

Physiology is Back in the Cath Lab! Should we Abandon Angiography in the Assessment of Intermediate Coronary Stenosis?

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For more than 40 years we have been able to evaluate *in vivo* the morphology of the coronary arteries by angiography, and angiographic contrast studies have come to be accepted as the gold standard for evaluating coronary artery disease in clinical practice. In addition, much of our knowledge of the natural history of the disease, and our capacity to modify the disease, comes from information that has been collected for years from angiographic studies. In the last 20 years the relation between anatomy and physiology has become better understood, thanks, among others, to the pioneering works of Gould et al who described, in an experimental model, the relation between the anatomic severity of stenosis and the resistance it offers to blood flow. In the experimental model it is accepted that a reduction of more than 75% in the vessel section (equivalent to a stenosis of 50% of the diameter) is necessary to produce a decrease in coronary blood flow capable of causing effort ischemia. This experimental evidence has been applied to clinical practice, and the use of levels of stenosis of more than 50% as theoretically capable of inducing ischemia has become generalized. Nevertheless, particularly in the last 15 years, we have learned the limitations of angiography, thanks to the development of new intracoronary imaging techniques like echography, and to the appearance of coronary guide wires with sensors for different physiological parameters. The difficulties of the

angiographic evaluation of lesions are maximal in intermediate lesions (e.g., 30-60%), where there is more interobserver variability and it is more difficult to make clinical decisions. In addition, the presence of diffuse disease, which is practically the rule in atherosclerotic disease, makes angiographic evaluation more difficult. Finally, angiography attempts to estimate the physiological significance of a lesion in accordance with its anatomical severity when it would seem conceptually more logical to directly measure its capacity to produce ischemia, as is done with noninvasive techniques. Habitually, a large group of patients have lesions in which the clinician or hemodynamics specialist has reasonable doubts about their significance, either because no noninvasive screening tests for ischemia have been made previously, because the results of these tests have been ambiguous, or because multivessel or multisegment disease exists, which makes it difficult to precisely locate the lesions responsible. Herein lies the interest of developing techniques that allow this information to be obtained during the intervention, before the patient leaves the catheterization table. At present, there are several methods for evaluating the physiological significance of a lesion in the catheterization laboratory, including calculation of the coronary flow velocity reserve with Doppler, pressure-flow ratio in hyperemia, and calculation of the myocardial fractional flow reserve (FFR). The first two parameters are dependent on hemodynamic conditions (heart rate, blood pressure, and myocardial contractility) and the state of the microvasculature, whereas the FFR has the advantage of being reasonably independent.

The development of the pressure guide wire is a clear example, unusual in medicine, of how a small group of investigators, led by Pijls and De Bruyne,

SEE ARTICLE ON PAGES. 251-7

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can take a technique from the phase of basic research to the phase of experimental validation and practical application in a relatively period short time without shortchanging development. The hemodynamic basis of its use is simple. An epicardial coronary stenosis that is capable of increasing resistance to blood flow produces a loss of distal pressure as a result of the loss of kinetic energy in viscous friction, turbulence, and separation of flow. As a result, a difference in pressure, or a gradient, develops in the segments just before and after the stenosis. Years ago, these gradients were used profusely in hemodynamics laboratories to assess the significance of intermediate lesions and, fundamentally, the result of balloon angioplasty. They were eventually abandoned because the angioplasty balloon catheters used produced a degree of obstruction to flow, and because it still was not known that this ratio only reaches its true expression in situations of maximum hyperemia, not at rest. In situations of maximum hyperemia, with maximum coronary arteriolar vasodilation, the relation between coronary blood pressure and flow is linear, which allows FFR to be calculated. FFR is defined as the ratio between maximum coronary flow in the presence of a stenosis and the maximum coronary flow that would exist in the vessel in the absence of stenosis. That is to say that it is the fraction of maximum coronary flow that can be delivered by the stenotic vessel. The calculation of FFR in clinical practice involves simply dividing the pressure distal to the stenosis by the mean aortic pressure in a situation of maximum hyperemia induced by a pharmacological stimulus. In normal arteries without stenosis, and consequently without any fall in pressure, FFR is equal to 1.

Several models of pressure guide wire are available on the market, all based on a 0.014-inch guide wire. At present, guide wires are reasonably guidable, although not fully comparable to a normal angioplasty guide wire, and are reasonably stable with regard to the pressure signal. Signal instability is still an occasional problem (although it occurred more frequently in early models), which can generate erroneous results if the study is not carried out meticulously. After passing the lesion with the guide wire, a hyperemic stimulus is administered to elicit maximum arteriolar vasodilation, and FFR is calculated as the ratio between the mean pressure distal to the stenosis, measured through the pressure guide wire, and the mean pressure proximal to the

lesion, measured through the catheter guide wire. An FFR value of less than 0.75 is considered pathological. In addition, during an interventionist procedure the measurement of the pressure distal to the inflated balloon reflects the wedge pressure, which serves to evaluate collateral circulation. To summarize, the pressure guide wire provides a large amount of information on the pathophysiology of the coronary artery studied.

The present article of López-Palop et al is the first Spanish study to be published in the REVISTA ESPAÑOLA DE CARDIOLOGÍA on the clinical use of pressure guide wires. The study was a retrospective review over a 2-year period of 253 lesions, mainly (82%) to assess the significance of lesions that were unclear on angiography. More than half of the angiographically ambiguous lesions were characterized as nonsignificant by the FFR, so no coronary intervention was performed. However, no follow-up data are available, which would have been particularly interesting. The sensitivity and specificity of any diagnostic test are influenced by the selection of the study population, and it is possible that in this initial experience of the center a large number of lesions with a low probability *a priori* of inducing ischemia were included. In any case, it is relatively common to find lesions that would be characterized angiographically as significant, but have an FFR of more than 0.75. In 2000, 1183 procedures were performed with an intracoronary pressure guide wire in 40 centers in Spain. The present series is large, representing 10% of the interventionist cases of the center, and it indicates both the usefulness and some of the limitations to the clinical use of this diagnostic technique, which merits a specific discussion to put it into perspective.

In addition to methodological limitations, some of which I have commented briefly and can in fact be resolved with proper technique, there are conceptual limitations that should be considered. The calculation of FFR is based on the assumption of a linear relation between coronary pressure and blood flow when hyperemia is maximal. If maximum hyperemia is not achieved, the ΔP is underestimated, FFR overestimated, and lesions of physiological import can be considered nonsignificant and left untreated. One of the most important limitations of the technique is that, in spite of its rapid expansion, with a growth in Spain of 204% last year, the vasodilator and dose that consistently achieve maximum vasodilation are still

not absolutely clear. The 0.75 limit has been validated with intracoronary papaverine and intravenous adenosine, which is most frequently used in clinical practice, including the study by López-Palop et al. The large variation of the dose of intracoronary adenosine used in the study by López-Palop et al, with occasional doses up to 5 times greater than the recommended dose, merely confirms this. In addition, the categorical limit of 0.75 is probably too inflexible. At present, a gray area between 0.75 and 0.80 tends to be accepted for this technique. Another important limitation is that in the case of microvascular dysfunction, as can occur after infarction, or in patients with diabetes or left ventricular hypertrophy, maximum hyperemia cannot be achieved and FFR underestimates the severity of the lesion. Although it has been suggested that such vessels probably would not benefit from revascularization, since these lesions do not produce ischemia even at the maximum vasodilation attainable, there are no conclusive data that demonstrate that this is the case. There are doubts about the possible reversibility of microvascular damage, particularly since there is no assurance, given the current level of information, that the vasodilation is in fact the maximum vasodilation attainable. In the work of López-Palop et al, 17% of the patients were studied during acute infarction or in the postinfarction period, situations in which FFR must be interpreted with caution. Finally, it is important to note that most of the validation studies of the pressure guide wire, specifically, those in which the limit of <0.75 was established as capable of inducing ischemia, were made in selected, stable patients with single-vessel disease and normal left ventricular function. In contrast, most of the patients who undergo catheterization in Spanish hospitals have unstable angina. Although it is common practice to extrapolate the results obtained in a stable population to other types of patients, there are no consistent data for doing it reliably. In the series of López-Palop et al, only 11% of the patients had stable angina, which, as the authors recognized, was a limitation of the study. Independently of this point, the calculation of FFR is based on the assumption of a constant resistance to coronary flow and does not consider the possible dynamic nature of the lesion, which is frequent in patients with unstable angina, where vasoconstriction and the thrombus are important. For that reason, it is necessary to interpret FFR with caution in these

patients and to consider the clinical presentation and other complementary tests before deciding on a therapeutic strategy.

The measurement of physiological and, particularly, hemodynamic parameters has been an essential part of the work of cardiac catheterization laboratories for many years. Little by little, however, the trend in activity has been toward imaging techniques like angiography, as well as therapeutic interventions, shifting some of the measurement of these parameters to laboratories of noninvasive techniques. The development of the pressure guide wire for measuring gradients and estimating coronary flow seems to run counter to historical developments. Its true usefulness in day to day practice has not yet been established, although studies like that of López-Palop et al should help. Most hemodynamics specialists do not use the pressure guide wire routinely in the evaluation of angiographically dubious lesions. Its use is limited by the additional time that it undoubtedly requires, by the care needed to obtain trustworthy information, by the theoretical limitations previously commented, and by the present ease of treatment of this type of lesions. Ease of treatment means that such lesions are often treated, often within less time than the time needed to evaluate them, or that the decision to clinically evaluate its effect on the patient is deferred with confidence that it can easily be done if it becomes necessary. There are a variety of useful tools for assessing ambiguous stenoses by angiography (pressure guide wire, intracoronary echography, intracoronary Doppler), each of which has its advantages and disadvantages. The moment may have arrived in which each hemodynamics laboratory becomes comfortable with at least one of these techniques, and the pressure guide wire occupies an advantageous position among them.

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