The interventionalist’s dilemma: innocent intimal hyperplasia or in-stent restenosis?

Nico H.J. Pijls*

Department of Cardiology, Catharina Hospital, PO Box 1350, 5602 ZA Eindhoven, The Netherlands

This editorial refers to “Alpha-adrenergic receptor blockade and hyperaemic response in patients with intermediate coronary stenoses” by A. De Bruyne et al. on page 2034 and “Utility of the fractional flow reserve in the evaluation of angiographically moderate in-stent restenosis” by Lopez-Palop et al. on page 2040.

One of the remaining challenges in interventional cardiology is in-stent restenosis. In-stent restenosis is difficult to treat, often recurs, and may require repeated interventions including bypass surgery and is therefore often frustrating for both the patient and the physician.

If in-stent restenosis is severe and the relation with the patient’s complaints or proven ischaemia is clear, there will be little discussion about the necessity to use the full armamentarium of the interventionalist to treat the stenosis, including brachytherapy, drug-eluting stents, and ultimately surgery if intervention fails. However, not infrequently patients return to the out-patient clinic weeks to years after stent implantation, with only mild or moderate in-stent restenosis, leaving unanswered the question whether this is a physiological degree of intimal hyperplasia or true restenosis which can be held responsible for (the recurrence of) complaints. How should we proceed in such patients? Just ‘blindly’ irradiate the presumed in-stent restenosis with the risk of activating a quiet non-significant lesion? Place a drug-eluting stent within the previous stent with a recurrence risk of at least 20%? Or try to get some more specific information beforehand about the individual lesions? And how can such essential information be obtained?

This issue is systematically addressed by the interesting study by Lopez-Palop et al., published in this issue of the Journal. In this study, 65 in-stent restenotic lesions of moderate severity were studied. Fractional flow reserve (FFR) was measured in all of these lesions, and used for the decision of whether to treat. If FFR was <0.75, treatment by PCI was always performed; if the FFR was >0.75, no intervention was performed. The study by Lopez-Palop showed for the first time that quantitative coronary analysis was completely inappropriate for assessing the physiological significance of these moderate in-stent restenoses: in those vessels with a diameter stenosis >50%, half of the lesions were haemodynamically significant and the other half were not. More importantly, after 12 months follow-up, not a single adverse event occurred in relation to any of the deferred lesions. Had these lesions been treated instead of having measured fractional flow reserve, not only would a lot of money been wasted, but also repeated interventions with discomfort and potential risks for the patients would have been necessary in approximately 20% of them, no matter whether a drug-eluting stent or brachytherapy had been used. The ironic aspect is that neither the doctor nor the patient realise that the true, man-made restenosis in those 20% of patients is iatrogenic and could have been prevented by appropriate FFR measurement beforehand.

Even though the number of patients is limited, the study by Lopez-Palop is convincing and extends our knowledge of moderate stenosis in native coronary arteries to in-stent restenosis. In this respect, it has been shown convincingly in two important randomized studies...
by Davies et al.4 (ACIP-study) and Bech et al.5 (DEFER study), that the most important criterion to treat a particular stenosis, is not its anatomical aspect but the presence of inducible ischaemia.4,5 The ACIP-study demonstrated that if a stenosis is associated with inducible ischaemia, irrespective of whether it is anatomically significant and even if no symptoms are present, the outcome of the patient is significantly improved by interventional treatment. The other side of the coin was addressed in the DEFER study, showing that when a stenosis is not associated with ischaemia, the risk of that particular stenosis to cause acute myocardial infarction or death, is approximately only 1% per year during the next two years. Therefore, as in many patients with coronary artery disease encountered nowadays in the cath-lab, multiple lesions are present and can be considered for treatment, it is of paramount importance to select which of the many lesions are responsible for ischaemia and to treat those specific stenoses. Conversely, angiographic lesions not causing reversible ischaemia should not be stented, even not by drug-eluting stents, because they cannot be held responsible for symptoms and because the risk of such individual stenosis to cause an acute coronary syndrome is extremely small and is not decreased by stenting.5,6

A second paper published in this issue of the Journal addresses the importance of maximum hyperaemia and pharmacological stimuli to induce it.7 For reliable assessment of fractional flow reserve, maximum hyperaemia is paramount and the present gold standard to achieve it is infusion of adenosine in the femoral vein (140 μg/kg/min) or intracoronary injection of papaverine (10–15 mg). Validation studies of these hyperaemic stimuli have been performed years ago by the seminal work of Wilson et al., and De Bruyne et al.6,9

It has been suggested that in some patients with diffuse and extensive disease, additional α-blockade would further reduce coronary resistance and enhance hyperaemia.10 This issue, as a matter of fact, is important: if arteriolar vasodilation and the resulting hyperaemia is not maximal, fractional flow reserve will be overestimated and stenosis severity underestimated. Barbato et al., studied the additional effects of different α-adrenergic blockers on top of i.v. adenosine infusion and showed that, although a small increase of hyperaemia occurred in approximately 10% of the patients, this was not clinically relevant because none of these patients had a fractional flow reserve value that shifted from above 0.80 to below 0.75. In other words, no patient crossed the grey zone.

Therefore, administration of α-adrenergic blockers in addition to classical vasodilators would not have changed the decision to intervene or not in any of these patients. For clinical practice, this work implicates that the clinical routine in the majority of catheterization laboratories, i.e., PCI in case of an FFR <0.75 and deferral of PCI in case of FFR >0.80, still stands firmly.

For all kinds of reasons, non-invasive stress testing is often not performed in patients undergoing PCI.11 The papers by Lopez-Palop and Barbato further corroborate the use of FFR as a better alternative for obtaining functional information, which is desirable in many patients encountered nowadays in our cathlabs. FFR provides similar information to non-invasive testing yet with an unsurpassed spatial resolution and is available for ad hoc decision making. It should therefore belong to the diagnostic tools of ‘good clinical practice’ in today’s catheterization laboratory.

References