

# TROPONIN AND THE NEW DEFINITION OF MYOCARDIAL INFARCTION

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**Abstract:** In 2000, the diagnosis criteria of myocardial infarction were redefined. The new definition recognizes the fact that neither anamnesis, nor electrocardiographic changes have sufficient sensibility or specificity. In the centre of the new definition, there is the utility of troponin for detecting the myocitary necrosis. The new definition brought to a dramatic increase of the cases of myocardial infarction. The increased level of troponin is now the most used marker for selecting patients with acute coronary syndrome without ST elevation for coronarography. The interest for an early determination of the myocardial injury has increased. As long as clinicians will be more familiarized with the testing, troponins will dethrone the role of creatinases regarding the diagnosis, but also the reperfusion, the re-infarction and the estimation of the infarction proportions. There are also cases of false positive results, but a good clinical assessment, together with a follow-up of the level of troponin, will orientate the diagnosis. This new definition sustains the necessity of dosing the troponin.

**Cuvinte cheie:** infarct miocardic, noua definiție, biomarkeri, troponina

**Rezumat:** În 2000, criteriile de diagnostic ale infarctului miocardic au fost redefinite. Noua definiție recunoaște faptul că nici anamneza, nici modificările electrocardiografice nu au suficientă sensibilitate sau specificitate. În centrul redefiniției s-a situat utilizarea troponinei pentru a detecta necroza miocitară. Redefiniția a condus la o creștere dramatică a cazurilor de infarct miocardic. Troponinele crescute sunt astăzi instrumentul cel mai utilizat în selecționarea pacienților cu sindrom coronarian acut fără ST supradenivelat pentru coronarografie. A crescut interesul pentru determinarea precoce a injuriei miocardice. Cu cât clinicienii se vor familiariza cu testările, se anticipează că troponinele vor detrona creatinaza din punctul de vedere al diagnosticului, dar și al reperfuziei, reinfarctizării și estimării mărimii infarctului. Există și cazuri de rezultate fals pozitive, dar contextul clinic și schimbarea în dinamică a nivelurilor de troponină orientează diagnosticul. Această nouă definiție se sprijină puternic pe necesitatea utilizării troponinei și disponibilitatea dozării ei devine chiar o problemă de interes național.

## New versus traditional in the myocardial infarction definition

During years, there have been used several definitions for the myocardial infarction. Hospitals from the same town and doctors from the same hospital have used different definitions. Patients with same types of myocardial infarction were calm or terrified, some were under medication with four or five drugs, some were not under any medication, some capable to drive, some not, based by the “caprices” of a doctor who was on duty in that “memorable” day when an atherosclerotic plaque has been broken. In the same direction, the statistics have been conducted using different criteria. It is necessary to have precise and general accepted criteria for diagnosing the myocardial infarction in the conditions in which the clinical trials appreciate it as an entity with diverse definitions.(1)

The classical definition uses two out of the three following criteria: history of coronary thoracic pain, electrocardiogram changes and an increase and decrease (in dynamic) of the cardiac biomarkers. An important variability exists in approaching the myocardial infarction using these three criteria, as the statistics say. ST elevation and Q waves on the electrocardiogram (ECG), two elements with high specificity, are only present at half of the patients. For the diagnosis of myocardial infarction, the ECG sensibility is situated

somewhere between 55 and 75%.

Approximately a quarter of the patients with myocardial infarction do not present thoracic pain, and the ECG shows not specific changes in almost a half of the patients who come at the emergency room with suggestive thoracic pain and who, are lately diagnosed with myocardial infarction. So, in most of the patients, the doctors should obtain repeated measures of the cardiac biomarkers in order to exclude the myocardial infarction. These measures can be also important for appreciating the dimension of the infarction. The cardiac biomarkers, with a high sensibility for myocardial affection will make possible the diagnosis in about one third of the patients who did not meet the old criteria. The increasing of the use of these biomarkers together with the development of new and more precise imagistic tools brought to the necessity of establishing new diagnostic criteria.(2)

In 2000, the diagnosis criteria of myocardial infarction were redefined. The new definition recognizes the fact that neither anamnesis, nor the electrocardiographic changes have sufficient sensibility or specificity. In the centre of the new definition, there is the utility of troponin for detecting the myocitary necrosis, troponin taking the place of the old creatinase-MB (CK-MB). Troponin proved to be more sensitive and specific (as a marker of myocardial necrosis) than CK-MB, which was dethroned from the “gold criteria” of the

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myocardial infarction.(3)

The increasing of the troponin levels are pathognomonic for the myocardial necrosis (having diagnostic value starting 9 years ago, and prognostic value starting 8 years ago). In the general population, increased levels of troponin may appear, but they are rare, less than 1% (Dallas study). These increased levels of troponin have a relation with a minimum myocardial necrosis, which occurs in the patients with diabetes mellitus, left ventricular hypertrophy, congestive cardiac failure or chronic renal failure. In the absence of the clinical or ECG signs of ischemia, these increased levels of troponin will not be interpreted as myocardial infarction.(4)

The determination of the troponin concentration will give the clinicians the opportunity of identifying small quantities of necrotic myocardium (in the presence of some clinical or ECG criteria). It can even identify infarctions which are too small and inaccessible. In the conditions in which troponin identifies infarctions even smaller than those CK-MB positive, the prognosis on a short period of time is better than in those patients with positive CK-MB and positive troponin. An early diagnosis can be established in 80% of the patients in the first 3-4 hours. A late diagnosis is also facilitated, in the conditions in which troponin remains higher, about 4-7 days after the infarction.(5)

The new definition brought to a dramatic increase of the cases of myocardial infarction and this increase can hide the descending trend of the incidence of myocardial infarction. As a result, the epidemiological studies were confronted with a substantial increased number of patients who were diagnosed with myocardial infarction and apparently with a prognostic amelioration (because of those patients with important transmural infarction, exposed at remodulation and cardiac insufficiency). On the other hand, even before being accepted, the new definition is put under question: only half of the doctors accept the diagnosis of myocardial infarction based on symptoms and increased troponin levels (in the absence of the ECG changes or the increased CK or CK-MB). It is important to accept the new definition, so that a number of infarctions which would have been missed using the old criteria, to be able to be recognized and to benefit from revascularization and modern antithrombotic therapy.(6)

Still, there were expressed some doubts regarding the new definition, including the failing in covering some fatal cases in the first hours from the onset of the symptoms of ischemic myocardium, before giving sufficient time for the troponin level to increase or regarding the fatal cases in which the tests are missing. The new definition, adopted in 2007, adds the imagistic criteria (a new loss of viable myocardium or new kinetic regional abnormalities) at the increased troponin level (in the presence of the signs or symptoms of ischemia).

The definition includes the sudden death due to the myocardial infarction – there is a major criticism in the redefinition. There are some patients who die before the first 3-4 hours from the onset of the symptoms and ECG changes, giving the troponin level not enough time to increase. According to the new definition, the myocardial infarction appears when there are symptoms of ischemia and ST elevation or major block of left branch, or angiographic criteria (the existence of a thrombus) or when death appears before some biological samples are taken, or before the increasing of the necrosis markers. It is also added the myocardial infarction associated with by-pass. In table 1 there is exposed the new definition of myocardial infarction (table 1).(7)

**Table no. 1. The new classification of myocardial infarction**

Type I – Spontaneous myocardial infarction	Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring or dissection
Type 2 – Secondary myocardial infarction	Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
Type 3 – Sudden cardiac unexpected death	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new left branch block, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
Type IVa – myocardial infarction associated with PTCA Type IV b – myocardial infarction associated with stent thrombosis	They are needed for diagnostic levels of biomarkers three times higher than the normal range.
Type V – myocardial infarction associated with CABG	They are needed for diagnostic levels of biomarkers five times higher than the normal range.

For patients with PTCA or aortal-coronary bypass, when there are anyway detected higher values of troponin, the admitted values, with a diagnostic value, are those over three times higher than normal range for PTCA, and over five times higher than the normal range for CABG (7). It is also clear that modest increased levels of troponin are also due to the myocardial necrosis. The increased levels of troponin are frequent in the intensive care units. The cardiac complications during hospitalization are frequent, and the patients who suffer from myocardial infarction during hospitalization for other reasons differ significantly regarding the evolution and prognosis, as compared with those who suffer initially from acute myocardial infarction.(9)

The American guidelines for the treatment of the patients with instable angina and acute coronary syndrome (ACS) without ST elevation (NSTEMI) promote an aggressive attitude in front of these entities, but without particularizing the recommendations for type 2 of myocardial infarction. The optimal therapeutic strategy for these patients remains unclear. By including a new diagnosis, such as type 2 myocardial infarction, it is possible to encourage the progress in the therapy of these patients and the interpretation with accuracy of the increased levels of troponin. It appears of extreme importance to clarify between: chronic increased levels of troponin, transitory increasing troponin associated with acute events and transitory increased levels associated with myocardial stress of other origin.

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The new classification is capable of differentiating the different types of therapies – focused on physiopathology mechanisms. For example, patients with type 2 myocardial infarction will not need an emergency angiography, as compared with patients with type 1 myocardial infarction. Type 2 infarction due to hypotension (in a context of general surgery, for example) will not need anti-thrombotic therapy, which will increase the risk of bleeding.(10) In addition, it is also justified the fear regarding the sensitivity and specificity of the samples. There are frequent questions like: “Have I justified hospitalized this patient?”, “Have I sent the right patient at home?”, “Troponin is high, but the angiography is normal. Will these patients receive counselling and treatment?” or “As I have a minimum of trust in one method, why should I trust in another?”

In this way, the current limitations of the specificity of troponin are completed with a clinical specific adequate context and with the changing in dynamics of the troponin levels. False positive results can be caused by alternative diagnostics (all from the table underneath, plus intense physical effort). The releasing of the cardiac biomarkers in the absence of a new coronary event was recognized. Low constant ascensions were detected in patients with renal failure, cardiac failure, left ventricular hypertrophy or diabetes mellitus.

The American guidelines regarding the unstable angina and the acute coronary syndrome without ST elevation use the terms of “secondary angina” or “non-thrombotic ascension” or “myocardial concomitant affection” or “acute coronary syndrome non-positive for troponin” or “secondary myocardial infarction”.

False positive results can occasionally appear during the nonspecific interaction between the anti-troponin antibodies and heterophilic antibodies, situation which can be judged by clinical consideration, by the lack of dynamics of the biomarkers and can be solved by the interrogation of the biochemistry lab. (11)

**Table no. 2. Troponin between acute myocardial infarction and non-ischemic injury**

cTnT >0,2microg/L	Acute myocardial infarction	Post-ablation Myocarditis
cTnT >0,1microg/L	NSTEMI (with positive markers)	
cTnT >0,05microg/l	NSTEMI (with negative markers)	TaKO-Tsubo syndrome Pulmonary thromboembolism Pacemaker implantation Cardiac failure Sepsis Renal failure
cTnT >0,01microg/l	Unstable angina Stable angina	Medicametos toxicity Neurological pathology End myocardial biopsy Severe aortic stenosis
cTnT <0,01microg/l	Reversible injury Population at risk	Left ventricular failure High age Masculine gender

The increased level of troponin is now the most used marker for selecting patients with acute coronary syndrome without ST elevation for coronarography. It is suggested that the patients with ACS without ST elevation, with high risk, would benefit from more early revascularization then it is provided in the guidelines. That is why the interest for an early determination of the myocardial injury has increased. There are still efforts made in order to find the “perfect biomarker”, which could make possible a better selection of the patients for an early revascularization. In fact, the troponin, as a surrogate marker for local thrombosis with distal consecutive emboli, became the “headstone” of the risk stratification in patients with ACS.

Moreover, the therapeutic decision in terms of conservative or invasive, together with the selection of the anti-thrombotic treatment will be guided by the results of troponin. From a clinical perspective, it is important to have tests with a higher specificity in order to eliminate the false positive results, incorrectly treated as myocardial infarction and with a higher sensibility, in order to eliminate the false negative results and to increase the number of patients correctly identified as myocardial infarction.(12)

It seems reasonably for the clinician to measure both troponins (cTnT and cTnI) in all patients with acute myocardial infarction. It is not necessary to measure both the troponins and CK-MB. At 8-12 hours, it will be sufficient to measure cTnT or cTnI or CK-MB. The retrospective diagnosis or the presence of the skeletal injury enforces the need for a troponin measurement. As long as clinicians will be more familiarized with the testing, troponins will dethrone the role of creatinases regarding the diagnosis, but also the reperfusion, the re-infarction and the estimation of the infarction proportions. Even though these considerations apply directly to the patients with unstable angina or with ACS without ST elevation, for patients with STEMI, the clinicians should not wait for the positivity of biomarkers, the rapid reperfusion being initiated as soon as possible (according to the ECG).

The effects of the use of the new definition, based on the determination of troponin are multiple. There was a dramatically increased number of cases diagnosed with myocardial infarction, and there was an amelioration of the prognostic if these patients, in the conditions in which the statistics added patients with small dimension infarctions, with positive troponin (in other conditions, interpretive as unstable angina) – a study shows a increased with 26.1% of the cases supplementary diagnosed, 33% were previously diagnosed as something else. There were also ascension with 74% of the cases diagnosed, as compared with the use of CK and an ascension with 41%, as compared with the cases previously diagnosed using CK-MB.

In conclusion, the “universal” nature of this new definition is hardly sustained by the necessity of a high quality dosing. The availability of dosing troponin becomes a problem of national importance.(13)

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