MORPHOLOGICAL DIAGNOSIS OF MYOCARDIAL INFARCTION - IN THE LIGHT OF THE CURRENT CLINICAL CLASSIFICATION

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MORPHOLOGICAL DIAGNOSIS OF MYOCARDIAL INFARCTION IN THE LIGHT OF THE CURRENT CLINICAL CLASSIFICATION (Abstract): Ischemic heart disease is one of the leading causes of morbidity and mortality worldwide. Diagnosis of myocardial infarction (MI) can be a challenge, especially in the absence of acute coronary occlusion. Accurate histopathological identification and timing of myocardial infarction in humans are of particular importance, especially for clinical practice or for legal medicine. The post-mortem diagnosis requires not only up-to-date knowledge of coronary and myocardial ischemic pathology, but also a correct interpretation of these features in relation to the clinical scenario of the disease. For these reasons, it is important for pathologists to know the different clinical types of MI and to differentiate myocardial infarction from other forms of myocardial injury. Keywords: ISCHEMIA, MYOCARDIAL INFARCTION, SMALL VESSEL DISEASE.

Acute ischemic cardiac syndromes, which are acute myocardial infarction (MI), unstable angina and sudden coronary death, are acute life-threatening diseases with high mortality rates (1). Coronary artery disease (CAD), which is the basis of most cases of MI, and also the ischemic myocardial pathology in various stages of injury and repair, is extensively studied to improve post-mortem diagnosis (2). Auxiliary techniques for highlighting ischemic injury have been developed or are now under investigation for improving diagnosis (3). Recent acquisitions, such as non- or minimally invasive post-mortem imaging techniques used to detect coronary occlusion and ischemic injuries, nowadays they attract much interest, as autopsy rates tend to decrease in many countries (4, 5). However, in some cases, these diagnostic modalities alone may prove inadequate or insufficient to explain a clinical suspicion of myocardial ischemia. Examples are sudden coronary death without thrombi, cases of peri-procedural myocardial ischemia after therapeutic coronary interventions or non-coronary causes of ischemia (6). Last but not least, there are certain types of myocardial injury, other than ischemic, that need to be considered. This is reflected in the current clinical classification of myocardial infarction, which differentiates various types of pathological mechanisms and evolving treatment strategies (7). Our paper proposed to review the previous MI appearances and to highlight the new concept.
in the light of the current clinical MI classification.

1. Definition. The 4th universal definition of myocardial infarction (2018), agreed by the members of the European Society of Cardiology, American Heart Association and World Heart Association Federation, etc., describes five distinct MI subtypes based on large variety in the pathophysiology aspects of MI encountered in clinical practice. The term acute myocardial injury should be used when there is evidence of increased cardiac troponin (cTn) values, what many doctors label as “troponin leakage”, “troponinemia” (8).

The known clinical diagnosis of MI is based on the presence of increased levels of cardiac troponin, in combination with prolonged chest pain, ECG records or regional wall anomalies indicative of recent onset ischemia or angiographic detection of a coronary thrombus, while the new concept proposes the need for differentiation of myocardial infarction from myocardial injury by highlighting the peri-procedural myocardial injury after cardiac and non-cardiac procedures and to use of cardiovascular magnetic resonance and computerized coronary tomographic angiography in diagnosis of suspected myocardial infarction (4, 5).

2. The new MI classification. In 2018, a group of pathologist experts differentiate five distinct MI subtypes (Table I) according with various pathophysiology MI appearances (9).

### TABLE I

<table>
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<tr>
<th>MI Types</th>
<th>ESC/AHA/ACC/WHF classification of MI 2018</th>
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<tr>
<td>Type 1</td>
<td>Acute atherothrombotic occlusion or mural thrombus with critical flow reduction initiated by plaque rupture or erosion</td>
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<tr>
<td>Type 2</td>
<td>Ischemic injury due to a myocardial oxygen supply-demand mismatch, which is not caused by coronary atherothrombosis (tab. II)</td>
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<tr>
<td>Type 3</td>
<td>Cardiac death in a clinical setting suggestive of ischemic injury (chest pain, ECG changes) but without definitive cardiac biomarker evidence</td>
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<td>Type 4</td>
<td>PCI-related ischemic injury &lt; 48 hrs. after procedure. Includes also cases of MI due to late stent thrombosis or restenosis</td>
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<tr>
<td>Type 5</td>
<td>CABG-related ischemic injury &lt; 48 hrs. after the procedure</td>
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Type I of MI is the result of acute coronary atherothrombosis. In clinical studies, coronary thrombotic events can be observed in approximately 80% of patients with acute coronary syndromes (ACS). They are still classified based on ECG findings as either ST elevation types of MI (STEMI) or non-ST elevation types of MI (non-STEMI).

The most common cause of acute myocardial ischemia is atherothrombotic occlusion of a coronary artery (10). This implies that, in cases of sudden death, acute coronary occlusion may explain the arrhythmic death. The underlying pathology of mural or occlusive coronary thrombosis may be due to rupture or erosion of the plaque, or less frequently, to protruding calcified nodules. Also, intraplaque bleeding contributes to the acute flow reduction in these
Irreversible damage of myocardial cells is the hallmark of MI also known as ischemic necrosis, which is histologically a “coagulative” type necrosis. It should be differentiated from other types of necrosis, which can be found at autopsy, the type of contraction band necrosis, which is a feature of many other forms of myocardial injury (12).

The onset of ischemic necrosis is not immediate. The acute ischemic lesion develops in the “area at risk” (area of perfusion of the obstructed artery). Ischemic necrosis of myocardial cells can be detected with the current diagnostic methods after about 2-4 hours, but the onset depends on many variables, such as collateral circulation and microvascular pathology. After the onset of occlusion, myocardial necrosis evolves in a wave front-like pattern over several hours from the endocardium to the epicardium in the “risk area”, eventually causing a transmural MI. During the wave evolution of the myocardial necrosis, ventricular arrhythmias may occur in the subendocardium, even in the earliest stage of still reversible damaged myocardium, but also several hours after occlusion, when the wave of necrosis has evolved substantially. This is also important for pathologist to realize that early onset arrhythmia and SCD is an early sign of myocardial injury in the absence of any other changes, prior to the development of myocardial necrosis wave. It should be noted that later stages of myocardial necrosis, including fibrous scars may serve as a substrate for life-threatening arrhythmias (13).

**Topographic distribution of MI in the heart.** According to the involved myocardial region, MI is classified as regional when it involves the area of perfusion of one epicardial artery or circumferential when it affects a large part of the circumference of the ventricular wall. Regional MI can be either transmural, usually associated with ST segment elevations on ECG (STEMI), or only subendocardial (non-STEMI). Circumferential MI is mostly due to the general decrease in coronary perfusion pressure that interests the three major coronary artery branches and is localized in the subendocardial region only (fig. 1).

![Fig. 1. Topographic distribution of MI in the heart.](image-url)
The location of the MI is related by the perfusion territory of the three large epicardial arteries, such as: (a) obstruction of the anterior descending left coronary artery determines an antero septal AMI located in the anterior wall of the LV, 2/3 anterior IVS and the apex of the heart (40%); (b) obstruction of the posterior descending coronary artery causes a postero-inferior AMI, located in the posterior or inferior wall of the LV and 1/3 posterior of the IVS (30%); (c) obstruction of the circumflex branch of the left coronary artery gives a lateral AMI, located in the lateral wall of the LV, except the heart apex (20%); (d) obstruction of the left coronary artery before artery branching causes a massive antero-lateral AMI (10%) (14).

**Other MI locations.** Atrial infarctions occur in relation with ventricular infarctions and have a variable incidence in patients with MI ranging from 0.7 to 42%. Isolated atrial infarctions are rare (15). The main cause of atrial MI is coronary atherosclerosis. The pathological significance is related by the two potential complications of atrial MI: the first is the mural thrombus formation followed by thromboembolization, especially in patients with atrial fibrillation (16); the second is the rare atrial rupture that can result in cardiac tamponade (15).

Postmortem diagnosis of MI is based on gross and histological changes. Clinical-pathological correlations can be made by differentiating four evolutive stages of the lesions, which are related to the important clinical scenarios of ischemic morbidity and mortality (9).

a. **The earliest stage of cell death (the first hours).** Under experimental conditions, transmission electron microscopy (TEM) reveals ischemic changes (mitochondrial swelling and cardiomyocyte interruptions already occurring 10 minutes after onset). This method is not useful for detecting early human ischemia due to similarities between early ischemic changes and autolysis. The earliest light microscopic changes are regional wavy pattern of myocytes as a result of stretching of dead non-contractile myocytes due to adjacent functional myocardium during the cardiac cycle (8). In the first hours, the interstitial edema appears, and early onset of coagulative necrosis shown by cytoplasmic hyper-eosinophilia also develops, representing the early onset of coagulative necrosis (fig. 2). Enzymatic detection of early necrosis in fresh myocardium is made by using NBT reaction which is reported to be positive from 3 hours after the onset of ischemia. NBT stains only in the presence of intracellular lactate dehydrogenase (LDH). Nitro blue tetrazolium (NBT) staining of a fresh myocardial slice demonstrates early ischemic necrosis (due to leakage of enzymes from irreversibly damaged myocardium) while the vital myocardium is stained in deep purple (9, 14).

b. **Inflammatory stage (first week).** Neutrophil infiltration begins at MI border. Neutrophils can also invade the central area of a small MI, but this occurs much later depending on the size of the infarction. Coagulation necrosis continues by revealing the nuclear changes and myocyte disintegration. This is associated with heavy interstitial infiltrates of intact neutrophils and karyorrhexis of the neutrophils. Early phagocytosis of dead cells by macrophages, infiltration of other mononuclear cells, such as lymphocytes, and the onset of marginal fibrovascular response, show a further continuation of the healing process (fig. 3).

However, in large MIs, residual necrotic areas can still be detected even after many
weeks. Macroscopically, MI acquires a gray-yellowish color. At this stage, the necrotic myocardium is weak and vulnerable to septal, papillary muscles or free wall ruptures in case of transmural infarction, all with high mortality (9, 14).

Fig. 2. a- myofiber waviness; b- interstitial edema.

Fig. 3. c- hyper eosinophilia and coagulative necrosis of cardiomyocytes; d- heavy granulocyte infiltration.

c. **Granulation tissue stage (one week to several weeks).** This stage is characterized by capillary and fibroblasts proliferation with initial deposition of loose arranged collagen fibers and a persistent inflammatory infiltrate of lymphocytes, rare plasma cells, macrophages including siderophages, while the number of neutrophils decreases. Granulation tissue is most abundant at 2-3 weeks (fig. 4). Grossly, this tissue can be seen as a gelatinous hyperemic border around the necrosis (9, 14).

Fig. 4. e- macrophages infiltration; f- granulation tissue with formation of micro vessels.
d. Late fibrotic stage (scarring) (over several weeks). The granulation tissue gradually disappears and is replaced by dense collagen leading to fibrotic scars, which usually contain dilated vessels with thin walls (fig. 5). The rate of granulation tissue disappearance depends on the size of MI but is completed by the second month in most cases, leaving a hypocellular scar (9, 14).

![Fig. 5. g-fibroblast proliferation; h-dense fibrous scar replacing myocyte loss.](image)

**Type 2 MIs** are heart attacks that result from an imbalance between myocardial oxygen demand and oxygen supply and are not due to acute disruption of coronary plaque and thrombosis (tab. II). In general, the frequencies reported by type 2 MI ranges from 10 to 30% of all patients with MI (17).

For example, MI with normal or low-grade angiographic stenosis (stenosis ≤50%) is a clinically recognized syndrome (called MI with non-obstructive coronary arteries, MINOCA), caused by a variety of pathology in and outside the heart. In a case of a fixed stenotic stable plaque of > 75% stenosis, exercise or spasm, can cause irreversible myocardial injury (18). Stenosis of 90% or more causes myocardial ischemia, even at rest, can be observed as a point-like/pinpoint lumen, less than 1 mm in diameter. Many of these stenoses are caused by fibro-calcified plaques but without thrombus. In these cases, microscopy of the malperfused territories of the myocardium can be a helpful adjunct in diagnosis.

### TABLE II.

<table>
<thead>
<tr>
<th>Causes of MIs without atherothrombotic coronary artery disease</th>
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<tr>
<td>Fixed coronary atherosclerotic plaques</td>
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<tr>
<td>Non-atherosclerotic coronary artery disease</td>
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<tr>
<td>Non-coronary cardiac oxygen demand-supply imbalance</td>
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<tr>
<td>Extra cardiac oxygen demand-supply imbalance</td>
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<tr>
<td>In combination with non-coronary causes of oxygen demand-supply imbalance</td>
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<tr>
<td>Spasm/SVD, vasculitis, dissection, embolism, congenital anomalies, fibromuscular dysplasia, iatrogenic (stent or graft restenosis), PCI-related no-reflow</td>
</tr>
<tr>
<td>Sustained tachyarrhythmias, bradyarrhythmia, LV hypertrophy and/or dilatation</td>
</tr>
<tr>
<td>Respiratory failure, severe anemia, hypovolemic shock</td>
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Morphologically, there are no distinctive gross or histologic hallmarks of coronary artery spasm (CAS). Drugs (androgenic anabolic steroids), physical and mental
stress are considered as precipitating factors of spasm (18). The presence of an area of regional myocardial infarction could indicate spasm in the artery when no other explanation for infarction is provided. It can affect either the normal or atherosclerotic epicardial arteries or the microcirculation, or both. It is the result of vascular smooth muscle cell hyper-reactivity as a pathophysiological substrate for spasm.

Microvascular dysfunction (MVD) is a functional impairment of flow in intramyocardial vessels and may cause MI. It is especially seen in hypertrophic and dilated hearts, preferentially in the subendocardial areas of the myocardium. Moreover, microvascular embolization can occur in patients with atrial fibrillation (19).

**Type 3 MI.** The patients presenting with type 3 MI have new ECG changes or are in ventricular fibrillation (VF), but who die before cardiac biomarkers of ischemia can be identified. A frequency of 3-4% of total MI has been reported. HP study of the myocardium reveals coagulative myocyte necrosis as a hallmark for VF (20).

**Type 4 MI** is diagnosed by a significant increase in cardiac biomarkers related to percutaneous coronary revascularization procedure. It can be temporally linked to the procedure (within 48 hours) leading to critical reduction of myocardial blood flow; it may be also due to acute complications of a device, such as in-stent thrombosis, coronary dissection or the late stent complications, such as restenosis and late-onset thrombosis (21).

Prompt restoration of coronary blood flow preserves the myocardium. Histological changes include hemorrhage, contraction band necrosis, endothelial swelling, and vascular plugs.

**Type 5 MI** is due to ischemic injury associated with coronary artery bypass grafting (CABG) that occurs within 48 hours of the procedure. It can be related to the procedure or to low-flow or reperfusion injury (9).

3. Ischemia and reperfusion and other forms of injury. After coronary intervention, PCI or CABG, the myocardial and microvascular pathology is characterized by peri-procedural ischemia, myocardial reperfusion injury and no-reflow phenomena, in association with pre-existent ischemic pathology of the myocardial risk area at (22).

Contraction band necrosis (CBN) of myocytes is the earliest sign of myocardial injury, arising at 10 min after onset of ischemia and reperfusion, and is characterized by the occurrence of thick eosinophilic bands in the cytoplasm of cardiomyocytes due to clustering of hypercontracted contractile proteins (fig. 6). After flow restoration (reperfusion), dying cardiomyocytes with ischemic damaged cell membranes are exposed to high serum Ca$^{2+}$ concentrations, leading to massive Ca$^{2+}$ influx followed by irreversible hypercontraction (CBN). CBN occur frequently in the periphery (the ‘border zones’) of ischemic infarctions, which is due to microvascular collateral perfusion from adjacent vital myocardium (23).

![Fig. 6. Contraction band necrosis](image-url)
of ischemic infarction alone. They can also be observed after CPR including defibrillation and other trauma. CNB are related to PCI, but they also are observed in situations of catecholamine excess, free radical injuries, etc. CBN is accompanied by microvascular injury leading to endothelial swelling, microvascular obstruction and interstitial hemorrhages (9, 24).

4. Experts appreciation. The 2018 New Concepts in differentiation of myocardial infarction from myocardial injury consists (7) in: (a) Highlighting peri-procedural myocardial injury after cardiac and noncardiac procedures; (b) Use of cardiovascular magnetic resonance in suspected myocardial infarction; (c) Use of computed tomographic coronary angiography to define the etiology of myocardial injury.

In both cases of MI associated with PCI or CABG (clinical types MI 4 and 5), the application of post-mortem coronary angiography should be considered. This method allows to localize stents, to visualize the patency of stents and grafts and to evaluate the distal arterial bed and presence of collateral vascularization. Histological sampling of the involved myocardium is crucial for investigating the presence of myocardial injury.

CONCLUSIONS

Histopathological exam represents the first and last opportunity to make an accurate diagnosis in AMI and SCD. The methods of investigation has been updated including not only a protocol for examination of the heart and histological sampling, but, when necessary, toxicology, microbiology, biochemistry, genetic, molecular investigation and imagistic methods.

REFERENCES


