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Fractional Flow Reserve: Should be the Gold Standard for Therapeutic Definition of Coronary Artery Disease?

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The ideal Coronary Artery Disease (CAD) treatment strategy should be defined based on the results from functional and anatomical examinations according to current guidelines [1]. However, this concept is apparently being overlooked by some centers, where percutaneous coronary intervention (PCI) is used to treat coronary lesions with ≤50% diameter stenosis, regardless of their functional repercussion [2-8].

Concern about the unnecessary revascularization of the myocardium motivated some cardiologists to develop the concept of functional PCI, where through the measurement of coronary fractional flow reserve (FFR) the therapeutic decision can be made [9].

Validated for clinical use in 1996 by Nico Pijls [10], FFR has gained popularity in interventional cardiology since then. It is important to note that its indications were strengthened by three studies with a small number of patients (1375 in total) and using different methods: the pioneering study by Nico Pijls the DEFER trial, and the FAME 1 trial [10-12]. Several maximal coronary hyperemia induction methods and cut- off values were used along these studies. Thus, this editorial aims to provoke a reflection to consider if FFR with all this fragility of measurement methodology should be considered gold standard to define a percutaneous treatment.

The FAME 1 trial showed that routine application of FFR to therapeutic decision-making in patients requiring multiple stents with a 0.80 cut-off resulted in a significant decrease in adverse events and hospital costs compared with the strategy guided only by angiography [12]. Such evidence had already been reported in the DEFER trial, wherein the event-free survival of patients with non-ischemia-causing lesions (FFR> 0.80) was high after one and 5-year follow-up, and was similar between groups that performed or did not perform PCI (92 vs 89% and 80 vs 73%, respectively) [11].

The 0.75 value of FFR has high sensitivity and specificity for positive and negative results in identifying ischemia in intermediate coronary stenoses when compared with three noninvasive functional methods [bicycle exercise testing, myocardial perfusion scintigraphy (MPC), and stress echocardiography (ECHO stress)], using intravenous injection of adenosine at the dose of 140 µg/kg/min as an inducer of maximal hyperemia, according to Pijls et al [10].

Adenosine-induced maximal coronary hyperemia has been widely discussed, with no apparent consensus as to the best way to perform this method, as shown in the DEFER II trial (026 test), which evaluated 325 patients using the FFR with a cut-off value of 0.75. Adenosine-induced maximal coronary hyperemia was performed differently from that proposed by Pijls et al. [10]., through an intravenous injection of 140 µg / kg / min combined with 15 µg doses in the right coronary artery and 20 µg in the left coronary artery during intracoronary (IC) infusion. The FAME[12] trial proposed adenosine-induced maximal coronary hyperemia at a dose of 140 µg/kg/min infused into the femoral vein (central access) and using 0.80 as cut-off value [13,14].

The hyperemia induction method for FFR measurement has not yet been carefully standardized (Intravenous (IV), Continuous (CI), Peripheral (PI), or Central Infusion (CI), combined doses, duplicate doses), Lastly, which is the FFR reference value for defining the treatment of a disease as aggressive as CAD?

What is the optimal (FFR) cut-off point for ischemia detection?

According to Pijls et al [10], the cut-off point for ischemia detection with 93% accuracy is 0.75, showing that values assessed by FFR measurement lower than 0.75 are always virtually associated with myocardial ischemia, whereas values higher than 0.75 are almost never associated with ischemia. Shal and cols [15] analyzed 18 studies that used noninvasive, functional tests (Bicycle exercise testing + MPC + ECHO stress), comparing the

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results assessed by FFR measurement, and the cut-off values ranging from 0.67 to 0.75 were best associated with ischemic areas. However, the cut-off point was set at 0.80 to increase ischemia detection sensitivity to almost 100%, based on the FAME trial [12].

It should be noted that FFR was validated as class IA in guidelines [16] using two cut-off points, 0.75 and 0.80, creating a dichotomy, and the concept termed the grey zone. Thus, stenoses with FFR values within this range are ultimately interpreted as dubious among the interventionist community. Consequently, keeping patients on conservative treatment under these circumstances is known to have a worse prognosis [17].

Petraco et al [18] suggested that the grey zone of the FFR measurement ranges from 0.75 to 0.85. In clinical practice, this means that each time a single FFR measurement falls within these two values, the recommendation for revascularization guided by this method might change if the measurement is repeated 10 minutes later. The closer to 0.80 the FFR result is, the higher this likelihood will be. Furthermore, in 2013, Tarkin et al [19] published a study showing that FFR measurements should only be performed when a stable hyperemia state is reached for ≥ 60 seconds during intravenous adenosine infusion. This study assessed that changes in systemic Blood Pressure (BP) caused by intravenous adenosine may lead to changes in the classification of the lesion based on the FFR measurement, affecting the clinical decision. Such changes were observed in 9% of cases, with differences when performing the measurements at peak values and under stable hyperemic conditions,using the threshold of 0.80 and in 5.2% of cases using the threshold of 0.75. This method was used in the DEFER and FAME trials, according to the authors [11,12]. However, there is no reference to microcirculation, nor to changes in peripheral resistance and compliance with changes in coronary perfusion pressure, nor to the FFR measurement at different time points in the aforementioned studies methodology. As an example, the DEFER trial[11]used two adenosine infusion methods, IV and CI. It should be noted that such situations are not included in the current guidelines [16].

Another key issue that was ignored or overlooked in the main protocols is the caffeine regimen for FFR measurement. Caffeine is known to attenuate the effects of adenosine, and its use should be contraindicated prior to these measurements [20-25]. Sparv et al showed that using caffeine 6 hours before FFR measurement by adenosine-induced maximal coronary hyperemia might significantly affect the results.

For reflection

This editorial note discussed the use of FFR measurement as the gold standard method for defining the treatment of coronary artery disease. This is motivated by the concern regarding an unfavorable outlook of percutaneous treatment for CAD, considering the fact that many patients are no longer being treated based on the information provided by FFR measurement, which remains less reproducible, either because the hyperemia induction method is still not standardized, or because of the lack of an objective definition of a cut-off point. These issues must be discussed along with the need for conducting studies with a direct comparison between FFR measurements and noninvasive functional methods in patients with moderate and severe coronary disease. There is a risk of an exponential increase in the number of cardiac adverse events, which could be avoided through improved evaluation, having them great impact on health care. Finally, should we forgot the results of ischemia detected by non-invasive methods and just accept those detected by FFR?

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