C-Reactive Protein in the Emergency Department: Has It Found a Clinical Application?

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For now, CRP remains innocent until proven guilty.
Scirica BM, Morrow DA

The investigation of the risk factors, of the thrombotic phenomena, and more recently of the role of vascular inflammation has been fundamental in advancing our knowlege, both of the etiopathology and the pathophysiology of atherosclerotic disease. Thus, we have understood how a stable atheromatous plaque is established and developed and how it is transformed into a "vulnerable" one, which represents the commonest underlying commonest cause of acute coronary syndrome (ACS). Since in both processes inflammation has a preponderant role, numerous studies, either individually or combined, have investigated if the use of markers of the inflammatory process can improve the diagnosis, the prognosis, stratification, or even the treatment in a convincing form, so that they can be used in daily clinical practice.[1]

We know that in the ACS, thus defined since the eruption into clinical practice of the troponin biomarker, a very complex series of highly overlapped inflammatory and thrombotic phenomena lead to the fissure of an atheromatous plaque, which until then had been stable. A series of reactions begin that will conclude with the partial or total occlusion of one or more coronary arteries, and the known clinical consequences.[2]

A key question, which the investigators have been formulating as often as the clinical physicians in the last decade, is if the inflammatory markers can be used to improve the clinical risk stratification in the patients with ACS. Among inflammatory markers, C reactive

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protein (CRP) has been studied in healthy individuals[3], in stable patients[4] and in subjects with ACS.[5] Among the reasons for its use is the fact that this marker is one of the few that has several of the essential requirements that makes a biomarker of practical utility in a clinical scenario.[6] It is possible to point to the following ones: it can be determined by means of a robust test with a good coefficient of variability; it is related to the ethiopathogenic process (in this case, the inflammatory process); it provides independent information, and it has an acceptable cost-effectiveness ratio, a suitable standardization, a validated cut-point, a high sensitivity, as well as simple stability, and storage conditions.

In spite of all these advantages, the validity of some of the initial studies conclusions, those that considered it a useful marker to discriminate the risk in different populations has recently been put in doubt.[7]

Criticism has been centered fundamentally in that, although it is recognized to be associated with an independent risk factor, it has not been able to entirely demonstrate—perhaps by its strong association with the well-known risk factors—that the use of CRP in clinical models improves discrimination of risk in the individual patient, since its incorporation does not seem to significantly increase the area under the ROC curve, which is a form to evaluate objectively the utility of clinical markers.

As far as methodology, it is considered necessary that the incorporation of a variable that demonstrates in a certain statistical model to be an independent risk factor show a predictive effectiveness superior to that offered by classic risk factors; that is to say, that improves in a significant way the area under ROC curve.

Proof of this is the conclusion of the last consensus of the American Heart Association/American College of Cardiology of 2003,[8] that considers that there is no type I indication—there are scientific tests and general agreement in which the procedure or treatment is useful and effective—for the use of the CRP in ACS, although it indicated that CRP has a class IIa indication–the scientific tests available are controversial and/or divergent as far as its efficacy as a procedure or treatment, but the weight of the scientific opinion tests is in favor of the procedure or treatment.

In spite of this, CRP is not used systematically, in Europe in general and Spain in particular, as a marker for cardiovascular risk in the general population. It is not employed as a risk marker or diagnostic tool in the emergency departments nor in patients with ACS admited to coronary units. Nevertheless, the search for a precise clinical utility for CRP continues at the present time in different centers around the world.

In this number of *Revista Española de Cardiología*, Lozano et al[9] communicate the results of an elegant study on the value of the serial determination of CRP in patients with chest pain who go to the emergency department without displaying electrocardiographic changes and with normal troponin values. The authors part from the hypothesis that "the concentration of CRP would rise if the symptoms were caused by coronary endothelial damage and the rupture of the atherosclerotic plaque."

The results of the study indicate, on the one hand, that the variation between both samples is significantly related to the presence of coronary disease, and on the other hand, that the absence of a difference between the 24 h CRP levels and those measured upon arriving at the emergency room allows the clinician to identify a sub-group of patients that does not present a cardiovascular event at least during a 1 month follow-up.

The authors indicate that, in this type of patients, 2 serial measurements in 24 h that do not show differences, allow the safe discharge from the hospital and rules out the presence of significant coronary disease. The patients included in this study are "low risk," although we know that "low risk" does not mean "absence of risk," and that this population has an important number of events in the 4 weeks following the discharge from the emergency room.[10]

Therefore, every effort made to improve the identification of the sub-group of patients with a greater possibility of developing coronary events is widely justified.

In order to try and propose a solution, among others, to this important problem, a functional units of chest pain unit (CPU) was proposed, which demonstrated a low incidence of events in the type of patients included in this study, when a treadmill test (TT) is negative.[11,12]

A problem of the functional CPU, beyond the logistic difficulties that many hospitals, in Europe in general and Spain in particular, present is that a high proportion of the patients who go to the emergency department with evident pain (older patients, with complete heart block, ventricular pacemakers, left ventricular hypertrophy, joint problems, etc) cannot undergo a TT, with the added problem that other tests that can adequately replace it —such as stress echocardiography require trained personnel, and others—like the radionuclide studies, the computerized tomography, or magnetic resonance are expensive and are unavailable in most hospitals. Recently the utility of "a structural" CPU has been published (with round the clock facilities available), that has established the prevalence of the motives for thoracic pain in a Spanish population. This is important data, unknown until this moment and that, in addition, demonstrates the necessity of a larger effort on the part of the authorities to extend this type of units to all territories.[13] Nevertheless, this study also made the limitations of the TT stand out, solved by the presence of a 24 h cardiologist, in addition, to doing others tests for the detection of myocardial ischemia.

The population studied by Lozano et al[9] could benefit from the finding of a simple and practical biological marker that allowed certain exclusion of the vulnerable patients. If the important findings communicated by these investigators[9] were confirmed in future studies with a greater number of patients, representative of the general population in Spain and also in other countries, would have an important clinical tool for the stratification of patients in the emergency departments.

Identifying the low risk patients, who can be discharged in a safe manner, is as important as identifying to those at high risk that require an urgent intervention. With respect to the CRP, its low predictive value is known when it is determined at the moment of arrival at the emergency room and we also know that in ACS its concentration increases from 12 h after the beginning of symptoms, reaching its maximum concentration at 48 h. In Spain, Sánchez et al[14] have pointed out to these kinetic characteristics of CRP and the necessity to consider these variations at the time of designing studies on inflammation markers. In the same way, Domínguez et al[15] have shown circadian changes in the values of CRP and cytokines, that should also be evaluated when determining the number and the hours since extraction of the blood samples. Also Strachan's group,[16] in London, has demonstrated the importance of the circadian variations of the inflammation and coagulation markers, which can introduce errors in the analysis of risk factors in epidemiological studies related to coronary disease.

In addition to these considerations, one of the limitations of this interesting study of Lozano et al[9] is the adjustment that the authors have made in the logistical regression model. The significant elevation of this acute phase reactant in the 24 h determination since the onset of chest pain in the patients who only had coronary disease obtains an area under the ROC curve of 0.68; that is to say, it has a little predictive capacity. The difference in CRP levels between the 2 samples, on the contrary, present in the model of logistical regression shows a very robust odds ratio (OR), after adjusting for a history of hypertension, preexisting coronary disease, and treatment with anti-inflammatory drugs. For a better statistical analysis it is necessary that the models are

adjusted for other known risk factors, although these have not reached statistical significance. Surely, if it had been done in this case, the value of the OR would have been lower and the area under the ROC curve would diminish, in comparison with the value communicated in the study (0.77),[9] which can be considered as of acceptable predictive capacity.

Another limitation of the method proposed by this study, that must be evaluated, constitutes the fact that the patient must remain hospitalized an entire day, increasing the costs, and generating logistical problems in already overflowing emergency departments, unless the hospital has as structural CPU.

Also the authors emphasize another limitation of their investigation: the lack of cardiac catheterization to establish the presence of real obstructive coronary disease, establishing bias that must be evaluated. The well-known high sensitivity of CRP does not hide its low specificity; finally, the insufficient sample size prevents definitive conclusions. The study of Lozano et al[9] is of clinical interest and must serve like a stimulus to generate multicentre studies, with adequate size samples, so that they allow to define with certainty if the proposal of these authors is of true clinical utility. This step is essential to obtain a definitive answer to the interesting question that opens this study.

The present situation in which markers of inflammation are in the land of prognostic stratification can be defined as one of uncertainty, since up to the present moment its use in clinical practice is not authenticated by solid scientific tests.

Gaps in the standardization of the analytical methods prevents the comparison and implementation of the findings. CRP is best positioned, but the problem continues to be its inability to add additional prognostic information to that contributed by conventional risk factors; or, in other words, its inability to improve the area under the ROC curve and to demonstrate that it increases the discriminative power of conventional biomarkers.

Although its relation with the inflammatory process is undeniable and its capacity as an independent risk factor is widely demonstrated, its ability to improve the prognostic stratification in the individual patient continues to be controversial.

In relation to markers of inflammation in general, including PCR, additional effort is required on the part of the investigators to manage standardization of methodology, to establish cut-off points that separation of populations with different risks, and to determine cost-effective timing and frequency of measurements.

Future investigations require stablishment of more suitable methodology inclunding, in addition, of the previously discussed analytical considerations, appropriate statistical analysis. The Inflammation Group of the Section of Ischemic Cardiopathy of the Spanish Society of Cardiology is elaborating a document with methodological recommendations that will allow the optimization of our limited resources on which we often rely for this type of research, in an attempt to make the effort of the investigators as profitable as possible.

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