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Original Article

Troponin levels within the normal range and probability of inducible myocardial ischemia and coronary events in patients with acute chest pain

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ABSTRACT

Background/Objectives: Patients with suspected acute coronary syndromes and negative cardiac troponin (cTn) levels are deemed at low risk. Our aim was to assess the effect of cTn levels on the frequency of inducible myocardial ischemia and subsequent coronary events in patients with acute chest pain and cTn levels within the normal range.

Methods: We evaluated 4474 patients with suspected acute coronary syndromes, nondiagnostic electrocardiograms and serial cTnI levels below the diagnostic threshold for myocardial necrosis using a conventional or a sensitive cTnI assay. The end points were the probability of inducible myocardial ischemia and coronary events (i.e., coronary death, myocardial infarction or coronary revascularization within 3 months).

Results: The probability of inducible myocardial ischemia was significantly higher in patients with detectable peak cTnI levels (25%) than in those with undetectable concentrations (14.6%, $p<0.001$). These results were consistent regardless of the type of cTnI assay, the type of stress testing modality, or the timing for cTnI measurement, and remained significant after multivariate adjustment (odds ratio [OR] 1.47, 95% confidence interval [CI] 1.21–1.79, $p<0.001$). The rate of coronary events at 3 months was also significantly higher in patients with detectable cTnI levels (adjusted OR 2.08, 95% CI 1.64–2.64, $p<0.001$).

Conclusions: Higher cTnI levels within the normal range were associated with a significantly increased probability of inducible myocardial ischemia and coronary events in patients with suspected acute coronary syndromes and seemingly negative cTnI.

1. Introduction

Cardiac troponin (cTn) is the recommended biomarker for detection of myocardial necrosis, and should be determined in all patients with acute chest pain suggestive of ischemic origin [1]. The optimal cutoff point for the diagnosis of myocardial infarction has been a matter of controversy [2]. The use of sensitive cTn assays has been proven to allow an earlier and more accurate detection of myocardial infarction [3,4]. However, lowering the cutoff for the detection of myocardial necrosis has raised concerns about the possibility of false-positive diagnoses, and the clinical significance of detectable cTn levels below the diagnostic threshold for myocardial necrosis has been debated [5–7]. Furthermore, there is scarce data on the association of cTn levels within the normal range with the development of inducible myocardial ischemia and coronary events in patients with suspected acute coronary syndromes, and the influence of cTn assay sensitivity on this association has not been well characterized.

Our purpose was to assess the effect of plasma cTn levels on the frequency of inducible myocardial ischemia and coronary events in patients referred to a chest pain unit for acute chest pain, nondiagnostic electrocardiograms (ECGs) and cTn levels below the diagnostic cut point for myocardial necrosis.

2. Methods

2.1. Patients

A total of 5723 patients with non-traumatic acute chest pain suspected of having an ischemic origin, nondiagnostic ECGs at rest and serial cTnI levels below the diagnostic threshold for myocardial necrosis were referred to our chest pain unit between July 2007 and April 2014. Exclusion criteria were as follows: contraindications or inability to

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exercise on a treadmill, obvious alternative causes for patients' symptoms, any cTnI measurement above the diagnostic threshold for myocardial necrosis between arrival at the emergency department and exercise stress testing, symptoms and/or signs of acute heart failure, hemodynamic instability, end-stage renal disease requiring chronic hemodialysis, and a history of an acute coronary event or a coronary revascularization procedure within the preceding 2 weeks. The final study population consisted of 4474 patients (Supplementary Fig. 1). This study was approved by the *Comité Autonómico de Ética na Investigación de Galicia*, our regional research ethics committee.

2.2. Clinical variables

Demographics, clinical data and stress testing results were entered in a dedicated database prospectively. Diabetes mellitus, hypertension and hypercholesterolemia were defined on the basis of prior known history and/or taking antidiabetic, antihypertensive or lipid-lowering drugs, respectively. Chest pain was classified as typical angina, atypical/probable angina and nonischemic chest pain as previously described [8]. Pretest probabilities of coronary artery disease were estimated by an updated version of the Diamond-Forrester prediction rule [9] based on sex, age and type of chest pain, and were classified as low (<15%), intermediate (15–85%) and high (>85%) [10]. Betablockers were withdrawn from the time of patient's arrival at the emergency department.

2.3. cTnI assays

All patients underwent at least two cTnI determinations, i.e., on arrival of the patient at the emergency department and ≥6 h later. A detectable cTnI concentration was defined as a cTnI level higher than the limit of detection of the assay.

During the study period, two different assays were employed. The diagnostic threshold for myocardial necrosis was set at the 99th percentile concentration or at the lowest concentration that showed to have a 10% coefficient of variation if not fulfilled at the 99th percentile [11,12]. First, a conventional cTnI assay (Siemens Dimension® RxL) was used in a subcohort of 2898 patients who were referred to our unit between July 2007 and November 2011. The limit of detection of this assay was 0.04 μg/L, the 99th percentile concentration was 0.07 μg/L, the coefficient of variation at 99th percentile was 20%, and the lowest concentration that showed to have a 10% coefficient of variation was 0.14 μg/L according to the manufacturer and 0.20 μg/L under local laboratory conditions; the latter was employed as the diagnostic threshold for myocardial necrosis.

In November 2011, a sensitive cTnI assay (Siemens Dimension® EXL) was implemented in our hospital. This assay has a limit of detection of 0.017 μg/L, a 99th percentile cutoff point of 0.056 μg/L, a coefficient of variation of 10% at 0.05 μg/L and a percentage of coefficient of variation at 99th percentile of 10%, as specified by the manufacturer; thus, according to the universal definition of myocardial infarction [12], a diagnostic threshold of 0.056 μg/L was employed. This assay was used in a subcohort of 1576 patients included in this study from November 2011 to April 2014.

2.4. Exercise testing

All patients underwent treadmill exercise stress testing the following working morning after negative serial cTnI concentrations were ascertained. The ECGs were considered interpretable (i.e., valid for exercise ECG interpretation) in the absence of left bundle branch block, preexcitation, ventricular paced rhythm, left ventricular hypertrophy with strain, treatment with digoxin or other repolarization abnormalities [13]. Exercise ECG (without imaging) was performed in 2567 patients (all of them with interpretable ECGs), whereas a subset of 1907 patients underwent exercise echocardiography as an add-on to exercise ECG, of whom 1479 had interpretable ECGs. Thus, electrocardiographic evidence of myocardial ischemia could be assessed in a total of 4046 patients.

Heart rate, blood pressure and serial ECGs were obtained at baseline and at each stage of the exercise protocol. Exercise end points included physical exhaustion, significant arrhythmias, severe hypertension (systolic blood pressure >240 mm Hg or diastolic blood pressure >110 mm Hg), severe hypotensive response (decrease >20 mm Hg), or limiting symptoms during exercise. A positive exercise ECG (i.e., electrocardiographic myocardial ischemia) was defined as the development of ST-segment deviation of ≥1 mm which was horizontal or sloping away from the isoelectric line at 80 ms after the J point, in patients with interpretable baseline ST segments. The test was considered negative if this criterion was not met, the ECG was interpretable and the patients achieved ≥85% of the maximum age-predicted heart rate. The Duke Treadmill Score was estimated as previously reported [14,15] and the corresponding predicted risks were classified as low (score ≥5), intermediate (4 to −10) and high (≤−11).

In patients undergoing exercise echocardiography, imaging acquisition was performed in 3 apical views (i.e., long axis, 4-, and 2-chambers) and 2 parasternal views (i.e., long and short axis) at baseline, at peak of exercise and in the immediate post-exercise period, as previously reported [16,17]. The acquisition of images at peak of exercise was performed with the patient still exercising on the treadmill, when signs of tiredness appeared or an end point was reached. Regional wall motion abnormalities were evaluated with a 16-segment model of the left ventricle. Each segment was graded on a 4-point scale (normal wall motion = 1, hypokinesia = 2, akinesia = 3, and dyskinesia = 4), and wall motion score index was calculated at rest and at peak of exercise as the sum of scores divided by the number of segments visualized. A positive exercise echocardiogram (i.e., echocardiographic myocardial ischemia) was defined as the appearance of new or worsening wall motion abnormalities with exercise, with the exceptions of exercise-induced dyskinesia of an akinetic segment at rest and isolated hypokinesia of basal inferior and/or inferoseptal segments. Severe myocardial ischemia was defined as echocardiographic myocardial ischemia involving ≥3 myocardial segments [18].

For the purposes of this study, any evidence of exercise-inducible myocardial ischemia was defined as either a positive exercise ECG, a positive exercise echocardiogram, or both.

2.5. Coronary angiography findings

Coronary angiographies were performed at the discretion of the referring physicians. Significant coronary stenoses were defined as a ≥50% lumen stenosis of the left main coronary artery or a ≥70% diameter stenosis of any other major epicardial coronary artery.

2.6. Outcomes

Follow-up data were collected from hospital databases, electronic medical records, death certificates and telephone interviews. The end point was the cumulative rate of coronary death, nonfatal myocardial infarction or coronary revascularization within 3 months. Coronary death was defined as any death due to a definite or possible acute coronary event in the absence of an obvious noncoronary cause, including sudden deaths of unknown causes. Myocardial infarction was defined as recurrent chest pain and/or ischemic electrocardiographic abnormalities accompanied by an increase in troponin levels above the aforementioned cutoffs for myocardial necrosis.

2.7. Statistical analysis

Categorical variables were reported as percentages and comparison between groups based on the chi-square test. Continuous variables were reported as mean ± standard deviation and differences were