Epicardial versus microcirculatory dissociation

Unlike window-based computer applications, where ‘what you see is what you get’, the angiographic results of percutaneous coronary intervention do not always correlate with long-term clinical outcome. Extrapolation of a perfect angiographic result, typically achieved with stent implantation, to long-term freedom from major adverse cardiac events is hindered by a number of factors. Firstly, disruption of the epicardial artery may lead to thrombosis and acute or subacute vessel closure. This complication has been nearly eradicated by adequate stent deployment and prolonged dual antiplatelet therapy. The second component of the dissociation between angiographic and clinical outcome relates to microcirculatory dysfunction. Virtually every coronary manipulation, and stent implantation in particular, is associated with microembolization of plaque material to the distal bed, as demonstrated by studies employing emboli-protection devices. Platelet-thrombus occurs as primary embolic material or in response to microscopic atherosclerotic debris lodged in the microvasculature. If obstruction occurs, myonecrosis and impaired coronary flow reserve ensue.

In this issue, Nishida et al.[1] examine microcirculatory dysfunction in a post-hoc fashion in a subset of patients enrolled in the Doppler Endpoint STenting INternational Investigation (DESTINI) trial. Among the 735 patients enrolled in the study, 448 had stent implantation, either as a planned (71%) or provisional (29%) strategy. They show that although the average coronary flow reserve in patients with and without subsequent target lesion revascularization is not statistically different, a coronary flow reserve <2.0 identifies a group of patients with a doubling of need for revascularization (22% vs 11%, P=0.01). This association remains statistically robust after adjustment for all angiographic and clinical parameters associated with revascularization (adjusted odds ratio 2.0, P=0.007) and positions coronary flow reserve as one of the four independent predictors of revascularization in this study together with hypertension, vessel reference diameter and total length of stented segment. Interestingly, none of the more accepted predictors of target lesion revascularization, such as diabetes and extent of coronary disease figure prominently in this analysis.

This exploratory analysis from a well-executed trial of provisional coronary stenting raises two important issues. The first is why should 26% of patients with successful stent implantation have an abnormal coronary flow reserve? Obviously, it is not because of significant residual stenosis (13 ± 12%) or untreated major dissections (4-4% type C or D), but probably because of the ubiquitous dispersion of microemboli to the arterial bed supplied by the stented artery. This is supported by a number of observations.

Coronary flow reserve is a ratio between the average hyperaemic and basal flow velocity. An increase in the denominator and/or a decrease in the numerator of this fraction can decrease the coronary flow reserve. Indeed, the authors report that, as compared with patients with a normal coronary flow reserve and no revascularization, basal velocity was significantly higher in patients with coronary flow reserve <2.0 and subsequent revascularization (24 ± 12 vs 21 ± 10 cm . s⁻¹, P=0.04, respectively). Unlike in previous reports, the abnormal coronary flow reserve was also associated with a lower hyperaemic flow velocity. While some of these changes can be attributed to temporary loss of autoregulation of the distal coronary bed after relief of the epicardial stenosis, this alone cannot be responsible for the frequent abnormality of flow, as it occurs less often in patients treated with balloon angioplasty alone. More likely, stenting is associated with more distal microembolization, which leads to elevated basal flow and reduced coronary flow reserve. The higher incidence of coronary microembolization after stenting, manifesting as peri-procedural creatine kinase-MB elevation, was clearly demonstrated in the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial[2] and other reports[3]. Although a low coronary flow reserve characterizes both patients with epicardial stenosis and microcirculatory dysfunction, the mechanism is different. After relief of the flow-limiting epicardial lesion, there is hyperaemia at rest in an attempt to offset the partially obstructed resistance vessels, causing a heightened basal flow and partial use of the flow reserve.

The second question is even more germane to the whole issue of recurrent ischaemic events in patients with coronary artery disease and pertains to the interaction between the quality of epicardial revascularization and microcirculatory function. Why should microcirculatory dysfunction after coronary intervention predict future revascularization in the presence

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of satisfactory angiographic epicardial results? How do coronary emboli, responsible for diminished coronary flow reserve after percutaneous coronary intervention, relate to upstream restenosis? Is impaired coronary flow reserve a cause of recurrent ischaemia or a marker for more severe coronary artery disease?

The authors imply that achievement of normal coronary flow reserve predicts lack of future adverse events irrespective of the use of balloons alone or stents. Yet, in the only study that prospectively addressed this issue (Doppler Endpoints Balloon Angioplasty Trial Europe — DEBATE II), patients undergoing stenting despite normal coronary flow reserve had a significantly lower incidence of revascularization (4%) than those who achieved normal coronary flow reserve with balloon angioplasty (12%)\[4\]. It means that normal microcirculatory function is not sufficient to prevent revascularization and both components of percutaneous intervention — excellent treatment of the epicardial narrowing and preservation of the microcirculation — need to be properly addressed.

Two possible mechanisms can account for the association between impaired coronary flow reserve after coronary intervention and subsequent revascularization. The simpler one relates to the burden of atherosclerosis in the epicardial artery. The more complex and diffuse the lesion, the more likely it is that recurrent revascularization will be needed. As the plaque burden increases, the likelihood of distal embolization is enhanced and so is the chance for neointimal formation and restenosis. Thus, low coronary flow reserve after coronary intervention serves as a marker for diffuse coronary artery disease and future events. Indeed, in this paper\[13\], the authors report that total length of stented segment is independently associated with revascularization with an excess of 48% for each additional 10 mm of stent. Although it is difficult to separate the impact of a longer stent from that of the more diffuse lesion, it is convincing that the need for long stents is associated with revascularization. These observations are in concert with the higher incidence of adverse events in diabetic patients, known to have much more diffuse coronary artery disease\[9\].

A second mechanism may involve the inflammatory response to coronary microembolization. It is well demonstrated that percutaneous coronary intervention is associated with a marked increase in C-reactive protein, interleukin-6 and other markers of inflammation\[6\]. We can postulate that the higher the inflammatory response, incited by coronary microembolization, the higher the propensity for leukocyte-mediated accumulation of cytokines and attraction of smooth muscle cells and subsequent neointimal formation at the site of arterial injury. The same inflammatory response may be responsible for episodes of plaque rupture at distant sites and may explain the higher incidence of myocardial infarction in patients with more extensive coronary artery disease\[7\].

Indeed, a number of small studies demonstrated that measures that reduce the inflammatory response after percutaneous coronary intervention are associated with improved outcome. Neumann et al. found that MAC-1 activation after primary angioplasty for acute myocardial infarction was reduced in patients treated with abciximab, compared with placebo, paralleling the lower incidence of adverse events in this group\[8,9\]. Lincoff et al. also reported that treatment with abciximab before percutaneous coronary intervention reduces the increase in C-reactive protein and interleukin-6 both immediately and at 4 weeks after the procedure\[10\]. Other interventions, such as statin therapy, also modulate the effects of an intense inflammatory response and reduces subsequent adverse events\[11\].

In summary, it appears that simple angiographic assessment of percutaneous coronary intervention results in the epicardial artery is insufficient to provide prognostic information with regard to future ischaemic events, i.e. ‘What you see is NOT (necessarily) what you get’. Intense research in strategies geared to prevent distal embolization by mechanical means (emboli protection devices) and their interaction with the microcirculation via pharmacological therapy (glycoprotein IIb/IIIa inhibition, statins, etc.) is under way and greatly needed.

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References