Troponins and Other Markers of Cardiac Damage. Miths and Realities

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When the myocytes necrose, or suffer important cellular damage, the integrity of the membrane is lost and macromolecules can pass to the interstitial tissue, from where they are absorbed by the capillaries and lymphatic system, finally reaching the systemic circulation.[1] The macro-molecules released by the myocytes receive the name of biological markers of myocardial damage and, with no little controversy, have acquired an enormous clinical relevance, especially since techniques have become available to identify and quantify proteins that are specific to the myocardium. In the 1960s it was possible to determine the plasmatic concentrations of CK, GOT, LDH. Although these determinations are not specific to cardiac tissue, they changed the criteria used to diagnose acute myocardial infarction (AMI).[2] These criteria, with time, were either adapted or shown to be adulterated, according to the best-considered opinion of different groups of investigators.[3] More recently, it has been demonstrated that some cardiac proteins, especially troponin I, troponin T and, to a lesser degree, CK-MB isoforms[4,5] present an amino acid sequence exclusive to myocytes and can be identified using monoclonal antibody techniques. Therefore, they are very specific for myocardial damage and, in addition, very sensitive,[1,4-7] which led to yet another change in the definition of acute myocardial infarction[8] and a new controversy.[3]

The present number of the REVISTA ESPAÑOLA DE CARDIOLOGÍA includes four articles on troponins,[9-12] three of which demonstrate its clinical utility. In the article by Moríñigo et al.,[9] high troponin I concentrations were examined in relation with the long-term prognosis of the patients hospitalized with the initial diagnosis of unstable angina. Roldán Torres et al.[10] analyzed patients with acute coronary syndrome without ST-segment elevation and observed in this study that patients who had elevated concentrations of troponin T at 3 months of follow-up also had a worse evolution. In a third article, Paschal Figal et al.[11] relate the combined measurement of both troponins (I and T) with the effectiveness of treatment of patients with precordial pain in the emergency room and, ultimately, with the reduction of costs. The conclusions of these articles are not unique or original. The relation with prognosis and the usefulness of the new markers of myocardial damage had already been studied in various investigations, with the same results. What is interesting is to analyze the last of the studies,[13] in which the Section on Ischemic Heart Disease of the Sociedad Española de Cardiología (Spanish Society of Cardiology) analyzes the findings of a national survey on the applicability of the new definition of myocardial infarction in Spanish hospitals. In half of them, no specific measurements of markers (troponins, CK-MB mass) were available. Even when their determination is possible, their use is limited or they are not considered adequate for the diagnosis of infarction, although it is probable that perceptions of the utility and use of troponins, CK-MB mass, and myoglobin are changing progressively. In fact, although it is not mentioned in the article, in some hospitals the simultaneous determination of several markers and repetition of the determinations in populations with or without a well-founded suspicion of acute coronary syndrome has become an important care and economic problem.

The new markers can be used for three purposes: the diagnosis of infarction, assessment of the prognosis, and as a guide for therapeutic actions. In these three cases, the markers of myocardial damage can either be very useful or lead to important clinical errors.

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DIAGNOSIS OF MYOCARDIAL DAMAGE OR ACUTE MYOCARDIAL INFARCTION

The new definition of infarction proposed by the American Heart Association, American College of Cardiology, and European Society of Cardiology is based on the demonstration of abnormal plasma concentrations of troponin (I or T) or CK-MB mass. Both molecules are very specific to myocardiocyte injury and also very sensitive, especially troponins. Using these determinations, more infarctions can be identified and a certain number of false positives can be avoided, compared with the use of earlier criteria. Nevertheless, the use of troponins for the diagnosis of AMI has several drawbacks or limitations, which is why their interpretation should be cautious. In first place, values can be different in different laboratories, depending on the method of determination (differences of up to 100 times within the limits of normality)[14,15] and quality controls used (or, sometimes, not used). In other words, the physician may rely on false results for guidance, believing that the laboratory report is infallible. Secondly, the elevation of troponin values indicates myocardial damage, not necessarily ischemic necrosis. Increased troponin due to myocardial damage can be found in myocarditis, pulmonary embolism, stroke, renal insufficiency, sepsis, aortic dissection, heart failure, chemotherapy, after strenuous physical exercise, and ventricular hypertrophy.[16-19] Plasma concentrations may even increase in the absence of myocardial damage,[20] so troponin concentrations can only be interpreted in relation to the general clinical context of the patient. On the other hand, the practical utility of the troponins in the diagnosis of infarction is limited to doubtful cases, in which this determination can identify myocardial necrosis in situations that otherwise would be classified as angina without myocardial necrosis. It is likely that one third of the patients diagnosed as unstable angina can be classified as myocardial infarction using troponin determinations, which are more sensitive than conventional markers of myocardial damage.[21] An interesting aspect of the different biological markers is their plasma elimination. In this sense, although there are no clinically significant differences in the speed of appearance (with the exception, perhaps, of myoglobin, which appears earlier: 1-2 h), elevations in the troponins persist longer (up to 7 days for cTn-I and 14 days for cTn-T), whereas the other markers (CK-MB mass, CK-MB isoenzymes, and myoglobin), although not specific, are eliminated more quickly, beginning to descend in 24-48 h. For that reason, the troponins are useful for identifying myocardial necrosis several days after the initial clinical episode. In contrast, the other markers are especially useful in the diagnosis of preinfarction, when plasma troponin concentrations are still high.[22-28] Finally, a frequent error of inexperienced physicians is to consider that the presence of normal troponin values excludes the diagnosis of acute coronary syndrome, an error that requires no further commentary.

ASSESSMENT OF THE PROGNOSIS

All the serum markers of myocardial damage provide prognostic information. Elevation of any of the markers is associated with an increase in the mortality and morbidity of patients with suspected acute coronary syndrome, and the relative increase of plasma concentrations in cases of infarction is also associated with a worse clinical evolution.[22,29] Why is there a special interest in the prognostic value of the troponins? Perhaps the response is that plasma troponin concentrations provide prognostic information in addition to that obtained from clinical parameters,[30-32] even when the classic markers are normal,[21] which supports the new diagnosis of AMI. No clear differences have been demonstrated in the prognostic relation of troponin T and I,[29] but there is an association with various biological markers, including C-reactive protein and atrial natriuretic peptide.[33,34] The question, in this case, is whether several determinations should be made of different markers. At present, the response is negative. The prognosis of patients with suspected acute coronary syndrome or confirmed infarction is multifactorial and cannot be ascertained from the analytical determination of markers of myocardial damage alone. The clinical characteristics of the patient, as a whole, are what determine prognosis.[35-38]

TROPONINS AS A GUIDE TO THERAPEUTIC ACTION

Patients with abnormal troponin values obtain more benefit from certain therapeutic interventions than patients without troponin elevation. Although there is no study in which this hypothesis has been directly analyzed, subanalyses of the FRISK[39] and TIMI 11B[40] studies suggest that anticoagulation with low-molecular-weight heparins is more effective in the subgroups that have high concentrations of markers (and, in contrast, loses clinical effectiveness in groups with negative concentrations of markers). The findings were similar when the subgroups that benefited from inhibitors of the glycoprotein IIb-IIIa receptors were analyzed. In practically all the studies, the benefit of their use in patients with acute coronary syndromes is greater in the presence of abnormal troponin concentrations and is lost again in patients without elevation of the concentrations of markers.[41-43] Nevertheless, as occurs with the diagnosis of myocardial infarction and the prognostic assessment of patients,

treatment cannot be determined by a single parameter. The combined assessment of patient characteristics is what makes the correct diagnosis, adequate risk assessment, and selection of the best therapeutic strategy possible.

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