Side Branch

The left main coronary artery (LMCA) needs special consideration. It has been suggested that the true FFR of a LMCA lesion can be obtained by placing the pressure guide wire in a large unobstructed side branch [12••, 13••, 14, 15]. This seems appropriate as these studies have shown that in the majority of cases, LMCA FFR is unaffected by downstream disease when the wire is placed in the disease-free vessel, even in the presence of obvious disease. With the wire placed in a disease-free side branch, if the FFR is greater than 0.85, then it can be assumed that the LMCA stenotic area is physiologically non-significant. This approach is restricted to LMCA lesions only, where serial disease is restricted to one daughter vessel [12••, 13••, 14, 15].
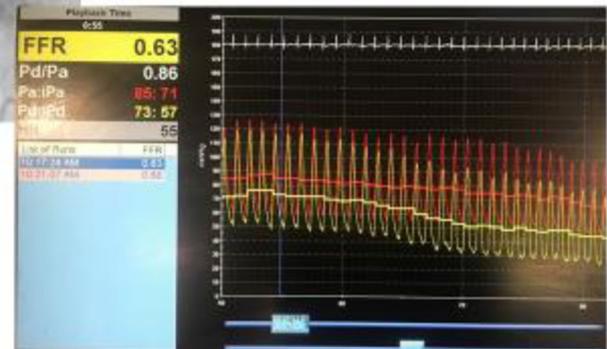
Currently Deployed Physiological Approach for Assessment of Multiple Lesions

There are several steps in the assessment of a vessel which contains multiple stenotic lesions, the process beginning with the measurement of the summed FFR. The summed FFR is the pressure distal to the furthest stenosis in the vessel and represents the aggregate of all intervening lesions. If this resultant FFR value amounts to more than 0.80, then deferment of PCI is a feasible option. However, if it is less than this value, then pressure wire pullback during adenosine-induced hyperemia is advised. As individual FFR is not reflective of the changes in pressure along the entire vessel, or Pd/Pa, a single FFR measurement is not valid for serial lesions and it is critical to measure changes in pressure at key points along the artery to discern the individual contribution of each isolated lesion to the total resistance to flow in the vessel. Once a cutoff value is established which warrants intervention, the sequential step is to address the lesion with the largest pressure

Fig. 1 **a** Console showing drop in FFR along a distal long LAD stenosis, in physiological coregistration with the coronary angiogram. The *yellow arrows* point to stenotic lesions (Reproduced with permission from TTHSC-El Paso Cath Lab, Dr. T. Siddiqui.). **b** Console showing drop in FFR along a tortuous mid RCA stenosis, in physiological coregistration with the coronary angiogram. The *yellow arrow* points to a stenotic lesion (Reproduced with permission from TTHSC-El Paso Cath Lab, Dr. T. Siddiqui)
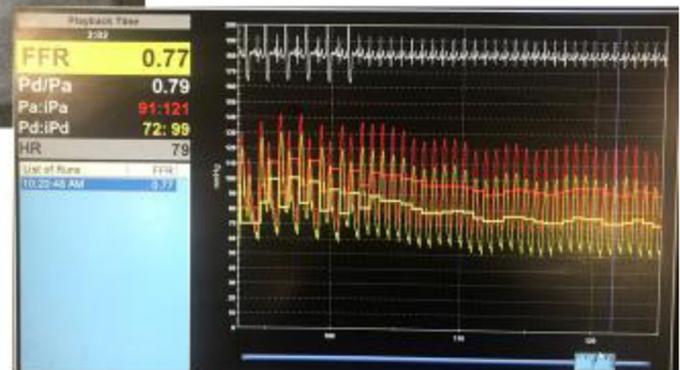

gradient. After successful treatment of the most significant lesion, an individual FFR should be measured on the remaining lesion(s) and if found to be less than 0.80, these too should be stented. Once all lesions identified as physiologically significant by this method are successfully treated, a final summed FFR and full vessel pressure guide wire pullback from distal to the most proximal end of the artery should be performed, to ensure that no lesions of significance are missed [12••, 13••, 14, 15]. One proposed benefit of iFR is that pressure pullback using this method does not have the drawbacks of individual FFR, as resting flow across lesions is assumed to be constant and the interplay between lesions negligible. During iFR assessment, the units are plotted against

Fig. 2 Console showing Instantaneous Wave-Free Ratio difference along a stenosed right coronary artery during pullback in cardiac catheterization, in physiological coregistration with the coronary angiogram. Each *yellow dot* represents a change in iFR of 0.01, with the graphic pullback on the right of the figure. The *white line* denotes the segment of stenosed vessel over which the pullback registers an increase in the iFR (Reproduced by permission courtesy of Royal Philips)

angiographic location, and the segment(s) with the higher iFR would attain candidacy for treatment [5••].

Resting Versus Hyperemic Pressure Gradient

With regard to this common procedural quandary, it can be stated that if detection of the pressure gradient is the best practice, then a hyperemic milieu will magnify this gradient, and therefore may enhance identification of the physiologically significant lesion. Furthermore, pressure signal drift can impact flow indices. Pressure signal drift, a source of error that decreases the accuracy of transstenotic pressure measurements during physiological stenosis assessment, due to multiple factors and which can be difficult to eliminate, with a clinically acceptable threshold of ± 2 mmHg in which repeat normalization and physiological assessment is not necessary, is a relatively frequent occurrence, occurring in close to one-fifth of all laboratories, and a greater spread of values reduces this [16••]; however, this phenomenon has a greater effect on resting than on hyperemic indices, suggesting the use of hyperemic measures for its minimization [17••]. Serial lesions, particularly in the context of crosstalk and interaction, in addition to challenging the FFR concept, witness enhancement in hyperemic states and are minimized at rest, the hyperemic state only being achievable in just under 60% of those undergoing adenosine administration [18, 19••].

Instantaneous Wave-Free Ratio, Resting Pd/Pa Ratio

iFR utilizes the same system and pressure wire to determine the physiological significance of coronary stenoses. This
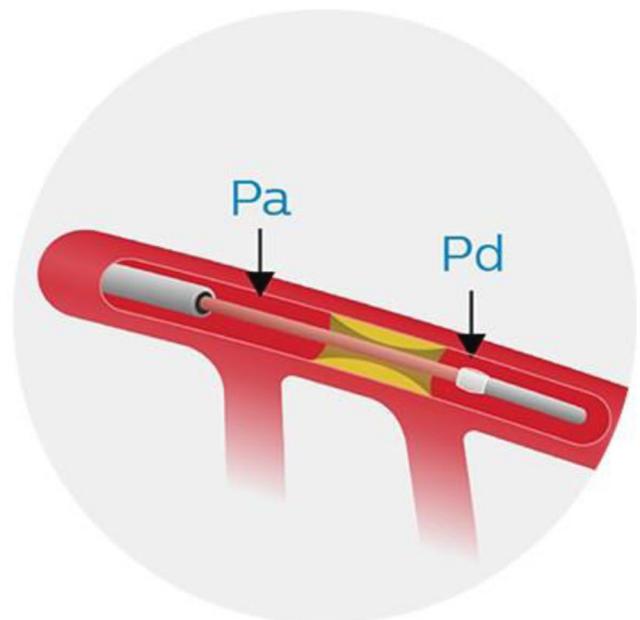
Fig. 3 Schematic showing translesional pressure gradient along a coronary artery; values on either side being measurable by the pressure guide wire. Pa, aortic pressure; Pd distal coronary pressure; Pd/Pa, distal coronary pressure to aortic pressure ratio (Reproduced with permission courtesy of Royal Philips)

Table 1   Table showing comparison of FFR to iFR [22••]

	FFR	iFR
Supporting studies	DEFER, FAME,	VERIFY, ADVISE, ADVISE II, ADVISE-Registry, CLARIFY, DEFINE-FLAIR, iFR-SWEDEHEART
Flow limitation cutoff	< 0.75–0.80	< 0.86–0.90
Accepted pressure wire drift	± 2 mmHg	± 2 mmHg
Calculation	Pd/Pa in adenosine-induced hyperemia	Pd/Pa during wave-free diastolic period
Adenosine pretreatment required	Yes	No
Revascularization deferral MACE rate	4.05%	4.12%
Revascularization deferral clinical outcome	Unknown	Unknown

particular pullback method analyzes the last segment of diastole called the wave-free period. It is only during this period of coronary flow that competing waves are quiescent and the relationship between flow and pressure is linear, and mitigates the interlesional interplay. Not only does this method not require hyperemia but it may be a better assessment of serial stenoses as the flow effects of serial lesions is not contributory to the result. This allows for measurement of resting flow and does not require hyperemia induction [6••, 7••]. This is a significant advantage as adenosine not only adds to cost and time of procedure but it can cause patient discomfort.

Further iFR-guided revascularization outcome studies are necessary but excellent correlation with FFR was noted in 94% of subjects in the ADVISE II trial [20]. The VERIFY and CONTRAST studies have also found near perfect correlation of iFR and Pd/Pa. These encouraging findings have led to an increased interest in resting indices and data for the potential application of iFR in serial disease is greatly anticipated [21, 22••] (see Figs. 2 and 3).

Current Best Practices Involve Physiology Assessment

Serial stenotic lesions, unlike their solitary counterparts, are difficult to assess. Nevertheless, it is clear that physiology-guided assessment of the coronaries is distinctly superior to angiographically guided treatment alone, and better outcomes are anticipated with increased utilization and acceptance of same; it should be noted that the harnessing of manual pullback and disease-free side branch method in the context of the LMCA, both when using FFR appear to confer the greatest level of accuracy, with emphasis on constant pullback speed in the case of the former [5••].

Despite a number of these approaches being controversial, it should be noted that measuring the pressure gradient during pressure wire pullback in a hyperemic state remains the current best practice; the change in iFR pressure pullback method being the latest addition to the options available but again

being mired in controversy as some believe it may have theoretical benefits over the former hyperemic approach, given the altered hemodynamics generated with agents such as adenosine; however, the official clinical trial data of this method are not yet available for practitioner perusal, engendering the current clinical quandary as to what could be futuristically considered as best practice [23••].

New Developments

Recently, the results of a study on the deferral of revascularization based on iFR and FFR showed these two approaches to be equally safe, this study involved patients from the DEFINE-FLAIR and SWEDEHEART trials, with them being stratified on the basis of Acute Coronary Syndrome (ACS) versus stable angina pectoris (SAP), with primary study endpoint being major adverse cardiac events (MACE). The MACE rate at 1 year between these two techniques was virtually equal at just over 4%, and the observation was made that lesions were more frequently deferred when iFR was used to assess their physiology. However, the 1-year risk of a MACE in the group with ACS and deferral of revascularization was about 2% more than the SAP counterpart, using these two techniques Table 1. This new data has already generated some debate, reflective of the richness, quality, and diversity of subspecialist opinion in this regard [24].

Conclusion

Identification of the physiological significance of individual stenotic lesions where they occur in series and the decision whether or not to intervene continues to present a challenge. Assuming that recent research findings hold true, this would give the coronary angiographer a lot more space to safely make clinical decisions based on reliable physiological intracoronary assessments; however, in the meantime, while a new consensus is being arrived at, an interim focus on a

combination of current available technical methods that are appropriate to best assess intracoronary morbidity has been necessitated until further research developments and technological enhancements better facilitate this unmet need. At this time, clinicians should use guidance form the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention which states that FFR is reasonable to assess angiographic intermediate coronary lesions (50% to 70% diameter stenosis) and can be useful for guiding revascularization decisions in patients with stable ischemic heart disease [25].

Compliance with Ethical Standards

Conflict of Interest Christopher S. G. Murray, Tariq Siddiqui, Norma Keller, Solaiman Chowdhury, and Tamanna Nahar declare that they have no conflict of interest with regard to this publication.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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