

## Annexin V Levels in Young Patients with Acute Myocardial Infarction: New Answers Bring New Questions

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The sharp reduction in coronary blood flow produced by a thrombus generally precipitates acute or unstable coronary syndromes (ACS). Unlike venous thrombosis, arterial thrombosis takes place in areas where the vessel wall is damaged in some way. In the coronary arteries, the lesion usually is a fissured or ruptured atheroma plaque, endothelial denudation of an atherosclerotic lesion, or, as recently reported, a calcified eruptive nodule.<sup>1</sup> However, only a small percentage of the coronary lesions associated with thrombosis (complicated lesions) originate clinical manifestations. Postmortem studies of young patients who die from non-cardiovascular causes have demonstrated ruptured or simply eroded coronary plaques on which thrombi have formed that do not limit coronary flow and do not cause acute clinical manifestations.<sup>2,3</sup> Generally speaking, these thrombi, known as mural thrombi, show monocyte-macrophage invasion, are organized, and incorporated into the underlying plaque that further protrudes into the vascular lumen. Repetition of this process is one of the mechanisms by which atheroma plaques progressively narrow the coronary lumen.<sup>4</sup> Nevertheless, sometimes the mural thrombi serves as a basis for a new thrombosis originated days after formation, giving rise to an unstable coronary syndrome.<sup>4</sup>

What factors influence the final size and attendant clinical manifestations of a coronary thrombus? The degree of thrombosis will depend on the balance between anticoagulant and procoagulant activity present in a given moment. On the one hand, the type of vascular lesion has an influence as a prothrombotic factor: for example, a large plaque rupture that exposes the lipid nucleus to circulating blood is an important thrombotic stimulus that would give rise to a larger, possibly occlusive, thrombus. Another important factor is the thrombogenicity of the blood, understood as the amount of thrombus that an individual develops in res-

ponse to a given stimulus, and depends on the procoagulant and anticoagulant balance of plasma and blood elements. Differences in blood thrombogenicity between different patients would explain the development of occlusive coronary thrombosis on overflow thrombogenic plaques, such as those that present only endothelial loss.<sup>1</sup>

Blood thrombogenicity depends on all the factors involved in coagulation, although the pathophysiology differs in venous and arterial thrombosis. For example, none of the genetic risk factors for venous thrombosis (Leiden factor V, deficits in C-protein, S-protein, or antithrombin, and the 20210G >A mutation of the prothrombin gene) are risk factors for arterial thrombosis. In the arterial bed, thrombosis occurs in a high-pressure and high-flow system in which platelets and factors such as fibrinogen or von Willebrand factor play a key role.<sup>5</sup>

Much evidence demonstrates the contribution of thrombogenicity to the appearance of thrombotic complications of arteriosclerosis, such as ACS. For example, persons with von Willebrand's disease or hemophilia tend to have a low incidence of ACS. In contrast, patients with high fibrinogen concentrations or thrombocytosis (essential or reactive) have an increased risk of acute coronary events. Cardiovascular risk factors like diabetes, hypercholesterolemia,<sup>6,7</sup> and smoking are associated with increased blood thrombogenicity, which contributes, in part, to cardiovascular risk. The circadian pattern of ACS coincides not only with greater platelet activation, which, together with other factors, increases the probability that an occlusive thrombus will develop on a coronary lesion or previous mural thrombus at certain times of the day.

Young patients with myocardial infarction present a series of differentiating characteristics compared with older patients. Most patients are men who smoke heavily and have a family history of ischemic heart disease. In general, they have few obstructive arteriosclerotic coronary lesions, which partly explains the good prognosis of survivors.<sup>8-11</sup> Several studies have suggested that increased blood thrombogenicity is important in young patients with acute myocardial infarction.<sup>8-12</sup> Recently, the presence of occlusive coronary thrombo-

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sis on mildly thrombogenic atheroma plaques has been reported to be more frequent in smokers under the age of 50 years,<sup>1</sup> lesions over which a mural rather than an occlusive thrombi would be more expected to develop.<sup>3</sup>

In this issue of the *REVISTA ESPAÑOLA DE CARDIOLOGÍA*, Rodán et al<sup>13</sup> publish an interesting study in which they describe a prothrombotic factor present in a group of patients who suffered acute myocardial infarction before the age of 45 years: their plasma annexin V concentrations were significantly lower than those of a control group of 23 persons of similar age.

How would lower annexin V concentrations favor the appearance of an ACS in these patients? In the presence of a complicated atherosclerotic lesion, platelets form a plug by linking together and adhering to the exposed surface, covering the lesion with a strongly bound layer that resists arterial blood flow. While this platelet plug is forming in the vascular lumen, the interaction of tissue factor (TF) with circulating factor VII/VIIa activates the coagulation system. TF-VIIa complex (tenase complex) activates factor X (Xa) and factor IX. Factor Xa binds to factor Va, forming the so-called prothrombinase complex that catalyzes the formation of thrombin from prothrombin. The tenase-complex chain reaction that gives rise to factor Xa and the prothrombinase complex, forming thrombin, are the key to the initiation of the coagulation reaction and, particularly, its expansion. These two reactions require the presence of negatively charged phospholipids (anions), such as phosphatidyl serine, so that the proteins can couple together to function in the presence of calcium. The main source of these phospholipids, which enable the reaction to take place, is the platelet membrane forming the coronary platelet plug, which is rich in phosphatidyl serine. The thrombosis expands over this catalytic membrane surface. Under normal conditions, these anionic phospholipids of the cytoplasmic membranes have an asymmetrical distribution, being arrayed toward the cytoplasmic face of the cell membrane. This distribution impedes their contact with the proteins of the coagulation system. In response to a specific stimulus, these phospholipids turn and are exposed to the outer surface, thus allowing coagulation reactions to take place.

Annexin V is a plasma glycoprotein that has a high affinity for these anionic phospholipids, and is bound to them when they are exposed on the outer cell surface. The result of this union is to block the reactions of the tenase and prothrombinase complex, thus inhibiting the activation of the coagulation cascade at its onset and preventing its expansion. Clinical evidence of the importance of this thrombosis regulation pathway can be found in at least two situations. In the Scott syndrome, activated platelets do not change phospholipid distribution (phosphatidyl serine remains on the cytoplasmic face) and there are not enough anionic

phospholipids to allow coagulation to be activated, thus originating a hemorrhagic tendency. In the antiphospholipid antibody syndrome, the Rand group have shown that auto-antibodies keep annexin V from binding to the anionic phospholipids and generating its inhibitory effect. At the same time, tenase and prothrombinase complex binding is unaffected, which is associated with the appearance of arterial and venous thrombosis. The work of Roldán et al. published in this issue of the journal<sup>13</sup> explores this pathway in young patients with a history of acute myocardial infarction. Although antiphospholipid antibodies are detected only in a small percentage of persons, it is very likely that the fact that annexin V values are lower in the group of patients reflects a predisposition toward occlusive coronary thrombosis in the presence of coronary arteriosclerosis, because thrombin formation is inhibited less than in normal persons. Lower concentrations of this circulating glycoprotein may also favor the formation of a more exuberant and obstructive acute thrombosis than would appear in the presence of normal concentrations, thus meeting the theoretical requirement of favoring the formation of a greater thrombus in response to the same stimulus, that is to say, a similar lesion of the coronary wall.

The patients in this study included a smaller proportion of smokers than other published series and a low rate of cardiovascular risk factors, although only four factors were recorded. Perhaps the fact that the patients were selected during clinical follow-up in the outpatient clinic meant that some of those risk factors ceased to exist. For example, smoking is no longer a factor in patients who stop smoking. Still, this approach has the advantage of avoiding the acute phase of the infarction, in which treatment and other uncontrolled variables could reduce the validity of the finding. Many questions are raised by the results of this study. It would be interesting to know if there are factors that modify annexin V concentrations and if the concentrations of this glycoprotein are influenced by any of the measures used in the secondary prevention of ACS. This could explain some of the clinical benefit, or the absence of any clinical benefit, in some patients. If another control group formed by patients with a history of myocardial infarction and a typical age for developing this condition (about 65 years in Spain) had been available, we would have been able to determine if annexin V plays a specific role in young patients with infarction compared with other patients with ischemic heart disease. The influence of genetics and environment on annexin V concentration, and what relation annexin V has with a familial history of early arterial thrombosis or venous thrombosis, are other points to consider. In summary, more studies are needed to assess the value of this potential «annexinopathie»,<sup>14</sup> and its clinical importance.

In any case, in spite of its limitations, this study des-

cribes a factor that could be involved in the appearance of ACS in younger patients, in which prothrombotic factors may have a key role. Findings like those described by Roldán et al tell us more about ACS while opening up an interesting field for future investigation into the possible influence of annexin V factors on the appearance of ACS.

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