Invasive Techniques for Intermediate Coronary Lesions Assessment

Subjects: Cardiac & Cardiovascular Systems

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Intravascular ultrasound has been used for many years in the assessment of intermediate coronary lesions. This technique uses a piezoelectric transducer that produces ultrasound signals allowing the assessment of the vessel wall and characterizing the atherosclerotic lesions, eliminating the disadvantages of angiography and FFR/iFR. Its main indications in the American College of Cardiology guideline as class IIa recommendation are the assessment of angiographically intermediate stenosis of the LMCA or the mechanisms of stent failure (thrombosis or restenosis) as well as guidance of coronary stent implantation, especially in LMCA or complex coronary artery disease.

functional assessment | intermediate lesions | fractional flow rate | intravascular ultrasound

1. Fractional Flow Reserve and Instantaneous Wave-Free Ratio

Due to the inconveniences derived from the visual estimation of percentage diameter stenosis, both American and European guidelines recommend functional evaluation either in the form of FFR or instantaneous wave-free ratio (iFR) for intermediate lesions in stable coronary artery disease. Some authors suggest even larger intervals for functional approach than those defined in the mentioned guidelines in the 3V FFR FRIENDS study, as 8.7% of lesions with diameter stenosis have less than 50% presented ischemic FFR value [1]. There are other indications of FFR/iFR apart of intermediate lesions' functional assessment, specifically the identification of significant (culprit) lesions in multivessel coronary artery disease or in multiple consecutive stenosis in the same vessel due to its high spatial resolution, and measurement of the functional significance of a stenosis in the presence of a distal collateral flow. The estimation of FFR/iFR can also be achieved non-invasively, derived from computational simulations comparable to those invasively measured [2].

Fractional flow rate is calculated as the ratio between the distal coronary pressure in the presence of a stenosis and the proximal coronary pressure in the absence of a stenosis during maximal hyperemia. The importance of inducing maximal hyperemia is crucial, as this minimizes the resistance of the microcirculation and therefore represents a good approximation of the coronary blood flow. Herewith, it is worth remembering that FFR is a pressure measurement, not a direct coronary flow determination, and that ischemia potential of a stenosis is also influenced by the total morphology of the lesion, the energy loss to turbulence, friction and separation caused by stenosis, and that all these are drawbacks of the technique. Apart from FFR, another parameter for the functional evaluation of a stenosis is coronary flow reserve is the flow ratio during maximal hyperemia and blood flow at rest.

However, there are many limitations of the technique, including left ventricular contractility, heart rate, blood pressure or unsuitable Doppler waves, and therefore no clear cut-off to base the clinical indications. Another important issue to consider in intermediate coronary lesions is microvascular disfunction, as it can induce severe ischemia that can be invasively evaluated in the form of coronary vasoconstrictor as well as vasodilator abnormalities [3]. A recent study from the ILIAS registry (Inclusive Invasive Physiological Assessment in Angina Syndromes) shows a possible role of coronary flow reserve (CFR) in subjects with intermediate FFR of 0.75 to 0.8, where those with CFR ≤ 2.0 and deferred PCI had lower risk of target failure defined as cardiac death, target vessel revascularization or myocardial infarction, compared with those with normal CFR > 2, proving to be a supplementary criteria to strategy patients [4]. Apart from CFR, the index of microvascular dysfunction (IMR) is a better parameter for the evaluation of microvascular resistance and has become the gold standard for the evaluation of microcirculation dysfunction [5][6]. Current commercial wires allow the measurement of both indices of epicardial disease (FFR, RFR) and microvascular dysfunction (CFR, IMR), which are integrated in the same guidewire assuring a more comprehensive evaluation of the intermediate coronary lesions.

Fractional flow reserve or instantaneous wave-free ratio is considered the gold standard for assessing the ischemic potential of a stenosis in stable ischemic heart disease, predicting the clinical benefit of revascularization, but despite the evidence from different clinical trials showing significant reduction to the primary endpoint (death urgent revascularization and myocardial infarction) [7][8][9], and the major indications from the European [10] and American [11] guidelines, its usage is low. In a study by Parikh et al., it is shown that the percentage of subjects with no stress test and intermediate lesions at angiography is very high (61.3%), while in these cases only 16.5% were investigated with FFR [7]. Interestingly, in the same report, reduced FFR usage in daily practice was not dependent on the absence of documented ischemia or the presence of symptoms as expected, revealing that the main reason for underuse remains operator belief in the futility of the technique and not reimbursement policies or training.

2. Intravascular Ultrasound

Intravascular ultrasound has been used for many years in the assessment of intermediate coronary lesions. This technique uses a piezoelectric transducer that produces ultrasound signals allowing the assessment of the vessel wall and characterizing the atherosclerotic lesions, eliminating the disadvantages of angiography and FFR/iFR. Its main indications in the American College of Cardiology guideline as class IIa recommendation are the assessment of angiographically intermediate stenosis of the LMCA [12] or the mechanisms of stent failure (thrombosis or restenosis) as well as guidance of coronary stent implantation, especially in LMCA or complex coronary artery disease. The European guidelines on myocardial revascularization have similar indications, recommending IVUS for approaching the severity of unprotected LMCA, the mechanisms leading to stent restenosis and guiding PCI. As observed, there is no indication to use IVUS to assess intermediate lesions in non-LMCA, mainly because studies showed only moderate correlation between IVUS-derived parameters and FFR values; for non-LMCA intermediate stenosis physiological assessment remains the gold standard.

Minimal lumen area (MLA) is the best parameter calculated using IVUS correlating with a major adverse cardiovascular event (MACE) [13]. If MLA has a good negative predictive value (75–96%), it has low positive predictive value (28–67%), indicating that it is a good parameter to defer intervention, but should not be used as the only indicator for the indication of revascularization, as this induces unnecessary procedures for lesions without significant functional impact. Although many studies have aimed to find an IVUS cut-off equivalent to the ischemic FFR of 0.8 or 0.75, the MLA thresholds largely differ between studies both in LMCA or non-LMCA. Despite the implementation of different IVUS-MLA cut-offs and refinements according to the type of vessel, location and size [14], the accuracy of detecting an ischemic FFR did not surpass 70%. The accuracy of MLA in the evaluation of LMCA stenosis is higher, most probably due to the simple morphology and dimension of this vessel with no branch involvement in the pure disease of LMCA, its functional significance decreasing when there is complex involvement of the ostial left anterior descending or circumflex artery. For LMCA, the MLA largely varied from 4.5 to 5.9 mm^2, with guidelines suggesting 6–7.5 mm^2 threshold for Western subjects according to some prospective multicentric studies showing that a value of 6 mm^2 or greater is safe to defer revascularization in Western patients [15][16] and 4.5–4.8 mm^2 more appropriate in Asian patients [17]

3. Optical Coherence Tomography

Optical coherence tomography is the light modality analogue of IVUS, a technique using near-infrared spectroscopy to detect the structure of the vessel wall. Optical coherence tomography brings several benefits over IVUS such as a quicker acquisition of images with higher resolution, characteristics that allow a better identification of dissection, thrombus, plaque ulcerations, stent malapposition and under-expansion. On the other hand, the reduced wavelength of infrared light and the obligatory flush of the catheter to create a blood-free lumen are associated with decreased depth of imaging, mainly in large vessels such as the LMCA, and the impossibility to assess aorto-ostial stenosis, ectacic or tortuous arteries. The procedural time is increased compared with the setting of the system, but automated workflows are imaged to reduce the total times with automated stent identification, lumen or external elastic membrane contour delimitation. The superiority of OCT over FFR in appreciating the severity of coronary lesions is not proven, and therefore not recommended [18][19]. The OCT-MLA cut-offs are smaller compared with IVUS-MLA, and correspond to the true lumen dimensions [20], being superior as ischemia predictors in non-LMCA in some trials [21][22]. On the other side of the coin, the smaller measured diameters in OCT may lead to smaller stent diameters and worse long-term outcomes. To overcome this limitation of OCT, several strategies have been proposed such as measurement based on the external elastic membrane rounded to the nearest 0.25 [23] or adding 10% or 0.25 mm to the mean lumen diameter [24]. The OCT guided percutaneous interventions showed decreased edge dissection, malapposition and under-expansion with increased final MLA compared with coronarography, resulting in better post-procedural FFR values in the survey DOCTORS [25]. The high axial resolution of OCT allows the measurement of the thin fibrous cap associated in histopathological studies with increased risk of erosion and rupture. In the COMBINE study, which made use of OCT and FFR, a thin cap fibroatheroma of 60 µm or less was associated with more MACEs in diabetic subjects with intermediate coronary lesions, pinpointing the ability of OCT to detect plaque vulnerability. One trial still recruiting patients is researching vulnerable plaque markers in OCT after acute coronary syndromes, collecting in a prospective manner data about OCT characteristics of plaque vulnerability and their correlation with outcomes [26]. The identification of vulnerable plaques and guidance of medical or interventional treatment intensification upon these might be very useful in the future, although there are no randomized trials showing the improvement of cardiovascular adverse events.

4. Emerging Artificial Intelligence Techniques

The emergent new artificial intelligence algorithms for machine learning might overcome the poor accuracy of IVUS or OCT-derived morphological criteria in predicting ischemia-inducing lesions showing good performance without the expenditure of pressure wires [27]. Mathematical fluid dynamics allows the calculation of several flow reserves, including an OCT-based FFR that has excellent accuracy (95.2%) in predicting the need for revascularization in intermediate coronary stenosis [28], or IVUS-based [27]. Another parameter derived by mathematical assumptions of FFR is virtual flow reserve, with its accuracy being investigated in the FUSION trial (NCT04356027), whose results are still awaited. One limitation to these parameters is that collateral flow is not considered, and might have significant impact in the calculation formula. One non-invasive method to detect ischemia is FFR computer tomography angiography (CTA) using novel computational fluid dynamics. Its good accuracy in predicting lesion-specific ischemia has been evaluated in many trials, such as NXT [29] or DISCOVER-FLOW [30]. Quantitative flow ratio (cQFR) is a parameter obtained from two different angiographic projects that generate a three-dimensional quantitative coronary angiography. Using the Gould formula, the pressure drop is calculated in each segment based on geometry and hyperemic flow velocity. In the FAVOR study, three models were used to compute hyperemic flow, and all of these showed good agreement with FFR [31]. Currently, the cQFR based on the TIMI count analysis without pharmacologically induced hyperemia is the standard displaying better accuracies. Although there is much evidence supporting FFR CTA more than CTA alone in the diagnosis of an ischemia-inducing stenosis, its application is limited due to accessibility, technical limitations and costs to intermediate, calcified stenosis or in cases with artefacts. The coupled CTA and FFR CTA proved to be useful even in subjects with intermediate stenosis and Agatston calcium score of above 400 [29].

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