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REVIEW

#FullPhysiology: a systematic step-by-step guide to implement intracoronary physiology in daily practice

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ABSTRACT

#FullPhysiology is a comprehensive and systematic approach to evaluate patients with suspected coronary disease using PressureWire technology (Abbott Vascular, Santa Clara, CA, USA). This advancement in technology enables the investigation of each component of the coronary circulation, including epicardial, microvascular, and vasomotor function, without significantly increasing procedural time or technical complexity. By identifying the predominant physiopathology responsible for myocardial ischemia, #FullPhysiology enhances precision medicine by providing accurate diagnosis and facilitating tailored interventional or medical treatments. This overview aims to provide insights into modern coronary physiology and describe a systematic approach to assess epicardial flow-limiting disease, longitudinal physiological vessel analysis, microvascular and vasomotor dysfunction, as well as post- percutaneous coronary intervention (PCI) physiological results.

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KEY WORDS: Myocardial ischemia; Physiopathology; Technology.

Coronary physiology, which includes indexes for the assessment of epicardial vessels and microcirculation, has been introduced and validated to support physicians in their daily clinical decision-making for patients with coronary artery disease (CAD). Despite numerous randomized clinical studies and high levels of recommendation in both European and American guidelines, the integration of coronary physiology into everyday clinical practice remains limited. The low uptake of coronary physiology is likely attributed to a combination of factors, in-

cluding operators' mindset, additional costs and lack of reimbursement, increased procedural time, and perceived difficulties in the interpretation of pressure traces.[1] However, recent studies and technological advancements offer an opportunity to overcome these barriers, transforming coronary physiology from a simple diagnostic tool into a comprehensive assessment of each individual component of the coronary circulation. It is now possible to efficiently integrate the assessment of epicardial, microvascular, and vasomotor function within a single procedure, enabling the definition and optimal management and procedural planning for various challenging clinical conditions.

The aim of this overview is to provide insights into modern coronary physiology and to describe a systematic approach for implementing coronary physiology into daily practice, specifically referred to as #FullPhysiology.

#FullPhysiology

The #FullPhysiology approach consists of a systematic step-by-step assessment of each component of the coronary circulation, including epicardial, microvascular, and vasomotor function (Figure 1). The #FullPhysiology approach is optimized using Coroflow Coroventis platform with PressureWire X guidewire (Abbott Vascular, Santa Clara, CA, USA). It is important to acknowledge that not every step is mandatory for every clinical case, and the approach should be tailored to the patient's clinical presentation and condition.

Step I: epicardial vessel

The first step involves evaluating the epicardial vessel. The evaluation begins with the measuring the non-hyperemic pressure ratio (NHPR). Various NHPR measurements are available, and current data suggest overall equivalence among these indexes. In the Coroflow Coroventis platform, the resting full-cycle ratio (RFR) is the available NHPR measurement. Unlike other NHPR measurements, RFR evaluates the entire cardiac cycle and not just the diastolic phase. Following this, fractional flow reserve (FFR) should be assessed. Hyperemia can be induced by administering intracoronary adenosine (200 µg for the left coronary artery, 100 µg for the right coronary artery), and/or intravenous adenosine (140 mg/kg/min), and/or papaverine (15 mg for the left coronary artery, 10 mg for the right coronary artery), and/or contrast media. Intravenous adenosine should be preferred over intracoronary adenosine as it allows for more reproducible assessments and longitudinal pullback in case of positive value. In cases where pharmacological hyperemia is to be avoided, the contrast fractional flow reserve (cFFR) can be used, which takes advantage of the vasodilatory properties of contrast medium and has proven to be the most efficient surrogate of the FFR.[2] Systematically using both non-hyperemic and hyperemic physiology offers the advantage of a comprehensive assessment that includes the vasodilatory response to the hyperemic stimulus. Importantly, there are clinical scenarios where NHPR/FFR discordance occurs, and measuring both provides a complete picture of the functional status of the coronary vessel. For vessels showing positive NHPR and/or FFR values, longitudinal assessment of the disease is essential to optimize patients' management and PCI procedural planning.[3] The pressure wire pullback technique provides a point-by-point physiological map of the vessel and should be performed in every case to define the predominant pattern of disease (focal, diffuse or mixed pattern) and to exclude significant drift of the pressure trace.[3] Pressure wire pullback can be performed at rest or during steady-state hyperemia, with the latter offering the advantage of highlighting even minor pressure gradients that are often disregarded using NHPR-based techniques.

Step II: microcirculation

More than 50% of patients referred for coronary angiogram due to anginal symptoms and evidence of inducible myocardial ischemia on non-invasive tests do not exhibit angiographic obstructive CAD (ANOCA).[4-6] Coronary microvascular dysfunction (CMD) plays a significant role in the pathophysiology of ANOCA patients, and it is present in nearly 30% of the cases with negative FFR (FFR >0.80).[4-6] In addition, since

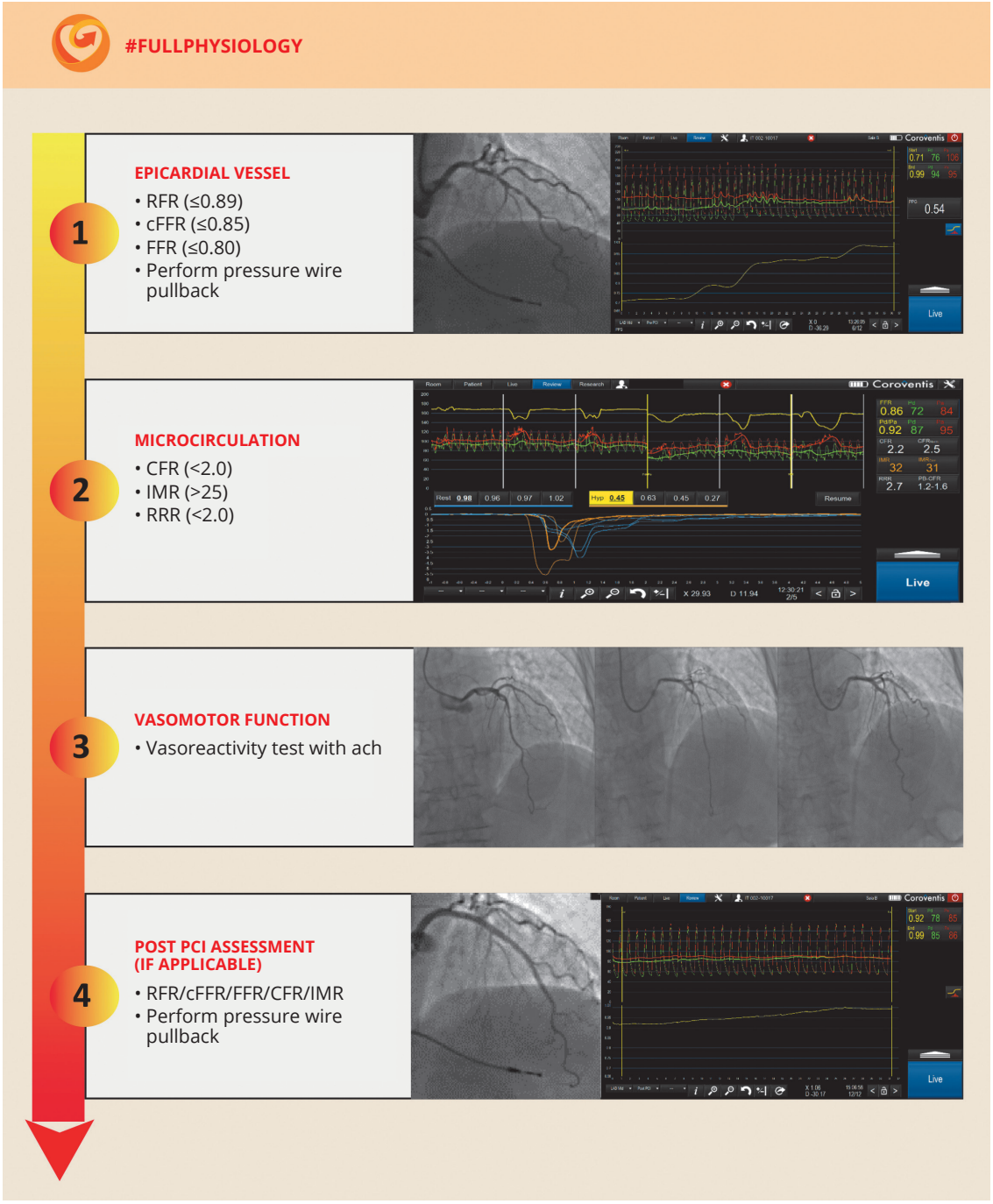

Figure 1.—#FullPhysiology step-by-step assessment of coronary circulation.

CMD and endothelial-dependent vasomotor dysfunction are early manifestations of atherosclerosis that can progress to obstructive CAD, the assessment of microcirculatory function could also be considered in patients with epicardial coronary disease.[7]

Thermodilution-based assessment of CMD involves injecting 3 mL of room-temperature saline

through the guiding catheter and observing the corresponding thermodilution curve on a dedicated monitor. Three injections are performed at baseline and subsequently after inducing steady-state hyperemia. Bolus thermodilution enables the measurement of two invasive indexes: coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR). A detailed description of these indexes is beyond the scope of this overview and can be found in more detailed sources.[8] In summary, CFR reflects the ability of the entire coronary circulation, encompassing both epicardial and microvascular components, to adapt to increased myocardial oxygen request. Pathological CFR values are considered to be less than 2.0 and serve as a hallmark of CMD in the absence of obstructive CAD. Conversely, IMR is a specific index of microcirculatory resistance that exhibits relative independence from hemodynamic conditions. Values equal to or exceeding 25 units are suggestive of CMD.

Step III: vasomotor function

Up to three quarter of ANOCA patients exhibits identifiable disorders of coronary vasomotion, including epicardial or microcirculation vasospasm.[9] It is noteworthy that coronary vasomotion disorders often coexist with CMD and/or obstructive CAD (Figure 2). The assessment of vasomotor function constitutes the third step of the #FullPhysiology approach and relies on specific provocative tests. Vasospastic angina is a clinical condition characterized by enhanced reactivity of vascular smooth muscle, resulting in spasm or impaired vasodilatation of the microvascular and/or epicardial compartments.[9] These conditions are frequently misdiagnosed due to their transient nature. Therefore, a systematic diagnostic assessment including vasoreactivity tests is recommended, especially in absence of obstructive CAD. Impaired microcirculatory vasodilation can be attributed to two primary subtypes: endo-

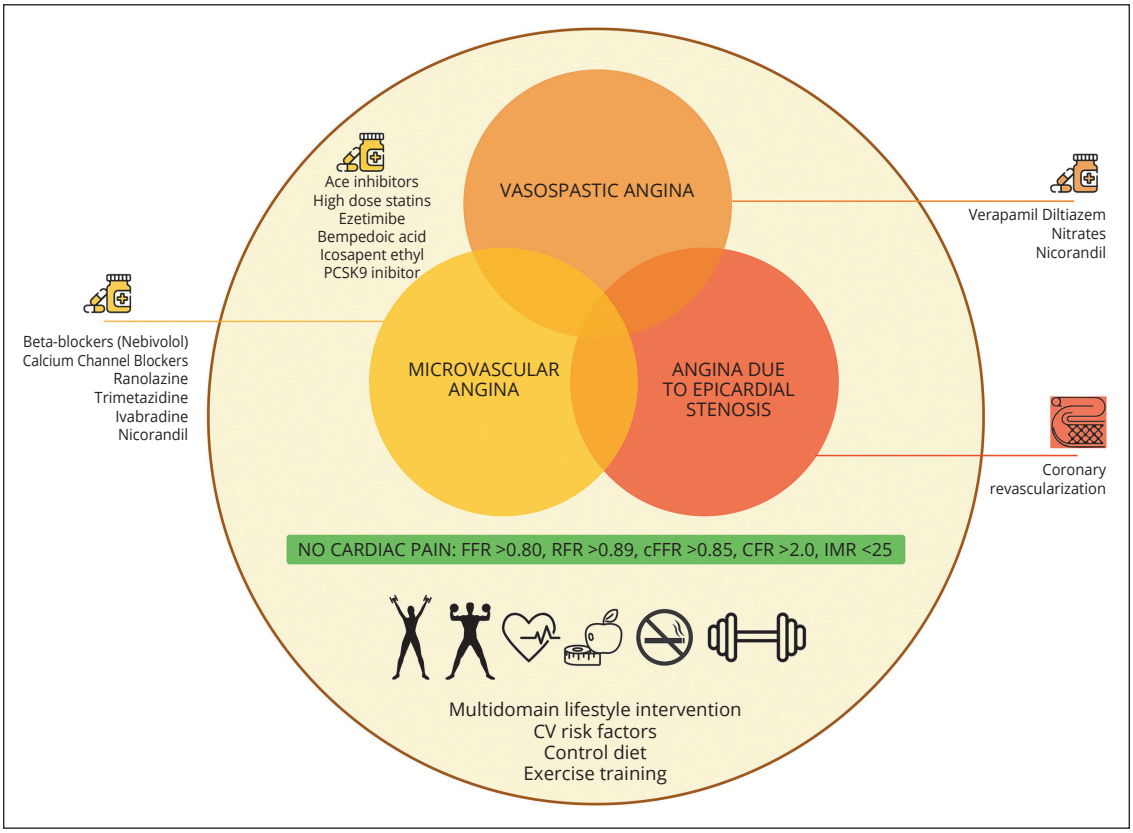

Figure 2.—#FullPhysiology-based precision medicine.

TABLE I.—*Vasoreactivity test.*

Step	ACh dose	Time	Action
Step I	20 µg	2	At the end of each step ask for symptoms, record ECG and repeat angiography
Step II	50 µg	2	
Step III	100 µg	2	

LCA: left coronary artery; RCA: right coronary artery; RFR: resting full-cycle ratio; Ach: acetylcholine, IMR: index of microcirculatory resistance.
Three sequential manual infusions of acetylcholine over a period of two minutes *via* the guiding catheter for assessment of the LCA. Although discouraged, vasoreactivity test can be performed also on RCA at lower doses (maximum 50 µg). The infusion should be slow and controlled in order to avoid excessive, variable volume altering coronary flow. If spasm persists for more than 1-2 minutes or if hemodynamic instability occurs, it is recommended to administer intracoronary nitroglycerin injection (100-200 µg) to alleviate the condition. The vasoreactivity test can be conducted by keeping the pressure wire in the same vessel where microcirculation has been assessed. In this case, RFR can be used to monitor epicardial spasm (significant reduction from baseline value) at the end of each Ach infusion (avoiding repeating angiography after each step), while IMR and the mean transit time (Tmn) can be used to monitor microvascular spasm (significant increase in the Tmn values).

thelium independent and endothelium dependent. The assessment of endothelium-independent function involves the use of thermodilution-based indexes, namely the index of IMR and CFR, as described at step 2. Conversely, the evaluation of endothelial-dependent vasomotor function entails intracoronary vasoreactivity testing primarily utilizing incremental doses of acetylcholine (ACh) infusion (Table I). ACh, acting as a neurotransmitter, primarily mediates the production of nitric oxide (NO) by the endothelium, playing a crucial role in flow autoregulation. In the presence of endothelial dysfunction, ACh primarily binds to vascular smooth muscle cells, leading to paradoxical vasoconstriction. The vascular response to ACh demonstrates endothelial dysfunction and/or hyperreactivity of vascular smooth cells if paradoxical vasoconstriction occurs after Ach infusion.[6] The clinical vasoreactivity test typically entails coronary angiogram, 12-lead ECG, and symptoms monitoring during Ach intracoronary infusion at incremental dosage (Table I).

Step IV: post-PCI assessment

In vessels treated with PCI, it is imperative to repeat the functional assessment using the same approach prior to the procedure. In particular, pressure wire pullback should be repeated before the end of the procedure, as pullback may highlight residual focal drop inside and/or outside the stent, which may require further treatment and optimization.

The objectives of #FullPhysiology

#FullPhysiology aims to clarify nine crucial aspects outlined below. The operator must customize the intracoronary physiology assessment for each patient to obtain the necessary information for accurate diagnosis and treatment.

Diagnosis of obstructive coronary artery disease

The most commonly used tool for determining flow-limiting coronary lesions in the epicardial vessels is FFR. Deferring coronary lesions with FFR value >0.80 is considered safe and it is recommended by international guidelines.[10,11] RFR and cFFR are viable alternatives to FFR, with deferral thresholds of >0.89 and >0.85, respectively.[12] It is advisable to collect more indexes (hyperemic and not). RFR and cFFR should be assessed at the beginning of the procedure, prior to inducing hyperemia for FFR and microcirculation assessment. In cases where there is disagreement between RFR and FFR, the decision on which parameter to rely on should be based on the patient's clinical history, functional pattern of CAD, and microcirculation status (see below for further details).

Functional patterns of CAD

Evaluating longitudinal assessment of CAD distribution pattern provides an additional dimension for characterizing the disease beyond angiography and functional evaluation of lesion significance. Functional patterns of CAD include focal stenosis, serial stenoses, diffuse disease and mixed patterns. Focal stenosis is defined at pressure wire pullback as an abrupt pressure drop (delta FFR ≥0.05 or delta RFR ≥0.03) over a short vessel segment (≤20 mm) (Figure 3). Serial lesions are defined as two or more focal stenoses separated by a non-diseased vessel segment >20 mm (Figure 3). Conversely, diffuse disease

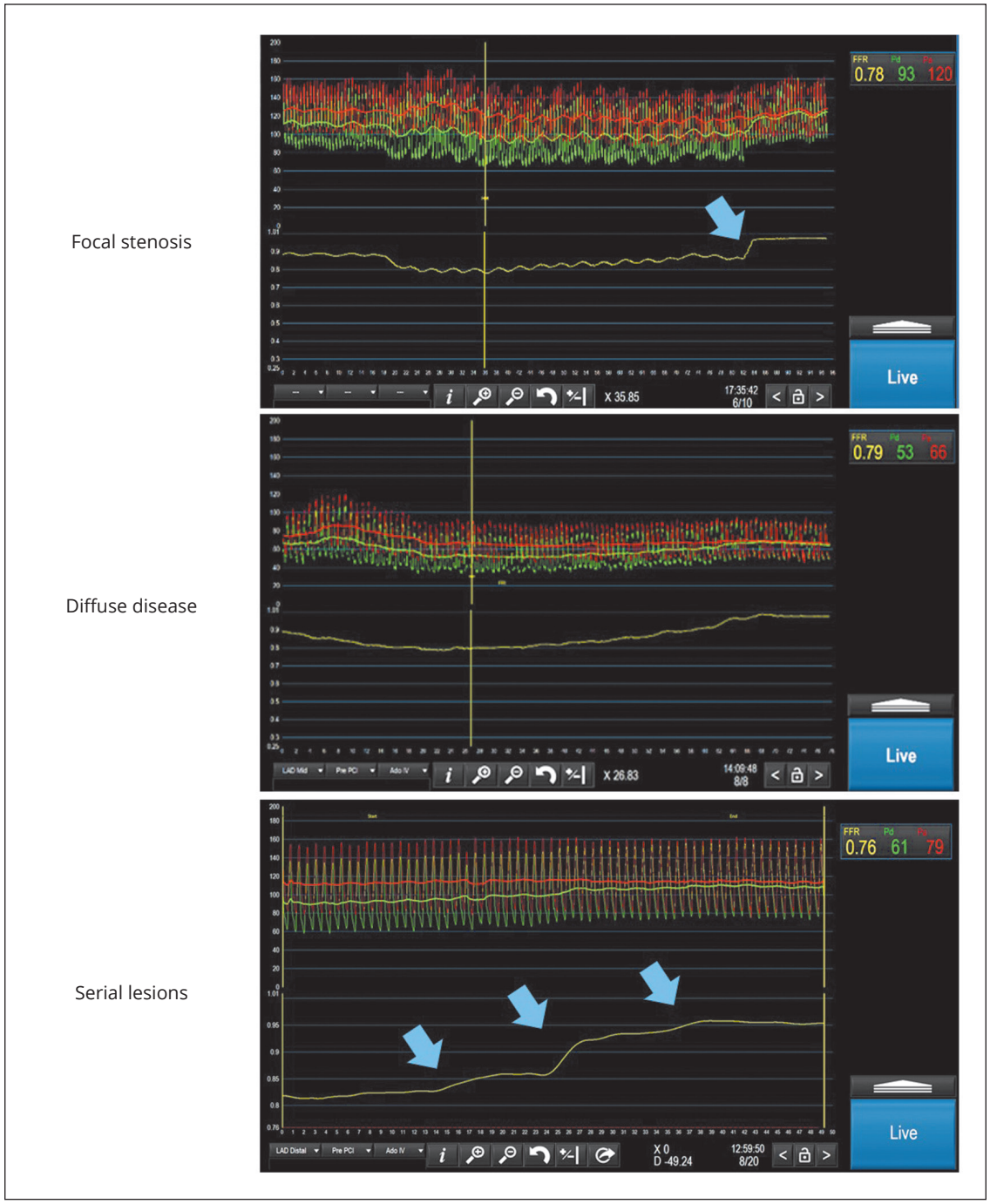

Figure 3.—A PressureWire pullback interpretation of different pattern of coronary artery disease.

is characterized by a progressive decrease of the pressure gradient in a diseased segment ≥20 mm, without clearly identifiable focal lesions (Figure 3). However, the observed distribution pattern often exhibits features of both the focal and diffuse disease patterns. Mixed patterns have been classified in predominantly focal (type I), predominantly diffuse (type II), and balanced

focal/diffuse distribution (type III). Distinguishing between predominantly focal *vs.* diffuse disease has significant implications in the clinical management. Diffuse disease is associated with unfavorable procedural outcomes in terms of both intracoronary physiology and imaging[13] and suboptimal patient-reported outcomes after PCI.[14] Moreover, the disease pattern represents an important determinant of RFR/FFR discordance. In case of discrepancy, abnormal RFR tends to be associated with predominantly diffuse disease, whereas abnormal FFR tends to be associated with predominantly focal pattern of disease.[3] Several tools have been developed to improve the characterization of the distribution pattern of CAD. Currently, none of these tools demonstrated superiority over qualitative assessment. Therefore, until further studies and data are available, we recommend incorporating qualitative information into daily practice.

Structural coronary microvascular dysfunction

Structural CMD is consequent result of adverse arteriolar remodeling, which includes capillary rarefaction and perivascular fibrosis. This leads to increased microcirculatory resistance and insufficient coronary flow increase in response to myocardial oxygen demand. Structural CMD is defined in presence of impaired CFR (<2) and IMR (>25) values.

Functional coronary microvascular dysfunction

Functional CMD is characterized by an impaired vasodilatation with a CFR (<2), but with a preserved IMR (≤25 units). This suggests the inability of coronary microcirculation to enhance coronary flow adequately through vasodilation in response to increased myocardial oxygen demand, despite having low microvascular resistance.

Compensated (initial) structural coronary microvascular dysfunction

In daily clinical practice, it is not uncommon to encounter patients with normal CFR values (>2) but abnormal IMR values (>25 units). This condition is less well-defined and standardized compared to the previously mentioned dysfunctions, and ongoing studies are necessary to gain a better understanding of its prognostic implications. Nevertheless, it is plausible that this condition reflects an early damage to the microvascular structure, which is still compensated as indicated by CFR values slightly above the pathological threshold. Although further confirmation is needed, it is possible that early identification of this condition, along with appropriate treatment and lifestyle interventions, prevent its progression into more severe and permanent forms of CMD.

Epicardial vasospasm

Epicardial spasm is defined as the presence of all the following: typical chest pain, ischemic ECG changes and ≥90% epicardial coronary artery vasoconstriction compared to angiography after nitroglycerin administration (Table I).[15] If the pressure wire is left in place and RFR is monitored, a significant reduction in the RFR value from baseline can be observed (Table I). The test result is considered inconclusive if only one or two of these criteria are met.

Microvascular spasm

Microvascular spasm is defined as the presence of typical chest pain, ischemic ECG changes, but without evidence of epicardial spasm (Table I).[16] During conventional angiography, a slowing of contrast media flow in the epicardial vessel can be observed. If the pressure wire is kept in place and bolus thermodilution is performed, an increase in microvascular resistance can be observed (Table I). Patients with myocardial bridging are prone to both epicardial spasm and microvascular dysfunction.

Post-PCI epicardial vessel assessment

Coronary revascularization is performed with the goal of restoring blood flow and preventing residual myocardial ischemia. PCI should be considered successful if both these conditions are satisfied. However, it is unfortunate that even when angiographic results appear satisfactory, up to 30% of cases exhibit suboptimal physiological findings after PCI.[17] Based on available data, it is crucial to achieve a final post-PCI FFR value >0.90 (or higher) to ensure optimal outcomes. Recent evidence suggests that this

specific cutoff is considerate appropriate for the right coronary artery and left circumflex, but its applicability to the left anterior descending artery (LAD) is uncertain. Due to the distribution and hydrodynamic effects associated with the position of the LAD, a post-PCI FFR value >0.86 should be considered acceptable. Suboptimal post-PCI physiology may be attributed to several factors, including stent-related complications, residual focal or diffuse disease in the untreated segments of the vessel, coronary spasm, or increased vasomotor tone. Understanding the mechanism of abnormal post-PCI physiology is key in optimizing procedural outcomes. In this regard, pressure wire pullback provides essential information, and it is recommended to spot residual pressure gradients. When the residual pressure gradient is localized within the stented segment of the vessel, intracoronary imaging has revealed that several factors such as geographical miss of the plaque, stent malapposition, stent underexpansion, plaque or thrombus in-stent prolapse, and major stent edge dissection may contribute to suboptimal post-PCI FFR.[18] The Oxford Optimization of PCI (OxOPT) study addressed stent-related anomalies by employing additional stenting and/or post-dilatation, resulting in a significant FFR increase in most cases (from 0.80±0.02 to 0.88±0.01). In case of residual diffuse disease beyond the stent, it may be necessary to accept because further intervention is unlikely to improve the functional result and it may increase the risks associated with overstenting.[3,19] However, in cases where the residual pressure gradient is attributed to focal stenoses that were initially overlooked during the initial angiographic or functional pre-PCI assessment, further PCI can lead to improved procedural outcomes. To identify the location of any potential pressure drop, it is advisable to mark the distal and the proximal stent edges during the pullback maneuver.[20]

Post-PCI assessment of microcirculation

After PCI, there are potential risks such as distal embolization of plaque debris and thrombotic aggregates, side branch occlusion or flow-limiting dissection, which can lead to myocardial damage. Moreover, pre-existing microvascular dysfunction has been linked with myocardial injury after PCI.[21] Both baseline and post PCI-IMR values are associated with PCI-related myocardial damage. Notably, PCI-related microvascular dysfunction can influence post-PCI FFR and it may hamper the accuracy of post-PCI FFR prognostic stratification. Murai *et al.* demonstrated that IMR was an independent predictor of post-PCI FFR.[22] Therefore, pre- and post-PCI microcirculation assessment could provide a more complete picture of the physiological findings and contribute to better risk stratification for cardiovascular events of patients undergoing revascularization.[23] Patients with negative post-PCI FFR and IMR values have a higher likelihood of being free from adverse events and residual angina. Conversely, patients with positive post-PCI FFR values are at higher risk of target vessel failure, whereas those with positive post-PCI IMR values may experience residual angina.

In-depth exploration #FullPhysiology in daily cases

Patient with ANOCA

Patients who are admitted to cath-lab with angina symptoms and exhibit non-obstructive coronary artery disease during conventional coronary angiography require a comprehensive assessment. This assessment aims to identify the underlying pathophysiological mechanism and facilitate the implementation of personalized medical therapy.[4,5] Invasive functional assessment plays a pivotal role in guiding the therapeutic approach in such cases, allowing the selection of appropriate pharmacological classes based on the main physiopathology pathway involved. The advantages of this approach lie in angina relief and quality of life, and the potential reduction of hospital admissions and healthcare costs. Although the evidence is limited ongoing studies are further contributing to our understanding of ANOCA diagnosis and guiding the development of tailored treatment strategies, which can be summarized as follows:

- a multidomain lifestyle intervention should be implemented to manage cardiovascular risk factors, including smoking cessation, angiotensin converting enzyme inhibitor, lipid-lowering

treatment, dietary modifications, weight control, and exercise training;

• in patients with compensated, structural, or functional CMD, beta blockers (BB) are the first-line therapy. BB are effectively control angina, especially if effort-angina is the predominant. Moreover, they showed to improve exercise tolerance. Nebivolol, in particular, has been suggested due to its ability to promote nitric oxide production at the endothelial level. Similarly, non-dihydropyridine calcium channel blockers (CCB) are effective antianginal therapies and may be used in patients who are intolerant to BB or when concurrent microvascular spasm has been identified. Conversely, nitrates should be avoided due to the potential stealing effect related to vasodilation. Additional treatment options include nicorandil (a potassium channel activator with effective coronary microvascular dilatory effects), ranolazine (a selective late-sodium current inhibitor that showed beneficial effects in patients with impaired CFR[24]), ivabradine, trimetazidine, and low doses of tricyclic antidepressants, such as imipramine and xanthine derivates;[6]

• in patients with positive vasoreactivity test, dialtiazem or verapamil are considered first-line therapies due to their demonstrated effect in improving angina status and reducing major adverse cardiovascular events (MACE). It is important to note that discontinuing CCB therapy in this context has been associated with increased risk of MACE.[8] While long acting-nitrates have been traditionally used as anti-anginal management of vasospastic angina, their benefits have come into question.[25] Conversely, BB should be avoided in patients with vasospastic angina, as they may potentially worsen vasospasm by unmasking coronary alfa-receptors.

Patients with recurrent angina despite complete revascularization

Patients with obstructive CAD who underwent complete revascularization continuing to experience recurrent angina require a comprehensive evaluation using #FullPhysiology to determine the underlying pathological mechanism causing these recurring symptoms. Initially, pressure wire pullback should be performed in the treated vessel. It is preferable to perform FFR pullback because it amplifies the gradients and improves the signal to noise ratio, enabling the detection of residual functionally significant lesions even in the presence of minor angiographic narrowing. Furthermore, thorough evaluation of microcirculatory and vasomotor function is essential in this scenario, particularly if angina occurs at rest. It should be noted that symptoms may not solely be attributable to epicardial narrowing caused by atherosclerosis, as CMD and/or vasomotor dysfunction often coexist with obstructive CAD. Tailoring medical therapy based on invasive functional results (CFR, IMR, ACh vasoreactive test) can lead to improved control of symptoms and enhance overall quality of life for patients. Furthermore, this approach can facilitate better patient understanding of their coronary disease, reduce the need for multiple noninvasive ischemia-inducing tests, and minimize the requirement for repeated coronary angiography.

Non-culprit lesion of patients with myocardial infarction and multivessel disease

The utilization of coronary physiology to guide non-culprit revascularization in patients with myocardial infarction and multivessel disease has been the subject of extensive discussion due to conflicting results.[26,27] Nonetheless, coronary physiology guided revascularization of non-culprit lesions can help avoid unnecessary procedures in case of non-ischemic findings, thereby reducing the risk of procedure-related complications. #FullPhysiology serves as a valuable tool in enhancing the accuracy of intracoronary functional assessment of non-culprit vessels. In the subacute phase of MI, the coronary microcirculatory function of non-infarct related arteries may show transient abnormalities that tend to recover over time. A substudy of the Reducing MicroVascular Dysfunction in Revascularized STEMI Patients by Off-target Properties of Ticagrelor (REDUCE-MVI) trial revealed noteworthy findings regarding coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) in non-culprit vessels. Specifically, one month following the index procedure, CFR showed a significant increase, while IMR tended to decrease. Interestingly, during the acute phase

of myocardial infarction, there was an observed blunted hyperemic response to adenosine, leading to a significant decrease in FFR in the non-culprit vessel at the 1-month follow-up.[28] Conversely, Mejía-Rentería *et al.* observed that the hyperemic flow was preserved in the subacute phase of myocardial infarction, supporting the use of FFR in this setting.[29] Notably, non-culprit vessels exhibited similar IMR values compared to a matched cohort of stable patients, whereas CFR was lower in the non-culprit lesions. Interestingly, the reduction in CFR was primarily attributed to an increase in resting coronary flow. This observation may have implications for NHPR in non-culprit vessels. In particular, a tendency for overestimation of lesion severity was observed in the iSTEMI study using iFR, where the classification agreement between the acute phase and follow-up iFR values was only modest (78%).[30] In practice, applying #FullPhysiology may assist the operator in selecting the most appropriate tool to guide the decision-making. FFR should be preferred over NHPR if IMR is normal (≤25 units), the hyperemic response to adenosine is preserved (RRR>2) and CFR is impaired because of significantly increased resting transit time. Conversely, NHPR may be preferred over FFR in case of significant increase of microcirculatory resistance (IMR >25 units) or a blunted hyperemic response to adenosine.

Conclusions

#FullPhysiology represents a comprehensive, step-by-step, systematic approach to patients with suspected coronary disease, aiming to overcome the simplistic and underutilized application of pressure wire indexes. The ultimate objective of #FullPhysiology is to advance precision medicine by enabling accurate diagnosis and tailored treatments through maximizing the potential of the pressure/thermodilution wire. Importantly, the implementation of #FullPhysiology does not significantly increase costs or procedural time compared to standard coronary functional assessment. By adopting a systematic use of #FullPhysiology, we can enhance our understanding of each patient's specific pathophysiology and tailor interventional procedures and medical therapy. This approach has the potential to reduce angina relapsing, hospital admissions, and improve patients' overall quality of life.

Key messages

- Identifying the predominant pathophysiology responsible for myocardial ischemia enhances precision medicine by providing accurate diagnosis and facilitating tailored interventional or medical treatments.
- #FullPhysiology is a comprehensive and systematic approach for the evaluation of patients with suspected coronary disease using PressureWire technology, embodying precision cardiovascular medicine.
- Such refined methodology entails assessing epicardial flow-limiting disease, longitudinal physiological vessel analysis, microvascular and vasomotor dysfunction, as well as post-percutaneous coronary intervention physiological results.

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