CARDIOLOGY Rounds®

As presented in the rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

Universal Definition of Myocardial Infarction

By TONY C. LEE, MD, MSc, and JUAN CARLOS MONGE, MD, FRCPC

Coronary artery disease is a major cause of morbidity and mortality worldwide. During the natural progression of atherosclerotic plaque, an abrupt and potentially catastrophic event may occur, namely plaque disruption, leading to exposure to substances that promote platelet activation and aggregation, and subsequently thrombin formation.[1-3] Interruption of blood flow and the imbalance between oxygen supply and demand, if severe and persistent, leads to myocardial necrosis. Myocardial ischemia usually occurs in the setting of coronary atherosclerosis, but may also reflect dynamic elements of coronary vascular resistance, embolic phenomena, and conditions that cause a mismatch between the perfusion pressure within the coronary arteries and myocardial oxygen demand (eg, aortic stenosis, aortic regurgitation, or hypertrophic cardiomyopathy). Conditions such as anemia, sepsis, and thyrotoxicosis may also worsen oxygen delivery and increase oxygen requirements. In addition to the clinical consequences, the term myocardial infarction (MI) also carries major psychological and legal implications for the individual and society. It further serves as an important enrolment criterion and outcome measure in clinical trials. The pathological diagnosis of MI requires evidence of myocardial cell death due to prolonged ischemia. After the onset of myocardial ischemia, cell death is not immediate, but takes a finite period of time to develop; it depends on the presence of collateral circulation to the ischemic zone, persistent or intermittent coronary artery occlusion, the sensitivity of the myocytes to ischemia, pre-conditioning, and the demand for myocardial oxygen.[4,5] During the acute phase of the infarct, the majority of myocyte loss in the infarct zone occurs via coagulation necrosis and then proceeds to inflammation, phagocytosis of necrotic myocytes, and repair leading to scar formation.[6] In contrast, the clinical diagnosis of MI has traditionally required an integrated assessment of the history, with some combination of indirect evidence for myocardial necrosis using biochemical, electrocardiographic, and imaging modalities. This issue of *Cardiology Rounds* reviews the recently published "Universal Definition of Myocardial Infarction" and highlights key differences in the context of previously published guidelines.

World Health Organization (WHO) Criteria

For many years, the diagnosis of MI relied on the criteria established by the WHO in 1979.[7] Two of the following three criteria were required for diagnosis of an acute ST elevation MI (STEMI):

- Chest discomfort characteristic of ischemia
- Typical electrocardiographic pattern including development of Q waves
- Typical elevations in serum markers of myocardial injury, usually creatine kinase (CK)-MB isoenzyme

Patients with typical chest pain and elevated CK-MB, but no evidence of ST elevation or Q waves, would have a non-ST elevation MI (NSTEMI), whereas patients with an unstable pattern of chest pain, no ST elevation or Q waves, and normal CK-MB would have unstable angina (UA).

St. Michael's Hospital
30 Bond St.,
Suite 7049, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5941

Table 1: Universal Definition of Myocardial Infarction (MI)[10]

Criteria for acute MI

The term "myocardial infarction" should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for MI:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the URL, together with evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia;
  - ECG changes indicative of new ischemia (new ST-T changes of new LBBB);
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia; accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus. Thrombus may be obtained by coronary 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.
- For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile of the URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than 3 $\times$ 99th percentile of the URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.
- For CABG surgery in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than 5 $\times$ 99th percentile of the URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.
- Pathological findings of an acute MI.

Criteria for prior MI

Any one of the following criteria meets the diagnosis for prior MI:

- Development of new pathological Q waves with or without symptoms
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Pathological findings of a healed or healing MI

URL = upper reference limit; ECG = electrocardiogram; LBBB = left bundle branch block; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting

European Society of Cardiology (ESC) / American College of Cardiology (ACC) Consensus Definition

The development of more sensitive and specific serologic biomarkers allows detection of very small infarcts that previously would not have been considered an MI.[8] Indeed, a patient with ischemic symptoms, no ST elevation or Q waves, and a normal CK-MB, but elevated serum troponins, would be considered to have UA based on the WHO criteria. In response to these limitations, the ESC and ACC established a revised definition of MI in 2000.[9]

An acute, evolving, or recent MI is diagnosed if there is a typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) in these biochemical markers of myocardial necrosis with at least one of the following:

- Ischemic symptoms
- Development of pathologic Q waves on the electrocardiogram (ECG)
- ECG changes indicative of ischemia (ST elevation or depression)
- Coronary artery intervention (eg, coronary angioplasty)

Alternatively, the diagnosis could also be made on the basis of pathologic findings of an acute MI.

Either of the following criteria satisfies the diagnosis for an established MI:

- Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
- Pathologic findings of a healed or healing MI.

Universal Definition of MI[10]

Given the considerable advances in the diagnosis of MI, since the previous consensus document was published in 2000, a global task force was formed to update the 2000 consensus document. This task force was composed of experts within the fields of biomarkers, ECG, imaging, interventions, clinical investigations, global perspectives, and implications. The new ESC/ACC/American Heart Association (AHA)/World Heart Federation (WHF) consensus report was published in 2007 (Table 1). The report refines and expands on the definition of MI, recognizing five separate categories based on pathophysiology and whether percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery is involved (Table 2). Troponin is emphasized as the biomarker of choice and now there are specific criteria for the diagnosis of MI as a cause of sudden death. The new consensus guidelines also incorporate findings from imaging techniques into the diagnostic criteria.

According to the new guidelines, the term "myocardial infarction" should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. This may occur in a number of clinical situations. Clinically, the various types of MI are classified as shown in Table 2. It is important to note that patients may present with more than one type of MI simultaneously or sequentially and that the term does not include myocardial cell death associated with mechanical injury from CABG, nor does it include myocardial necrosis due to miscellaneous causes, including renal failure, heart failure, cardioversion, electrophysiological ablation, sepsis, myocarditis, cardiac toxins, or infiltrative diseases.

Spontaneous MI (Type 1) is related to ischemia due to a primary coronary event such as plaque rupture, whereas Type 2 MI is due to either increased oxygen demand or decreased supply in the absence of a primary coronary event (eg, coronary artery spasm, coronary embolism, anemia, arrythmias, hypertension, or hypotension). The diagnosis of an acute MI under these circumstances requires the detection of a rise and/or fall in cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia. Myocardial ischemia may manifest as typical symptoms of cardiac ischemia, ECG changes indicative of new ischemia, development of pathological Q waves, or imaging evidence of a new loss of viable myocardium or new regional wall motion abnormality. An acute MI may also be diagnosed based on pathological findings. Criteria for a prior MI are summarized in Table 1.

Patients who suffer sudden cardiac death represent a challenging diagnostic group. These individuals may die before blood samples for biomarkers can be obtained and before pathological changes can develop in the myocardium. However, if they present with symptoms suggestive of ischemia, accompanied by new ST elevation or new left bundle branch block (LBBB), and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, then they should be classified as having had a fatal MI (Type 3).

Table 2: Clinical classification of different types of myocardial infarction[10]

Type 1 Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2 MI secondary to ischemia due to either increased oxygen demand or decreased supply; eg, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension
Type 3 Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, 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 4a MI associated with PCI
Type 4b MI associated with stent thrombosis as documented by angiography or at autopsy
Type 5 MI associated with CABG surgery

Table 3: Elevations of troponin in the absence of overt ischemic heart disease[10]

- Cardiac contusion, or other trauma, including surgery, ablation, pacing, etc.
- Congestive heart failure – acute and chronic
- Aortic dissection
- Aortic valve disease
- Hypertrophic cardiomyopathy
- Tachy- or bradyarrhythmias, or heart block
- Apical ballooning syndrome
- Rhabdomyolysis with cardiac injury
- Pulmonary embolism, severe pulmonary hypertension
- Renal failure
- Acute neurological disease, including stroke or subarachnoid hemorrhage
- Infiltrative diseases; eg, amyloidosis, hemochromatosis, sarcoidosis, and scleroderma.
- Inflammatory diseases; eg, myocarditis or myocardial extension of pericarditis/endocarditis
- Drug toxicity or toxins
- Critically ill patients, especially with respiratory failure or sepsis
- Burns, especially if affecting >30% of body surface area
- Extreme exertion

Multiple events take place during either PCI or CABG that can lead to myocardial necrosis, and it is logical that the limitation of such damage would be beneficial to patients and their prognosis.[11-13] In the setting of PCI, in patients with normal baseline troponin values, elevations >3 times the 99th percentile of the URL are defined as PCI-related MI (Type 4a). In the setting of CABG, elevations of >5 times the 99th percentile of the URL, plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium are designated as evidence of the patient having had a CABG-related MI (Type 5). A separate subcategory of MI (Type 4b) related to stent thrombosis, as documented by angiography or autopsy, must meet the criteria for spontaneous MI as well.

Biomarker evaluation

The preferred biomarker is cardiac troponin (I or T) that has nearly absolute myocardial specificity and high clinical sensitivity reflecting even microscopic zones of myocardial necrosis.[8,14] However, biomarkers reflect the presence of myocardial necrosis and not its mechanism; as a result, an absence of clinical evidence for ischemia should prompt a search for other etiologies of myocardial necrosis (eg, myocarditis, aortic dissection, pulmonary embolism) listed in Table 3.[10] If troponin assays are not available, the best alternative is CK-MB.[15]

Table 4: ECG manifestations of acute myocardial ischemia (in absence of LVH and LBBB)[10]

ST elevation
New ST elevation at the J-point in 2 contiguous leads with the cut-off points: ≥0.2 mV in men or ≥0.15 mV in women in leads V_2-V_3 and/or ≥0.1 mV in other leads.

ST depression and T-wave changes
New horizontal or down-sloping ST depression ≥0.05 mV in 2 contiguous leads; and/or T-wave inversion ≥0.1 mV in 2 contiguous leads with prominent R-wave or R/S ratio >1

LVH = left ventricular hypertrophy

Electrocardiographic detection of MI

Acute or evolving changes in the ST-T waveforms and the presence of Q waves suggest the timing of the event, the infarct related artery, and provide estimates for the amount of myocardium at risk (Tables 4 and 5).[16] Although an ECG is an integral part of the diagnostic workup of patients with chest pain, it alone is often insufficient to diagnose MI, since ST deviation is observed in other conditions (Table 6).[17] Q waves may also

Table 5: ECG changes associated with prior MI[10]

- Any Q wave in leads V_2-V_3 ≥0.02 s or QS complex in leads V_2 and V_3
- Q wave ≥0.03 s and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V_4-V_6 in any 2 leads of a contiguous lead grouping (I, aVL, V_6; V_4-V_6; II, III, and aVF)*
- R wave ≥0.04 s in V_1-V_2 and R/S ≥1 with a concordant positive T wave in the absence of a conduction defect

* The same criteria are used for supplemental leads V_7-V_9, and for the Cabrera frontal plane lead grouping.

Table 6: Common ECG pitfalls in diagnosing MI[10]

False positives

- Benign early repolarization
- LBBB
- Pre-excitation
- Brugada syndrome
- Pericarditis/myocarditis
- Pulmonary embolism
- Subarachnoid hemorrhage
- Metabolic disturbances such as hyperkalemia
- Failure to recognize normal limits for J-point displacement
- Lead transposition or uses of modified Mason-Likar configuration (24)
- Cholecystitis

False negatives

- Prior MI with Q-waves and/or persistent ST elevation
- Paced rhythm
- LBBB

occur in nonischemic cardiomyopathy due to the presence of myocardial fibrosis.

Imaging techniques

Regional myocardial hypoperfusion and ischemia lead to a cascade of events that include myocardial dysfunction, cell death, and healing by fibrosis. A number of imaging modalities have been applied, both in the acute phase, as well as in the healing or healed phase of MI. These include echocardiography, myocardial perfusion scintigraphy, cardiac computed tomographic (CT) angiography, magnetic resonance imaging (MRI), and positron emission tomography (PET).[18-22] Imaging techniques are particularly useful if, for some reason, biomarkers are not drawn or may have normalized. In this situation, loss of myocardial viability or new regional wall motion abnormality in the absence of a nonischemic cause would be sufficient to make a diagnosis of MI.[10] However, if biomarkers are measured at appropriate intervals and are normal, they would take precedence over the imaging criteria.

Conclusions

The revised definition of MI has important implications, not only for clinical care of patients, but also for documenting epidemiological trends, initiating public policy, and developing clinical trials. Indeed, the definition of MI determines the characteristics of patients entering clinical trials, as well as the number of outcome events. The use of nonuniform infarct definitions impairs comparison and generalization among trials. A universal definition allows for trial-to-trial comparisons and improves the accuracy of meta-analyses involving multiple investigations. Ideally, investigators should ensure that a trial provides comprehensive data for various types of MI and quantifies the extent of myocardial damage.[10] Improved precision of diagnostic criteria will allow more detailed interpretations of major clinical trials and aid in the development of treatments tailored to specific subsets of patients. Increasing the sensitivity of the diagnostic criteria will result in the identification of more events, thereby allowing for appropriate secondary prevention and improved outcomes. However, this may entail adverse consequences, with respect to psychological status, professional career, and eligibility for life insurance, for some individuals and their families who are not currently labelled as having had an infarction. There are also significant societal implications related to diagnostic coding, hospital reimbursement, and mortality statistics. Cardiovascular disease is a global epidemic and the application of this revised definition of MI will potentially have a substantial impact on the identification, prevention, and treatment of cardiovascular disease throughout the world.

The vast majority of our knowledge in the diagnosis and management of MI comes from Type 1 MI, the term indicated in the new universal classification. In the absence of evidence, management is often extrapolated from this type of MI to the other types. For instance, we frequently tend to manage a perioperative MI, which is more likely to be a type 2 event related to a supply-demand imbalance as opposed to a type 1 MI due to spontaneous plaque rupture, by applying the evidence of clinical trials that did not include this type of patient and were conducted overwhelmingly in what we would now classify as type 1 MI. Therefore, another potential benefit of the new classification is that it will force physicians to think in terms of the mechanism underlying the MI and, hopefully, will spur clinical studies to further our understanding of the prevention and management of the other, perhaps less frequent, but also highly relevant, types of MI (types 2 through 5).

References

1. Ohtani T, Ueda Y, Mizote I, et al. Number of yellow plaques detected in a coronary artery is associated with future risk of acute coronary syndrome: detection of vulnerable patients by angioscopy. *J Am Coll Cardiol.* 2006;47:2194-2200.
2. Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA.* 1999;282:2035-2042.
3. Rosenberg RD, Aird WC. Vascular-bed-specific hemostasis and hypercoagulable states. *N Engl J Med.* 1999;340:1555-1564.
4. Bardales RH, Hailey LS, Xie SS, et al. In situ apoptosis assay for the detection of early acute myocardial infarction. *Am J Pathol.* 1996; 149:821-829.
5. Buja LM. Modulation of the myocardial response to injury. *Lab Invest.* 1998;78:1345-1373.
6. Fishbein MC, Maclean D, Maroko PR. The histopathologic evolution of myocardial infarction. *Chest.* 1978;73:743-749.
7. Report of the Joint International Society and Federation of Cardiology/World Health Organization Task Force on Standardization of Clinical Nomenclature. Nomenclature and criteria for diagnosis of ischemic heart disease. *Circulation.* 1979;59:607-609.
8. Antman EM, Grudzien C, Mitchell RN, Sacks DB. Detection of unsuspected myocardial necrosis by rapid bedside assay for cardiac troponin T. *Am Heart J.* 1997;133:596-598.
9. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined – a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *J Am Coll Cardiol.* 2000;36:959-969.
10. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol.* 2007;50:2173-2195.
11. Brener SJ, Lytle BW, Schneider JP, et al. Association between CK-MB elevation after percutaneous or surgical revascularization and three-year mortality. *J Am Coll Cardiol.* 2002;40:1961-1967.
12. Ricciardi MJ, Davidson CJ, Gubermikoff G, et al. Troponin I elevation and cardiac events after percutaneous coronary intervention. *Am Heart J.* 2003;145:522-528.
13. Croal BL, Hillis GS, Gibson PH, et al. Relationship between postoperative cardiac troponin I levels and outcome of cardiac surgery. *Circulation.* 2006;114:1468-1475.
14. Apple FS. Tissue specificity of cardiac troponin I, cardiac troponin T, and creatine kinase MB. *Clin Chim Acta.* 1999;284:151-158.
15. Morrow DA, Cannon CP, Jesse RL, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical characteristics and utilization of biochemical markers of acute coronary syndromes. *Circulation.* 2007;115:c352-c355.
16. Zimetbaum PJ, Josephson ME. Use of the electrocardiogram in acute myocardial infarction. *N Engl J Med.* 2003;348:933-940.
17. Wang K, Asinger RW, Mariott HJ. ST-segment elevation in conditions other than acute myocardial infarction. *N Engl J Med.* 2003;349: 2128-2135.
18. Korosoglou G, Labadze N, Hansen A, et al. Usefulness of real-time myocardial perfusion imaging in the evaluation of patients with first time chest pain. *Am J Cardiol.* 2004;94:1225-1231.
19. Dakik HA, Howell JF, Lawrie GM, et al. Assessment of myocardial viability with 99mTc-sestamibi tomography before coronary artery bypass graft surgery: correlation with histopathology and postoperative improvement in cardiac function. *Circulation.* 1997;96:2892-2898.
20. Gosalia A, Haramati LB, Sheth MP, et al. CT detection of acute myocardial infarction. *Am J Roentgenol.* 2004;182:1563-1566.
21. Buda AJ. The role of echocardiography in the evaluation of mechanical complications of acute myocardial infarction. *Circulation.* 1991;84 (3 Suppl):I109-I121.
22. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible necrosis, infarct age, and contractile function. *Circulation.* 1999;100:1992-2002.

Upcoming meetings

16 – 20 March 2008
The 24th Annual Cardiovascular Conference at Lake Louise
Lake Louise, Alberta
Contact: www.acclakelouise.com/
Carol Cox/ Hallmark Meeting Concepts
Tel. (905) 814-1112
carol151@sympatico.ca

29 March – 1 April 2008
American College of Cardiology Annual Meeting ACC.08
Chicago, Illinois
Contact: www.acc.org

1 – 3 May 2008
European Society of Cardiology (ESC) Euro Prevent 2008
Paris, France
Contact: ww.escardio.org/

30 August – 3 September 2008
ESC Congress 2008
Munich, Germany
Contact: www.escardio.org/

Disclosure Statement: *Dr. Lee and Dr. Mongé have stated that they have no disclosures to announce in association with the contents of this issue.*

Change of address notices and requests for subscriptions to *Cardiology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Cardiology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above. Publications Post #40032303

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Canada Inc.