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New insights in the pathophysiology of acute myocardial infarction detectable by a contemporary troponin assay

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ABSTRACT

Objectives: ST-elevation and non-ST-elevation myocardial infarction (STEMI, NSTEMI) are considered two distinct pathophysiologic entities. We evaluated cardiac troponin I (cTnI) release in STEMI and NSTEMI using a "contemporary" (CV > 10 to 20% at the 99th percentile concentration) cTnI assay for patients undergoing early percutaneous coronary intervention (PCI).

Design and methods: 856 patients with suspected acute coronary syndrome consecutively admitted to the Emergency Department of the Maggiore Hospital of Novara (225 STEMI and 135 NSTEMI) were selected according to: 1) early (≤4 h from admission) and successful PCI; and 2) cTnI measurements at ED presentation and within 24 h. The influence of the MI type on cTnI concentrations at baseline and after PCI as well as the velocity of cTnI [cTnI V = absolute increase (after log conversion of cTnI measurements) / delay between the two measurements] was studied by multiple regression analysis, adjusting for patient parameters.

Results: A statistically significant interaction between MI type and time from symptoms was reported on cTnI concentrations ($p < 0.0001$): STEMI and NSTEMI differed for cTnI releases at admission and after revascularization. Higher cTnI V in STEMI was detectable in patients admitted within 6 h from symptoms. Baseline cTnI concentrations were lower in patients with a history of coronary artery disease (CAD) and increased with aging ($p < 0.0001$). In the elderly (>75 years), the cTnI V was significantly increased.

Conclusion: STEMI and NSTEMI patients have different patterns and dynamics of cTnI release influenced by the interaction with time from symptoms, by aging and history of CAD.

Introduction

Several studies currently evaluate the prognostic performances of cardiovascular biomarkers measured in the acute phase of a myocardial infarction (MI) on case series including both patients with ST-elevation myocardial infarction (STEMI) and MI with non-ST-elevation at electrocardiogram (ECG) (NSTEMI) [1,2]. However the mixing of these two populations of patients contrasts with the definition of acute MI stating STEMI and NSTEMI as two distinct pathophysiologic entities according to the presence/absence of electrocardiographic ischemic changes [3]. ECG currently represents the sole clinical tool able to early catch the main difference between pathological mechanisms underlying MI types. In fact, although advancements have been made in imaging techniques (i.e., cardiac magnetic resonance), these may still fail in the assessment of heterogeneous and small infarct size in NSTEMI, resulting below the threshold of detection [4].

Biomarkers can provide important information for both STEMI and NSTEMI pathophysiologic mechanisms. Reports have suggested that STEMI and NSTEMI have different patterns of release of inflammatory and neurohormonal markers [5,6]. Inflammatory markers show a remarkable prognostic value in NSTEMI whereas cardiac troponins (cTns) are associated with better risk prediction for STEMI [7]. This may reflect differences in the pattern of cTn release between STEMI and NSTEMI and thus in the underlying biochemical and protein expression profiles.

Current generation cTn assays [8,9] have led to an appreciation that increased cTn concentrations can be associated with myocardial necrosis independent from myocardial ischemia [10]. In particular,

Abbreviations: MI, acute myocardial infarction; STEMI, ST-elevation myocardial infarction; ECG, electrocardiogram; NSTEMI, no ST-elevation at electrocardiogram myocardial infarction; cTnI, cardiac troponin I; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; ED, Emergency Department; CCU, Cardiac Care Unit; CK-MB, creatine kinase MB isoenzyme; LoD, limit of detection; CVa, analytical coefficient of variation; CAD, coronary artery disease; cTnI V, velocity of cTnI release; CI, confidence interval.

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the availability of sensitive cTn detection [namely "high sensitive" assays (CV ≤ 10% at the 99th percentile) and "contemporary" assays (CV > 10 to 20% at the 99th percentile)] [9] could contribute more relevant information about the biochemical substrates underlying STEMI and NSTEMI. Within this context, we sought to compare the average patterns and the dynamics of cTnI release in STEMI and NSTEMI patients undergoing early percutaneous coronary intervention (PCI). The second aim was to investigate the effect of patient characteristics on cTnI release occurring within the first 24 h from admission in each MI type.

Materials and methods

Patients

Eight hundred and fifty-six patients with chest pain and suspected acute coronary syndrome (ACS) were consecutively admitted to the Emergency Department (ED) and then to the Cardiac Care Unit (CCU) of the Maggiore Hospital of Novara from August 2006 (when a cTnI new generation assay was introduced) to January 2009. From this case series, 360 MI patients (225 STEMI and 135 NSTEMI) were retrospectively selected according to the following criteria:

1) PCI performed early after admission (within 4 h) [11,12] according to risk stratification gauged on ECG findings and clinical evaluation reported by running guidelines [12,13]. The resting 12-lead ECG was obtained within 10 min after first medical contact upon arrival of the patient in the emergency room and immediately interpreted by a qualified physician. The finding of persistent (>20 min) ST-elevation suggested STEMI. In the absence of ST-elevation, additional recordings were obtained in symptomatic patients. NSTEMI patients were preliminary selected according to ECG criteria and/or creatine kinase MB (CK-MB) typical increase with at least one value ≥ 99th percentile reference limit. High-risk NSTEMI patients undergoing early reperfusion were identified according to the following criteria: a) ST-segment depression >0.5 mm (0.05 mV) and <1.0 mm (0.1 mV) in two or more contiguous leads, in a clinical context of typical symptoms and coexisting cardiac disorders or previous MI; b) ST-segment depression >1 mm (0.1 mV). Only a small percentage of cases (~2%) were not classified accounting for inconclusive data and were excluded from the case series;
2) successful PCI according to TIMI score;
3) availability of the first cTnI measurement performed at ED presentation and of a second measurement performed at CCU after PCI within 24 h from admission;
4) detectable cTnI concentrations.

Exclusion criteria were successful thrombolysis, unsuccessful PCI (TIMI from 0 to 2 at the end of the procedure) and emergency surgery.

The time from symptoms and the time elapsed between the two cTnI measurements were reported for all patients. In particular, the time from symptom onset (namely duration of pre-hospital delay) was defined as the time interval between the onset of signs and symptoms suggestive of MI and arrival in the ED (reported in h, assuming a tolerance of ±0.5 h). The delay time was obtained by the cardiologist at patient's ED presentation during the clinical evaluation and reported in the medical record together with other risk factors.

Hypertension was defined as systolic tension higher than 140 mm Hg and/or diastolic tension higher than 90 mm Hg or use of antihypertensive drugs. Diabetes was defined as fasting venous plasma glucose concentrations ≥7.0 mmol/L or venous plasma glucose 2 h after ingestion of 75 g oral glucose load ≥11.1 mmol/L. Hypercholesterolemia was defined as fasting plasma cholesterol concentration ≥5.0 mmol/L. A positive family history for coronary artery disease (CAD) was defined as presence of a CAD in a first degree family member before the age of 55 years in males and 60 years in females. Chronic renal failure was defined according to the presence of severely reduced kidney function with an estimated glomerular filtration rate ≤29 mL/min/1.73 m. Coronary and peripheral vasculopathy was defined as wall narrowing resulting in ischemia or non-inflammatory vascular lumen occlusion resulting from thromboembolic disease.

The study was approved by the Institutional Review Board of the Maggiore Hospital of Novara and informed consent was obtained from all patients. Authors have complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects.

Sample processing and measurements

Venous blood samples were drawn via direct venipuncture into tubes containing lithium heparin to obtain after centrifugation (5 min, 1500 *g* at 4 °C) specimens of plasma for cTnI determination.

cTnI was determined by Advia Centaur TnI-Ultra™ assay [8] with an analytical range of measurement of 6–50,000 ng/L, a limit of blank of 6 ng/L, and a 99th percentile value (cut-off) of 40 ng/L. From a 6-month retrospective evaluation of the two-level control materials supplied by the manufacturer, the intra-laboratory analytical coefficient of variation (CVa) was 15% at 80 ng/L and 5% at 9000 ng/L.

Statistical analysis

The patient features were reported as dichotomous and continuous variables. Accordingly, the statistically significant differences between these parameters in STEMI and NSTEMI were assessed by F exact test and Mann–Whitney test. The results were adjusted by adopting the Bonferroni correction for multiple comparisons.

The LOESS method (*locally estimated scatterplot smoothing*) was used to visually assess the relationship between the two variables (i.e., cTnI concentrations and time) in this large dataset where multiple trends (i.e., thin lines from dataset points to arrows) can be hard to visualize. LOESS is the most flexible non-parametric regression technique. This smoothing function, by making minimal assumptions about the relationship among variables, can capture general patterns while reducing the noise. The result of LOESS application is the solid gray line through the moving central tendency of the relationship between cTnI measurements and time. The smoothness parameter (i.e., span) was set at 0.75: this means that each smoothed value was determined through 75% of the neighboring points [14].

Descriptive analyses were employed to define the distributions of cTnI concentrations in STEMI and NSTEMI patients. Because of the skewed distributions, cTnI concentrations followed a logarithmic transformation. The marker changes in STEMI and NSTEMI patients were estimated as velocity of cTnI release (cTnI V) as follows:

$$[\log(\text{cTnI concentration after PCI}) - \log(\text{cTnI concentration at admission})] / \text{time elapsed between the two measurements.}$$

Multiple regression analysis was used to study the dependence from MI type of:

1) cTnI concentrations detected at baseline;
2) cTnI concentrations detected after PCI;
3) cTnI V.

The analysis was adjusted for patient parameters as time from symptom onset, age, gender, renal failure, and history of CAD. Age and time from symptoms were included into the models as continuous variables, accounting for possible non-linear effects by restricted cubic splines [15]. In addition, the interaction between the time from symptoms and AMI type was tested. The software used is the R-library Design by Harrell (http://CRAN.R-project.org/package=rms).