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Fractional flow reserve and non-hyperemic indices: Essential tools for percutaneous coronary interventions

Amine Mamoun Boutaleb, Chadi Ghafari, Claudiu Ungureanu, Stéphane Carlier

Abstract

Hemodynamical coronary artery lesions evaluation is an important diagnostic step to assess the functional impact of an intermediate coronary artery stenosis. Fractional flow reserve (FFR) received a class IA recommendation from the European Society of Cardiology for the assessment of angiographically moderate stenosis. FFR evaluation of coronary artery disease offers improvement of the therapeutic strategy, deferring unnecessary procedures for lesions with a FFR > 0.8, improving patients' management and clinical outcome. Post intervention, an optimal FFR > 0.9 post stenting should be reached and > 0.8 post drug eluting balloons. Non-hyperemic pressure ratio (NHPR) measurements have been validated in previous studies with a common threshold of 0.89. They might overestimate the hemodynamic significance of some lesions but remain useful whenever hyperemic agents are contraindicated. FFR remain the gold standard reference for invasive assessment of ischemia. We illustrate this review with two cases introducing the possibility to estimate also non-invasively FFR from reconstructed 3-D angiograms by QFR or vFFR. We conclude introducing a hybrid approach to intermediate lesions (DFR 0.85 – 0.95) potentially maximizing clinical decision from all measurements.

INTRODUCTION

Coronary artery angiography remains the cornerstone for coronary artery disease (CAD) assessment confirming stenoses or occlusions of epicardial coronary arteries. These are often subjectively estimated by the operator who visually evaluates the percentage of intraluminal narrowing of the artery. Quantitative coronary angiography improves this guess work, optimizing devices sizing by accurately measuring the length and reference diameter of coronary stenoses [1]. However, this anatomic evaluation remains often insufficient requiring adjunctive information provided by a functional assessment. The presence of inducible ischemia in patients with CAD has been associated with adverse clinical outcome with risk stratification based on the extent of myocardial ischemia [2, 3]. However, this was not confirmed in the more recent Ischemia trial where the severity of ischemia was not associated with an increased risk after adjustment for CAD severity [4].

Medical treatment is efficient in relieving anginal symptoms related to myocardial ischemia while revascularization improves downstream coronary blood flow and therefore relieves myocardial cells from the changes related to anaerobic metabolism[5].

Although current guidelines have implemented non-invasive stress testing prior to percutaneous interventions (PCI), the frequency of upstream testing remains low [6].

Fractional flow reserve (FFR) is used during coronary artery angiography to directly measure the pressure drop across an epicardial stenosis [7]. It is nowadays considered as the gold standard for the detection of myocardial ischemia and is recommended by the ESC 2018 myocardial revascularization guidelines [8]. This invasive diagnostic tool is the current standard of care for the functional assessment of lesion severity in patients with intermediate grade stenosis (40%-90%) without evidence of ischemia. FFR-guided PCI has been shown to be superior to angiographic guided PCI as well as its safety for PCI deferral of non-functionally significant stenosis [9, 10] [11].

With the increasing use of physiological assessment for CAD, new pressure-derived indices have emerged to guide PCI and to overcome some of the issues of FFR. Non-hyperemic pressure ratios (NHPR) are now an integral part of most current pressure wire systems and are widely used in the majority of catheterization laboratories. These

indices evaluate coronary artery functional severity over either the diastolic phase or the whole cardiac cycle. A good correlation with FFR was found for the instantaneous wave free ratio (iFR), the first NHPR developed, with an 80% approximative accuracy [12–14]. Numerous NHPR are now available and are numerically equivalent with a common threshold [15].

I. FRACTIONAL FLOW RESERVE:
1. Definition of FFR:

Fractional flow reserve is defined as the maximal achievable blood flow in the presence of an epicardial coronary stenosis divided by the maximum flow in the same healthy vessel if there was no obstructive epicardial disease[16]. It can be estimated by the simplified ratio of the coronary artery pressure downstream an epicardial stenosis over the aortic pressure during maximal hyperemia, taking into account the central venous pressure, hence FFR estimates the percentage of maximal blood flow limited by the presence of an epicardial stenosis. It is expressed by the following relationship, considering a constant and minimal coronary arterial bed resistance:

$$FFR = (Pd-Pv)/(Pa-Pv)$$

where Pd is the pressure recorded downstream the epicardial stenosis, Pa is the aortic pressure and Pv the central venous pressure (Figure 1) [17].

Maximal hyperemia is generally obtained by intravenous or intracoronary perfusion of adenosine. Other agents such as Regadenoson or Papaverine can also be used [18, 19]. The coronary vasodilator agent dose and side effects perfusion are presented in Table 1. Intracoronary Adenosine is the preferred vasodilator agent inducing a quick (5-10 s) response to maximal hyperemia, however it may cause transient atrioventricular block, chest discomfort and shortness of breath and is contraindicated in patients presenting

with chronic pulmonary obstructive disease. A more stable hyperemia is achieved using an intravenous perfusion [20]. Regadenoson (Rapiscan) is a selective agonist of the receptor A2 of adenosine with a 10-fold lower affinity for the A1 adenosine receptor. Its injection produces coronary vasodilatation and increases coronary blood flow. Given its selectivity for the A2 receptor, cardiac conduction sides effects are less frequently observed and is generally well tolerated in patients with chronic obstructive pulmonary disease (COPD) [21, 22]. A good correlation between both agents has been reported in multiple trials [23, 24].

The first proposed FFR threshold was 0.75. The issue of a grey-zone decision between 0.75 and 0.80 has been solved recommending now a threshold of 0.80[25]. An accuracy of 90% was reported in the FAME trial [10]. To revascularize between 0.75 and 0.80 remains debatable but should be considered in function of the potential MACE rates of the patients presenting proximal or mid coronary artery stenosis [26].

The cutoff threshold values have been validated in multiple trials comparing non-invasive measurements to FFR and the reversal of the presence of ischemia after PCI [7, 25, 27, 28].

2. Technical aspect of FFR measurement:

The majority of PCI are performed using 6 French guiding catheters (GC). All FFR systems are with a low profile allowing to use already 5 Fr GC but care must then be taken to optimize the quality of phasic pressure recordings, flushing the catheter with saline solution.

FFR systems are based either on a piezoelectrical or an optical sensor. Both types of pressure sensors generate a membrane deflection through the pressure, inducing either an electrical charge or a phase delay in a reflected light beam.

These systems have been well validated, with a reduction in pressure drift reported with the optical method [29, 30]. Moreover, the latest versions of optical pressure

guidewires enable its use as a workhorse guidewire for PCI by disconnecting and reconnecting the system.

The first step consists of zeroing the fluid-filled aortic pressure and the FFR pressure system *ex vivo* to the atmospheric one, ideally at the level of the right atrium. The pressure wire is then advanced few millimeters beyond the tip of the GC. Both pressure curves are equalized with the introducer needle off the Y connector [31]. Contrast may dampen the catheter waveform pressure, hence flushing the system with saline is mandatory before pressure measurements.

After intracoronary administration of isosorbide dinitrate, FFR and NHPR can be measured with the wire advanced at least 3 vessels diameters distal to the stenosis. In case of multiple stenosis and diffuse disease, a recording of the pressure during a pull back of the wire identifies spots with significant pressure changes where a PCI might be useful. At the end, a possible drift (significant if >3 mmHg) of the FFR system is carried out [32]. Figure 2 represents the display screen of the POLARIS monitor (Boston Scientific, Marlborough, MA, USA) using the COMET™ wire, showing a non-significant FFR value of 0,82.

Several intracoronary pressure systems are currently available on the market: WaveWire™ (Philips Inc, Eindhoven, the Netherlands), COMET™ (Boston Scientific, Marlborough, MA, USA), PressureWire™ (St. Jude/Abbott, St. Paul, MN, USA), NAVVUS RXi® (ACIST Medical Systems, Inc, Eden Prairie, MN), TruePhysio™ (Insight Lifetech) and OptoWire Deux (Opsens medical, Quebec, Canada) with fewer drift [30]. The COMET trial comparing the COMET™ and the PressureWire™ found similar results in terms of safety and performance [33]. The RIPCORD 2 trial was a large prospective, multicenter study where investigators used the COMET™ wire to evaluate a FFR-guided revascularization strategy in patients presenting with stable CAD or NSTE-ACS.

In most guidewires, the pressure sensor is usually located at the proximal part of the radiopaque tip. In the case of the NAVVUS RXi®, the pressure sensor is located 5 mm above the distal tip of the microcatheter.

Conventional pressure wires have generally less torque control, flexibility and crossing ability than workhorse or specialized guidewires. Therefore, the NAVVUS RXi® and TruePhysio™ are microcatheters to be used with any workhorse wire to overcome these issues, with debatable opinions [34–36]. In vitro assessment of the novel 0,014'' OptoWire™ showed improved pushability, steerability and torquability in comparison with regular PCI wires, offering reliable pre and post PCI hemodynamic assessment [37].

3. Validation of Fractional Flow Reserve measurement:

Myocardial ischemia is defined as a lack of coronary blood flow with electrical, functional, metabolic and structural consequences for the myocardium. The imbalance between oxygen supply and myocardial oxygen need is the central point of interest that should be improved with optimal medical therapy and/or coronary artery revascularization [38].

The FFR was first introduced by De Bruyne & Pijls and their colleagues who demonstrated the initial threshold of 0.75 demonstrating reversal of non-invasive stress tests after performing PCI[7].

The DEFER trial investigated the appropriateness of not stenting a functionally non-significant coronary stenosis and showed the safety to defer PCI when the FFR was > 0.75 [39].

Tonino et al. showed in the FAME I trial that FFR-guided PCI is associated with fewer major adverse cardiovascular events (MACE) and less resource utilization compared with angiography-guided PCI in patient with multivessel disease using a threshold of 0.80 [40].

De Bruyne et al proved in the FAME II trial that the addition of FFR measurements to optimal medical therapy in patients presenting stable CAD is superior to best medical therapy alone [41].

In the context of non ST-elevation acute coronary syndrome (NSTE-ACS) FFR guided revascularization of non-culprit lesions may be used during the index procedure to evaluate the need for further revascularization therapy [42].

The meta-analysis of Knuuti *et al* evaluated the performance of non-invasive stress test to rule-in and rule-out significant CAD choosing as reference invasive coronary angiography with FFR measurements. They concluded that imaging methods are clearly superior to stress ECG. Functional imaging techniques including positron emission tomography (PET), cardiac magnetic resonance (CMR) and single-photon emission computerized tomography (SPECT) offer the best diagnostic performance even if the anatomical correlation is poor as shown in table 2 [43].

All these major trials support the class IA recommendation to assess the hemodynamic relevance of intermediate coronary artery disease by FFR and as class IIB in multivessel disease evaluation [44]. In fact, both the European and American guidelines state that patients undergoing coronary angiography without prior ischemia assessment should have invasive hemodynamic test (FFR or NHPR) to optimize the revascularization strategy [45].

4.FFR features and applications:

The theoretical value of FFR is 1 in a normal healthy epicardial coronary artery. FFR decreases with increasing epicardial stenosis severity. This index is not influenced by systemic hemodynamics and remain stable in case of systemic pressure, heart rate and left ventricular contractility changes [46]. In addition, Jonhson *et al* found a 98% reproducibility rates [47]. Among its other advantages, FFR takes into account the contribution of collaterals by reflecting both antegrade and retrograde blood flow during maximal hyperemia [48].

Considering the critical prognostic importance of left main (LM) stem disease and its difficult angiographic assessment, the revascularization of intermediate LM should be guided by FFR or intravascular imaging [49]. Generally, LM disease is frequently associated with other stenoses of the coronary artery tree. FFR could therefore stratify

patients for surgical or percutaneous revascularization taking into account downstream lesion implication[50, 51].

FFR can guide revascularization of non-culprit lesions in patients presenting with acute coronary syndromes (ACS). The FAME trial demonstrated that the benefits of FFR-guided PCI were similar in patients with unstable angina or NSTEMI and chronic coronary syndrome [52]. However, controversial findings were reported by Liou *et al.* advocating in depth assessment of FFR guided PCI in ACS context [53].

Tandem lesions are defined by two 50% or more stenosis separated by an angiographically normal segment. In serial lesions, FFR measurements of all stenoses is carried out, followed by a slow pull back of the FFR wire under steady state hyperemia and fluoroscopic view to determine the exact drop of pressure localization [53]. These cases remain challenging to interpret considering the interaction of downstream coronary artery stenosis: the FFR value of the proximal lesion might be overestimated and equations to predict FFR for each stenosis have been reported using the coronary wedge pressure, measured with an inflated balloon[54, 55]. For a tandem lesion, NHPR are easier and more precise in assessing the respective significance of each stenosis. Table 3 summarizes the major trials evaluating the outcomes of FFR in intermediate coronary lesions of LM and non LM lesions.

5. FFR post-interventions:

In an otherwise healthy vessel with only a short stenosis, the FFR after stenting should theoretically revert to 1. However, atherosclerosis affects diffusely most of the coronary vessels and FFR values will therefore be affected by a mix of potential sub-optimal stenting (e.g. a remaining sub-expansion of the stent in a calcified lesion), issues at the edges (e.g. a dissection), or a remaining stenosis outside the stented segment. In the DKCRUSH VII registry the only statistically significant predictor of target vessel failure (TVF) at 3-year was a post-PCI FFR <0.88[56]. Hwang *et al* reported an optimal cut-off post-PCI FFR predicting TVF of <0.82, associated with a 10.9% rate of events while it was only 2.5% when the post-PCI FFR was ≥0.82 in the left anterior descending artery

(LAD). Similarly, a FFR post PCI<0.88 was associated with 8% of TVF, but 1.9% with a FFR$\geq$0.88 in a non-LAD vessel [57]. Conversely, Diletti *et al* more recently reported among 1000 patients that a sub-optimal FFR<0.90 was measured in 38% of the treated vessels. At 2-year follow-up, in a patient level analysis, there were no increase in major adverse cardiac events. A vessel level analysis demonstrated a significant doubling of target vessel revascularization (P = 0.030) and a trend towards a higher stent thrombosis rate (HR, 2.89 [95%CI, 0.88–9.48], P = 0.08) [58]. After balloon angioplasty without stenting, favorable outcomes have been associated with a final FFR ranging between 0.90 and 0.75. An optimal FFR cut-off of 0.80 was reported for drug eluting balloon angioplasty without stenting[59].

II. NON-HYPEREMIC PRESSURE RATIOS:

1. Rational of instantaneous wave-free ratio

FFR has become the gold standard invasive diagnostic tool to guide coronary artery revascularization. Understanding the mechanisms of fractional flow measurement is essential before performing any physiological assessment of CAD. Coronary resistance fluctuates during the cardiac cycle in a phasic pattern, due to the compression and decompression of the myocardium. A specific period, not affected by forward and backward effects, named instantaneous wave free period, has been identified [60]. The instantaneous wave free ratio (iFR) concept relies on the theory that intracoronary resistance is naturally low and constant during this wave free period allowing to compute a reliable pressure index. This particular cardiac window has been defined in the ADVISE (Adenosine vasodilator independent stenosis evaluation) trial to start 25% after the start of the diastolic phase and ends 5 ms before the systolic phase start. iFR is measured without the need of hyperemia/adenosine and the 0.89 threshold corresponding to ischemia has been validated *vs* FFR measurements[61].

2. Validation studies:

The ADVISE study assessed the accuracy of iFR compared with FFR. A close correlation was found between both indices with good diagnostic performance (receiver-operating characteristic (ROC) area of 93%, at FFR< 0.8) with specificity, sensitivity, negative and positive predictive values respectively at 91%, 85%, 85% and 91% [61].In the CLARIFY study, an agreement of 92% between iFR and FFR values was found. In the four lesions with mismatch between the two indices, the hyperemic stenosis resistance (HSR) was correlated either to FFR or iFR[62]. In addition, the SWEDEHEART trial highlighted the noninferiority of iFR-guided PCI compared with a FFR-guided PCI [12]. The same finding were reported in the DEFINE FLAIR trial with a reduction in adverse procedural symptoms related to adenosine infusion and shorter time of procedures [13]. A better agreement between iFR than FFR and coronary flow velocity reserve (CVFR) was reported in JUSTIFY-CFR. In 4% of their non-significant iFR values (>0.90) a significant drop in FFR value (<0.75) was noted [63]. Multiple trials have reported an approximative 80% accuracy between iFR and FFR [14, 61, 64].

The ADIVSE II trial reported a strong correlation between iFR and FFR and identified 0.89 as the optimal iFR threshold with an area under the ROC curve of 0.90. This cut-off correctly classified 82,5% of coronary artery stenoses with a sensitivity and specificity of respectively 73% and 87,8%. The hybrid iFR-FFR approach based on a iFR treatment value below 0.85 and deferral above 0.94 showed a better correlation rate of 94,2% [65].

Using respectively 0.89 and 0.80 as cutoffs for iFR and FFR, Modi reported a 25% discordance rate, which is in line with the previous studies. This discrepancy can be lowered to 11% using respectively 0.86 and 0.75 cutoffs[66]. Table 4 presents these different studies.

In contrast, the VERIFY trial revealed only a moderate overall correlation between iFR and FFR with a weak correlation in the clinically important range for decision making, between 0.60 and 0.90. The authors do not recommend the use of iFR for clinical decision making for PCI[67]. We will also personally guide our clinical decisions to revascularize or defer an intervention in our patients using the results of their FFR that

we will always assess in any doubtful result of a NHPR in a grey zone between 0.84 and 0.94.

3. Novel non-hyperemic pressure indices (NHPR):

With the increasing use of invasive hemodynamic assessment of CAD severity, novel non-hyperemic pressure ratios (NHPR) have been proposed by different manufacturers. These indices have been compared to iFR and are summarized in Table 5.

Figure 4 shows the different periods used for NHPR calculation over the cardiac cycle. These indices can be separated into two groups, the ones using the whole cycle and the others using calculating diastolic indices.

The retrospective VALIDATE study showed the diagnostic comparability between resting full-cycle ratio (RFR) and iFR. It is important to note that 12,2% of RFR were measured outside the diastolic phase with a predominant discrepancy rate between both measurements when iFR was > 0.93. This difference was found to be more important in waveforms acquired in right coronary arteries (6,5%)[68]. The REVALIDATE RFR study had the same purpose using a prospective analysis methodology showing a 97,8% overall diagnostic accuracy, sensitivity and specificity. Thus RFR is an alternative diagnostic tool for the guidance of PCI reducing time and cost procedures by avoiding hyperemic agents need [69].

The dPR study found a strong linear correlation between the diastolic pressure ratio and iFR ($r = 0,997$, p<0,001) on one hand and FFR ($r = 0,77$, p<0,001) on the other[70]. The dPR measured with the Optowire (Opsens, Quebec City, Quebec, Canada) showed strong correlation with other NHPR (RFR, iFR) in the RPG study with an $r = 0,84$ [71].

A novel Opsens dPR algorithm using the mean of 4 consecutive beats Pd/Pa ratio at diastole was highly correlated to iFR ($R^2=0,99$) with high accuracy to predict iFR at 95,6%, with a sensitivity of 93,5% and specificity of 96,7% [72]. As reviewed by De Marie *et al.* among the major advantages of the resting indices is the hyperemia drug free evaluation[73].

The cut-off for these non-hyperemic indices is 0.89 with a proportion of discordance ranging between 15 to 20% particularly in proximal vessel subtending large myocardial areas[60]. Theses resting indices were not evaluated in randomized controlled trials but have only been compared in studies to support their clinical use[74, 75].

4. Indications for the use of non-hyperemic pressure ratios:

Following the validation studies described above, NHPR share similar indications than FFR but additional specific clinical scenario's have been investigated. For example, a retrospective study reported how to decide to perform a PCI with iFR in non-culprit lesions of patients presenting with ACS[76].

The iLITRO study found an agreement of 80% between iFR and FFR in left main intermediate stenosis. Intravascular ultrasound imaging (IVUS) was used in cases with discrepancy, using the threshold of 6 mm^2 as a cut-off for revascularization. In discordant FFR/iFR measurements, IVUS showed an MLA <6mm^2 in 69% of the cases of FFR+/iFR-, while in FFR-/iFR+ cases, 40% only had an MLA< 6mm^2. The patients deferred from revascularization with discordant hemodynamic measurements and a negative IVUS evaluation had a low incidence of MACE at follow-up, leading to an iFR-guided LMCA revascularization strategy combined with IVUS in the discordant cases (hybrid approach)[49].

An iFR pullback enables the operator to predict an iFR value after the treatment of a selected stenosis[77]. The comparison of functional PCI results using NHPR in the REFINE-RPG study showed comparable results between RFR, dPR and iFR while reducing the total length of treated lesions using NHPR pullback PCI-guided strategy compared to angiography-guided PCI. The correlation between predicted and actual post PCI NHPR was high ($r = 0,73$) with no difference among NHPR groups [71].

III. THE HYBRID APPROACH:

In multiple scenarios, the use of FFR or iFR alone may not suffice to take the proper therapeutic decision. Hence, a hybrid approach is useful in some clinical scenarios.

Using FFR as the gold standard, NHPR has an average accuracy of 80% resulting in stenoses misclassifications. A combined physiological assessment without adenosine in the first line demonstrated a reduction of the need of intracoronary vasodilator in more than half of the CAD patients in need of functional assessment. Furthermore, the use a 0.86-0.93 cut-off range for iFR improve its positive and negative predictive value to respectively 92% and 91% [63].

The technical aspect of PCI optimization involves proper use of diagnostic and guidance imaging, equipment, techniques, and antithrombotic therapy to achieve optimal patient outcomes. Recently, the value of low post PCI FFR has been linked to poor outcomes related to suboptimal stent placement or remaining disease[78]. In this specific setting, intravascular imaging may be helpful to understand the mechanisms behind inadequate functional improvement. The FFR REACT trial used a post PCI threshold of 0.90 and randomized 291 patients for IVUS or traditional standard of care. This strategy resulted in the improvement of post PCI FFR in 20% of the vessels with a trend for lower target vessel revascularization in the IVUS guided arm ($P = 0,06$).[79]

Intermediate left main coronary artery lesions can be evaluated more thoroughly with either intracoronary imaging (using intravascular ultrasound (IVUS)) or physiological assessment (using fractional flow reserve (FFR) pressure wire). These invasive tools can provide more detailed information on the anatomical severity and hemodynamic significance of the lesions to be discussed in the heart team to improve the decision of the revascularization strategy and its optimization. Park has reviewed in detail the role of pre and post PCI role of IVUS and FFR are well detailed.[80] The ILITRO-EPIC07 study showed that FFR and iFR had an average agreement of 80%, while IVUS was more likely to match FFR's classification of stenosis significance in discrepant cases. Therefore, from a clinician's viewpoint, the best approach for determining if revascularization can be safely deferred in intermediate left main coronary artery lesions is a combination of IVUS and physiology[49].

IV. QUANTITATIVE FLOW RATIO AND FRACTIONAL FLOW RESERVE COMPUTED TOMOGRAPHY:

More recently, physiological coronary assessment has been evaluated with virtual tools computing the flow ratio. Quantitative flow ratio (QFR) is based on the analysis of two angiography views 25° apart at least with minimal superposition between the main and side branches. The QFR uses a mathematical model, the three-dimensional reconstruction and coronary contrast product progress in order to determine the coronary flow. The FAVOR trial was the first to assess this technique, and showed significant correlation with FFR (r = 0,77; p<0,001) with an 80% accuracy using an FFR threshold of 0,80 [81]. Along with these promising results, the FAVOR II Europe-Japan Study found that QFR is superior to angiographic assessment of intermediary coronary artery stenosis using FFR as standard reference [82]. Kasinadhuni *et al* showed that QFR has a superior diagnostic performance compared to the benchmark FFR in evaluating intermediate lesions physiologically outperforming the anatomical percentage diameter stenosis with a significant difference (p < 0.001) [83].

QFR and FFR have excellent consistency and alignment. The ability of QFR to determine the functional impact of coronary disease has been demonstrated in the meta-analysis and systematic review of Cortés *et al* [84]. This new tool, and a similar one, vFFR implemented in the CAAS Worstation (Pie Medical Imaging, Maastricht, the Netherlands) are independent predictors for MACE with beneficial effect of PCI for low QFR / vFFR values[85, 86].

The SYNTAX III REVOLUTION study showed that using Computed coronary tomography angiography to decide between CABG and PCI for coronary artery disease, based on the predicted four-year mortality as indicated by the SYNTAX score II, resulted in high agreement (93%) in treatment decisions, with an "almost perfect kappa" of 0.82, compared to decisions made using ICA [87].

FFR-Computed Tomography (FFR-CT) allows for the measurement of flow across the entire coronary artery bed unlike the usual method which assess the functional significance of a specific coronary stenosis and its upstream segments [88].

These new concepts open new tracks for a better risk stratification and prognosis prediction of patients presenting with coronary artery disease. Their use is increasing in the context of stable CAD for the guidance of percutaneous interventions, but some authors have demonstrated the prognostic implication of a post interventional pan-coronary-QFR evaluation in patients with ACS [89].

We hypothesize that further improvement of these techniques might help the physicians to discriminate atherosclerotic NSTE-ACS from type II Myocardial infarction and myocardial infarction with non-obstructive coronary disease.

A hybrid approach, with a combined use of both anatomical (IVUS) and functional methods to determine the significance of coronary stenosis, could provide a more comprehensive and accurate assessment enabling the operators to take more targeted and individualized decisions. However, the hybrid approach does require additional imaging and testing, which can increase the cost and complexity of the evaluation. Using QFR and IVUS simultaneously, or FFR-CT before, seems appealing as they combined only one invasive evaluation with a noninvasive one, lowering the cost.

We illustrate this concept in a recent clinical case we performed. A stable patient with suspected myocardial ischemia after dobutamine stress test had a coronary angiogram demonstrating a LAD with a moderate long lesion in the proximal and mid part (figure 4) that was evaluated by QFR at 0.83 (figure 5). Regarding these intermediate values, a complementary IVUS evaluation was performed (figure 6) showing a non-significant lesion with a minimal lumen area of was 4.7 mm².

The good agreement between QFR and FFR is illustrated in another case summarized on Figures 7 to 9. On the coronary angiogram of a patient with recurrent clinical

symptoms, we noticed multiple intermediates lesions in the proximal, mid, and distal LAD (Figure 7).

The FFR was positive in the distal LAD at 0,78 and also the DFR was 0,86 (figure 8). The QFRof 0.75 was well aligned with these measurements (figure 9). The relationship between QFR and clinical outcomes, and its cost-effectiveness, requires further prospective validation.

CONCLUSION

Invasive hemodynamic assessment of coronary artery disease is a critical component of a patient evaluation. Today, fractional flow reserve and non-hyperemic pressure ratios guide the physician in optimizing coronary artery tree revascularization therapy. Their development has been backed up by extensive validation studies and physiology and they obtained a class I indication during PCI. The possibility to assess the spatial distribution of epicardial resistances and determine the focal or diffuse characteristics of coronary artery disease is crucial for revascularization therapy decisions. In the case of a difference between the measured fractional flow reserve and any non-hyperemic pressure ratio, we recommend following the results of the FFR and defer an intervention when it will be >0.80.

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