REVIEW

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Diagnostic and Therapeutic Implications of Type 2 Myocardial Infarction: Review and Commentary

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ABSTRACT

The Task Force for the Universal Definition of Myocardial Infarction recently published updated guidelines for the clinical and research diagnosis of myocardial infarction under a variety of circumstances and in a variety of categories. A type 1 myocardial infarction (MI) is usually the result of atherosclerotic coronary artery disease with thrombotic coronary arterial obstruction secondary to atherosclerotic plaque rupture, ulceration, fissuring, or dissection, causing coronary arterial obstruction with resultant myocardial ischemia and necrosis. Patients with a type 2 MI do not have atherosclerotic plaque rupture. In this latter group of patients, myocardial necrosis occurs because of an increase in myocardial oxygen demand or a decrease in myocardial blood flow. Type 2 MI has been the subject of considerable clinical discussion and confusion. This review by knowledgeable members of the Task Force seeks to help clinicians resolve the confusion surrounding type 2 MI.

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In 2007, the Task Force for the Universal Definition of Myocardial Infarction simultaneously published an international consensus document in the *Journal of the American College of Cardiology*, the *European Heart Journal*, and *Circulation*.[1-3] The 2007 document was an updated revision of the original document from this group that had first been published in 2000.[4] In this second communication, the task force defined 5 subtypes of myocardial infarction (MI), which were retained in the 2012 revision.[5]

Type 1 MI is usually the result of atherosclerotic coronary artery disease with thrombotic coronary arterial obstruction secondary to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection. However, an occasional patient may demonstrate normal luminal coronary anatomy at catheterization despite the clinical syndrome of a type 1 MI. In contrast, patients with type 2 MI do not usually have atherosclerotic plaque rupture, but rather, myocardial necrosis secondary to an increase in myocardial oxygen demand or a decrease in myocardial blood flow. Type 3 MI is the result of coronary arterial thrombosis with early demise, and types 4 and 5 MI are related to complications of percutaneous coronary intervention and coronary bypass surgery.

Type 2 MI has been the subject of considerable clinical discussion and confusion. All of the co-authors of the present report have been questioned repeatedly by colleagues concerning the criteria for diagnosing this latter entity and distinguishing it from type 1 MI and from myocardial injury with necrosis secondary to a variety of entities other than myocardial ischemia. This review and commentary will seek to clarify some of the confusion surrounding the distinction between type 1 and type 2 MI and nonischemic myocardial injury with necrosis. Clarification in this area is needed badly because multiple efforts are now ongoing to define the frequency and prognosis of type 2 MI despite the absence of clear operational criteria. Such efforts have the potential to distort the information that will guide clinical care.

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TYPE 1 VS TYPE 2 MI

Distinguishing patients with type 2 MI from those with type 1 MI often is not difficult. This distinction can be straightforward in many patients but challenging at other times. Patients with type 1 MI usually present with spontaneous symptoms with or without associated ischemic electrocardiographic (ECG) changes and in the *absence* of a cause for increased myocardial oxygen demand, for example, tachycardia with heart rates in excess of 120 beats per minute or decreased myocardial blood flow, for example, hypotension secondary to marked bradycardia. Patients with type 1 MI often demonstrate ECG changes such as ST elevation or depression.

CLINICAL SIGNIFICANCE

- Considerable clinical confusion continues to exist concerning the diagnosis of type 2 myocardial infarction (MI) as well as a nonischemic myocardial injury.
- Daily requests for cardiology consultation occur involving patients with these 2 entities, which must be distinguished from type 1 MI so that appropriate therapy can be administered to the latter group of patients.
- Criteria are given enabling clinicians to distinguish type 1 from type 2 MI and from a myocardial injury not involving myocardial ischemia.

Blood troponin levels rise and fall in a manner diagnostic of acute MI.[1-5] Troponin blood levels tend to be higher in patients with type 1 MI compared with individuals with type 2 MI. During coronary angiography, type 1 MIs often are found to have new or presumptive new coronary arterial occlusion or the angiographic criteria for plaque rupture, fissure, or thrombus within a coronary artery (**Table**). However, angiographic criteria are not specific for acute events and occur in patients with chronic coronary artery disease as well.[6] More invasive techniques, such as intravascular ultrasound and optical coherence tomography, all have the potential to refine the invasive criteria that might be helpful in further clarifying diagnoses in this important area.

The perioperative setting provides a good opportunity to consider a common clinical situation where it is important to distinguish type 1 from type 2 MI. It appears, from clinical studies on the pathophysiology of MI following noncardiac surgery, that the vast majority of these patients have a non-ST-elevation MI, which is almost always a type 2 MI.[7-9] Some autopsy studies suggest a higher prevalence of type 1 MI in this setting than is suspected from the clinical findings. Recent data suggest that nearly 50% of these patients have coronary abnormalities consistent with acute lesions.[10] However, we know that such lesions also can be seen in individuals with stable coronary artery disease, although these latter patients are apparently at higher risk if elevated high-sensitivity troponin levels are found.[6] Nevertheless, it would appear that most perioperative MIs are indeed type 2 MIs, although those with more morbid events may have had a type 1 MI.

Distinguishing type 1 perioperative MI from a type 2 MI is often challenging. When the MI occurs spontaneously during the postoperative period, particularly if there is ST elevation on the electrocardiogram, a type 1 MI is likely. On the other hand, if the patient has had an alteration in hemodynamic status, for example, intraoperative hypotension, then a type 2 MI has probably occurred. A potentially confusing situation can arise when a type 1 perioperative MI results in hypotension or tachycardia, thereby demonstrating some of the characteristics of a type 2 MI. On occasion, both type 1 and type 2 perioperative MIs can be associated with a hypertensive response, particularly if heart failure or severe postoperative discomfort is present.

THE ESSENCE OF A TYPE 2 MI

In the most recent publications from the task force, type 2 MI was categorized as a myocardial infarction secondary to an ischemic imbalance between blood supply and myocardial oxygen demand.[4,5] Patients may or may not have atherosclerotic coronary artery disease. Instances of ischemic myocardial injury with necrosis where an imbalance between myocardial oxygen supply or demand occur include coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy. Recently, Saaby et al[11] in Denmark studied more than 500 patients with an acute MI. They categorized these patients into the 5 subsets described in the task force documents from 2007 and 2012.[1-3,5] These investigators identified patients with an acute MI admitted to the hospital during a 1-year period (2010-2011). Seventy-two percent of the patients had type 1 MI and 26% had type 2. Type 2 patients were older, more likely to be female, had lower blood troponin values, and had more comorbidities. Nearly 50% of the patients with a type 2 MI had a normal coronary angiographic study.[11] Only 12% of type 1 MI patients had normal coronary angiography. However, peak cardiac troponin (cTn) was lower in individuals with type 2 MI, thereby suggesting that as more sensitive cTn assays come into use, the proportion of patients with type 2 AMI will increase.[11]

An example of a typical patient with a type 2 MI would be an individual with known coronary atherosclerosis presenting with ischemic symptoms during an episode of rapid atrial fibrillation, for example, a heart rate >150 beats per minute for a substantial period of time, for example, 30-60 minutes. In such individuals with rapid atrial fibrillation, one frequently observes ischemic ST-segment depression or nonspecific ST-segment or T-wave abnormalities on the electrocardiogram, accompanied by subsequent modest

Table Distinctions between Type 1 MI, Type 2 MI, and Nonischemic Myonecrosis

Type 1 MI
Usually spontaneous in onset with associated ECG changes such as ST-segment depression or elevation;
Patients often describe ischemic chest discomfort or equivalent;
Associated abnormal blood troponin levels tend to be higher than in type 2 MI, but this is not invariably the case;
Absence of conditions leading to elevated myocardial oxygen consumption or decreased myocardial blood flow;
Plaque rupture, ulceration, fissuring, erosion, or dissection with complex plaque and coronary arterial thrombus often seen during coronary angiography.
Type 2 MI
Usually associated with conditions that lead to elevated myocardial oxygen demand, for example, tachycardia with heart rate >150 beats per minute for a time, or decreased myocardial blood flow, for example, hypotension (BP <90 mm Hg) secondary to blood loss;
ECG changes are often minimal, absent or non-specific;
Associated blood troponin levels often but not always minimally elevated;
Ischemic chest discomfort or equivalent may be absent;
Angiography often does not demonstrate plaque rupture with associated thrombus.
Nonischemic myocardial injury with necrosis:
Usually occurs in patients with critical illness, for example, sepsis or respiratory failure, or in patients with chronic conditions associated with low grade on-going myocardial injury, for example, severe heart failure or renal failure;
ECG changes are often minimal, absent or non-specific;
Associated blood troponin levels often minimally elevated and usually without a rise or fall;
Ischemic chest discomfort or equivalent usually absent;
Angiography usually does not demonstrate plaque rupture with associated thrombus.

BP = blood pressure; ECG = electrocardiographic; MI = myocardial infarction.

elevations in blood troponin levels. If there are initial ischemic symptoms followed by atrial fibrillation, the patient may be classified as having had a type 1 MI. If the atrial fibrillation initiates the presentation, then the authors classify these latter patients as having had a type 2 MI secondary to markedly increased myocardial oxygen demand resulting from the tachycardia. In the clinical setting, it is often not known whether ischemia precipitated the atrial fibrillation or atrial fibrillation precipitated the ischemia. It is a more challenging task to make a diagnosis of acute myocardial infarction if the exact same patient had less clear-cut symptoms or less classical ECG findings. Importantly, although incidental, patients with atrial fibrillation and an elevated cTn are at markedly increased risk for both mortality over time and arterial embolism.[12]

TYPE 2 MI VS NONISCHEMIC MYOCARDIAL INJURY WITH NECROSIS

Distinguishing type 2 MI from nonischemic myocardial injury with necrosis represents another challenging problem for the clinician. Nonischemic myocardial injuries are common in patients with severe illness, for example, bacteremia secondary to pneumonia. Problems with the diagnosis of type 2 MI usually do not arise in relatively straightforward patients, but rather in complex medical and surgical patients with multiple comorbidities (**Table**). An example of such a complex patient would be a middle-aged individual with no clinical history of coronary artery disease and without prominent atherosclerotic risk factors who is admitted to the hospital with a serious infection accompanied by myocardial infarction systemic sepsis. An elevated troponin level is often noted in such individuals in the absence of ischemic symptoms or ECG changes, and the clinical question often posed at this point is "Does this patient have an acute myocardial infarction that requires urgent therapeutic intervention?" We suggest that such patients have *not* had a coronary artery disease, but rather a myocardial injury secondary to various factors associated with the serious illness, that is, a nonischemic myocardial injury with necrosis.

Factors suggested in such situations as causative of myocardial necrosis include elevated circulating levels of inflammatory cytokines such as tumor necrosis factor-α as well as catecholamines, combined with marked electrolyte abnormalities, acute renal insufficiency, hypotension, and tachycardia. This patient should not be labeled as having a type 2 MI but rather, as an individual having a myocardial injury due to the direct toxic effects of factors elaborated with sepsis. It is unlikely that the patient needs emergency intervention for a type 1 MI. In addition, acute intervention in such critically ill patients is undoubtedly high risk, and hence, may not be prudent. Regardless of the diagnosis, patients with elevated biomarkers are at increased risk both acutely and longer term.[13-16]

As just noted, the diagnosis given to patients with myocardial necrosis not felt to be secondary to ischemia is myocardial injury with necrosis, which is usually secondary to a critical illness. However, if such patients demonstrate myocardial ischemic symptoms or ischemic ECG changes, or have known severe coronary artery disease, it may be very difficult for the clinician to decide if the patient has had a myocardial injury with necrosis or a type 1 or 2 myocardial infarction. If a biomarker were available that could identify accurately the presence of a ruptured plaque, and the need, therefore, for angiography and possible

intervention, or if standardized clinical criteria for diagnosing type 2 MI were developed, it would be helpful in devising therapy. Unfortunately, such a biomarker is not available at present, but studies about clinical criteria are under way, as noted above.[11] The distinction between a type 2 MI and a myocardial injury with necrosis usually has less immediate therapeutic implications. Once the critical illness has resolved, it is up to the clinician to determine whether a test for possible coronary ischemia or coronary angiography is indicated.

Additional diagnostic problems involved in making the correct diagnosis of myocardial infarction arise when the seriously ill patient has a history consistent with prior coronary artery disease or important atherosclerotic risk factors. Has such a patient had myocardial injury or a type 2 MI? As noted above, it is often very difficult to answer this question without lingering doubt as to the veracity of the eventual diagnosis applied. Factors that should be taken into account include any associated symptoms consistent with the presence of myocardial ischemia or new electrocardiographic changes such as 0.5 mm or more of horizontal ST-segment depression in 2 contiguous leads as well as serial troponin measurements demonstrating the presence or absence of a rising or falling pattern as opposed to a less dynamic pattern of elevation. In the latter circumstance, that is, an unchanging pattern of troponin elevation, the diagnosis is more likely to be myocardial injury with necrosis, for example, in patients with chronic renal failure.

If a type 2 MI is suspected, the next clinical conundrum develops. Should the patient undergo coronary angiography; should aspirin, a P2Y12 inhibitor, and antithrombotic therapy be administered; should the patient be treated with beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, an angiotensin receptor blocker, a statin, ranolazine, or nitrates? At this time, there is a dearth of scientific information that can help physicians make clinical decisions in this setting. Cardiac catheterization almost certainly is associated with significant risk in such critically ill patients, as is antithrombotic therapy. Often, beta-blockers, nitrates, and low-dose aspirin are given, *but without a strong sense on the part of the clinician involved that this therapy is beneficial in this setting.* Clinical research involving patients with type 2 MI or myocardial injury is needed desperately to assist in differentiating these 2 entities and determining what, if any, specific therapy is indicated.

In conclusion, the authors feel that careful weighing of the clinical situation is important in guiding further diagnostic testing and possible therapy in patients with type 2 MI or a nonischemic myocardial injury with necrosis. Thus, a patient with one of these syndromes and a poor prognostic outlook might not undergo any further testing following recovery from an acute illness where blood troponin values were elevated, while a patient with a reasonably good prognosis would be offered additional diagnostic evaluation to assess the likelihood of important underlying coronary artery disease and to guide therapy.

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