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Original article

Type 2 myocardial infarction: A descriptive analysis and comparison with type 1 myocardial infarction

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ABSTRACT

Background: While 'plaque rupture' is the paradigm of type 1 myocardial infarction (T1MI), T2MI is myocardial necrosis secondary to oxygen supply-demand mismatch. Being a heterogeneous and rather newly defined group, data are lacking about T2MI.

Methods: A retrospective review of medical records of patients diagnosed with T2MI in the Rabin Cardiology Center, Israel between the years 2007 and 2012 was performed. Following a descriptive analysis, we used multivariate time dependent models to estimate the association of T2MI with the risk for 30-day, 1-year, and 5-year all-cause-mortality and major adverse cardiovascular events (MACE), and compared it to a T1MI group matched for age, gender and electrocardiographic changes.

Results: The study included 107 T2MI (and 107 T1MI) patients. Sepsis, anemia, and atrial fibrillation were the most common etiologies. Triple anti-thrombotic therapy was given to 22% of T2MI patients (vs. 82% of T1MI patients, $p < 0.001$). Twenty-five percent were managed using urgent percutaneous coronary intervention. Angiography unmasked acute plaque rupture in 29% of T2MI patients group. Compared to T1MI, T2MI was associated with higher all-cause-mortality rate: adjusted-hazard-ratio 7.14 (1.31–38.9) at 30 days, 3.42 (1.51–7.75) at 1 year, and 2.08 (1.14–3.81) at 5 years follow-up. MACE risk was consistent between T2 and T1MI patients.

Conclusions: The most common T2MI triggers are sepsis, anemia, and atrial fibrillation. Compared to a T1MI population, T2MI is associated with higher short- and long-term mortality rates but equal cardiovascular mortality and MACE risk. As many as 30% may harbor plaque rupture and in fact have T1MI.

Introduction

Type 2 myocardial infarction (T2MI) is defined as cardiomyocyte necrosis caused by conditions other than atherosclerotic coronary artery disease (CAD) and secondary to decrease in oxygen supply (e.g. hypoxemia, anemia, hypotension, and endothelial dysfunction) and/or increased demand (e.g. tachycardia, arrhythmia, and sepsis) [1]. Although believed to constitute as many as 25% of all MIs in hospitalized patients [2] and strongly associated with a high mortality rate [3,4], as a heterogeneous and relatively newly defined group, little is known about T2MI patients. Since 2007, when the diagnosis was first introduced by the Universal definition, it raised awareness, documentation and quality review programs, and holds promise to improve outcome for these patients in the future [5]. While plaque rupture is the designation paradigm of T1MI, it is often difficult to exclude atheroembolic acute coronary events in patients thought to suffer T2MI. Whether and when to attempt revascularization among patients hospitalized with severe sepsis and ischemic electrocardiographic (ECG) changes with new elevated troponin level is based on clinical judgment. The magnitude of benefit, if any, of anti-platelets and anti-coagulant medications in these patients has yet to be defined. Apart from treating the underlying condition, there are neither guidelines nor a consensus on the optimal management of T2MI

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patients [6]. Better characterization of T2MI patients may help to predict which patients suffer pure secondary MI and which harbor acute coronary events. The objective of our study was to characterize T2MI patients concerning baseline characteristics, clinical presentation, management, and outcome, with a comparison to a T1MI patient group matched for age (±2 years), sex, and ST-elevation (STE).

Methods

In our cardiology department at Rabin Medical Center in Israel, we used electronic medical, pharmacy, and laboratory record systems to review records of patients admitted and diagnosed with T2MI between the years 2007 and 2012. We validated the diagnosis and included only patients who fulfilled both of the following criteria:

1. Detection of a rise and/or fall of cardiac troponin T (cTnT) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
   A. Symptoms of ischemia.
   B. New or presumed new significant ST–T changes, left bundle branch block (LBBB), or pathologic Q waves.
   C. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (RWMA).

   cTnT assay was performed on Roche Elecsys 2010 (Basel, Switzerland) and Roche Cobas e 411 instruments, using the electrochemiluminescence immunoassay. Between 2007 and 2010 we used cTnT 4th Gen. The limit of quantification (functional sensitivity) was 30 ng/L, and the URL (99th percentile) was 10 ng/L. From 2010 until the end of the study we used cTnT hs (high sensitive). The limit of quantification (functional sensitivity) was 13 ng/L, and the URL (99th percentile) was 14 ng/L.
2. At least one of the following conditions considered to trigger imbalance between myocardial O_2 supply-demand (supported, partially, on data from the literature [2,5,7–9]):
   A. Sepsis-systemic inflammatory response syndrome (SIRS) which consists of ≥two of the following: fever > 38 °C, tachypnea > 24 breaths/min, tachycardia > 100 beats/min, leukocytes > 12 K/μL, in the context of clinically suspected/documented infection.
   B. Shock – defined as systolic blood pressure (BP) < 90 mmHg and/or diastolic BP < 60 mmHg together with evidence of systemic hypo-perfusion (lactatemia).
   C. Anemia (severe) – defined as a fall in ≥2 g/dL hemoglobin (Hb) and/or Hb < 10 g/dL and/or a need to use blood products.
   D. Active bleeding – visualization of blood in stool, vomit, gastric aspirate, or endoscopy.
   E. Tachyarrhythmia – ventricular rate > 120/min excluding sinus tachycardia.
   F. Bradyarrhythmia – requirement of medical treatment or cardiac pacing.
   G. Respiratory failure – requirement of mechanical ventilation (invasive or non-invasive).
   H. Hypertensive crisis – systolic BP > 180 mmHg and concomitant progressive retinopathy and/or encephalopathy.

We then used a matching algorithm which sequentially searched a 4524 T1MI patient cohort (all T1MI patients admitted to our department between years 2007 and 2012), matching for sex, ST segment elevation, and searching for the closest match for age (year ±2). Each selected pair was then removed from the search algorithm until a 1:1 matching process was completed. T1MI diagnosis was validated according to the first of the two above-mentioned criteria.

The study protocol was approved by the Helsinki Committee of the Rabin Medical Center.

Definition of covariates:

After descriptive analysis of baseline characteristics and clinical presentation, we used multivariate time dependent Cox regression models to estimate the association of T2MI with the risk for 30-day, 1-year, and 5-year major adverse cardiovascular events (MACE) [cardiovascular (CV)-death, urgent percutaneous coronary intervention (PCI), stroke, and re-MI] and all-cause-mortality. CV mortality was defined as death due to acute coronary and/or aortic syndrome, cardiac arrhythmias, congestive heart failure (CHF), stroke, pulmonary emboli, or during cardiac interventions. All other deaths were considered non-CV. The cause of death was adjudicated blindly with respect to MI type. Re-MI was defined as recurrence of chest pain or ECG changes and new cTnT elevation. Urgent PCI was defined as PCI for re-MI or unstable angina during follow-up. CHF was defined as left ventricular ejection fraction (LVEF) < 40% and/or a history of CHF. Patients without history of CHF but with missing LVEF data were excluded from the CHF analysis. ECG changes were considered ischemic when there was evidence of new ST segment deviation, T wave inversion, LBBB, or pathologic Q wave. We conducted angiographic characterization of coronary lesions morphology using features of complexity previously described by Ambrose et al. [10–13]. Lesions were considered 'complex' if they exhibited either: (A) An intraluminal filling defect consistent with thrombus, defined as abrupt vessel cutoff with persistence of contrast or filling defect observed in multiple views; (B) Plaque ulceration, defined by the presence of contrast beyond, but contiguous to the vessel lumen; or (C) Two or more of the following: (a) fissuring, defined by intra-plaque dye penetration not meeting definition of ulceration; (b) plaque irregularity, defined by irregular margins or overhanging edges; or (c) intraluminal haziness. Lesions not meeting these criteria were considered to be 'noncomplex.' The angiographic analysis and interpretation were carried out by an experienced cardiologist blinded to the original angiographic interpretations and to the MI type as well as to the clinical outcome. We only analyzed lesions that were associated with at least 50% stenosis.

Statistical methods

Categorical data were reported as numbers (percentages), and continuous data were reported as means [±standard deviations (SD)] and medians [±interquartile ranges (IQRs)]. Comparisons between groups for categorical data were made with the Chi-square or Fisher's exact tests, whereas continuous data were compared using two-sample *t*-tests or Mann–Whitney test. Univariate Cox proportional hazards models were used to assess the impact of MI type and other variables on all-cause-mortality, CV-mortality, and MACE. MI type and variables with $p < 0.2$ in the univariate analysis were included in the multivariate analysis. Cox proportional hazards models were used to assess the impact of MI type on all-cause-mortality, CV-mortality, and MACE, while controlling for confounders. As the groups were matched for age (±2 years), sex, and STE, the only other covariates included in the multivariate analysis, specifically: ischemic heart disease (IHD), diabetes mellitus, chronic kidney injury (CKI), LVEF at presentation, pulmonary congestion, Hb level (g/dL), creatinine (Cr) level (mg/dL), and cTnT level (ng/mL). Analyses were repeated separately in patients with or without sepsis, with or without anemia, and with or without arrhythmia. These stratified analyses allowed us to explore the associations between T2MI and the primary outcomes differences according to T2MI major subgroups. Kaplan–Meier curves were constructed to estimate the survival function of all-cause-mortality, CV-mortality, and MACE within T2MI