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Original Contribution

Role of copeptin in dual–cardiac marker strategy for patients with chest pain presented to ED☆

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ABSTRACT

Objective: The objective of the study is to evaluate the role of copeptin in the diagnosis of acute coronary syndrome (ACS) and its role in dual–cardiac marker diagnostic strategy with troponin.
Design: A prospective cohort study was carried out from May 2012 to October 2012.
Setting: The study was conducted at the emergency department (ED) of a public hospital in a cluster of Hong Kong.
Methods: Patients aged at least 18 years presented with chest pain to ED who have intermediate or high likelihood of ACS were included. All patients had blood taken in the ED for copeptin and troponin I. The adjudicated diagnoses of ACS were made by 2 independent physicians based on the universal definition. Diagnostic characteristics were calculated. Receiver operating characteristic curves were created. Areas under the curves were compared for copeptin, troponin I, and dual-marker strategy with copeptin and troponin I.
Results: A total of 637 patients were recruited. Seventy-eight had been diagnosed to be ACS. The negative predictive value of copeptin for ACS was 0.881 (0.849-0.907) compared with troponin I, 0.937 (0.913-0.956). The areas under the receiver operating characteristic curves of copeptin, troponin I, and dual-marker strategy were 0.68, 0.859, and 0.880, respectively.
Conclusions: Addition of copeptin to troponin does not have significant improvement of the diagnostic accuracy of ACS in patients presented with chest pain.

1. Introduction

Patients presenting with chest pain to emergency department (ED) remain a great challenge in clinical practice. Unlike in ST-elevation myocardial infarction, where electrocardiogram (ECG) and clinical criteria are sufficient to set the diagnosis, biomarkers are crucial to facilitate the diagnostic process in case of unstable angina (UA) and non–ST elevation myocardial infarction (NSTEMI). The introduction of biomarkers such as troponin and high-sensitivity troponin in the past decades has made significant advancement in acute coronary syndrome (ACS) diagnosis [1-3]. However, there are still many limitations on troponin usage from possible sensitivity and specificity deficit to the delayed release pattern after the onset of myocardial ischemia [4]. Second measurement of troponin is necessary, due to its delay in release during acute myocardial infarction (AMI), and creates economic burden and extra workload to ED. Thus, it is essential to increase accuracy of troponin assay in the detection of ACS as early as possible [5-7]. Identification of single perfect biomarker in this context is questionable. Multimarker testing for ACS diagnosis has been advocated [8-10]. Studies on multimarker testing seem to show encouraging results, especially regarding the combination of copeptin and troponin, but there are still many controversies.

The main pathophysiological process in AMI is cardiac necrosis. It is accompanied by the release of many stress hormones. Among them, copeptin, the C-terminal part of vasopressin, is proven to be an indirect marker of vasopressin [11]. Copeptin concentration elevates in AMI [8-10], heart failure [12,13], and shock [14,15]. The release of vasopressin and, therefore, copeptin in AMI is much faster than the release of troponin [10]. Unlike vasopressin, which decays 20 minutes after its release to circulation, copeptin is a stable peptide providing time frame for

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biochemical measurement [11]. Detection of copeptin may add diagnostic value in UA and NSTEMI patients, especially in patients presenting shortly after the onset of chest pain.

The aim of this prospective trial is to evaluate the clinical role of copeptin in daily practice in the ED of Chinese population in Hong Kong by a new economic commercial kit. The study aims at investigating the diagnostic value of copeptin alone and its combination use with troponin in early detection of UA and NSTEMI.

2. Methods

2.1. Study population and design.

This is a prospective cohort study for consecutive patients presenting to the ED with chest pain. The enrollment was conducted in Tuen Mun Hospital between May 2012 and October 2012. The inclusion criteria were older than 18 years, chest pain suggestive of ACS, and nonconclusive ECG. Patients were assessed by the in-charge emergency physician with relevant history, physical examination, and ECG findings to stratify into high, intermediate, or low likelihood of ACS (Table 1) [1]. Patients with high or intermediate likelihood of ACS were taken cardiac biomarkers and enrolled in the study.

Exclusion criteria were ST-elevation myocardial infarction, cardiac arrest, sepsis, end-stage renal failure, trauma, or major surgery within 4 weeks before admission; pregnancy; and drug abuser. Patients were also excluded if the in-charge physician suspected aortic dissection or pulmonary embolism as the cause of chest pain after initial workup.

The study was performed according to the principles of the Declaration of Helsinki. Approval was obtained from the local institutional review board and ethics committee. Informed consent was obtained from all participating patients. The study was funded by the research grant of the Hong Kong College of Emergency Medicine.

2.2. Clinical evaluation

All patients underwent standard clinical evaluation at admission by the attending emergency physician, including medical history; physical examination; 12-lead electrocardiogram; chest x-ray; and laboratory tests including troponin I, full blood count, aminotransferases, and creatinine.

Cardiac markers of troponin were repeated in selected patients in various time frames as judged by the attending physician after admission. Echocardiogram, coronary angiography, and cardiac stress test were carried out in selected patients according to the judgment by the attending physician or cardiologist.

2.3. Laboratory methods

2.3.1. Troponin I

Blood samples for troponin I were collected from patients while they are presenting chest pain in the ED shortly after admission and were transferred to the laboratory in serum gel tubes. Troponin I assay measurements were performed with sandwich 2-step chemiluminescent immunoassay of (ADVIA Centaur XP Immunoassay system; Siemens, Erlangen, Germany). The cutoff for the detection of myocardial ischemia was 0.06 ng/mL (the 99th percentile of a normal population); detection limit was 0.01 ng/mL, with a measuring range of 0.01 to 50 ng/mL; and coefficient of variation level was less than 10%.

2.3.2. Copeptin

Blood samples for copeptin were collected simultaneously with troponin I from patients while they are presenting chest pain in the ED and were transferred to the laboratory in EDTA tubes and then centrifuged for 15 minutes at 1000*g* in room temperature within 30 minutes of collection. The samples were than stored at −20°C. Assays were transported to the accredited laboratory. The samples are thawed and centrifuged in batches, and the assays were performed with enzyme-linked immunosorbent assay method. We used a commercial enzyme-linked immunosorbent assay kit (CSB-E12130h; Cusabio Biotech Co, Ltd, DE, Wuhan, China). Copeptin assay was calibrated with normal subjects from healthy local Chinese population of Hong Kong Chinese and diseased subjects confirmed with ACS. The lower detection limit of the assay is was 19.53 pg/mL; the detection range was 19.53 to 5000 pg/mL; and coefficient of variation level was less than 10%. The adopted cutoff was 64.5 pg/mL (18.9 pmol/L), which was based on the recommendation from the manufacturer and previous study [9].

2.4. Adjudicated final diagnosis

The final diagnosis was adjudicated at discharge by 2 independent cardiologists. Disagreements were settled by the opinion from a third cardiologist. Acute myocardial infarction was diagnosed according to the universal definition of myocardial infarction [16]. Myocardial necrosis was diagnosed if at least 1 value of troponin was positive (above the 99th percentile) and/or a rising and/or falling pattern of troponin I was present. Unstable angina was diagnosed in the presence of typical angina at rest at admission or a sudden increase in episodes of a previously stable angina (elevation of at least 2 classes according to the Canadian Cardiovascular Society classification) with normal troponin level and no evidence of myocardial necrosis. Patients diagnosed with NSTEMI and UA were considered as ACS.

Table 1
Likelihood of an ACS secondary to coronary artery disease according to clinical characteristics

Features	High likelihood	Intermediate likelihood	Low likelihood
	Any of the following:	Absence of high-likelihood features and presence of any of the following:	Absence of high- to intermediate-likelihood features but may have:
History	Chest or left arm pain or discomfort reproducing prior documented angina Known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom Age older than 70 years old Male sex Diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate-likelihood characteristics Recent cocaine use
Examination	Transient MR murmur, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (≥1 mm) or T-wave inversion in multiple precordial leads	Fixed Q waves ST depression 0.5-1 mm or T-wave inversion >1 mm	T-wave flattening or inversion <1 mm in leads with dominant R waves Normal ECG
Cardiac markers	Elevated cardiac TnI, TnT, or CK-MB	Normal	Normal

Abbreviations: CAD, coronary artery disease; MI, myocardial infarction; MR, magnetic resonance; TnI, troponin I; TnT, troponin T; CK-MB, creatine kinase-MB.