ESC European Society of Cardiology

European Heart Journal (2018) **39**, 3757–3765
doi:10.1093/eurheartj/ehy655

CARDIOPULSE

What's new in the Fourth Universal Definition of Myocardial infarction?

When myocardial infarction (MI) was redefined in 2000 it was stated that myocardial injury detected by abnormal cardiac biomarkers in the setting of acute myocardial ischaemia should be labelled as myocardial infarction. Since then, this principle has remained a fundamental component of the Universal Definition of Myocardial Infarction including the Fourth Universal Definition of Myocardial Infarction Consensus Document.

Even though myocardial injury is a prerequisite for the diagnosis of MI it is also an entity in itself and is now considered a separate condition. Myocardial injury is said to be present when blood levels of cardiac troponin (cTn) are increased above the 99th percentile upper reference limit (URL). The injury may be acute, as evidenced by a newly detected dynamic rising and/or falling pattern of cTn values above the 99th percentile URL, or chronic, in the setting of persistently elevated cTn levels.

There are numerous situations such as infection, sepsis, and kidney disease that can cause myocardial injury which is diagnosed when patients demonstrate elevated cTn values. For example, a patient admitted with chest trauma following a motor vehicle accident may demonstrate a typical rising and falling set of cTn values as a result of a myocardial injury. A substantial number of patients with chronic renal failure demonstrate low grade, persistently elevated cTn values which imply a negative long-term prognosis for these individuals. It is thought that the persistently elevated cTn levels are the result of a number of factors including ongoing, low-grade myocardial injury.

Myocardial injury may also be related to coronary revascularization procedures. Both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) can lead to elevation of cTn values that may be related to the procedure itself or secondary to complications from the procedure.

The presence of an acute myocardial injury in the setting of acute myocardial ischaemia meets the clinical definition of MI. There are five different subtypes of MI that are based on pathological, clinical, and prognostic differences and require different treatment strategies.

Type 1 MI is the traditional clinical picture of a heart attack. The underlying pathophysiology involves atherosclerotic plaque disruption complicated by intraluminal thrombosis resulting in decreased oxygen and nutrient delivery to heart muscle. Depending on the ECG findings, Type 1 MI can be classified as either an ST elevation MI (STEMI) or a non-ST elevation MI (NSTEMI) in order to direct appropriate, guideline established therapy.

In Type 2 MI, oxygen deprivation is not caused by atherosclerotic plaque rupture in a coronary artery but rather by an acute stressor such as an acute gastrointestinal bleed with a precipitous drop in haemoglobin, or a sustained tachyarrhythmia with clinical manifestations of myocardial ischaemia. Each of these settings and many others may result in a supply/demand imbalance of myocardial oxygen and nutrient supply leading to ischaemia and a myocardial injury. However, individual ischaemic thresholds may vary substantially from one patient to another depending on the magnitude of the stressor, the presence of non-cardiac comorbidities, the extent of underlying coronary artery disease (CAD), and cardiac structural abnormalities. Coronary atherosclerosis is commonly seen in patients with Type 2 MI who undergo coronary angiography. However, atherosclerotic plaque rupture with accompanying thrombosis is not seen.

Patients with Type 2 MI are treated by managing the underlying illness that has led to the ischaemic imbalance of oxygen supply and demand. Therapy may include volume adjustment, blood pressure management, blood transfusion, heart rate control, and respiratory support. Depending on the clinical situation, a coronary angiographic evaluation may be indicated once a patient is stable in order to assess the likelihood of clinically important CAD. Patients with atherosclerotic CAD should be managed according to current guidelines.

Type 2 MI and myocardial injury are frequently encountered in clinical practice and both entities are associated with poor outcome. Both Type 1 and Type 2 acute MI require a rising and/or falling pattern of cTn values. Acute myocardial injury may also manifest such a pattern. However, in patients with chronic myocardial injury related to structural heart disease the cTn values may be elevated and stable without the rising and falling pattern. Type 2 MI and non-ischaemic myocardial injury may coexist in the same patient.

The detection of cardiac biomarkers in blood is fundamental for establishing the diagnosis of MI. However, patients can manifest a typical presentation of myocardial ischaemia/infarction including presumed new ischaemic ECG changes or ventricular fibrillation and die before it is possible to obtain blood for cardiac biomarker determination. Such patients are designated as having a Type 3 MI, when suspicion for an acute myocardial ischaemic event is high, even when cardiac biomarker evidence of MI is lacking.

Percutaneous coronary intervention-related increases of cTn values establish a diagnosis of procedure-related myocardial injury, but cTn elevation alone does not meet the diagnosis of Type 4a MI. The Type 4a MI also requires an elevation of cTn values >5 times the 99th percentile URL in patients with normal baseline values or in patients with elevated pre-procedure cTn in whom the cTn levels are stable (≤20% variation) or falling. In addition, evidence of new myocardial ischaemia is required, either recognized from ECG changes, findings on imaging procedures, or as a result of a procedure-related complication that leads to reduced coronary blood flow. Other subcategories of PCI-related MI are stent/scaffold thrombosis, Type 4 b MI, as documented

by angiography or autopsy or in-stent restenosis, Type 4c MI, detected at angiography. Both Types 4b and 4c MIs are applying the same diagnostic criteria utilized for Type 1 MI.

Numerous factors can lead to procedural myocardial injury during a CABG procedure. Many of them are related to various aspects of myocardial preservation, direct traumatic injury to the myocardium, as well as any potential ischaemic injury. For that reason, increases in cTn values should be expected after all CABG procedures. However, for diagnosing type 5 MI, it is suggested to use a cTn value >10 times the 99th percentile URL as the cut-point during the first 48 h following CABG, occurring from a normal baseline cTn value (≤99th percentile URL), together with accompanying ECG, angiographic, or imaging evidence of new myocardial ischaemia or new loss of myocardial viability.

Perioperative MI is one of the most important complications involving major non-cardiac surgery. Most patients who have a perioperative MI will not experience ischaemic symptoms due to anaesthesia, sedation, or pain-relieving medications. Post-operative cTn surveillance is recommended for high-risk individuals. In order to properly interpret the aetiology of elevated post-operative cTn values, a baseline pre-operative value is needed in order to determine whether the increase is acute or chronic. A diagnosis of MI, however, still requires, in addition to an increase of cTn values, evidence of myocardial ischaemia during the immediate peri- and post-operative period, e.g. ECG changes on telemetry, repeated episodes of hypoxia, hypotension, etc., or imaging evidence of MI. In the absence of evidence for acute myocardial ischaemia, a diagnosis of acute myocardial injury is more appropriate.

Takotsubo syndrome (TTS) can mimic MI and is found in approximately 1–2% of patients presenting with suspected STEMI. The onset of TTS is often triggered by intense emotional or physical stressors, and over 90% of patients are post-menopausal women. ST-segment elevation is frequently seen beyond that of a single coronary artery blood flow distribution. The rise and fall in cTn levels support an acute myocardial injury, secondary to high catecholamine surges which are known to trigger cTn release from cardiomyocytes.

It is increasingly recognized that there is a group of MI patients without angiographic obstructive CAD. Clinically important coronary arterial obstruction is defined as a stenosis ≥50% of the luminal diameter of a major epicardial vessel. These patients are said to have suffered an MI without significant coronary arterial narrowing. The term used to describe these patients is 'myocardial infarction with non-obstructive coronary arteries (MINOCA)'. This entity is more common in women than in men and usually presents as a NSTEMI rather than a STEMI.

Many patients with advanced kidney disease have chronic elevations of cTn values denoting chronic injury to the myocardium. The mechanisms for this injury state include increased ventricular pressure, small-vessel coronary obstruction, anaemia, hypotension, and probably direct toxic effects on the myocardium associated with the uraemic state. Studies suggest that serial changes in cTn levels are equally effective in diagnosing MI in patients with chronic kidney disease as in those with normal renal function. When the level of elevated cTn values is unchanging, this reflects chronic myocardial injury. However, if a rising and/or falling pattern is present, and it is accompanied by ischaemic symptoms, new ischaemic ECG changes, or loss of viable myocardium on imaging, a diagnosis of acute MI is likely.

Asymptomatic patients who develop new Q wave criteria for MI detected during routine ECG follow-up or reveal evidence of MI by cardiac imaging that cannot be directly attributed to an interim coronary revascularization procedure or to an admission to hospital for an acute coronary syndrome, are said to have had a 'silent or unrecognized MI'.

In addition to the clinical sections of the Consensus Document on the Fourth Universal Definition of Myocardial Infarction, it also contains a considerable amount of detailed information regarding analytic issues of cTn, about the use of ECG, and the application of imaging for diagnosing myocardial injury and MI.

Myocardial injury

- Cardiac troponin (cTn) values above 99th percentile of upper reference limit (URL).
- Acute or chronic.
- Different causes.
- Iatrogenic after PCI and CABG.
- Occurrence in the setting of acute myocardial ischaemia denotes myocardial infarction.

Myocardial infarction

- Type 1: reduced blood supply to myocardium due to coronary atherothrombotic obstruction to blood flow.
- Type 2: reduced oxygen supply or increased demand secondary to other causes unrelated to acute coronary atherothrombosis.
- Type 3: Cardiac event and death before biomarkers measured.
- Type 4a: PCI-related increases of cTn values >5 times the 99th percentile URL together with new myocardial ischaemia evidenced by ECG, imaging or complications leading to reduced coronary blood flow.
- Type 4b: stent/scaffold thrombosis.
- Type 4c: in-stent restenosis at angiography.
- Type 5: CABG-related increases of cTn values > 10 times 99th percentile URL together with new myocardial ischaemia or new loss of myocardial viability.

Kristian Thygesen MD DSc
Co-chairman
Joint ESC/ACC/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction.
Department of Cardiology, Aarhus University Hospital
Palle Juul-Jensens Boulevard
DK-8200 Aarhus N, Denmark
Tel: +45 78452262
Email: kthygesen@oncable.dk
kristhyg@rm.dk

Conflict of interest: none declared.