Endothelial Function in Infarct-Related Arteries: Does the Type of Reperfusion Therapy Matter?

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The endothelium plays a fundamental role in regulating circulatory homeostasis through the secretion of substances with vasoactive effects, such as nitric oxide, prostacyclin, and endothelin, the expression of surface molecules that modulate the adhesion and activation of leukocytes and platelets, and the release of regulatory factors that control cell proliferation. Endothelial dysfunction is one of the initial events in the development of atherosclerosis—and of ischemic heart disease in particular—and could play a causal role in the onset and progression of the disease. In support of this potential influence, it is a well-known fact that endothelial function is altered in most of the situations in which there is risk of atherosclerosis, such as advanced age, smoking, hypertension, diabetes, and menopause, and that certain changes in lifestyle or pharmacological interventions that reduce the incidence of cardiovascular events also improve endothelial function. Moreover, there is a large body of laboratory data indicating that the endothelium influences leukocyte chemotaxis, lipoprotein oxidation, and thrombogenesis, all of which are key aspects in the development and progression of atherosclerosis.

The method most widely utilized to assess coronary endothelial function is the analysis of the response to intracoronary infusion of acetylcholine, which, under normal conditions, produces vasodilation mediated by the release of nitric oxide, whereas in patients with risk factors or established coronary artery disease, it frequently triggers a vasoconstrictor response. In healthy individuals, acetylcholine infusion also induces an increase in coronary blood flow and a decrease in distal vascular resistance, and these effects are considered to be indicators of microvascular endothelial function. The ultrasound analysis of the changes in the diameter of the brachial artery during reactive hyperemia and venous occlusion plethysmography are less aggressive and more widely available techniques for the study of endothelial function, the results of which, in expert hands, correlate quite well with those of coronary angiography with acetylcholine. Finally, determinations in blood or urine of substances released by normal or dysfunctional endothelium, such as nitric oxide metabolites, von Willebrand factor, certain inflammatory markers, or the soluble forms of a number of adhesion molecules, have also been utilized for the indirect evaluation of endothelial function.

Endothelial function deteriorates in acute myocardial infarction. In experimental models, hypoxia and acidosis change the function of endothelial cells in culture, and during reperfusion following prolonged coronary artery occlusion, there is a reduction in the coronary vasodilator response to acetylcholine and in microvascular function, both in the infarct-related artery, and in more remote regions. There are a number of mechanisms involved in postischemic endothelial dysfunction, from the oxidative stress that occurs during the initial minutes of reperfusion to the leukocyte and platelet deposition that takes place over the following hours and days, with the ultimate release of vasoconstrictor substances by these cells. In patients with acute myocardial infarction, a decrease in the coronary vasodilator response has been reported, both in the infarct-related artery and more remote regions. A few years ago, Iràculis et al observed, in 16 patients with acute myocardial infarction successfully treated with thrombolytic agents at Hospital Universitario de Bellvitge in Barcelona, Spain, that the infusion of acetylcholine into the infarct-related artery 9 (2) days after the infarction produced a more marked vasoconstrictor response, which was significantly greater than that observed in a control group of patients with stable ischemic heart disease, and the magnitude of which was correlated with the size of the infarct. The examination was repeated 1 year later in those patients in whom it was possible, and a considerable improvement in the response to acetylcholine was observed.

The question as to whether the different reperfusion strategies applicable in acute myocardial infarction can produce distinct effects on coronary endothelial function...
is pertinent, and, until recently, there has been no information on this subject. Recently, Obata et al. analyzed the response to acetylcholine infusion 2 weeks after infarction in 29 patients who underwent a primary percutaneous coronary intervention, and observed that those treated with sirolimus-eluting stent implantation developed a more pronounced vasoconstrictor response and a less marked increase in the coronary blood flow than those who had undergone implantation of a bare metal stent.9 The authors attributed these differences to a reduced secretion of vascular endothelial growth factor in the reperfused territory of patients with a drug-eluting stent.9

In the study published in the present issue of Revista Española de Cardiología, González-Costello et al., also from the Hospital Universitario de Bellvitge, refer to this question, analyzing coronary endothelial function in a series of patients with infarction that was successfully reperfused using metallic stents, and comparing it with a historical series of patients treated with thrombolytic agents.8 The 2 series were similar both in terms of the number of patients included and the moment in which the endothelial function was analyzed and the study protocol employed. The vasoconstrictor response to acetylcholine was significantly reduced in the patients who underwent stent placement than in the earlier series treated with thrombolytics (−4% [5%] vs −20% [21%] reduction in the diameter with respect to the baseline value at the maximum acetylcholine concentration evaluated). The authors conclude that primary angioplasty is associated with a lower degree of early endothelial dysfunction than thrombolysis. This offers still another argument in favor of said strategy for the treatment of infarction, and they point out that the study of coronary endothelial function could be useful in the evaluation of the efficacy of different therapeutic interventions during the acute phase of infarction.10

The difference observed is of great interest in pathophysiological terms, and leads one to consider the possible explanations, looking in depth into the discussion of the results provided by the authors of the study. The most fundamental finding is that this difference is invalid, given that the comparison of two nonrandomized series with so much time elapsed between them would appear to be improbable. On the one hand, the study seems to be exquisitely carried out and the authors have very carefully selected a sample of patients similar to those of the previous series, the measurements were made in the ignorance of the study protocol and it has been shown that the adjustment of the results for possible confounding variable does not change the conclusions. Moreover, it is significant that the mild degree of vasoconstriction in the patients treated with a metallic stent was very similar to that reported by Obata et al.9 in the subgroup of patients in their series with this same type of stent, a circumstance that strengthens the validity of the measurements. Nor does it appear that the series differ widely in terms of the time until reperfusion or the size of the infarction, although with respect to this aspect, the lack of correlation between the endothelial function and the infarct size in the patients who underwent primary interventionism, when compared with the series undergoing thrombolysis, is enigmatic. It is not probable either that the thrombolytic agents alone worsen the endothelial dysfunction that accompanies the coronary thrombosis that causes the infarction, or that the mechanical aggression of the intima inherent to primary intervention improves it.11,12 The authors point out that the more immediate and permanent reperfusion achieved by primary angioplasty as compared to thrombolysis could help to explain its apparent protective effect over the endothelial function. However, it appears that, in this respect, the endothelium behaves similarly to the myocardium, whose possibility of surviving following prolonged ischemia increases significantly with intermittent reperfusion.13

The 2 series differed in 2 aspects that may critically affect endothelial function. On the one hand, the severity of the lesion—which may enable the estimation, at least approximate, of the amount of residual thrombus—was, as expected, much greater in the group treated with thrombolytics. On the other hand, concomitant antiplatelet therapy was much more aggressive in the series subjected to primary interventional procedures (in addition to aspirin, clopidogrel in every case and abciximab in 73%). There is a great deal of evidence showing that thrombosis and activated platelets induce local and distant endothelial dysfunction,6,11,12 as well as the beneficial effect of different antiplatelet drugs on endothelial function.5,14,15 Thus, it is plausible that sealing the lesion with a stent, on the one hand, and aggressive antiplatelet therapy on the other, have contributed significantly to the relative preservation of endothelial function in these patients. The 2 series also differed in the frequency of the use of statins, with their known protective effect in the endothelium, but the administration of these drugs was discontinued 48 hours before the study, a circumstance that minimizes their potential influence.

What could the clinical implications of these results be? Today there is consensus in that primary angioplasty performed under the proper conditions is superior to thrombolysis with respect to reducing the recurrence of ischemic events, the need for revascularization and even the mortality, and the situations in which thrombolysis continues to be preferable are quite well defined.16 As a consequence, the fact that the deterioration of endothelial function in the infarct-related artery is less marked following reperfusion with a metallic stent than after thrombolytic therapy will probably have little influence when it comes to choosing one reperfusion strategy or another.

The same could be said for the potential clinical implications of the of drug-eluting stents in endothelial function soon after the infarction,9 taking into account the fact that there are large series comparing the incidence
of serious clinical events with one type of stent or the other, that identify the major predictors of complications associated with drug-eluting stents.\textsuperscript{17}

If it were demonstrated that post-infarction endothelial dysfunction independently predicted the development of adverse events, including those related to the stents, its evaluation—especially if it could be done as noninvasively as possible—could be highly useful, as pointed out by González-Costello et al, in terms of individualizing the management of the patients. In the mean time, our therapeutic decisions in acute myocardial infarction must be based on the large body of clinical information available. Recent trials with drugs like estrogens,\textsuperscript{18} antioxidants,\textsuperscript{19} or L-arginine\textsuperscript{20} oblige us to take certain precaution when it comes to drawing clinical implications from the studies of endothelial function, as it is seen that endothelial function and the prognosis of the patients do not always follow parallel paths.

REFERENCES