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VIEWPOINT

Supply/Demand Type 2 Myocardial Infarction

Should We Be Paying More Attention?

Yader Sandoval, MD,* Stephen W. Smith, MD,† Sarah E. Thordsen, MD,* Fred S. Apple, PhD‡

Minneapolis, Minnesota

Supply/demand (type 2) myocardial infarction is a commonly encountered clinical challenge. It is anticipated that it will be detected more frequently once high-sensitivity cardiac troponin assays are approved for clinical use in the United States. We provide a perspective that is based on available data regarding the definition, epidemiology, etiology, pathophysiology, prognosis, management, and controversies regarding type 2 myocardial infarction. Understanding these basic concepts will facilitate the diagnosis and treatment of these patients as well as ongoing research efforts. (J Am Coll Cardiol 2014;63:2079–87) © 2014 by the American College of Cardiology Foundation

In 2007, the second Universal Definition of myocardial infarction (MI) introduced and defined five different MI subtypes that were endorsed by the major cardiology societies (1). Type 1 MI (T1MI) corresponds to a spontaneous MI secondary to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus leading to decreased myocardial blood flow or distal platelet emboli with consequent myocyte necrosis (acute coronary syndrome, [ACS]), whereas type 2 MI (T2MI) was defined as MI due to supply/demand mismatch, without plaque rupture, but also with myocardial necrosis evidenced by a rise and/or fall of cardiac biomarkers above the 99th percentile reference value of a normal population, in addition to at least one of the other criteria for MI (2).

For numerous reasons, there is controversy and reluctance to use the term "T2MI" in clinical practice. Foremost, although the ACS classification of ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI), and unstable angina is widely adopted to guide revascularization and pharmacological treatment, not all have embraced the 5-MI subtype classification (1–6). Notably, recognizing limited availability of some cardiac biomarkers in many settings, the World Health Organization definition of MI limits its discussion on supply/demand MI (4). Another motive for the reluctance relies on the basis that the International Classification of Diseases coding system does not recognize T2MI, and often MI quality review programs (e.g., Centers for Medicaid and Medicare Services) rigorously evaluate for certain measures for anyone with a diagnosis of acute MI, which may be appropriate for ACS (T1MI), but may not be appropriate for an MI (T2MI) not caused by ACS (7).

Distinguishing different etiologies of ischemic myocardial necrosis is essential for clinical purposes, mainly because management differs when cardiac troponin (cTn) is elevated as the result of T1MI, as opposed to T2MI (5,6). The purpose of this article is to provide an evidence-based perspective on supply/demand T2MI.

Definition

The Third Universal Definition of MI consensus document defines MI by the evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia, in which there is a rise and/or fall of cTn with at least one value above the 99th percentile of a normal reference population; and the presence of at least one of the following: a) ischemic symptoms; b) new or presumed new significant ST-segment or T-wave changes or new left bundle-branch block; c) development of pathological Q waves in the electrocardiogram; d) imaging evidence of new loss of viable myocardium such as a new regional wall motion abnormality; or e) identification of an intracoronary thrombus by means of angiography or autopsy (2).

On the basis of the above criteria, T2MI is diagnosed in instances in which a supply/demand imbalance leads to myocardial injury with necrosis that is not caused by ACS, including arrhythmias, aortic dissection, severe aortic valve disease, hypertrophic cardiomyopathy, shock, respiratory failure, severe anemia, hypertension with or without left ventricular hypertrophy, coronary spasm, coronary embolism or vasculitis, and coronary endothelial dysfunction without significant coronary artery disease (CAD) (2,8).

From the *Division of Cardiology, Department of Medicine, Hennepin County Medical Center, Minneapolis, Minnesota; †Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, Minnesota; and the ‡Department of Laboratory Medicine and Pathology, Hennepin County Medical Center and University of Minnesota, Minneapolis, Minnesota. Dr. Apple is a consultant to T2 Biosystems and Instrumentation Laboratory; has received honoraria from Abbott Laboratories; and has received research funding, without salary, from the majority of manufacturers marketing cardiac troponin assays. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)

CAD = coronary artery disease

cTn = cardiac troponin

ED = emergency department

MI = myocardial infarction

NSTEMI = non–ST-segment elevation myocardial infarction

STEMI = ST-segment elevation myocardial infarction

T1MI = type 1 myocardial infarction

T2MI = type 2 myocardial infarction

It should be noted that in contrast with the 2007 Universal Definition of MI, the 2012 recommendations incorporated coronary endothelial dysfunction as one of the variables to consider when encountering supply/demand ischemia (1,2). Coronary endothelial dysfunction has been associated with myocardial ischemia and increased cardiac events, and certainly these patients may have cTn increases and meet the definition for MI (9–11). However, it is unclear if endothelial-dependent coronary flow reserve assessment with acetylcholine infusion is warranted in the acute MI setting.

From an electrocardiographic perspective, the use of the terms NSTEMI and STEMI has been applied to T2MI. Saaby et al. (12) recently reported 144 T2MI, of which 3.4% were categorized as STEMI and 96.6% as NSTEMI (12). The significance of applying these electrocardiographic classifications to T2MI is unclear, as they are clinically intended to guide reperfusion therapy in T1MI (ACS) (5,6).

The interpretation of cTn increases in conditions in which supply/demand is being considered can be challenging, largely due to the paucity of specific criteria for what exactly constitutes a T2MI. Several major expert opinion documents have provided some guidance in regard to what should be considered a T2MI, but none of these documents have defined specific criteria for T2MI (2,8,13).

Saaby et al. (12) have proposed certain novel, specific criteria for T2MI, in order to avoid the implicit subjectivity in the clinical diagnosis (criteria detailed in Table 1). However, the development of strict criteria for the diagnosis of T2MI is complicated by the multifactorial nature of supply/demand ischemia, as patients may have any number of factors leading to increased demand or decreased supply, which in addition may or may not be in the setting of distinct pre-existing conditions such as flow-limiting CAD. Thus, advocating for any strict criteria and cutoffs of variables such as heart rate or blood pressure may have its own limitations. Most studies have used adjudicators who can assess all contributing variables and give a subjective diagnosis of T2MI without applying strict parameters.

Among patients with no pre-existing conditions such as underlying CAD, a clearly recognizable acute and/or sustained supply/demand mismatch should be present to consider T2MI. Conversely, in patients with underlying comorbidities such as significant CAD and/or the presence of several supply/demand imbalances, lower thresholds of supply/demand mismatches may be required to elicit ischemia. In these patients, an individualized diagnostic approach should be favored.

The current "gold-standard" definition for T2MI remains undetermined, and any future MI consensus document should ideally provide further clarification in this challenging area to guide both clinicians and researchers and bring homogeneity to this field. Details including definitions used across selected heterogeneous studies, which have reported T2MI, are summarized in Table 1.

Epidemiology

With the use of current contemporary cTn assays, T2MI is frequently encountered in clinical practice (Table 1). It is expected that after the anticipated Food and Drug Administration (FDA) clearance (likely 2014) of high-sensitivity cTn assays, these assays will be as commonly used in clinical practice in the United States, as they currently are in the rest of the world. This use will likely lead to an increased incidence of cTn elevations above the 99th percentile in clinical settings consistent with T2MI (14). However, little epidemiologic data is available on T2MI, possibly due to the relatively recent introduction of this term, suspected underreporting, and confusion as to what specifically constitutes a T2MI given lack of specific criteria.

There are a limited number of studies addressing the frequency of T2MI. Morrow et al. (15) described the value of the Universal Definition of MI in the context of a clinical trial. In follow-up of 1,218 MIs, T2MI was infrequent and consisted of 3.5% (n = 43) of all MIs, in contrast to 32.6% T1MI and 49.5% (n = 603) peri-percutaneous coronary intervention (type 4A) MI. This study was limited because it was an ACS trial, which included a pre-selected population, and therefore was not reflective of the true epidemiology of T2MI. Javed et al. (16) performed a prospective study to identify the percentage of hospitalized patients with a positive cTn who fulfilled the criteria for MI and classified them according to the Universal Definition using a contemporary, sensitive cTn assay (ADVIA TnI-Ultra, 99th percentile: 40 ng/l) over a 3-month period. In this large, prospective study, cTnI was obtained in 2,979 patients, with 701 having at least one increased cTnI: 216 had MI according to the Universal Definition of MI, of which 143 (66.2%) had a T1MI and 64 (29.6%) had T2MI (the remaining 4.2% [n = 9] were type 3 and 4 MI). Melberg et al. (17) studied the implications of the Universal Definition of MI by retrospectively studying all patients hospitalized in 2004 with suspected MI using the 4th generation Roche cTnT assay. Their cohort of 1,093 patients with MI consisted of 967 (88.5%) with T1MI and 17 (1.6%) with T2MI (the remaining 9.9% [n = 109] were classified as type 3 to 5 MI).

Smith et al. (18), in a retrospective study of 662 consecutive patients with ischemic symptoms presenting to the emergency department (ED) in which cTnI was obtained with the use of the Siemens Stratus CS (Tarrytown, New York) (99th percentile: 99 ng/l), found that of 139 who had MI, 40 (28.8%) had T1MI and 99 (71.2%) had T2MI. In a subsequent study at the same institution, among 1,119