

## Editorial

## Multimarker Panel for Patients With Chest Pain: Case Closed?

## Panel multimarcador para pacientes con dolor torácico: ¿está todo dicho?

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Chest pain is one of the symptoms that most frequently compels patients to consult emergency services. When acute coronary syndrome is suspected, early diagnosis facilitates the immediate implementation of decision and treatment algorithms that favorably affect the prognosis. Thus, patients not showing electrocardiographic changes or pain conclusive for myocardial ischemia in the initial evaluation will remain under observation, awaiting a series of clinical, electrocardiographic, and biochemical evaluations that will help to stratify risk and establish the definitive diagnosis.

Diagnosis of acute myocardial infarction currently requires the finding of increased or decreased values of a specific biomarker of myocardial damage or necrosis; due to its high sensitivity and specificity, the biomarker of choice is troponin. An infarction is diagnosed when, in patients with clinical features indicative of or compatible with myocardial ischemia, at least 1 serially performed troponin measurement is above the 99th percentile of the upper reference limit according to the specific assay used in each laboratory.<sup>1</sup> If no troponin measurement is available, the best alternative is to search for a similar alteration in the creatine kinase MB fraction (CK-MB) (determined with the mass assay). Despite the indisputable progress that has enabled troponin to be measured in emergency department laboratories at any given moment, it is well known that many other clinical situations distinct from acute coronary syndromes can present with an increase in troponin<sup>2</sup> and that both its maximum values and its release kinetics can be influenced by diverse factors.<sup>3</sup>

The manufacturers of the troponin test kits have improved their ability to detect minute quantities, which has greatly increased their sensitivity in the diagnosis of small infarctions. Nowadays, the latest generation of highly sensitive or ultrasensitive methods for measuring troponin (usTn) are replacing the conventional methods that have been used thus far in Spanish hospitals.<sup>4</sup> The most important practical consideration is that conventional methods have relatively low or inadequate sensitivity during the first few hours after symptom onset, which can delay diagnosis and treatment administration and prolong patient stay in emergency departments. It is precisely these aspects that have been improved

with usTn use, particularly in the first few hours after symptom onset.<sup>5</sup> In fact, the latest clinical practice guidelines recommend usTn determination, if available.<sup>4</sup> Thus, when less than 6 h have passed from the chest pain episode, a second usTn measurement is recommended 3 h after patient arrival at the emergency department (the recommendation for conventional troponin is 6–9 h). If more than 6 h have passed since the chest pain episode, a single negative usTn result is sufficient to rule out myocardial necrosis. Furthermore, like its predecessors, usTn has demonstrated independent predictive value in short- and medium-term prognosis and mortality.<sup>6,7</sup>

However, as usual, usTn also has controversial aspects. Numerous publications argue that the enhanced sensitivity of this method is produced at the expense of its specificity and positive predictive value, with a consequent increase in the number of false positives.<sup>8</sup> Thus, out of every 100 patients attending emergency services with chest pain and showing usTn elevation in the first few hours after symptom onset, only 50%–80% (depending on the usTn test used) will receive a final diagnosis of infarction.<sup>5</sup> This can lead to excessive concern among physicians, unnecessary tests, and administration of inappropriate treatments in a considerable proportion of patients. The aim of these considerations is not to cast doubt on the tissue specificity of troponin (myocardiocyte-specific), but to stress the need to evaluate usTn values within a clinical context compatible with myocardial infarction and always after excluding other serious conditions that could have increased these values.

In this scenario, there is a renewed interest in identifying markers whose plasma concentrations are increased before the onset of myocyte necrosis. Natriuretic peptides, also called cardiac hormones, have been proposed as markers of myocardial ischemia. These peptides include atrial natriuretic peptide, largely secreted by atrial myocytes, brain natriuretic peptide (BNP), thus named because it was first isolated from pig brain, which is principally expressed by ventricular myocytes, and type C natriuretic peptide, predominantly expressed in endothelial cells. BNP and its inactive N-terminal fragment, NT-proBNP, are derived in turn from a precursor (pro-BNP) that is released into the circulation from ventricular myocytes in response to an increase in cardiac wall stress, such as from myocardial ischemia.<sup>9</sup> The physiological effects of BNP (the active form) include peripheral vasodilation, stimulation of natriuresis, and inhibition of the sympathetic nervous and renin-angiotensin-aldosterone systems. In heart failure, secretion of these peptides increases with disease

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progression, and measurement of their plasma concentrations has become a useful tool for determining diagnosis, prognosis, and treatment response. Thus, BNP or NT-proBNP measurement is included in the diagnostic algorithm of acute and chronic heart failure recommended by current clinical practice guidelines. The principal benefit of BNP determination lies in its high negative predictive value, which allows heart failure to be ruled out when BNP concentrations are not increased.<sup>10</sup>

Furthermore, in acute coronary syndromes, measurement of plasma BNP concentrations could provide additional prognostic information that is independent of classic risk stratification,<sup>11</sup> and there is a growing interest in the potential role of these peptides in the early diagnosis of acute chest pain of uncertain origin. From the pathophysiological point of view, ventricular wall stress increases during episodes of myocardial ischemia, resulting in the release of these markers into the plasma, where they can be detected even when myocyte necrosis is not occurring or is yet to occur. Accordingly, BNP are detectable in patients with acute coronary syndrome and normal, or still normal, usTn. In this regard, reports published several years ago indicated the additional value of BNP when added to the detection of traditional markers in increasing the sensitivity of early diagnosis of ischemic chest pain.<sup>12</sup> However, most of these studies were performed in the era of conventional troponin analysis and very little information is available on the usefulness of these markers in the current context of usTn use.

In an article published in the *Revista Española de Cardiología*, Sanchis et al.<sup>13</sup> present an excellent study into the benefits of including NT-proBNP in the determination of ultrasensitive troponin T (usTnT) in the diagnosis and short-term prognosis of patients with chest pain. Their study included 398 patients who presented to the emergency services of various Spanish hospitals with chest pain and who showed normal conventional troponin levels in 2 sequential measurements (on arrival and at 6–8 h). The authors concluded that, in this group of patients with chest pain of uncertain origin and low risk (without electrocardiograph changes and with normal conventional troponin values), NT-proBNP provided no additional information to usTnT in establishing the diagnosis or estimating short-term prognosis. The reasons put forward by the authors to explain this negative result are that they used one of the most sensitive methods for usTnT determination, the small sample size, the low risk of the patients included, the short follow-up, and the possibility that NT-proBNP may have been measured outside the period when it is most useful.

These results contradict those obtained recently and independently by 2 other studies with even smaller sample sizes and even longer blood sampling delays. Both studies concluded that the additional measurement of NT-proBNP improves diagnosis<sup>14</sup> and prognosis<sup>15</sup> in the initial management of patients evaluated with the same usTnT test as that used by Sanchis et al.<sup>13</sup> In addition to the different times chosen for NT-proBNP determination, other important differences between these studies may explain the discrepancies among the results. Chief among these differences are the disparities between the chosen inclusion and exclusion criteria and the cut-off points established as normal for NT-proBNP. For example, the presence of heart failure or renal insufficiency was an exclusion criterion in the studies by Sanchis et al.<sup>13</sup> and Truong et al.,<sup>14</sup> respectively, but neither disease was an exclusion criterion in the study by Melki et al.,<sup>15</sup> which could have significantly affected the results obtained, given that both conditions affect circulating NT-proBNP and troponin values. Moreover, the cut-off points chosen for NT-proBNP by Sanchis et al.,<sup>13</sup> Truong et al.,<sup>14</sup> and Melki et al.<sup>15</sup> were 125 ng/L, 50 ng/L, and 300 ng/L, respectively, which were arbitrarily selected because reference values remain to be established for the use of NT-BNP in the diagnosis of acute coronary syndrome. Additionally, none of

these studies included the multiple factors that affect the normal values of natriuretic peptides (eg, age, sex, lean body mass, renal insufficiency), all of which are difficult to adjust for with small sample sizes. Finally, another important consideration is that the results of the study by Sanchis et al.<sup>13</sup> were derived from a substudy; due to their idiosyncratic nature, such analyses have statistical limitations that make it difficult to obtain conclusive scientific evidence.

In view of the above, our opinion is that caution should be exercised when interpreting the results of these studies and, above all, when asserting the utility—or lack of utility—of NT-proBNP in the management of patients with chest pain and a negative usTn result. In the multimarker approach to patients with chest pain, the case is clearly not yet closed. There is a need for further studies, preferably specifically designed, to shed light on the clinical usefulness of other biomarkers, including the natriuretic peptides, in the initial diagnosis and prognostic stratification of patients presenting to emergency departments with chest pain. Because it will be difficult to beat the high sensitivity and negative predictive value (almost 100%) of the new usTn measurement methods in the detection of myocardial damage, efforts should focus on finding a specific and sufficiently sensitive marker for the early detection of myocardial ischemia. At present, NT-proBNP does not seem to be such a marker, unless—who knows?—in the future we obtain an ultrasensitive marker, possibly NT-proBNP, that permits the early detection of the increase in cardiac wall stress that occurs during myocardial ischemia. Meanwhile, patient history, physical examination, and electrocardiographic findings continue to be the mainstays of the initial management of patients presenting with chest pain who have normal usTn levels.

## CONFLICTS OF INTEREST

None declared.

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