

C-Reactive Protein in Acute Coronary Syndrome. Looking Back in Order to Move Forward

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Recent years have seen a spectacular rise in the importance of biomarkers in acute coronary syndrome (ACS). The most notable of these biomarkers is, without doubt, troponin. Its usefulness for diagnosis, decision making, and prognostic stratification have been fully validated, and its use in daily clinical practice is now widespread.¹ It should be pointed out that the kinetics of troponin release were studied in detail for different types of ACS right from the outset. This approach has clearly laid a solid foundation which has contributed to the current popularity of this marker.

However, it was soon evident that not all patients with ACS and elevated troponin had a very poor prognosis,²⁻⁶ and that patients with chest pain and normal troponin levels did not always have an excellent prognosis.^{7,8} It therefore became clear that other factors besides troponin levels and electrocardiographic findings needed to be taken into account. A full clinical evaluation of the patients using risk scales,⁷ early stress tests,⁸ and gathering all available information in dedicated chest pain units⁸ have proved decisive developments. Alongside these, the incorporation into daily practice of new biomarkers has provided another important tool.^{1,2} Biochemical information can currently be obtained for almost all pathophysiological processes implicated in ACS^{1,2,5} but, besides troponin, the marker that has deserved most attention in the last decade is C-reactive protein (CRP).²⁻⁶

Recognition of the importance of inflammation in the development of arteriosclerotic disease in general and ACS in particular has arisen in parallel with interest in CRP.^{1,2} After years of investigation, we now have fairly precise knowledge of the role this biomarker plays in non-ST-elevation ACS. Unlike

troponin, its use is essentially prognostic—it provides little diagnostic information and does not help to guide therapeutic decisions. Nonetheless, this does not detract from what this biomarker can offer. We should, after all, remember that our duty is not just to administer treatments but also advise the patients and their families of what they can expect in the future. To this end, CRP is a predictor of medium- to long-term mortality. Once adjusted for traditional risk factors, it implies that the risk of death in the following months doubles.³⁻⁶ The biggest advantage of this biomarker is probably that this quantifiable information can be obtained from a simple assay.

Joint analysis of troponin and CRP has shown that these markers are independent and additive. A simultaneous increase in the levels of both markers is associated with a very high risk, an increase in just one of them with an intermediate risk, and no increases in either with good prognosis.³⁻⁶ The addition of new markers to troponin and CRP is giving rise to the so-called “multimarker strategy” for assessing patients with non-ST-elevation ACS.^{2,5} C-reactive protein has also been useful in predicting risk in patients with ACS who undergo percutaneous revascularization, with a higher elevation being associated with more events in the following months.⁹

Most of the evidence has accumulated for cases of non-ST-elevation ACS, but increased elevation of CRP has also been associated with more complications in cases with ST-segment elevation. In such cases though, the greater increase in CRP is clearly dependent on greater necrosis and analysis of systolic function can make the information provided by this redundant.¹⁰

We should also highlight situations in which CRP does not provide any relevant information. This marker, unlike troponin, does not predict reinfarction.^{3-6,9} Likewise, it is not considered a reliable marker of ischemia or for confirming diagnosis of ACS in the emergency room; clinical assessment, electrocardiogram, troponin, and an early exercise test seem to be much more useful in this situation.^{1,7,8} Other markers such as natriuretic peptides seem to provide more information for of risk stratification in patients with no signs of ischemia (negative troponin or electrocardiogram).^{1,2} Although CRP elevation has been associated with greater short-term risk,¹¹ its role

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seems to be more consistent with predicting medium- to long-term risk. Finally, there are no conclusive data on its importance for guiding therapeutic decisions. Although CRP reduction with statin therapy is clearly associated with greater beneficial effects than would be expected from reduction in cholesterol levels alone,⁹ its role in other situations, such as invasive treatment, has not been proven.

Therefore, other markers, in particular, troponin should be used as indicators of diagnostic usefulness and to guide therapeutic decisions,¹² whereas the usefulness of CRP lies in predicting events, particularly mortality, after ACS.

Despite the intensive effort that has gone into investigation of CRP in ACS, it is striking that questions such as “When should the sample be taken?” “What cutoff should be used?” and, most importantly, “Why are CRP levels elevated?” have yet to receive a satisfactory answer.⁹ In the current issue of *REVISTA ESPAÑOLA DE CARDIOLOGÍA*, Sánchez et al¹³ present data that will help clarify these points.

The authors prospectively analyzed a group of 110 consecutive patients admitted for ACS. A strong point of their study design is that they analyze CRP kinetics separately for 3 groups of patients. These groups correspond to the type of ACS: ST-elevation infarction, non-ST-elevation infarction, and unstable angina. The serial analyses done during the stay in hospital enabled them to show that the 3 groups initially had similar CRP levels. These levels increased at around 6 hours and reached their peak values at between 36 hours and 48 hours. Peak levels are much higher in infarction with ST-segment elevation, intermediate in non-ST-elevation infarction, and low in stable angina. The increase in CRP levels followed that of troponin, but with a lag of a few hours, and peak values of both markers were directly correlated.

This study is a good example of a simple but appropriate design that clarifies an issue not satisfactorily answered by previous studies (and whose interpretation requires extensive knowledge of the field) without large populations or resorting to statistical tricks. Such studies can help drive research forward.

The data reported by Sánchez et al¹³ do not indicate when the sample for CRP should be taken in patients admitted for non-ST-elevation ACS or what cutoff to use, but the authors do provide some important clues. Although serial determination is ideal, this option cannot be applied to daily practice because of logistic reasons and the low cost-effectiveness ratio.

Of the 2 possibilities—sampling when the patient arrives in the emergency room or once after admission between 24 hours and 48 hours after onset—an early measurement can provide information on the patient’s baseline risk free from the influence of the current episode. Information may also be obtained on the

inflammation caused by rupture of unstable plaque. The cutoff in this early measurement should be low (<5 mg/L).⁹ However, early measurement does not provide information on the inflammatory state triggered by necrosis if this has occurred. On the other hand, it is hard to determine the exact onset of the current episode if our intention is to eliminate the influence of necrosis from our measurement. Finally, early measurement of CRP will not substantially influence the treatment given. This will depend more on the patient’s clinical status, the electrocardiogram, or troponin.

The biggest contribution of CRP to prognosis is in the prediction of medium- to long-term mortality.^{3-6,9} This information is not essential to have during the first few hours in the emergency room. The prognostic value has been demonstrated in studies in which the sample was taken at least 24 hours after admission.⁹ To improve the cost-effectiveness ratio, a single measurement of CRP from routine blood sampling the day after admission, close to the peak value, is probably sufficient for risk stratification in view of CRP kinetics. In our experience^{4,5} and that of other authors,^{6,9} CRP levels above 10 mg/L between 24 hours to 48 hours after onset of non-ST-elevation ACS are associated with a greater probability of events, particularly death, in the following months.

We therefore emphasize that interpretation of CRP levels will depend on when the sample was taken and that the cutoff applied for prognostic purposes will be different if sampling was early (lower cutoff) or late (higher cutoff). For ST-elevation ACS, the cutoff has to be even higher.¹⁰

The findings of Sánchez et al¹³ can also help interpret the mechanisms that lead to increased CRP in ACS. In short, it seems that 3 mechanisms are implicated:

1. Rupture of unstable plaque or high presence of unstable plaque in patients with ACS could trigger an inflammatory response and, as a result, release of CRP as an acute-phase mediator.¹⁴ It has even been suggested that CRP could exert direct effects on the arterial wall and trigger destabilization.⁹ This mechanism might contribute to elevated CRP in the first few hours of the episode, but can rupture of a plaque measuring a few millimeters explain an elevation of CRP to between 100 and 1000 times normal? Furthermore, why is CRP elevation much greater in patients with ST-elevation ACS than in those with non-ST-elevation ACS even though the characteristics of the unstable plaque are similar?

2. From the findings of Sánchez et al¹³ and previous studies,¹⁵ the principle mechanism responsible for CRP elevation in ACS is clearly necrosis. Levels are much lower in non-ST-elevation infarction ACS which has less myocardial damage. In patients with unstable

angina, levels are even lower, although the study did detect a certain CRP elevation perhaps in this case because of the type of plaque. However, this theory is not fully accepted and the small CRP elevations in cases classed as unstable angina might also result from undetected necrosis.

The correlation between major necrosis and large CRP elevation also explains the weak association between this marker and reinfarction. Patients with greater elevation are also likely to be those that have suffered more extensive necrosis and, therefore, new infarction is less likely.⁹ However, the correlation between CRP and extent of the infarction, although significant, is far from perfect.^{6,15} Unfortunately, the authors do not provide any imaging data which might help to better quantify the association between the size of the necrotic region and CRP elevation. Moreover, if CRP elevation were due only to infarct size, its predictive power would disappear once adjusted for necrosis markers or variables of systolic function. That this does not happen is probably due to the third mechanism implicated in CRP elevation in ACS.

3. Inflammatory response varies greatly from individual to individual. Recently de Servi et al⁹ have suggested that CRP elevation during ACS is partly determined by baseline CRP levels and, therefore, by the baseline inflammatory status. The higher the CRP levels before ACS, the larger the increase during the acute episode. Thus, a greater increase in this marker during ACS would also indicate that the arterial system is more inflamed, with a larger number of unstable plaques and, in short, a higher baseline cardiovascular risk.

From the outset, a large part of CRP research has focussed on the clinical usefulness of the marker, with little time for reflecting on its kinetics or the mechanisms that might lead to its elevation. As the saying goes, better late than never, and now is the moment to assimilate all the clinical information, take a step back, and interpret as best we can what we already know. We should therefore welcome the publication in REVISTA ESPAÑOLA DE CARDIOLOGÍA of the findings of Sánchez et al¹³ on the kinetics of this marker in the different clinical manifestations of ACS. The information they provide is novel, the study is not large but rarely has the question been approached with such an elegant and clear methodology. This step back will doubtlessly help us to continue to clarify the important points and, ultimately, to make progress.

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