

New Diagnostic Criteria of Acute Myocardial Infarction [54]

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Novos Critérios de Diagnóstico do Enfarte Agudo do Miocárdio

For the last four decades the diagnosis of MI has been based on the WHO criteria. The definition of MI required the presence of at least two of the following three factors: clinical history of ischemic chest pain; serial changes in ECG; a rise and fall in serum cardiac enzymes. These criteria have been extensively modified by the clinicians in their application: chest pain is often non-specific; the ECG criteria were based on evolving Q-waves. Today we know that about one-half of all infarcts are non-Q wave. However, ST-T changes without Q waves do not differentiate between myocardial ischemia and MI. We have come to rely heavily on biochemical markers which have been, for the last two decades, total CK and CKMB.

Refinement of this definition has expanded it to include the use of more sensitive and specific cardiac markers, including troponins. They are structural proteins of the sarcomere and would be released only with ischemia. So, biomarkers of myocardial necrosis have, in recent years, become the cornerstone of myocardial necrosis in the clinical context of ischemia.

A new definition of MI was needed.

The basic concept behind this definition is that any amount of myocardial necrosis caused by ischemia should be labelled as an infarct. Consequently any patient who was formerly considered as having angina pectoris, stable or unstable, could be diagnosed today as having a small MI.

The modern concept of the pathophysiology of acute coronary syndromes (ACS) has been previously explained in this session by Prof.

Paulo Ribeiro. The clinical picture of ACS may present with two different ECG patterns, ST elevation and non-ST elevation, that may progress to MI (*Fig. 1*). In the first situation the changes include new ST segment elevation at the J point in two or more contiguous leads with the cut-off points of 0.2mV in leads V1-V3 and 0.1 mV in the other leads. In patients without ST segment elevation, we may find ST segment depression or T wave abnormalities.

These ECG criteria reflect myocardial ischemia and are not sufficient by themselves to define MI. The final diagnosis of MI depends on the detection of elevated levels of cardiac biomarkers in the blood.

The time release of various biomarkers following myocardial necrosis is different and so we may choose the most appropriate to clarify the clinical picture according to its characteristics.

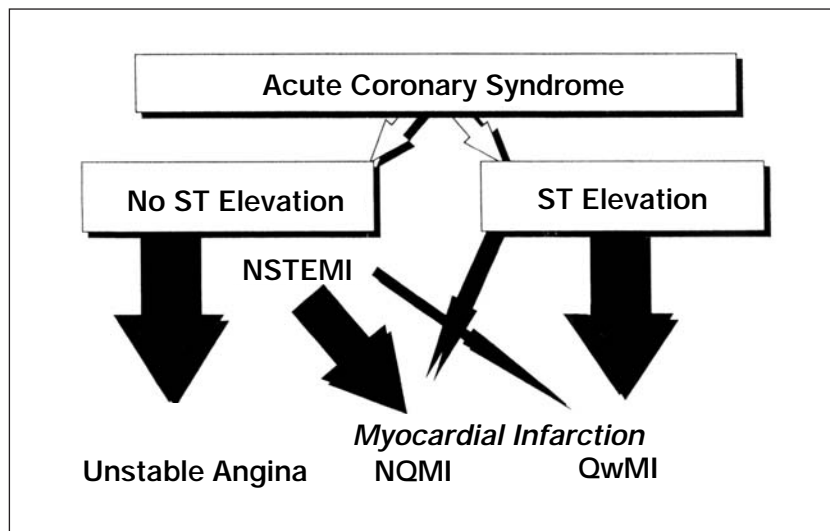
The most recently described biomarkers of myocardial damage are cardiac troponin (I and T) which are highly sensitive and specific, thereby reflecting even microscopic zones of myocardial necrosis. The value for troponin must present elevated on at least one occasion during the first 24 hours after the index clinical event.

In the absence of technology for detection of troponin, CK-MB is the best alternative. It is less tissue specific than troponins but has the advantage of earlier peak value and more robust data documenting its clinical specificity.

The other enzyme tests in current use in the sixties and seventies, namely total CK and lactate dehydrogenase and its isoenzymes, are no longer used due their low specificity.

Fig. 1 Clinical classification of acute coronary syndromes. NQMI - non-Q wave myocardial infarction; NSTEMI - non-ST elevation myocardial infarction; Q wave MI - Q wave myocardial infarction; ST - ST segment of ECG tracing.

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Alexander and co-workers for the PURSUIT trial studied the association between minor elevations of CK-MB level and mortality in patients with ACS without ST-segment elevation. 8250 patients were included, between November 1995 and January 1997. Mortality at 30 days and 6 months was assessed and multivariable logistic regression was used to determine the independent prognostic significance of peak CK-MB level. The mortality at 30 days and 6 months increased from 1.8% and 4.0%, respectively, in patients with normal peak CK-MB levels, to 3.3% and 6.2% at peak CK-MB levels 1 to 2 times normal, to 5.2% and 7.5% at peak CK-MB levels 3 to 5 times normal, and to 8.3% and 11.0% at peak CK-MB levels greater than 10 times normal ($p < 0.001$ for both). The authors found a strong relationship between a patient's peak CK-MB level during hospitalisation and both 30-day and 6-month mortality. The increased risk begins with CK-MB levels just above normal, and so even minor CK-MB elevations should be considered indicative of MI.

The relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease was evaluated in the FRISC trial, and compared with other early risk indicators. Nine hundred and seventy-six patients included in a trial of low-molecular-weight heparin in unstable CAD were followed for 5 months after the index episode. The results showed that the risk of cardiac events (death or MI) increased with increasing maximal levels of TnT obtained in the first 24 hours. There was an increase in the rate of the combined end-point from the lower to the high-

er quintiles of TnT. The three highest quintiles (0.18g/l) constituted a high risk group with 4.3%, 10.5% and 16.1% risk. The prognostic value of TnT was independent of the type of event, unstable angina or myocardial infarction.

From the same FRISC group a more recent paper, published in *JACC-2001*, was designed to study the mechanisms behind the prognostic value of TnT in unstable CAD. Clinical characteristics, findings at echocardiography and coronary angiography and prognosis were evaluated in relation to different TnT levels. The one-year risk of death in the non-invasive arm increased by increasing levels of TnT (1.6% to 4.6%) whereas the risk of MI showed an inverted U-shaped curve and was lower in the lowest (5.5%) and highest (8.4%) TnT groups than in the two intermediate groups (17.5% and 16.2%) – *Fig. 2*.

The conclusion is that any elevation of TnT raises the probability of significant coronary stenosis and is associated with an increased risk of MI and death. The incidence of infarction is modest in the highest group of TnT values. These patients have persistent occlusion of the culprit lesion, decreased LV function, and high mortality.

In a very elegant editorial comment to this paper, Elliot Antman emphasizes the importance of diagnosing episodes of micro-infarction that are below the accuracy provided by CK-MB. In an analysis from the TIMI-3B trial the TnI positive patients had a significantly higher risk of mortality by 42 days even when the analysis was restricted to the cohort of patients with a negative CK-MB assay.

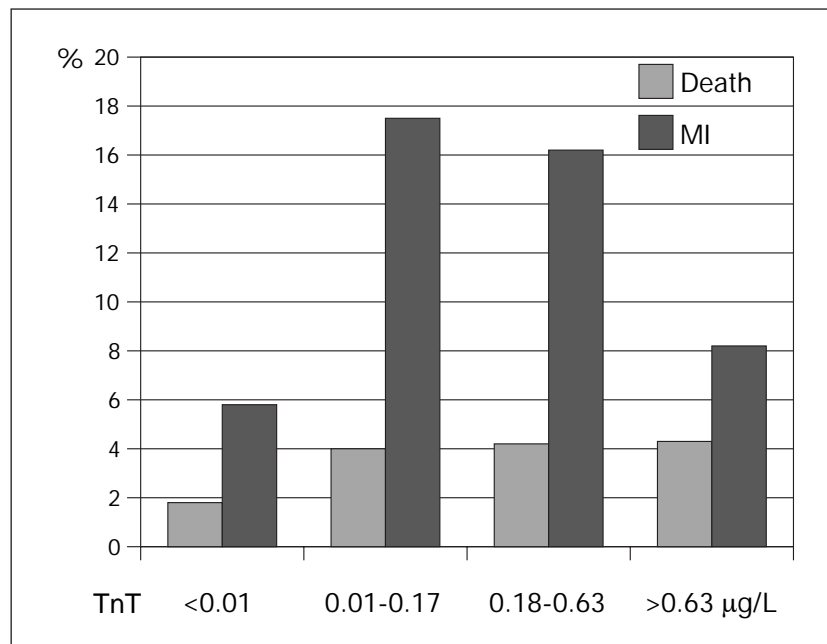


Fig. 2 Death and myocardial infarction (MI) rate at 12 months, respectively, in relation to troponin T (tnT) levels. Reproduced with permission of Elsevier Science from JACC 2001;38:979:86.

The relative risk for TnT positive patients was, in a meta-analysis reported by Heidenreich, 3.9 for mortality and 3.8 for death or non-fatal recurrent MI. Ottani et al. in a recent work (*Am. Heart J.* – 2000) conclude that the adverse prognostic significance of a positive troponin test has been demonstrated by multiple clinical investigators, across multiple trials, involving multiple patient groups from different countries, indicating that the observation is a robust one.

Patients with a positive TnT test are considered to benefit from aggressive pharmacological therapy with IIb/IIIa glycoprotein inhibitors and, according to some authors, should be selected for early invasive strategy. However, the FRISC study showed no correlation between the severity of underlying CAD and the TnT level but did show a progressive increase in the odds of TIMI-3 flow with increasing TnT levels. Based on these observations Antman describes a U-shaped curve relating TnT measurements and the rate of MI through one year. Patients with only slightly elevated levels of TnT or TnI do not benefit from IIb/IIIa GP inhibitors with respect to prevention of death or non-fatal MI by 30 days. Those with intermediate values of the troponins have the maximum benefit, whereas those with higher biomarker levels show progressively less benefit compared with the intermediate group. These results, according to this author, came from detailed observation of the results of both the FRISC-II study and the PRISMA-Plus trial.

Accordingly patients with intermediate elevation of troponin values have not yet lost substantial amounts of myocardium and are ideal candidates for more effective antithrombotic therapy and prompt referral for an early invasive approach supported by i.v. glycoprotein IIb/IIIa inhibitors. Those patients with higher levels of troponin have increasing amounts of completed myocardial damage and are less likely to benefit from i.v. GP IIb/IIIa inhibitors. They may have severe 3-vessel disease and decreased LV function and should be referred early for bypass surgery (*Fig. 3*).

PERCUTANEOUS CORONARY INTERVENTION

An increase of cardiac markers after coronary angioplasty or implantation of coronary artery stents, or both, is indicative of cell death (*Consensus Document-ESC/ACC – 2000*). This elevation occurs in a setting of myocardial ischemia and according to the new criteria should be labelled as an MI.

About five years ago, the group of E. Topol presented data on the prognostic significance of transient, uncomplicated in-laboratory coronary artery closure. In a population of about five thousands percutaneous coronary intervention (PCI) procedures, 88 had a transient, uncomplicated, in-laboratory vessel closure. When the procedure was associated with CK-MB elevation there was a significant correla-

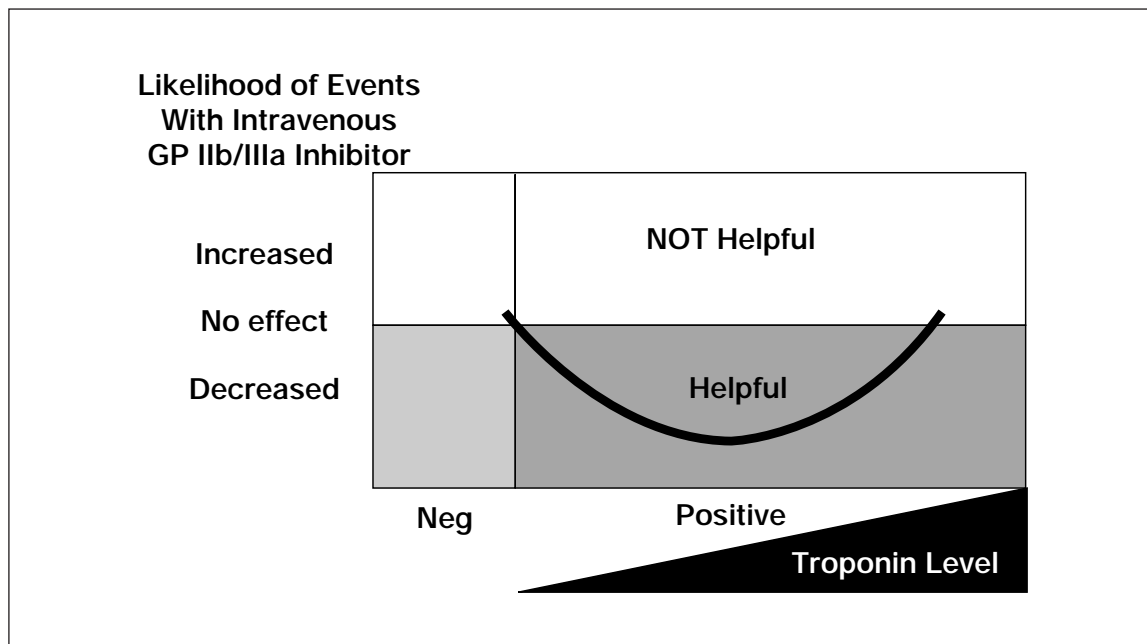


Fig. 3 Proposal for therapeutic decision making based on quantitative troponin results. The U-shaped relationship between absolute levels of troponin and the risk of death and myocardial infarction following administration of intravenous glycoprotein (GP)IIb/IIIa inhibitors is shown. Patients with undetectable troponin levels or just barely elevated troponin levels are at low risk and unlikely to benefit from an intravenous GPIIb/IIIa inhibitor. Those with intermediate levels of troponin derive the greatest benefit while those with progressively higher levels of troponin have increasing amounts of completed myocardial damage and are less likely to benefit from intravenous GPIIb/IIIa inhibitors. See text for further discussion. The relationship shown in this figure is in part based on data from Lindahl et al. (10) and Heeschen et al. (11). Reproduced with permission of Elsevier Science. JACC 2001;38:987-90.

tion with cardiac death (risk ratio, 1.25 $P < 0.0001$); an increase in CK-MB was also the most important correlate for major ischemic events on follow-up. The authors (Abdelmeguid et al) conclude that the determination of CK-MB in this subset of patients has important prognostic implications.

A study by Kini et al. was designed to evaluate the incidence and predictors of CK-MB elevation after successful coronary intervention, in 1,675 consecutive patients. CK-MB elevation was detected in 313 patients (18.7%). Procedural complications or ECG changes occurred in only 49% of the CK-MB elevation cases. Predictors of CK-MB elevation on multivariate analysis were diffuse coronary disease ($p = 0.02$), systemic atherosclerosis ($p = 0.002$), stent use ($p = 0.04$) and absence of beta-blockers therapy ($p = 0.001$). Adverse in-hospital cardiac events were more frequent in patients with more than 5 times CK-MB elevation. During a mean follow-up of one year the incidence of death was not statistically different between the two groups (1.6% versus 1.3%). The relevance and complexity of the real meaning of myonecrosis after revascularization procedures has been the subject of a

recent review article by Califf et al. and represents a consensus among a group of researchers with data on this subject. *Table I* summarizes the main mechanisms involved.

Table I
Elevated biomarkers after PCI

1. Minor branch occlusion
2. Thrombus in the vessel
3. Intimal dissection
4. Coronary spasm
5. Distal embolization

Heeschen et al. recently studied the cardiovascular risk and therapeutic benefit of coronary interventions for patients with unstable angina according to TnT status. Three hundred and fifty-one patients with unstable angina (UA) were included; TnT was elevated in 36%. In a follow-up of 30 days the TnT positive patients were more refractory to medical treatment (78% vs. 44%); had a higher incidence of cardiac events (6.4% vs. 0.4%); and the angiograms documented more severe CAD requiring revascularization (69% vs. 50%). The authors conclude that TnT identified high-risk patients with UA with a higher event rate prior to and in association with PCI.

In an editorial comment to this paper Brener and Topol raise the question why myocardial necrosis of such a limited extent should be associated with unfavourable outcome. They establish a link between the diseased epicardial artery and the events occurring in the microcirculation after plaque fissure or rupture. The ruptured atherosclerotic plaque disturbs epicardial flow and promotes the deposition and activation of platelets, with distal embolization and microvascular obstruction. The authors present a new pathophysiologic paradigm of plaque rupture, embolization and microcirculatory dysfunction which would explain the unfavourable prognostic of this limited necrosis (Table II).

Table II
Troponin, embolization and microvascular integrity

| |
|--|
| Ruptured atherosclerotic plaque |
| platelet deposition and activation |
| Distal embolization of the plaque-platelet aggregate |
| Microvascular obstruction |
| Myocardial necrosis |
| TnT elevation |

Brener and Topol. Eur Heart J 2000;21:1117.

What are the clinical implications of the new definition of MI? In the recent meeting of the ACC, Meier et al. presented data from the University of Michigan, collected for a period of 8 months. Three hundred and five patients with enzyme elevations were separated into 2 groups: Group A with positive CK-MB (n=264) regardless of troponin status and group B with negative CK-MB but positive TnI (n=41). Patients in group B had a shorter hospital stay and fewer events (without statistical significance). The decision to include troponins in the diagnostic criteria of MI resulted in a 16% increase in the annual number of MI diagnosed.

The GRACE investigators examined the MI rates and prognostic value of peak CK-MB and troponins (I/T) in 3,420 patients. The authors concluded that the addition of troponin leads to as many as 25% additional ACS patients meeting the criteria for the diagnosis of MI. This group of patients experiences a 3-fold increase in short-term mortality when compared to normal enzyme levels and a 1.5-fold increase compared to the traditional cardiac enzyme definition.

So, in conclusion, we may say that the new definition of AMI allows us for the first time to distinguish between unstable angina and myocardial infarction.

This is important on clinical grounds because any amount of myocardial damage implies worse prognosis for the patients and so allows appropriate secondary prevention.

The epidemiological implications are important and should be emphasized. The application of the new diagnostic criteria for MI will cause the recorded incidence of MI to rise and the case fatality rate to fall.

Modification of the definition of MI is going to have an impact on the selection of patients for clinical trials, but may enable us to separate, with more rigorous criteria, between unstable angina and myocardial infarction. The homogeneity of the population may help to analyze the results and clarify the conclusions.

REMARK 1

Biochemical testing is the only method by which non-Q wave AMI can be diagnosed and by which the majority of patients presenting with suspected ACS can have AMI excluded. P.O. Collinson Eur Heart J 1998; Suppl N-16.

REMARK 2

About one third of patients with ST-elevation who would previously have been diagnosed as experiencing UA on the basis of normal CK-MB levels are now diagnosed as having NSTEMI because of detectable troponin levels. Braunwald et al. JACC 2000;36:970.

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