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The New Definition of Myocardial Infarction—Can We Use It?

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Summary

Background: A joint committee of the European Society of Cardiology and the American College of Cardiology (ESC/ACC) recently redefined myocardial infarction.

Hypothesis: The objective of this study was to examine the outcome of diagnoses from more than 500 patients admitted to a university hospital coronary care unit (CCU), when the ESC/ACC committee cut-off levels were compared with the Swedish diagnostic criteria for acute myocardial infarction (MI), comparable with everyday practice in most countries.

Methods: Creatine kinase-MB, troponin I, and troponin T were measured in 525 patients admitted consecutively to the CCU, Huddinge University Hospital, with possible myocardial ischemia lasting < 12 h before arrival.

Results: The ESC/ACC definition of MI increased the number of MIs by 3–32% compared with the number achieved when Swedish diagnostic criteria for acute MI were used. A significant number of patients with elevated cardiac enzymes presented with acute heart failure, tachycardia, pulmonary embolism, and sepsis as initial symptom.

Conclusions: In this study of more than 500 patients with possible myocardial ischemia admitted consecutively to the CCU at a university hospital, the ESC/ACC definition of MI increased the number of MIs by 3–32% compared with the number achieved when Swedish diagnostic criteria for acute MI were used. A majority of the patients identified with ESC/ACC cut-off levels presented with myocardial ischemia as the primary symptom, whereas many of the other patients had acute heart failure and tachycardia as initial symptom. It is unclear whether patients in this latter group should be labelled as having MI; there are no clinical studies providing guidance in this situation.

Key words: myocardial infarction, troponin, definition, creatine kinase-MB

Introduction

Myocardial infarction (MI) is defined as myocardial cell death due to prolonged ischemia. A joint committee of the European Society of Cardiology and the American College of Cardiology (ESC/ACC) redefined MI in September 2000.[1] The cardiac-specific troponins are highly sensitive and specific markers of myocardial damage,[2,3] and therefore cardiac troponins (I or T) are recommended for the diagnosis of MI.[1] The committee states that a maximal concentration of troponin T or I exceeding the decision limit (99th percentile of the values of a reference control group) on at least one occasion during the first 24 h after the index clinical event indicate myocardial necrosis. Furthermore, the committee demands that the coefficient of variation at the 99th percentile for the assay used should be ≤ 10 %.

The change of definition has resulted from the demonstration that even very small detectable amounts of troponins are associated with increased cardiovascular risk.[4–6] However, our guidelines are based on clinical trials, using the old MI criteria as an inclusion criterion. The 99th percentile for cardiac troponin T (Elecsys 2010, Roche Diagnostics, Basel, Switzerland) was 0.01 µg/l in a reference population,[7] whereas 0.1 µg/l often has been used as a cut-off level in clinical studies.[8] The corresponding values for cardiac troponin I (Stratus CS, Dade Behring, Deerfield, Ill., USA) are 0.07 µg/l[9] and 0.40 µg/l,[10] respectively. Thus, there is often up to a 10-fold cut-off level in clinical studies.

Also, in the clinical setting, higher cut-off levels for cardiac enzymes than those suggested by ESC/ACC are often used. In the Swedish Register of Cardiac Intensive Care (RIKS-HIA),[11] the cut-off level for troponin T is suggested to be ≥ 0.05 µg/l, and for creatine kinase (CK)-MB at least one value ≥ 10 µg/l or two values exceeding 5 µg/l is suggested.

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Since the diagnosis of MI not only affects the decision making of the cardiologist but also the actual care given and, not least, the response by the patient, the aim of this study was to examine the outcome of diagnoses from more than 500 patients admitted consecutively to a university hospital coronary care unit (CCU), when the ESC/ACC committee cut-off levels were compared with the Swedish national cut-off levels, which are comparable with everyday practice in most countries.

Methods

Patients

All patients admitted to the CCU, Huddinge University Hospital, with possible myocardial ischemia lasting < 12 h before arrival, were examined according to the following schedule: (1) creatine kinase-MB (Stratus CS), troponin I (Stratus CS) and troponin T (Elecsys 2010) 6 h after the last chest pain episode; (2) troponin I (Stratus CS) and troponin T (Elecsys 2010) 12 h after the last chest pain episode. Patients with renal insufficiency (serum creatinine > 150 µml/l) were excluded. Since elevation of cardiac troponins indicates more than myocardial ischemia,[12] each patient, including laboratory data and the file of the patient, was retrospectively evaluated by two cardiologists as to the most dominant symptom when the patient was admitted to the hospital. The cardiologists used all available clinical data including catheterization data, file notes, laboratory reports, echocardiography reports, and so forth. In case of disagreement, a third cardiologist was consulted. The initial symptoms were categorized as follows: myocardial ischemia, acute heart failure, tachycardia, pulmonary embolism, sepsis, skeletal muscle origin, or other causes. All bedside assay measurements were performed immediately after a blood specimen was obtained. Troponin T STAT was analyzed on Elecsys 2010 immunoassay analyzer in the central laboratory of Huddinge University Hospital. The third-generation TnT test uses the same monoclonal antibodies (M11.7 and M7) as the second-generation test, but is standardized with human recombinant cTnT instead of bovine cTnT (Roche Diagnostics). Stratus CS (SCS) is a fluorometric enzyme immunoassay analyzer, based on solid-phase radial partition immunoassay technology, for quantitative measurement of CK-isoenzyme MB mass concentration (reference interval according to the manufacturer 0.6–3.5 µg/l), and troponin I (reference interval according to the manufacturer 0.00–0.06 µg/l) in whole blood samples collected using lithium heparinate as anticoagulant. The method has been described previously.[9]

Definition of Myocardial Infarction

Myocardial infarction was defined as elevated cardiac enzyme levels with at least one of the following: (1) ischemic symptoms, (2) development of pathologic Q waves on the electrocardiogram (ECG), (3) ECG changes indicative of ischemia (ST-segment elevation or depression), (4) coronary artery intervention. Relevant cut-off levels according to Swedish guidelines were 0.40 µg/l for troponin I (Stratus CS) and 0.05 µg/l for troponin T (Elecsys). These cut-off levels were compared with the cut-off levels suggested by ESC/ACC. The ESC/ACC guidelines (concentrations corresponding to 10% coefficient of variation (CV) imprecision and 99th percentile reference limit in a reference population) were 0.10 µg/l[13] for troponin I (Stratus CS) and 0.04 µg/l[13] for troponin T (Elecsys).

Results

In all, 525 patients with a mean age of 67 ± 10 years were included in the study. When troponin T ≥ 0.05 µg/l was used as cut-off level according to the national guidelines, 240 MIs were recorded. If the cut-off level for troponin T was lowered (> 0.03 µg/l) according to ESC/ACC guidelines, another eight MIs were identified. In these eight patients, the initial symptom was myocardial ischemia in six, acute heart failure in one, and tachycardia in one.

When national cut-off levels for troponin T were compared with those for troponin I, 11 patients had elevated troponin I but normal troponin T. Nine of these patients had myocardial ischemia as initial symptom, one had tachycardia, and one had acute heart failure. Seventeen patients had elevated troponin T but normal troponin I. Ten of these had myocardial ischemia as initial symptom, five had acute heart failure, and two had pulmonary embolism.

Table I compares the national cut-off levels for troponin T with ESC/ACC cut-off levels for troponin I. Forty-seven patients had elevated troponin I, but normal troponin T; 25 patients had myocardial ischemia, 6 had acute heart failure, 9 had tachycardia, 1 had pulmonary embolism, 3 had sepsis, and 3 were of other origin. Five patients had elevated troponin T and normal troponin I. Two patients had myocardial ischemia and three had acute heart failure as initial symptom. Figure 1 shows the correlation between troponin T and troponin I 6 h after the index event (r = 0.86).

Table II compares the national cut-off levels for troponin I with the ESC/ACC cut-off levels for troponin I. Forty-eight more MIs were diagnosed with the lower cut-off level; 25 patients had myocardial ischemia, 7 had acute heart failure, 7 had tachycardia, 3 had pulmonary embolism, 3 had sepsis, and 3 had skeletal muscle pain as initial symptom.

When national cut-off levels for troponin T were compared with those for CK-MB, 45 patients had elevated troponin T and normal CK-MB and 19 had elevated CK-MB and normal

TABLE I National cut-off levels for troponin T compared with European Society of Cardiology/American College of Cardiology (ESC/ACC) cut-off levels for troponin I

	Troponin I (ESC/ACC guidelines)	
	≥ 0.10 µg/l	< 0.10 µg/l
Troponin T (national guidelines)		
≥ 0.05 µg/l	235	5
< 0.05 µg/l	47	238

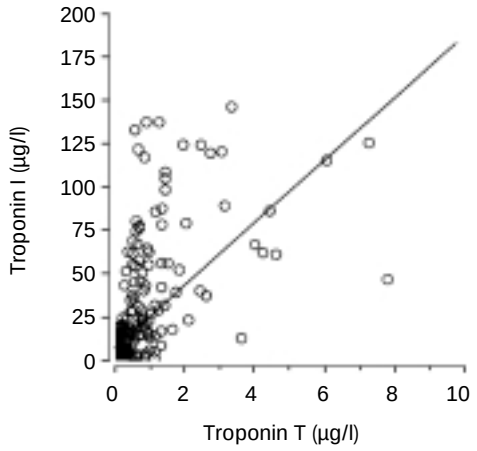

FIG. 1 Correlation between troponin T and troponin I 6 h after the index event (r = 0.86).

troponin T. Of these 19 patients, 3 had myocardial ischemia, 3 had acute heart failure, 2 had tachycardia, and 10 had skeletal muscle pain as initial symptom.

Table III compares ESC/ACC cut-off levels for troponin I with national cut-off levels for CK-MB. Eighty-one patients had negative CK-MB and elevated troponin I, whereas 13 patients had elevated CK-MB and normal troponin I. Of these 13 patients, 4 had myocardial ischemia, 1 had acute heart failure, 1 had tachycardia, and 7 had skeletal muscle pain as initial symptom.

Discussion

In this study of more than 500 consecutive patients with possible myocardial ischemia, admitted to the CCU at a university hospital, the ESC/ACC definition of MI increased the number of MIs by 3–32% compared with the number achieved when national guidelines,[11] comparable with everyday practice in most countries, were used.

If CK-MB ≥ 5 µg/l was used as a cut-off level for MI as the Swedish guidelines state, the number of infarctions increased by 32% when ESC/ACC criteria based on troponins were used. A similar observation was recently reported in other studies.[14, 15] In the study by Meier *et al.*,[15] the 6-month mortality was higher among patients with elevated troponin but normal CK-MB than among those with only CK-MB elevations. Thus, if the diagnosis of acute MI is based on CK-MB, we fail to put the correct diagnosis on a group of high-risk subjects. Another well known problem with CK-MB that was also observed in this study, is elevated CK-MB caused by skeletal muscle damage. Except for situations such as reinfarction diagnosis and renal insufficiency, CK-MB determination adds no information when troponins are measured in this group of patients.

Panteghini *et al.*[13] evaluated the imprecision of eight cardiac troponin assays at low-range concentrations and found that no assay was able to achieve the 10% CV recommendation at the 99th percentile reference limit defined by the manufacturer. In that study, the ratio of the 10% CV concentration to 99th percentile limit was 1.4 for Stratus CS and 4.0 for Elecsys 1010. In the present study, troponin I (Stratus CS) and troponin T (Elecsys 2010) were used. More patients presenting with myocardial ischemia had elevated troponin I than troponin T. Thus, our results together with Pathegini *et al.*'s results suggest that troponin I (Stratus CS) provides a more sensitive method with a higher reliability at low concentrations than troponin T (Elecsys).

How should we deal with the "new" MIs? In the Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction (TACTICS-TIMI) 18 study,[6] patients with cardiac troponin I between 0.1–0.39 µg/l had the benefit of an early invasive strategy compared with conservative management. The level of improvement after invasive treatment compared with conservative treatment was of the same magnitude in patients with troponin I between 0.1–0.39 µg/l and in patients with troponin I between 0.4–1.49 µg/l. However, it is important to point out that the inclusion criteria in TACTICS-TIMI 18 were ECG changes or elevated cardiac enzymes. Thus, it is very likely that the patients with the low enzyme levels discussed above were included because of ECG changes; therefore, we have no evidence-based data on how to take care of patients with slight troponin elevation but normal ECG.

A lower cut-off level presented another problem. Since elevation of cardiac troponins indicates more than myocardial ischemia,[12] each patient, including laboratory data and the file of the patient, was retrospectively evaluated regarding the symptom that had been most dominant at admission. The number of patients in this study with troponin I above the cut-off level increased from 234 to 282 with 0.4 µg/l and 0.1 µg/l as cut-off

TABLE II National cut-off levels for troponin I compared with European Society of Cardiology/American College of Cardiology (ESC/ACC) cut-off levels for troponin I

	Troponin I (ESC/ACC guidelines)	
	≥ 0.10 µg/l	< 0.10 µg/l
Troponin T (national guidelines)		
≥ 0.40 µg/l	234	0
< 0.40 µg/l	48	243

TABLE III European Society of Cardiology/American College of Cardiology (ESC/ACC) cut-off levels for troponin I compared with national cut-off levels for creatine kinase (CK)-MB

	Troponin I (ESC/ACC guidelines)	
	≥ 0.1 µg/l	< 0.1 µg/l
CK-MB (national guidelines)		
≥ 5 µg/l	199	13
< 5 µg/l	81	230

levels. Of these 48 patients, more than 50% presented with myocardial ischemia as the primary symptom, whereas the rest of this group had acute heart failure, tachycardia, pulmonary embolism, and sepsis as initial symptom.

Troponin T elevation is a prognostic variable among patients with sepsis,[16] and in patients with severe exacerbation of chronic pulmonary disease, elevated troponins are observed and, elevated troponins in this group of patients are an independent predictor of death.[17] It is likely that the presence of hypoxemia and the increased breathing effort may cause an infarction in this group of patients with a high prevalence of atherosclerotic disease. There are also data suggesting that tachycardia up to more than 200 beats/min may cause elevated troponins despite absence of coronary disease.[18] Cardiac troponin I is also associated with impaired hemodynamics and mortality in patients with severe heart failure;[19] such patients often have coronary heart disease, and worsened heart failure may very well be caused by MI. Thus, it is difficult to know whether a patient with acute worsened heart failure with slightly elevated troponin has had an MI or whether the troponin leakage is the result of an impaired hemodynamic situation. The same problem is an issue if the patient presents with tachycardia, sepsis, or exacerbation of chronic pulmonary disease as initial symptom in combination with troponin leakage.

Conclusion

We report that in this study of more than 500 consecutive patients with possible myocardial ischemia admitted to the CCU at a university hospital, the ESC/ACC definition of MI increased the number of MIs by 3–32% compared with the number achieved when Swedish national guidelines were used. A majority of the patients identified with ESC/ACC cutoff levels presented themselves with myocardial ischemia as the primary symptom, whereas many others had acute heart failure and tachycardia as initial symptom. It is unclear whether patients in this latter group should be labelled as having MI, and we do not really know how these patients should be treated; there are no clinical studies providing guidance in this situation.

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