Canadian Journal of Cardiology 31 (2015) 296–301

Clinical Research

Troponin Rise in Hospitalized Patients With Nonacute Coronary Syndrome: Retrospective Assessment of Outcomes and Predictors

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ABSTRACT

Background: Cardiac troponin is elevated in several clinical settings apart from thrombotic acute coronary syndrome (ACS) and is associated with increased adverse events. It is not clear whether troponin elevation in type II myocardial infarction (MI) is associated with increased cardiovascular events. Our objectives were to identify the cause of mortality in type II MI and to attempt to establish the threshold range of cardiac troponin-I (cTnI) elevation as well as clinical factors associated with adverse outcomes in type II MI.

Methods: This retrospective cohort study included 245 patients presenting with a noncardiac primary diagnosis associated with cTnI elevation at a single centre from January 2003 to December 2011. Primary outcome was a composite of cardiovascular and noncardiovascular mortality. Secondary outcomes included subsequent stroke, ACS, and heart failure (HF).

Results: At 1 year, ACS occurred in 13 patients (5.3%), stroke was seen in 10 (4.1%) patients, and HF occurred in 19 (7.8%) patients. Overall 1-year mortality included 102 events (41.6%), with 10 cardiovascular deaths (9.8%), 65 noncardiovascular deaths (63.7%), and 27 (26.5%) deaths from unknown causes. In multivariable analysis,

RÉSUMÉ

Introduction : La troponine cardiaque est élevée dans plusieurs contextes cliniques, mis à part le syndrome coronarien aigu (ACS) thrombotique, et est associée à des évènements défavorables accrus. Il n'est pas évident d'évaluer si l'élévation de la troponine lors d'un infarctus du myocarde (IM) de type II est associée à une augmentation dans le taux d'événements cardiovasculaires. Nos objectifs étaient d'identifier la cause de la mortalité lors d'IM de type II et de tenter d'établir l'intervalle du seuil de l'élévation de la troponine cardiaque I (cTnI) ainsi que les facteurs cliniques associés à des résultats défavorables dans l'IM de type II.

Méthodes : Cette étude de cohorte rétrospective a inclus 245 patients se présentant avec un diagnostic primaire non cardiaque associé à une élévation de la cTnI dans un seul centre de janvier 2003 à décembre 2011. Le point d'aboutissement principal était une combinaison de mortalité cardiovasculaire et non cardiovasculaire. Les points d'aboutissement secondaires incluaient les accident vasculaire cérébral (AVC), le syndrome coronarien aigu (SCA), et l'insuffisance cardiaque (IC).

Résultats : À un an, des SCA sont apparus chez 13 patients (5,3 %), des AVC ont été observés chez 10 (4,1 %) patients, et des IC ont eu lieu

Cardiac troponin (cTn) is the most sensitive and specific measure of myocardial injury. It is commonly elevated in the absence of acute coronary syndrome (ACS) and does not distinguish the cause of myocardial injury. The 2012 Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Health Federation Task Force defines myocardial infarction (MI) as type II MI when the myocardial injury with necrosis is induced by a condition other than coronary artery disease (CAD) that contributes to an imbalance between myocardial oxygen supply or demand, or both.[1] Type I MI is defined as spontaneous atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection, with resulting intraluminal thrombus in 1 or more coronary arteries, leading to decreased myocardial blood flow or distal platelet emboli and ensuring myocyte necrosis in the presence or absence of pre-existing CAD.

The mechanisms of cTn release in type II MI are not completely understood and may be disease specific. Management principles and guidelines for type II MI are not well established. The efficacy of traditional therapies, such as antiplatelet and antithrombotic medications, aimed at reducing risk in patients with cTn elevation in the absence of thrombotic ACS is unknown. There are no data to support an early invasive revascularization strategy in patients when the risk of thrombotic ACS is low. Additionally, it is not known if there

Received for publication September 10, 2014. Accepted November 28, 2014.

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See page 301 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2014.11.032

factors independently associated with increased overall 1-year mortality included cTnI elevation $\geq$ 4.63 μg/L (odds ratio [OR], 3.37; 95% confidence interval [CI], 1.55-7.34; $P = 0.002$), age $\geq$ 70 years (OR, 2.44; 95% CI, 1.40-4.29; $P = 0.002$), and estimated glomerular filtration rate $<$ 30 mL/min/1.73m^2 (OR, 2.40; 95% CI 1.31-4.40; $P = 0.005$).

Conclusions: Unlike the published literature, our study includes a variety of both operative and nonoperative clinical settings associated with troponin elevation. We illustrate that although overall mortality is high after type II MI, the majority of mortality is caused by noncardiovascular events.

pour 19 (7,8 %) patients. La mortalité globale à 1 an comprend 102 événements (41,6 %), dont 10 décès cardiovasculaires (9,8 %), 65 décès non cardiovasculaires (63,7 %), et 27 (26,5 %) décès de cause inconnue. En analyse multivariée, les facteurs indépendamment associés à l'augmentation de la mortalité globale à 1 an incluent l'élévation de la cTnI $\geq$ 4,63 μg/l (ratio d'incidence approché [RIA], 3,37; intervalle de confiance [IC] à 95 %, 1,55-7,34; $P = 0,002$), un âge $\geq$ 70 ans (RIA, 2,44; IC à 95 %, 1,40-4,29; $P = 0,002$), et un débit de filtration glomérulaire estimé $<$ 30 ml/min/1,73m^2 (RIA, 2,40; IC à 95 %, 1,31-4,40; $P = 0,005$).

Conclusions : Contrairement à la littérature publiée, notre étude comprend une variété de contextes cliniques à la fois opératoires et non opératoires associés à une élévation de la troponine. Nous illustrons que, bien que la mortalité globale soit élevée après un IM de type II, la majorité de la mortalité est causée par des événements non cardiovasculaires.

is a threshold level of cTn elevation that correlates with increased cardiovascular and noncardiovascular morbidity and mortality in type II MI. Accordingly, our objectives were to attempt to establish the threshold range of cTn-I elevation in patients with type II MI associated with adverse outcomes. We also explored clinical factors associated with increased morbidity and mortality events in the setting of type II MI and identified the distribution of mortality.

Methods

Study design and patients

The study protocol was approved by the Health Research Ethics Board at the University of Alberta before commencement. The requirement for written consent was waived. This was a retrospective population-based cohort study of adult patients ($\geq$ 18 years) admitted to noncardiology units in a single tertiary care centre—the University of Alberta Hospital in Edmonton, Alberta—with a non-ACS primary admission diagnosis associated with a cTnI elevation of $\geq$ 0.15 μg/L during the study period from January 2003 to December 2011 inclusive. Patients were initially triaged in the emergency department by an emergency medicine physician based on clinical presentation. The appropriate admitting service was then involved for what was documented as a non-ACS primary diagnosis. Expert opinion from a cardiology consultant was often, but not always, sought to verify that cTnI elevation was related to type II MI based on the absence of cardiac-related chest pain and the presence of an acute noncardiac clinical condition that provided an alternative explanation for cTnI elevation. The primary diagnosis remained something other than thrombotic ACS throughout the patients' documented hospital stay. Patients admitted with decompensated heart failure (HF) and cardiac arrhythmias were excluded because of the possibility of type I MI being the primary cause of such presentations. Patients receiving chemotherapy were excluded because of its potential for direct cardiac toxicity. Those undergoing organ transplantation were also excluded for the same reason. Finally, patients with another means of direct myocardial damage—including myocarditis, cardiac contusion, and cardiopulmonary resuscitation or after an electrophysiological procedure—were excluded. Study patients were identified through the International Classification of Diseases, 9th edition, Clinical Modification (ICD-9-CM) and ICD-10 Canada at the time of discharge.

Data extraction and outcomes

A detailed chart review was undertaken to extract baseline patient characteristics, including cardiovascular risk factors, peak cTnI elevation, laboratory data, in-hospital use of traditional cardioprotective and cardiotoxic medications, need for subsequent coronary revascularization, hospital length of stay, and clinical outcomes using standardized case report forms. A primary admission diagnosis associated with cardiac ischemic imbalance was verified by chart review. The levels of cTnI increase were separated into quartiles (Q) as follows: Q1, 0.15-0.57 μg/L; Q2, 0.58-1.74 μg/L; Q3, 1.75-4.62 μg/L; and Q4, 4.63-67.48 μg/L. Primary outcome included a composite of cardiovascular and noncardiovascular mortality. Secondary outcomes included stroke or transient ischemic attack, thrombotic ACS, and decompensated HF. All outcomes were verified by chart review and measured in the hospital, at 30 days, and at 1 year of follow up.

Operational definitions

Patients were said to have cardiac risk factors—including hypertension, hypercholesterolemia, coronary artery disease (CAD), familial premature CAD, or smoking—if these were documented in the medical records. Presence of diabetes mellitus was defined by previous documentation in the medical records or by preadmission or admission hemoglobin A1c levels $\geq$ 6.5%. Previous stroke, HF, ACS, valvular heart disease, and atrial fibrillation were confirmed based on the written records and preadmission imaging data. Significant valvular disease was defined as at least moderate to severe valvular stenosis or regurgitation. Previous coronary revascularization was confirmed based on written medical records or operative reports. Medications were documented as in-hospital use at the time of cTnI elevation. cTnI assessment was conducted using the Beckman Coulter chemiluminescent immunoassay (Beckman Coulter, Brea, CA) with an upper limit of normal at 0.15 μg/L (99th percentile upper reference limit). Any cTnI level $\geq$ 0.15 μg/L was designated as a