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gOVERVIEW

EDITORS' PAGE

New Universal Definition of Myocardial Infarction

Global Implications, Applicability, and Need for Flexibility

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Myocardial infarction (MI) is a pathological process but a clinical entity. For a pathologist, the presence of myocardial necrosis is fundamental to the detection of MI, but a clinician is usually fortunate to detect this condition in the living. Ideally, MI has to have ischemic source of injury, and for want of definite evidence of ischemia, clinical diagnosis of MI always remains presumptive and indirect. There are mimickers and associated comorbidities, which introduce uncertainty in diagnosis. Hence, early, accurate, and consistent diagnosis of MI remains a challenge despite discovery of cardiomyocyte-specific biomarkers. Elevated levels of troponin indicate myocardial injury, but not the mechanism of injury. Although uniform availability of the means to detect and define MI across the globe remains a challenge, the definition has implications for epidemiology, disease monitoring, content of registries, clinical research studies, clinical trials, quality assurance, economic analysis, medicolegal disputes, and estimation of healthcare costs [1].

HISTORICAL ASPECTS

Although the crude description of MI has been available for centuries, an exponential growth in its understanding, knowledge, and management has occurred only in the twentieth century. James B. Herrick, a Chicago internist, presented the first detailed description of non-fatal acute MI in 1912 [2]. However, a couple of years earlier, Obratzow and Straches (1910) had distinguished the clinical entity of coronary thrombosis from that of angina pectoris [3]. Parkinson and Bedford believed that coronary thrombosis was diagnosed in 1878 by Hammer and in 1879 by Ziegler who used the term myomalacia cordis [4]. However, a simple, clinically useful and robust definition of MI eluded clinicians long after the initial description. Definition of MI evolved over time with emphasis shifting from clinical presentation to electrocardiographic changes to the release of intracardiomyocytic macromolecules. The latter macromolecules are generally water-soluble and hence wash out because myocyte necrosis is accompanied by the loss of integrity of sarcolemma. Intramyocardial enzymes (including transaminases) and fragments of contractile protein apparatus (such as myoglobin, light chains of myosin, troponins) have been traditionally measured as the indicators of the severity of myocyte necrosis. Measurement of the cardiac troponins (or cTn, I, and T) offers high specificity and reproducibility, and high sensitivity assays accord high negative predictive value to the test [5,6]. Although highly sensitive and specific, myocardial injury with release of contractile apparatus proteins in circulation can be secondary to a variety of pathobiological processes; central to this theme is the presence of the clinical picture of myocardial ischemia. It is somewhat difficult to establish this relationship when one is dealing with sick and old patients with multiple comorbidities, and also following the procedures wherein the heart is manipulated. Hence, the introduction and perpetuation of the rise and/or fall of cardiac biomarkers above the 99th percentile of upper reference limits (URL) in this new definition is similar to the previous version of the Global MI task Force [7,8]. Is the new definition able to be generalized and what are its implications for low- and middle-income countries (LMIC)?

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GLOBAL HEART, VOL. 7, NO. 4, 2012
December 2012: 377-380

ANALYSIS OF THE CRITERIA

Broadly, the criteria have remained unchanged except for the diagnosis of procedure-related MI. As the new universal definition states, "the diagnosis of acute MI is a clinical diagnosis based on patient symptoms, ECG changes, and highly sensitive biochemical markers, as well as information gleaned from various imaging techniques" [8]. There is unlikely to be any major disagreement with regard to clinical and electrocardiographic criteria, which are essentially supportive rather than diagnostic. Use of any imaging technique for quick detection of MI shall remain limited because of unacceptable delay in conducting and interpreting any of the available tests. The key question in acute myocardial infarction is how to determine the evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Herein comes the pivotal role of the cardiac biomarkers (read as troponins). The key point of the *Third Universal Definition of MI* [8] is the detection of a rise and/or fall of cardiac biomarker values, with at least one of the values being elevated above the 99th percentile of upper reference limit for a particular assay. The minor increase in troponin previously called troponin disease or troponin bump has become all-important for the diagnosis of MI in the presence of myocardial ischemia. The improved assay sensitivity and precision has allowed the detection of the trace quantities of the troponin and hence allowed the detection of many undetected micro-infarcts. The latest definition makes it obligatory to test cardiac biomarkers at least twice to detect rising or falling levels before MI is diagnosed. By default, point-of-care bedside troponin tests, which are read as positive or negative, lose relevance for diagnosis of MI even if these are highly sensitive but may have prognostic value for a variety of conditions. However, quantitative point-of-care finger-stick tests, which have relevance in ER and primary care settings still may be useful.

SPONTANEOUS MI

Spontaneous MI, both type 1 and type 2, are the dominant occurrences in all societies. Pertinent questions, which the new definition raise have important implications for the developing world. The following points need emphasis and clarification:

1. It is imperative for every facility managing MI to have its own reference values so that there is clarity about the 99th percentile URL. Obviously, it will vary with the types of assay and the biomarker.
2. The point-of-care strip tests, which were read as positive or negative for cardiac troponin are meant for diagnosis but not for prognosis. However, in subjects with high pre-test probability of thrombotic coronary heart disease, single point-of-care tests may be accurate and useful in the situation of insufficient resources.
3. The definition implies that the cardiac biomarkers be tested twice or more to detect rising or falling trends.
4. In patients with suspected acute coronary syndrome who finally end up in the catheter lab or in the operating room, the tests will obviously be done at least three times; twice for making a diagnosis or risk stratification and at least once again for the detection of post-procedural complication.
5. We need to be certain that the dynamic troponin changes are only due to MI. Other conditions such as infection, arrhythmia, stress cardiomyopathy, etc., may also be responsible for dynamic changes.
6. The definition may also increase the workload of clinicians and introduce time delay, especially when a MI is almost certainly based upon the ECG criteria.
7. The new definition still would not differentiate MI from Tako-tsubo cardiomyopathy, which may be encountered in nearly 5% of the patients presenting with ACS.
8. Other biomarkers (including total CK, CK-MB activity, lactate dehydrogenase, aspartate aminotransferase, etc.) are relatively non-specific and have been deleted from the definition. Although elimination of various tests brings uniformity to the detection of MI universally, these tests have been commonly employed in LMIC for lower cost and easy availability. There will be a substantial lag time before these tests are phased out in the LMIC.
9. There is also the matter of access, equity, and the cost for the LMIC. Clinical decisions may be more difficult in resource-constrainted societies wherein an exponential increase in acute coronary events is being encountered. Making dynamic changes in troponin levels mandatory for the detection of MI will widen disparities with regard to treatment.
10. Local expertise would need to be augmented to develop cheaper assays to increase greater use of cardiac troponins in developing countries.
11. The incidence of MI is likely to rise with the newer definition and high-sensitive assays of the troponins. Including micro-infarcts in the definition will alter the trends in case fatality rates and initially create epidemiologic disparities.
12. The analytical sensitivity (lower detection limit) of the troponin assays is likely to increase in the future. This will detect still more micro-infarcts whose significance may be uncertain.

13. A single value of troponin above analytical sensitivity may still be useful in the LMIC in certain situations.

PERI-PROCEDURAL MI

MI after percutaneous coronary interventions (PCI, Type 4) and coronary artery bypass surgery (CABG, Type 5) is more common than believed or reported. There is unfavorable prognosis associated with raised biomarkers in these patients. The diagnosis of MI, however, has important diagnostic-coding, medico-legal, insurance, and quality-of-care issues. Stent thrombosis following PCI as the cause of MI is pretty much a uniformly agreed upon matter. With so many incidental and unintentional phenomena causing myocardial ischemia, which can and does occur during PCI, it is reasonable that peri-procedural MI should receive adequate attention. The new definition has raised the bar from three to five times URL of troponin levels so that unnecessary panic and worry on the part of both physicians and patients can be decreased. Using the previous definition, up to 24% of patients undergoing non-emergent PCI had MI by troponin criteria [9]. However, estimation of troponin is not routine after apparently uncomplicated elective PCI [10], especially in developing countries because of cost considerations. Even in the developed world there is a trend towards shorter hospital stay after elective PCI (< 24 h). Monitoring troponins will identify those patients who need to stay longer. The knowledge that troponin elevations occur even after otherwise uncomplicated procedures and are associated with a 20% increase in long-term mortality has triggered the need to define PCI-related MI separate from troponin bump [11]. Such a definition will help in monitoring efficacy of therapy, quality and standard of cardio-protection during the procedure, and development of newer techniques to reduce procedural MI. However, to identify PCI-related MI, at least one pre-procedure and one post-procedure troponin estimation shall become mandatory in all patients. In fact, to catch the peak troponin level, more frequent testing may be required. Although adding imaging to this difficult diagnosis is a good idea it would increase the cost.

Rise in troponin levels following CABG is more common [12], possibly because of ischemia-reperfusion injury pattern and hence the new definition (≥10 times URL of troponin) is more stringent with regard to type 5 MI. Nearly 21% of patients have >80 times URL rise in troponin [13] when cardiopulmonary bypass is used; myocardial injury and hence troponin release may be less pronounced in off-pump surgeries [14]. Because patients may be sedated following CABG, ECG changes may not be necessarily specific and imaging difficult in these situations; troponin release may play an important role in type 5 MI. A recent study has demonstrated a graded relationship between troponin rise and mortality following CABG regardless of the threshold [15]. Thus, one could argue for or against more stringent troponin criteria for definition of MI related to open heart surgery. Deleting CK-MB from the definition is also questionable since there is so much data relating CK-MB rise to intermediate and long-term mortality [15]. As troponin levels below the threshold of MI also affect prognosis, the purpose of defining MI by using more stringent criteria and dissociating it from prognosis could be misleading.

Overall, more reasoning has gone into the revised definition of MI. The biomarker cacophony has been eliminated and the clinician has to talk only in terms of troponins. Its impact on LMIC will need careful evaluation. Also, MI related to cardiac procedures would need greater emphasis and more refining.

REFERENCES

1. Mendis S, Thygesen K, Kuulasmaa K, et al. World Health Organization definition of myocardial infarction: 2008e09 revision. Int J Epidemiol 2011;40:139–46.
2. Herrick JB. Certain clinical features of sudden obstruction of the coronary arteries. JAMA 1912;27:100–16.
3. Obrastzow WP, Straschesko ND. Zur kenntis der thrombose der koronararterien des herzens [Toward understanding coronary artery thrombosis]. Zeitschrift für klinische medizin 1910;71:116–32.
4. Parkinson J, Bedford E. Cardiac infarction and coronary thrombosis. Lancet 1928;1:4–11.
5. Cummins B, Auckland ML, Cummins P. Cardiac-specific troponin-I radioimmunoassay in the diagnosis of acute myocardial infarction. Am Heart J 1987;113:1333–44.
6. Katus HA, Remppis A, Looser S, et al. Enzyme linked immunoassay of cardiac troponin T for the detection of acute myocardial infarction in

GLOBAL HEART, VOL. 7, NO. 4, 2012
December 2012: 377-380

patients. J Mol Cell Cardiol 1989;21: 1349–53.
7. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation 2007;116: 2634–53.
8. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Global Heart 2012;7: 275–95.
9. Novack V, Pencina M, Cohen DJ, et al. Troponin criteria for myocardial infarction after percutaneous coronary intervention. Arch Intern Med 2012;172:502–8.
10. Jeremias A, Kleiman NS, Nassif D, et al. Prevalence and prognostic significance of preprocedural cardiac troponin elevation among patients with stable coronary artery disease undergoing percutaneous coronary intervention: results from the Evaluation of Drug Eluting Stents and Ischemic Events registry. Circulation 2008;118:632–7.
11. Prasad A, Singh M, Lerman A, et al. Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality. J Am Coll Cardiol 2006;48: 1765–70.
12. Noora J, Ricci C, Hastings D, et al. Determination of troponin I release after CABG surgery. J Card Surg 2005;20:129–35.
13. Greenson N, Macoviak J, Krishnaswamy P, et al. Usefulness of cardiac troponin I in patients undergoing open heart surgery. Am Heart J 2001;141:447–55.
14. Peivandi AA, Hake U, Dahm M, Opfermann UT, et al. Coronary revascularization: off-pump versus on-pump—a comparison of behavior of biochemical cardiac ischemia markers. Z Kardiol 2002;91:203–11.
15. Domanski MJ, Mahaffey K, Hasselblad V, et al. Artery bypass graft surgery. JAMA 2011;305:585–91.