Myocardial injury, necrosis and infarction

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Faculty Disclosure

In accordance with the policy of the ESC the following presenter has indicated that they have a relationship, which in the context of their presentation, could be perceived as a real or apparent conflict of interest but do not consider that it will influence their presentation.

Research Grants

Sanofi Aventis; Eli Lilly; Medicines Company; NIH; Pfizer; Roche; Johnson & Johnson; Schering Plough; Merck Sharpe & Dohme; Astra Zeneca; GlaxoSmithKline; Daiichi Sankyo Pharma Development; Bristol-Myers Squibb

Advisory boards

Merck Sharpe & Dohme; Regado Biosciences
Definitions of injury, necrosis and infarction: Concise Oxford Dictionary

• Injury: Physical harm or damage

• Necrosis: Death of tissue caused by disease or injury

• Infarction: Dead tissue caused by an inadequate blood supply
Definition of myocardial infarction

Acute myocardial infarction is defined as myocardial cell death due to prolonged myocardial ischemia.

Pathology

Third Universal Definition of Myocardial Infarction
Biomarkers for detection of myocardial infarction

Preferably
Detection of rise and/or fall of cardiac Troponin (I or T) with at least one value above the 99\textsuperscript{th} percentile of the upper reference limit measured with a coefficient of variation \( \leq 10\% \)

When cardiac Troponin is not available
Detection of rise and/or fall of CKMB mass with at least one value above the 99\textsuperscript{th} percentile of the upper reference limit measured with a coefficient of variation \( \leq 10\% \)

Third Universal Definition of Myocardial Infarction
Elevations of cardiac troponin values because of myocardial injury

- Injury related to primary myocardial ischemia (MI type 1)
- Injury related to supply/demand imbalance of myocardial ischemia (MI type 2)
- Injury not related to myocardial ischemia
- Multifactorial or indeterminate myocardial injury
“Small amounts of myocardial injury with necrosis may be detected which are associated with heart failure, renal failure, myocarditis, arrhythmias, pulmonary embolism or otherwise uneventful percutaneous or surgical coronary procedures. These should not be labelled as MI or a complication of the procedures, but rather as myocardial injury.”
Myocardial injury: quote from the 3rd Universal definition document

“It is recognized that the complexity of clinical circumstances may sometimes render it difficult to determine where individual cases may lie (with respect to myocardial injury vs. myocardial infarction).”
Elevated troponin in the absence of overt ischemic heart disease

- 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 brady arrhythmias, or heart block
- Stress cardiomyopathy (takotsubo syndrome)
Elevated troponin in the absence of overt ischemic heart disease

- Rhabdomyolysis with cardiac injury
- Pulmonary embolism, severe pulmonary hypertension
- Renal failure
- Acute neurological disease, including stroke, or subarachnoid haemorrhage
- Infiltrative diseases, e.g., amyloidosis, haemochromatosis, sarcoidosis, and scleroderma
Elevated troponin in the absence of overt ischemic heart disease

- Inflammatory diseases, e.g., myocarditis or myocardial extension of endo-/pericarditis
- Drug toxicity or toxins
- Critically ill patients, especially with respiratory failure, or sepsis
- Burns, especially if affecting > 30% of body surface area
- Extreme exertion
### Elevation of cardiac troponins because of myocardial injury

#### Criteria for acute myocardial infarction
- Plaque rupture
- Intraluminal coronary artery thrombus formation

#### Injury related to supply/demand imbalance of myocardial ischaemia
- Tachy-/brady-arrhythmias
- Aortic dissection or severe aortic valve disease
- Hypertrophic cardiomyopathy
- Cardiogenic, hypovolaemic or septic shock
- Severe respiratory failure
- Severe anaemia
- Hypertension with or without LVH
- Coronary spasm
- Coronary embolism or vasculitis
- Coronary endothelial dysfunction without significant CAD
Elevation of cardiac troponins because of myocardial injury

Criteria for acute myocardial infarction

- Plaque rupture
- Intraluminal coronary artery thrombus formation
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### Universal classification of myocardial infarction

#### Type 1: Spontaneous myocardial infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

#### Type 2: Myocardial infarction secondary to an ischaemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.

#### Type 3: Myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

#### Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 X 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes, or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-reflow, or embolization or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

#### Type 4b: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

#### Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 X 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
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Universal classification of myocardial infarction

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In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.
Universal classification of myocardial infarction

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Universal classification of myocardial infarction

Type 4b: Myocardial infarction related to stent thrombosis

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
Universal classification of myocardial infarction

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 X 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
PCI-related MI is defined by elevation of cardiac troponin values >5 X 99th percentile URL. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality.
Myocardial Infarction Type 4a

PCI-related MI is defined by elevation of cardiac troponin values >5 X 99th percentile URL. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality.

If cardiac troponin values are not elevated >5 X 99th percentile URL, then the term myocardial injury should be used.

Third Universal Definition of Myocardial Infarction

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Myocardial Infarction Type 4b

Myocardial infarction related to stent-thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers with at least one value >99th percentile URL

Third Universal Definition of Myocardial Infarction
CABG-related MI is defined by elevation of cardiac troponin values $>10 \times 99^{th}$ percentile URL. In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Myocardial Infarction Type 5

CABG-related MI is defined by elevation of cardiac troponin values >10 X 99th percentile URL. In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

If cardiac troponin values are not elevated >10 X 99th percentile URL, then the term myocardial injury should be used.

Third Universal Definition of Myocardial Infarction
## Classification of potential types of mechanisms causing troponin elevations

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<tr>
<td>Type 2</td>
<td>Apoptosis</td>
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<tr>
<td>Type 3</td>
<td>Normal myocyte turnover</td>
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<tr>
<td>Type 4</td>
<td>Cellular release of proteolytic troponin degradation products</td>
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<tr>
<td>Type 5</td>
<td>Increased cellular wall permeability</td>
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<tr>
<td>Type 6</td>
<td>Formation and release of membranous blebs</td>
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White, HD. JACC 2011
Sections of left ventricle from dog with 6h of coronary occlusion without reperfusion

(a) Oedema and hypereosinophilia of myocytes in zone of necrosis
(b) immunostaining for troponin I showing decreased staining of necrotic myocardium
(e) accentuation of loss of troponin T at the edge of the infarct (arrows)
Type 2: Apoptosis

- Apoptosis with preserved membrane integrity associated with activation of caspases that mediate the cleavage of structural proteins that may lead to the release of troponin

White, HD. JACC 2011
Type 3: Normal myocyte cell turnover

- Study of the integration of carbon-14 into the DNA of myocardial cells, generated by nuclear bomb testing, has shown that cardiac myocytes regenerate.

- There is a decrease from 1% annual turnover at the age of 25 to 0.45% at the age of 75 with approximately 50% of cells exchanged during a normal life span.

- Whether such low grade turnover results in release of troponin to the systemic circulation is unknown.

White, HD. JACC 2011
Type 4: Cellular release of proteolytic troponin degradation products

- A potential cause of troponin release, without death of the cell and cellular membrane disruption, is the cellular release of proteolytic troponin degradation products.
- Thus proteolysis to create small fragments could allow these to pass through a cellular membrane with normal membrane integrity.
- Only 15 minutes of mild ischemia has been shown to cause development of troponin I degradation products.
Type 5: Increased cellular wall permeability

- Reversible injury to the cardiac myocyte membrane allowing permeability of troponins from the cytosol may occur due to myocardial stretch, or ischemia.

- Simulation of stretch-responsive integrins has been shown to result in release of intact troponin from cultured viable cardiomyocytes without an increase in lactate production inferring that release may occur without ischemia or necrosis.

- Also in a rat model increasing preload has been shown to be associated with release of troponin I, independent of ischemia.

White, HD. JACC 2011
Type 6: Formation and release of membranous blebs

- Active secretion of vesicles (blebs) or membrane expression with shedding has been hypothesised to be a mechanism to enable troponin to be released from cardiac cells.

- This mechanism has been described in liver cells, where large molecules can pass from intra- to extra-cellular spaces without necrosis occurring, by the formation of membranous blebs during ischemia.

White, HD. JACC 2011
Microbleb formation of adult cultured myocytes

Baseline

30 min of anoxia

Myocardial injury with cell death marked by cardiac troponin elevation

Myocardial Infarction

Clinical evidence of acute myocardial ischemia with rise and/or fall of cardiac troponin

Cardiac procedure

Non-cardiac major procedure

Tachy-/brady-arrhythmia

Heart failure

Renal failure
Myocardial injury, necrosis and infarction

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