Fractional Flow Reserve in Diabetics: Does It Have an Expiry Date?

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Assessing the clinical importance of intermediate coronary stenosis, defined as a luminal obstruction of 40% to 70%, is a challenge for the interventional cardiologist. Coronary angiography correlates poorly with the functional importance of epicardial coronary disease, especially in patients with stenosis at the threshold of significance. Post-mortem studies have demonstrated that the coronary lumen area only decreases when atherosclerotic plaque values are above 40%. This event is due to the vessel undergoing positive remodeling during the atherosclerotic process.[1] Another potential source of error lies in the actual methodology used in calculating the severity of coronary stenosis. Thus, the percentage of stenosis is normally calculated as the ratio between the minimum luminal diameter at the site of obstruction and a reference diameter considered "normal," that is, without disease.[2] Obviously, in the case of diffuse disease, it is very difficult to establish a disease-free reference diameter, which can lead to underestimating the degree of coronary obstruction. Other sources of error are stenosis in tortuous arteries, in bifurcations, with overlapping branches, or highly focal "diaphragm-like" stenosis. This is compounded by the not inconsiderable degree of variation between observers in the qualitative calculation of the degree of obstruction. The calculation of the fractional flow reserve (FFR) has helped to resolve many of these limitations. The FFR is defined as the ratio between the peak coronary flow in the stenotic artery and the peak coronary flow in the same vessel in the theoretical absence of obstruction.[3,4] This should be calculated during maximum arteriolar vasodilation, which establishes the minimum myocardial resistance in the area under study. This is usually achieved by the continuous intravenous administration of adenosine over 1-2 min. The FFR is independent of changes in heart rate and blood pressure and takes into account the collateral circulation.[5] An FFR value <0.75 correlates with ischemia detected using non-invasive tests.[3,6] Similarly, several studies[7,8] have demonstrated the safety of deferring revascularization for intermediate stenosis with FFR values >0.75. The calculation of FFR is limited by the presence of microvascular dysfunction. In this case, maximal hyperemia may not be achieved and thus the FFR value could be overestimated.

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Diabetic patients present some specific anatomical and functional characteristics that hinder their correct diagnosis. Atherosclerotic disease in diabetic patients is usually diffuse, with a tendency toward negative vessel remodelling,[9] which can lead to underestimating the degree of coronary obstruction due to the lack of actually "healthy" segments with which to compare them. On the other hand, diabetic patients present structural abnormalities of the microcirculation that can contribute to an abnormal response to coronary vasodilators. Thus, both the endothelium-dependent vasomotor response and the independent response have been described as impaired in diabetic patients, especially in those with poor glycemic control.[10,11] Such microvasculature impairment would be the cause of the difficulty in obtaining maximal hyperemia. To date, few data are available on the usefulness of the pressure-monitoring guidewire in diabetic patients. In a cohort of 96 diabetic patients, Yanagisawa et al[12] demonstrated that the classic cut-off value of 0.75 correlates with the presence of ischemia as assessed by TI-201 SPECT imaging. Similarly, sensitivity and specificity were comparable to that obtained in the control group of 149 non-diabetic patients assessed in the study. An exception to this were the diabetic patients with poor glycemic control (HbA_{1C} ≥7%), where specificity was significantly lower than in diabetic patients with good glycemic control.

In this issue of the *Revista Española de Cardiología*, Domínguez-Franco et al[13] present a valuable and original study in which the usefulness of this technique is assessed in diabetic patients with intermediate stenosis. This was a retrospective cohort study of consecutive patients assessed with FFR between 1997 and 2004. A total of 222 lesions were assessed in 206 patients. Initially, stenoses with an FFR value >0.75 did not undergo

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revascularization. Thus, revascularization therapy was deferred in 42 lesions in 40 diabetic patients and in 102 stenosis in 96 non-diabetic patients based on the results obtained using the pressure-monitoring guidewire. During long-term follow-up (average of 30 months), the need to revascularize stenotic lesions was greater in diabetic patients, although this did not reach statistical significance.

In my opinion, these results should be read taking into account a set of limitations (most of which have already been highlighted by the authors). First, the sample size (only 40 diabetic patients were assessed) prevents us from drawing any definite conclusions. Despite having insufficient statistical power, the rate of new revascularization procedures at follow-up was 40% lower in non-diabetic patients (8.8% vs 14.3% in diabetic patients). This should be corroborated by larger studies. On the other hand, the assessed lesions were angiographically focal (9-10 mm) in relatively large vessels (reference diameter 3 mm). Without doubt, this type of stenosis is hardly representative of atherosclerotic disease in diabetic patients. Thus, in the DIABETES[14] study, for example, the reference diameter was 2.3 mm and the average length was 15 mm. In fact, one-third of these patients had a reference diameter <2 mm.[15] A third aspect to take into account is that the degree of glycemic control in these patients was not known, which may be associated with the FFR having lower specificity.[12] This could be relevant, since indirectly we can see that most of the revascularizations in this cohort were performed in insulin-dependent patients, who could have worse glycemic control (non-demonstrable due to the lack of data in this regard) and a more impaired microvasculature. Finally, I would like to mention a conceptual problem. What is required of the pressure-monitoring guidewire is the functional assessment of a stenosis at a given moment to decide whether to revascularize the lesion or not. Thus, this diagnostic device, or any other (intracoronary ultrasound imaging, for example), was never intended to be used as an aid in the prevention of the long-term progression of stenosis, that is, in preventing atherosclerosis progression. Coronary disease undergoes progression, especially in poorly controlled diabetic patients. In comparison, at 2-year follow-up, around 10% of the diabetic patients included in the DIABETES study presented new revascularization in a vessel or segment remote and different from the one treated previously.[16] These data are comparable to those found in the cohort studied with pressure-monitoring guidewire.[13] It would seem somewhat unfair to attribute this long-term event to a flawed technique. Thus, it remains to be decided how long a technically correct functional measurement retains its validity, especially in poorly controlled diabetic patients.

In conclusion, calculating the FFR in diabetic patients with focal and proximal stenosis seems safe, and probably helps in preventing performing too many revascularization procedures in lesions that do not present functional ischemia. The authors of this work[13] should be thanked for contributing to the validation of this technique in this group of patients. The pressure-monitoring guidewire is probably not a tool that can be used in the secondary prevention of atherosclerosis in diabetic patients, especially those who are insulin-dependent. Strict metabolic control and controlling risk factors continues to be the best mechanism to keep the pressure-monitoring guidewire "negative" during the long-term follow-up of these patients.[17,18]

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