Original Articles

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Importance of Severe Lesions Left Untreated in Patients With Acute Coronary Syndromes and Angioplasty of the Culprit Lesion

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Introduction and objectives. Patients with acute coronary syndromes may have significantly stenotic nonculprit lesions that do not show complex lesion morphology. We investigated whether these lesions were prone to become unstable since they exist within a prothrombotic and inflammatory systemic milieu.

Patients and method. We evaluated the clinical course of 150 patients after successful angioplasty of a culprit lesion: 75 patients with a severely stenotic but uncomplicated nonculprit lesion (group A) and 75 patients without these lesions (group B).

Results. In group A, 1 patient (1.3%) required angioplasty of an initially nonculprit lesion, and in group B, 2 patients (2.6%) died in cardiogenic shock. After 1 year of follow-up, in group A, 4 patients (5.3%) died (cardiac deaths), 1 patient (1.3%) had a myocardial infarction, and 10 patients (13.3%) underwent a repeat revascularization procedure, which in 6 cases (8%) was angioplasty of an initially nonculprit lesion. In all 6 patients with angioplasty of the initially nonculprit lesion, revascularization was done within the first 4 months and was indicated for unstable angina. In group B, 1 patient (1.3%) died (noncardiac death) and 2 patients (2.6%) underwent a repeat revascularization procedure because of restenosis. Survival curves were significantly different between both groups. Belonging to group A was the only independent predictor for events, and within this group location of the lesion in the left anterior descending artery was the main predictor.

Conclusions. The presence of nonculprit lesions of uncomplicated morphology at the time of a percutaneous revascularization procedure for a culprit lesion in patients with acute coronary syndrome is a short- and middle-term predictor of a moderate rate of recurrent events when these initially innocuous lesions become unstable.

Key words: Unstable angina. Myocardial infarction. Coronary angioplasty.

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Importancia de las lesiones severas no tratadas en pacientes con síndrome coronario agudo y angioplastia de la lesión causante

Introducción y objetivos. Los pacientes con síndrome coronario agudo pueden presentar lesiones coronarias no causantes que pueden ser severas y sin morfología compleja. Evaluamos si, a corto plazo, estas lesiones son proclives a la inestabilización al encontrarse en un entorno sistémico protrombótico e inflamatorio.

Pacientes y método. Evaluamos la evolución clínica de 150 pacientes sometidos a angioplastia (ACTP) de la lesión causante, 75 pacientes (grupo A) con lesiones no causantes no complejas y 75 pacientes (grupo B) con lesiones no causantes con morfología estenótica no complicadas (LNC) y otros 75 pacientes (grupo B) con ausencia de estas lesiones.

Resultados. En el grupo A, un paciente (1.3%) precisó ACTP de una LNC y en el grupo B, 2 pacientes (2.6%) fallecieron por shock cardiogénico. Al cabo de un año de seguimiento, en el grupo A, 4 pacientes (5.3%) murieron por causa cardíaca, uno (1.3%) sufrió un infarto y 10 (13.3%) precisaron revascularización, en 6 casos ACTP sobre LNC. Estos 6 procedimientos se efectuaron en los primeros 4 meses por angina inestable. En el grupo B, un paciente (1.3%) falleció de causa no cardíaca y 2 (2.6%) precisaron revascularización por reestenosis. Las curvas de supervivencia libre de acontecimientos fueron significativamente diferentes en ambos grupos. La pertenencia al grupo A fue la única variable predictora de acontecimientos y, dentro de este grupo, la localización de la lesión en descendiente anterior (DA) fue el principal factor predictor de la necesidad de revascularización.

Conclusions. La presencia de LNC en pacientes con síndrome coronario agudo y ACTP de la lesión causante predice una moderada tasa de revascularización a corto-medio plazo por inestabilización.

Palabras clave: Angina inestable. Infarto de miocardio. Angioplastia coronaria.
INTRODUCTION

The basic cause of acute coronary syndromes is coronary thrombosis that is triggered by erosion or by rupture of an artherosclerotic plaque. This is often reflected in the complex appearance of the culprit plaque on angiography, showing thrombus, dissection, and/or ulceration being present. The plaque ruptures when it becomes unstable, owing in part to well-recognized systemic factors that affect the entire coronary vasculature. Such factors include inflammatory activity that weakens the fibrous layer of the plaque; factors that facilitate thrombosis; and mechanical intraluminal effects that are conditioned by sympathetic tone and catecholamine levels. The diffuse nature of coronary heart disease and the systemic effect of the factors just mentioned could trigger a state of multifocal destabilization of the coronary circulation. Some such factors might operate during prolonged periods (>1 month), as in the case of platelet activation. Elevated levels of C-reactive protein are seen in patients who have had recurrent episodes of acute coronary syndrome over a period of up to 4 years, as opposed to patients who have persistently remained clinically stable.

All of the above would explain the presence in patients with acute coronary syndrome of multiple complex coronary lesions whose negative influence on patients’ clinical course has been looked at in several studies. Nevertheless, non-culprit lesions, including those that are associated with the ischemic event, often fail to produce angiographic indicators of destabilization. On the other hand, despite the fact that the severity of the lesions is, in and of itself, predictive for events, this relationship is highly influenced by the morphology of the lesion on angiography and the patient’s stable or unstable clinical picture. Thus, angiographically significant lesions that are not complex will cause the greatest doubts during revascularization of the culprit lesion, since we do not know whether they are more likely to become unstable in the short or medium term after an acute coronary syndrome, or if they will only lead to a higher incidence of unstable angina. However, the most common approach in these patients is to revascularize only the lesion that is felt to be the cause of the acute coronary syndrome, even if non-culprit but significantly stenotic lesions are present, particularly if such lesions do not show complex morphology on angiography. It is felt that an intervention involving multiple vessels in an acute scenario may put the patient at greater risk, yet the isolated treatment of the culprit lesion in the presence of multivessel disease is associated with a higher rate of recurrent angina.

We designed this study in order to assess the potential impact on patient prognosis of the presence of significant non-culprit, non-complex lesions (NCL) after an acute coronary syndrome and PTCA of the culprit lesion.

PATIENTS AND METHODS

We performed a retrospective study with consecutive patients who fulfilled the following criteria:

1. Acute coronary syndrome, infarct or unstable angina, with referral for emergency coronary angiography. Patients with cardiogenic shock were excluded.

2. Absolute identification of the lesion that triggered the clinical picture.

3. Successful PTCA of the culprit lesion (visual stenosis <25% and TIMI III).

Two groups were defined according to the following criterion: the presence of a second non-culprit lesion in a different vessel (visual stenosis ≥75% and reference luminal diameter ≥2 mm), not to include truncal lesions, obstructive or subocclusive lesions, and lesions appearing to be complex on angiography, such as those with dissection, ulceration, or thrombus.

Group A included those patients with non-culprit lesions having these characteristics, and group B included those who did not have non-culprit lesions. Patients were followed clinically during their hospital stay and after discharge. Cases were selected without knowledge of the clinical course after the procedure. A researcher selected patients according to iconographic reports and records of hemodynamic status, and subsequently another researcher collected information on in-hospital events and follow-up data.

Given the larger number of patients in group B, inclusion in this group was limited to a number of consecutive patients equal to the number attained in group A during the same time period.

In these patients, who were asymptomatic after...
successful angioplasty of the culprit lesion, who did not have triple vessel disease or truncal artery disease and who had no other lesions that seemed complex on angiography, no test for residual ischemia was performed during hospitalization. Performing these tests during follow-up was left up to their cardiologists.

**Statistical analysis**

Quantitative variables are expressed in terms of the mean±standard deviation, and qualitative variables are expressed as percentages. The Student t test was used for inter-group comparison of means, and the $\chi^2$ test was used to compare percentages between groups. Kaplan-Meier survival curves were constructed for events in both groups, and comparisons were performed by means of the log-rank test. Multiple logistic regression, with all study variables included, was performed in order to establish which independent variables were predictive for events. For all analyses, associations for which $P<.05$ were considered significant. The statistical package used was SPSS v. 11.0.

**RESULTS**

Over a 2-year period, 150 patients were included, 75 in each of the groups. Patients’ clinical features are shown in Table 1. Both groups were comparable, and the only significant difference was the higher prevalence of hypercholesterolemia in group A. Table 2 shows the characteristics of the procedure. Group A had a somewhat higher frequency of use of abciximab (40%) than group B (30.6%), due to the greater prevalence of infarction as an indication for the procedure. The rate of stent utilization was comparably high in both groups. Table 2 describes the non-culprit lesions that were seen in group A patients. In both groups, all patients with stent implantation received treatment with aspirin and ticlopidine (250 mg/12 h) or clopidogrel (75 mg/day) for one month.

**In-hospital events**

There were no deaths or clinically detectable infarcts in group A. In one case (1.3%) it became necessary to revascularize the NCL, which was situated in the ADA, because of recurrent unstable angina. Two deaths (2.6%) occurred in group B. One of them was due to reinfarction and cardiogenic shock, and the other one to progressive, refractory heart failure in a patient who was not a candidate for heart transplant. No new revascularization procedures were required. No significant differences were found between both groups in the number of events.

**Events during the first year of follow-up**

All patients were followed for a period of one year or more (21±7 months in group A and 19±5 months in group B).

In group A, 4 patients (5.3%) died over this period. Three of them died from progressive heart...
failure and one experienced sudden death (Table 3). All were women over 70 years old whose ejection fraction was less than 35%. Also, 6 patients (8%) developed unstable angina that required hospitalization, and one patient (1.3%) suffered an infarct without a Q wave. A new revascularization procedure was performed on 10 patients (13.3%): there were 6 instances of PTCA of the NCL, 2 of PTCA of the restenosed lesion, and 2 of revascularization surgery after diffuse restenosis (Table 3).

All these events occurred during the first eight months. Among them, all cases of intervention on which was not initially the culprit lesion occurred during the first 4 months. The 6 patients developed unstable angina (class IIIB in 3 patients, IIB in 1 patient, and IB in 2 patients). All these patients had hypercholesterolemia, and 4 (67%) were diabetic. All of them had the lesion in the ADA. In the initial study there was 75% stenosis in 5 patients and 90% stenosis in one patient. Only 2 patients clearly showed progressive stenosis of the lesion on angiography, with signs of complex morphology at the time the PTCA was performed. At the end of the follow-up period, 71 patients (94.6%) are still alive. Of these, 51 (72%) are asymptomatic, and 20 (28%) have stable class II angina (Table 3).

In group B, one patient (1.3%) died over the same period of a non-cardiac cause (lymphoma); 2 patients (2.7%) were hospitalized for unstable angina and underwent revascularization, one by means of PTCA of a severe restenotic lesion and the other by surgical means. This last patient had severe diffuse restenosis involving the ostium of the ADA. These two procedures were performed 2 and 5 months after the initial episode. At the end of the follow-up period, 72 patients (96%) are still alive. Sixty-three of them (87.5%) are asymptomatic, and 9 (12.5%) have stable class II angina (Table 3).

Event-free survival curves for both groups are shown in Figure 1. These differ significantly with respect to the greater need for revascularization in group A, but no significant differences were found in mortality or infarction rates ($P=0.22$), though a trend was detected.

According to the logistic regression analysis that was performed in both groups, the only independent variable that was predictive for events (death from cardiac causes, infarct, and revascularization) was belonging to group A (Table 4). When the analysis was restricted to group A, the independent variables that were predictive for events were the presence of a non-culprit lesion in the ADA, which was associated with increased risk, and an initial procedure that was performed on a male patient who had suffered an infarct, which was associated with a lower risk (Table 5).

**DISCUSSION**

The instability of the plaque and subsequent thrombosis lead to the acute coronary syndrome. Among the physiopathologic factors that can trigger...
plaque destabilization are inflammatory activity, factors that facilitate thrombosis, and neurohumoral influences.\textsuperscript{10,14} Such factors can exert their influence mainly on coronary vessels,\textsuperscript{3,6} so that neutrophil activation is not confined to the culprit lesion.\textsuperscript{5} Similarly, their effect can be detected after the clinical episode has subsided, and platelet activation has been seen to occur as much as one month later.\textsuperscript{7} Increased levels of C-reactive protein on discharge in patients who have had an episode of unstable angina are predictive of a higher likelihood of clinical instability.\textsuperscript{16}

The prevalence of multiple lesions on angiography in patients with acute coronary syndrome, infarct or unstable angina has been studied recently. Goldstein et al. found complex multiple lesions in 40\% of patients who had suffered myocardial infarction.\textsuperscript{9} This prevalence is even higher in autopsy series.\textsuperscript{17} All these studies suggest that destabilization of the plaque is not merely a local accident, but rather that it reflects a more generalized process that can potentially destabilize multiple plaques.\textsuperscript{6} The concept of multifocal instability holds up in light of angiographic studies showing the natural course of patients with infarct or unstable angina and the progression of culprit and non-culprit lesions.\textsuperscript{18,19} The multifocal nature of the disorder bears an influence on patient prognosis and, as a result, the presence of multiple complex plaques in patients who have suffered an infarct is associated with a worse prognosis.\textsuperscript{9}

Serial angiographies that are performed in health care facilities having a long waiting list for angioplasty have shown that the progression of the lesions is more pronounced after unstable angina and is associated with clinical events.\textsuperscript{20,21} Complex culprit lesions progress faster than stable lesions, but the severity of the stenoses, morphology aside, accelerates the process. In these studies, multivessel disease was seen in 35\%-40\% of cases. Even though morphologic indicators of complexity correlate with a worse prognosis, angiography has very little sensitivity when it comes to detecting plaque erosion or rupture. Classic angiographic studies show that 30\%-35\% of cases of unstable angina do not show lesions that are complex in appearance on angiography.\textsuperscript{22} In the papers previously cited, 36\% of the culprit lesions did not look complex.\textsuperscript{20,21}

In light of the above, one can legitimately assume that non-culprit lesions in the presence of an acute coronary syndrome may be more prone to becoming unstable in the presence of systemic or regional inflammation that facilitates thrombosis, thus becoming potential triggers for a new acute coronary syndrome within a short time.

Despite the fact that all these observations cast doubts on the concept of an isolated culprit lesion, the usual strategy in such cases is to perform revascularization of the culprit lesion alone. However in the few instances where there is another lesion that does not appear to be connected to the current clinical picture but it is severely stenotic (>90\% diameter stenosis) or very complex in appearance (thrombus, dissection, or ulceration), this lesion usually is treated as well.

In our study we assessed the clinical course of patients with acute coronary syndrome who underwent emergency PTCA of the culprit lesion and who had another non-culprit lesion that was substantial but not complex. Our control group was composed of a series of patients who were treated over the same period and who had similar characteristics, only they had no other significant lesions. We noted in our study that the presence of a NCL, even without complex morphology, leads to a moderate chance of recurrence (10.6\%) of ischemic events in the short or medium term (\(<4\) months), so that the non-culprit lesion required intervention in 7 patients (9.3\%), one before discharge and 6 over the 4 ensuing months. It is worth noting that none of the patients who received abciximab during the initial procedure suffered any subsequent events. At the end of follow-up we found that 28\% of the patients had stable angina that was attributable to the untreated lesion and, in isolated cases, restenosis. The apparent lack of correlation between the severity of the lesions on angiography and the degree of revascularization noted was likely the result of the persistently stable nature of the majority of the lesions, medical treatment (knowing that such lesions are present leads to more aggressive treatment), and a revascularization strategy based on clinical parameters (whether destabilization or severe stable, refractory angina is present). Similarly, testing for ischemia early and systematically in asymptomatic patients after successful revascularization of the culprit lesion, having first ruled out anatomical features involving greater risk (trunk, triple vessel, or complex lesions), is not strictly necessary; it can be done later during follow-up in light of the patient’s overall clinical picture.

On the other hand, in the control group we found a very low frequency of events: only 2 patients had unstable angina, and these 2 patients were the only ones that required revascularization, in both instances on account of severe restenosis. At the end of the follow-up period, the great majority of patients were asymptomatic. Both groups are clinically comparable. As one might expect, however, group A, which had multiple lesions, had a greater burden of risk factors, which was
significant in the case of hypercholesterolemia.

The only independent variable that was predictive of events was belonging to group A and, within this group, the variables that were independently predictive of events were the location of the NCL in the ADA (which is associated with a greater risk), the initial procedure after the infarct, and being a male (both of which are associated with a lower risk). Considering the fact that NCL revascularization is the most common event and the one that differentiates both groups, it is easy to understand these results, with the exception of the ADA. One might argue that knowing that a lesion is located there makes the clinician more inclined to indicate revascularization, but it must be borne in mind that these procedures were performed when patients were clinically unstable, which points to a genuine predisposition. It is interesting to note that the degree of stenosis seen on angiography was not predictive of events, which underscores the role of plaque destabilization in these episodes. If we compare this study with the one performed by Goldstein et al., it is interesting to note that the annual rate of events in our patient series lies halfway between the rate for patients without multiple lesions (2.6%) and patients with multiple complex lesions (19%), this latter figure being high despite the fact that in this study complete revascularization was attempted in 60% of patients with multiple complex lesions, either during the first procedure or in subsequent ones. This underscores the prognostic significance of complex morphology in non-culprit lesions. The experience with patients having multiple vessel disease was very recently published for the TACTICS-TIMI 18 trial. In this study, which was performed with patients suffering from an acute coronary syndrome but without an elevated ST segment in the invasive branch, interventions were performed on 137 patients with single vessel disease and in 290 patients with multiple vessel disease. Of these latter patients, 66 (23%) underwent multiple PTCA, and 224 (77%) underwent PTCA of the culprit lesion only. The rates of death and infarction 6 months later were comparable in both groups. The rates of revascularization of non-culprit lesions in patients with multiple vessel disease were 6.3% in untreated cases and 1.5% in treated cases. When the cut-off point for defining significant coronary disease increased from 50% to 70%, the figures were 7.7% and 7.1%, respectively. This latter figure of 7.7% is comparable to the one observed in our study.

In the aforementioned serial studies, the rare progression (5%-10%) of non-culprit lesions probably resulted from the fact that patients had been medically stabilized and that the non-culprit lesions noted were severe (stenosis >25%). In our study, emergency angiography was performed on patients having an acute coronary syndrome that was not medically stabilized and whose non-culprit lesions appeared to be significant on angiography (visual stenosis ≥75%).

**Limitations**

This study has the limitations that are inherent to any retrospective study with a rather limited number of patients, even though statistically significant values are obtained. In order to reduce selection bias, patients were selected with strict adherence to the previously defined criteria and in consecutive order. The decision to revascularize during follow-up may have been influenced by the knowledge that...
an untreated lesion was present, but the fact remains that these procedures were performed in the presence of unquestionable unstable angina. It might be argued these patients could have been subjected to non-invasive tests in order to assess the lesions, but at the time it was felt that early and systematic tests for ischemia was unnecessary if patients were stable and asymptomatic after successful angioplasty of the culprit lesion and had no anatomical risk factor (complex lesions, truncal lesions, or triple vessel disease). Such tests can be performed on an individual basis during follow-up, depending on the patient’s clinical course. Early detection of ischemia by means of such tests would probably have made it possible to «choose» certain patients for a second revascularization procedure, but our results suggest that a severe appearance on angiography is not predictive for destabilization, and in fact, that the opposite may be true.

CONCLUSIONS

It is not unusual to find multivessel disease in patients who suffer from an acute coronary syndrome. In such cases, the standard approach is to treat the culprit lesion only. The presence of severely stenotic non-culprit lesions that are not morphologically complex, especially when they are located in the anterior descending artery, increases the need for revascularization in the short to medium term because of the risk of destabilization.

Clinical implications

These results do not invalidate the therapeutic approach to culprit lesions in patients suffering from an acute coronary syndrome, but, along with other studies,23 they open the subject to controversy. This approach is based on the results of interventionist thinking during the eighties. Over the past several years great strides have been made, such as the generalized use of increasingly sophisticated stents, direct implant of the stent, IIb-IIIa receptor inhibitors, intravascular sonograms, pressure guides, etc., which unquestionably make it possible to obtain better results, even in patients with multivessel disease and complex lesions, as well as to assess the physiologic and morphologic features of lesions whose severity is uncertain.23 The additional risk of treating «non-culprit» lesions during the procedure can be very low and clearly compensated for by the reduced recurrence of destabilization and an appreciably lower incidence of stable angina during follow-up. According to our results, this would apply particularly to lesions located in the ADA. The only discouraging factor may be fear of restenosis. Still, the availability — now a reality — of stents that are coated with cytostatic agents would considerably reduce the problem. Nevertheless, today patients can be offered complete initial revascularization with a high degree of safety. Performing a test for ischemia early on is a valid option, but in these cases it may not reveal which patients are at higher risk of developing an unstable lesion, but only which ones are more likely to develop stable angina at follow-up. In this sense, it may be that the use of markers, such as C-reactive protein, will help identify patients who are at greater risk of destabilization.

We would like to dedicate this study to the memory of our recently departed colleague, Dr. Isabel Gómez.

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