CLINICAL RESEARCH STUDY

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Determinants of High-Sensitivity Troponin T Among Patients with a Noncardiac Cause of Chest Pain

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ABSTRACT

BACKGROUND: It is unknown to what extent noncardiac causes, including renal dysfunction, may contribute to high-sensitivity cardiac troponin T levels.

METHODS: In an observational international multicenter study, we enrolled consecutive patients presenting with acute chest pain to the emergency department. Of 1181 patients enrolled, 572 were adjudicated by 2 independent cardiologists to have a noncardiac cause of chest pain. Multiple linear regression analyses were used to determine the important predictors of log-transformed high-sensitivity cardiac troponin T. Kaplan-Meier curve was used to assess the prognostic significance of high-sensitivity cardiac troponin T > 0.014 μg/L (99th percentile).

RESULTS: A total of 88 patients (15%) had high-sensitivity cardiac troponin T > 0.014 μg/L. Less than 50% of cardiac troponins could be explained by known cardiac or noncardiac diseases. In decreasing order of importance, age, estimated glomerular filtration rate, hypertension, previous myocardial infarction, and chronic kidney disease (adjusted r^2 0.44) emerged as significant factors in linear regression analysis to predict high-sensitivity cardiac troponin T. High-sensitivity cardiac troponin T was best explained by a linear curve with age as ≤ 0.014 μg/L. Patients with high-sensitivity cardiac troponin T levels > 0.014 μg/L were at increased risk for all-cause mortality (hazard ratio 3.0; 95% confidence interval, 0.8-10.6; $P = .02$) during follow-up.

CONCLUSION: Among the known covariates, age and not renal dysfunction is the most important determinant of high-sensitivity cardiac troponin T. Because known cardiac and noncardiac factors, including renal dysfunction, explain less than 50% of high-sensitivity cardiac troponin T levels among patients with a noncardiac cause of chest pain, unknown or underestimated cardiac involvement during the acute presenting condition seems to be the major cause of elevated high-sensitivity cardiac troponin T.

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KEYWORDS: Age; Chest pain; High-sensitivity cardiac troponin; Noncardiac; Renal dysfunction

Chest pain accounts for up to 5% to 10% of the consultations in emergency departments.[1] Improvements in cardiac troponin assay technology have allowed manufacturers to develop fully automated assays that meet the recommendations set by professional organizations to diagnose acute myocardial infarction. These assays have a lower limit of detection and a limit of quantification below the 99th percentile of a normal reference population.[2]

The more widespread application of sensitive and high-sensitivity cardiac troponin tests and the application of the

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99th percentile as the decision limit for acute myocardial infarction have led to a substantial increase in the detection of elevated levels of cardiac troponin even among patients diagnosed with a noncardiac cause of chest pain. Furthermore, concentrations below the 99th percentile, measured with several different assays, have been shown to provide robust prognostic information in low-risk patients and the general population.[3-8] Thus, a number of factors responsible for elevated cardiac troponin have been suggested.[2,9-12] However, the extent to which these noncardiac causes, including renal dysfunction, may contribute to elevated high-sensitivity cardiac troponin T levels, particularly among patients with no obvious cardiac cause, is still largely unknown.

The aim of this study was to evaluate the prevalence of elevated high-sensitivity cardiac troponin T (defined as the > 99th percentile of the healthy population) and to determine its association with known cardiovascular risk factors, and their relative clinical significance, among patients diagnosed with a noncardiac cause of chest pain at the emergency department. We were particularly interested in age and renal dysfunction because these are hypothesized as the major determinants of cardiac troponin levels.

CLINICAL SIGNIFICANCE

- Age and not renal dysfunction is the most important determinant of high-sensitivity cardiac troponin T among patients with a noncardiac cause of chest pain. This finding should caution clinicians not to falsely attribute elevated high-sensitivity cardiac troponin T levels to renal dysfunction.
- Unknown or underestimated cardiac involvement during the acute presenting condition seems to be the major cause of elevated high-sensitivity cardiac troponin T.
- Patients with a noncardiac cause of chest pain with high-sensitivity cardiac troponin T levels > 0.014 μg/L at presentation are at increased risk for all-cause mortality.

MATERIALS AND METHODS

Study Design and Population

The Advantageous Predictors of Acute Coronary Syndromes Evaluation is an ongoing prospective, international, multicenter study designed and coordinated by the University Hospital Basel, Switzerland.[13,14] From April 2006 to June 2009, consecutive patients who presented to the emergency department with symptoms suggestive of acute myocardial infarction, such as chest pain and angina pectoris with an onset or peak of symptoms within the last 12 hours, were recruited. Patients with terminal kidney failure requiring dialysis were excluded. The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committee at each participating institution. Written informed consent was obtained from all patients.

Clinical Assessment

On admission to the hospital, all patients underwent a detailed clinical evaluation, including medical history, 12-lead electrocardiography, standard blood tests, and chest x-ray. The necessity of additional investigations and medical treatment, and the decision to discharge or hospitalize the patients was left to the discretion of the attending physician.

Biochemical Analysis

Blood samples for the determination of Roche high-sensitivity cardiac troponin T (Roche Diagnostics, Indianapolis, Ind) and Siemens cardiac troponin I ultra (Siemens AG, Deerfield, Ill) were collected in serum and ethylenediaminetetraacetic acid tubes, respectively, at the time of a patient's presentation to the emergency department. Serial measurements were obtained 1, 2, 3, and 6 hours after presentation and were available in 77%, 62%, 52%, and 31% of patients, respectively, of the 572 patients included in this study. Serial sampling was discontinued when the diagnosis of acute myocardial infarction was certain and treatment required transferring the patient to the catheterization laboratory or coronary care unit. After centrifugation, samples were frozen at −80°C until they were assayed in a blinded fashion in a dedicated core laboratory. Cardiac troponin levels obtained at presentation were used for all analysis, except prognosis where serial measurements also were used to detect changing pattern.

The high-sensitivity cardiac troponin T assay was performed with the Elecsys 2010 system (Roche Diagnostics). Limit of detection has been determined to be 0.005 μg/L; an imprecision corresponding to 10% coefficient of variation was reported at 0.013 μg/L and the 99th percentile of a healthy reference population at 0.014 μg/L.[15]

The cardiac troponin I ultra assay was performed with the ADVIA Centaur immunoassay system (Siemens AG). Limit of detection has been determined to be 0.006 μg/L; a 10% coefficient of variation was reported at 0.030 μg/L with the 99th percentile cutoff point of 0.04 μg/L.[16,17]

Adjudicated Final Diagnosis

To determine the final diagnosis responsible for acute chest pain in each patient, 2 independent cardiologists reviewed all available medical records (including patient history, physical examination, results of laboratory testing including local cardiac troponin values, radiologic testing, electrocardiography, echocardiography, cardiac exercise test, and coronary angiography) pertaining to the patient from the time of emergency department presentation to the 60-day follow-