Acute Coronary Syndromes and Multivessel Coronary Artery Disease

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The current issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA includes an article by De la Torre et al[1] that describes a retrospective study of 75 consecutive patients with acute coronary syndrome (ACS), with and without ST segment elevation, who underwent coronary angiography and angioplasty. These patients (Group A) hade the peculiarity that, other than the treated culprit lesion, theyhad at least one severely stenotic lesion (≥75%) different from the one that caused the ACS and was not complex in appearance (no thrombus, ulceration, or dissection present and showing normal flow). The control group included 75 patients (group B) with ACS who underwent angioplasty of the lesion that caused the ACS and who had no other coronary lesions. Both groups were followed clinically for one year. During follow-up, mortality was noted to be higher in group A, even though the differences were not statistically significant (5.3% vs 1.3%). Similarly, more patients in group A required a new revascularization procedure (13.3% vs 2.6%; *P*=.04). Among patients in group A, 8% had to undergo new angioplasty on lesions other than the ones that had caused the ACS and that had not been treated initially.

The results of this study make sense, since multivessel coronary heart disease is predictive for cardiovascular events in patients with ACS, whether complete revascularization is performed or not, as opposed to single vessel disease. In a retrospective analysis of patients in the TACTICS study,[2] patients with single vessel disease had fewer cardiovascular events (death and AMI) than patients with multivessel disease over a 6-month follow-up (17.5% vs 22.2%; *P*=NS). Among patients with multivessel disease who underwent angioplasty of the culprit lesion only, the frequency of such events was higher, though not to a statistically significant degree, than among those who underwent multiple revascularization procedures (23.2 vs 21.2%; *P*=NS). Nonetheless, the need for a new revascularization procedure during follow-up was significantly greater in patients with multivessel disease who underwent revascularization of the culprit lesion only, compared to patients with single vessel disease or with multivessel disease and a history of multiple revascularization procedures (6.3%; 1.5%, and 1.5%, respectively; *P*=.04). The authors of this study believe that the differences noted between the results of this study and those of previous studies,[3] where multiple angioplasties were predictive for cardiovascular events in patients with ACS, is due to the systematic use of glycoprotein IIb/IIIa inhibitors before angioplasty in the TACTICS study. Several retrospective studies have shown that revascularization of the culprit lesion only in patients with ACS and multivessel disease is associated with a low rate of major cardiovascular events (death or AMI), but a greater number of interventions is required during follow-up.[4,5] In any event, no prospective controlled randomized studies have been performed to assess the advantages and disadvantages of complete revascularization versus revascularization of the culprit lesion only in patients with ACS and multivessel disease. Current recommendations under the guidelines of the AHA/ACC for percutaneous coronary interventions (PCI) are based on nonrandomized studies and advocate multiple attempts at revascularization in the presence of «significant (>50%) coronary stenoses that are anatomically amenable to angioplasty, are unlikely to develop complications, and threaten a moderately large or large portion of the myocardium.»[6] The *Sociedad Española de Cardiología* (SEC) guidelines (also based on retrospective nonrandomized studies[4,5]) are even more specific: «In patients with unstable angina, two PTCA approaches can be followed, depending on whether the procedure is performed because the problem is refractory to medical treatment or because the patient fulfills "high risk" criteria. In the first instance, percutaneous treatment of the culprit lesion can be very useful, even in a patient with multivessel disease, for stabilizing the patient in preparation for full revascularization at a future date, if necessary. In the second instance, it seems more rea-

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sonable to perform as complete a revascularization procedure as possible.»[7]

An interesting aspect of the paper by De la Torre et al is the low rate of events during follow-up in the group of patients with multivessel disease who underwent PCI of the culprit lesion only, despite the severity of the lesions in untreated vessels (in 73% of the untreated lesions, coronary stenosis was ≥75%, and in 26% it was ≥90%). In a paper by Goldstein et al, patients with AMI and multivessel disease who had undergone primary angioplasty were studied.[8] Of such patients, 60% underwent multiple coronary revascularizations (with angioplasty or surgery), either at the time of the acute event or later. Notwithstanding, 19% of these patients suffered a new ACS during the year of follow-up, and 32% required new angioplasty. It is interesting to note that cardiovascular events were substantially more frequent in Goldstein's study than in the study performed by De la Torre et al. These differences could have something to do with patient selection. In Goldstein's study, all non-culprit lesions looked complex and unstable on angiography (they were ulcerated and irregular in shape, and they showed thrombi as well as decreased coronary flow). In De la Torre's study, the patients that were chosen had non-culprit lesions which did not appear complex on angiography. These differences between the two studies suggest that the vulnerability of an atheromatous plaque and its ability to trigger new ischemic events do not correlate with the severity of the stenosis it produces, or, at least, that the degree of stenosis is not the only factor with which they correlate.

Traditionally, the diagnosis of coronary heart disease has involved identifying those coronary stenoses that significantly reduce the lumen of the blood vessel and coronary blood flow, either acutely or chronically. For years, this diagnosis has been based on coronary angiography. Thus, the treatment of coronary heart disease has rested on this mechanical concept, which favors treating only severely stenotic lesions. However, angiographic studies have shown that most acute myocardial infarctions (AMI) happen in coronary segments where only slightly stenotic or moderately stenotic coronary lesions were formerly present.[9] Histologic studies in patients with coronary heart disease who died suddenly show that the coronary occlusion produced by the ACS is due to thrombosis after rupture or erosion of atheromatous plaques without severe stenosis.[10]

In recent years, performing coronary angiography at progressively earlier stages in patients with ACS, with or without ST segment elevation, has made it possible to determine that many patients have angiographically complex and unstable coronary lesions in coronary segments that are not related to the acute event. Using coronary angiography, Goldstein et al found that almost 40% of patients with AMI had complex and unstable coronary lesions that were different from the ones that caused the infarct.[8] Still, coronary angiography has serious limitations when it comes to detecting ruptured atheromatous plaques, since such plaques rarely produce severe coronary stenosis. Rioufol et al used intravascular ultrasound to explore the coronary arteries of patients with ACS and found that 79% of such patients had a ruptured atheromatous plaque in a coronary artery that was different from the one that caused the ACS.[11] Thus, it would appear that that destabilization of atheromatous plaques leading to their erosion, rupture, or both, and to a subsequent occlusive thrombus is not a local event that involves a single coronary segment, but rather a global process affecting the entire coronary vasculature. On the other hand, how a plaque behaves after it becomes destabilized may have nothing to do with the severity of the stenosis it produces, but rather, to certain passive features of the plaque, such as the presence of a large lipid nucleus and a thin fibrous sheath, or to active features. These include the presence of inflammation mediated by activated monocytic macrophages that not only facilitate rupture of the plaque by liberating metaloproteinases, but that cause a state of hypercoagulability (mediated by tissue factor) sometimes leading to thrombosis of the plaque after it suffers a slight erosion without necessarily rupturing. Some markers for inflammation, such as elevated plasma levels of C-reactive protein (CRP), reflect this inflammatory state and have been correlated with a greater incidence of cardiovascular events in patients without a history of ischemic heart disease,[12] and with a greater recurrence of ischemic events after an ACS.[13]

Therefore, several studies have shown that in patients with ACS, multiple unstable atheromatous plaques are often found, even in vessels that did not cause the ACS, and that the presence of these plaques is associated with a greater frequency of cardiovascular events during follow-up.[8] However, to date no randomized trials have shown the benefits of performing preventive revascularization of these other unstable plaques when they are not severely stenotic.

Currently, cardiology faces the challenge of identifying vulnerable atheromatous plaques, that is, those that are prone to becoming unstable and rupturing, thereby causing ACS and, potentially, sudden death.[14] Angiography has serious limitations when it comes to detecting these vulnerable plaques that are rarely severely stenotic. Other techniques, such as intravascular ultrasound,[11] intracoronary thermography[15] and angioscopy,[16] may be more sensitive tools for detecting vulnerable atheromatous plaques that are prone to destabilization, and are currently being investigated. In the future, these tools could potentially be used to detect vulnerable atheromas at risk for destabilization such as would justify treatment with angioplasty, regardless of the degree of stenosis they may cause. The use of drug-

coated stents, with which restenosis is rarely seen, would make preventively treating these vulnerable plaques even more justifiable.

Until there is enough evidence in favor of treating unstable (ruptured or vulnerable) lesions that are insignificant, current treatment by means of percutaneous coronary intervention in patients with ACS should target hemodynamically significant culprit lesions and non-culprit coronary lesions that are severely stenotic and amenable to revascularization.[6,7]

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