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Copeptin Improves Early Diagnosis of Acute Myocardial Infarction

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Objectives Early identification of myocardial infarction in chest pain patients is crucial to identify patients at risk and to maintain a fast treatment initiation.

Background The aim of the current investigation is to test whether determination of copeptin, an indirect marker for arginin-vasopressin, adds diagnostic information to cardiac troponin in early evaluation of patients with suspected myocardial infarction.

Methods Between January 2007 and July 2008, patients with suspected acute coronary syndrome were consecutively enrolled in this multicenter study. Copeptin, troponin T (TnT), myoglobin, and creatine kinase-myocardial band were determined at admission and after 3 and 6 h.

Results Of 1,386 (66.4% male) enrolled patients, 299 (21.6%) had the discharge diagnosis of acute myocardial infarction, 184 (13.3%) presented with unstable angina, and in 903 (65.2%) an acute coronary syndrome could be excluded. Combined measurement of copeptin and TnT on admission improved the c-statistic from 0.84 for TnT alone to 0.93 in the overall population and from 0.77 to 0.9 in patients presenting within 3 h after chest pain onset (CPO) ($p < 0.001$). In this group the combination of copeptin with a conventional TnT provided a negative predictive value of 92.4%.

Conclusions In triage of chest pain patients, determination of copeptin in addition to troponin improves diagnostic performance, especially early after CPO. Combined determination of troponin and copeptin provides a remarkable negative predictive value virtually independent of CPO time and therefore aids in early and safe rule-out of myocardial infarction.
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Early identification of myocardial infarction (MI) in chest pain patients is crucial to maintain a fast treatment initiation. Diagnosis of acute myocardial infarction (AMI) relies, besides clinical symptoms and electrocardiographic (ECG) findings, primarily on biomarker levels. Markers of myocardial necrosis such as cardiac troponin and creatine kinase-myocardial band (CK-MB) are the gold standard in detection of AMI, and their use is recommended by current guidelines (1). In particular, cardiac troponin provides excellent specificity (2,3).

The delayed release of necrosis markers after cell disintegration might explain the weakness in diagnostic performance of conventional troponin assays early after chest pain onset (CPO) (4). Therefore, markers with pathophysiologic background independent of cell necrosis might improve rapid diagnosis of AMI.

The antidiuretic hormone arginin-vasopressin (AVP) is secreted neurohypophyseal and controls osmotic homeostasis (5). Release of AVP is regulated by hyperosmolality, hypovolemia (6), hypotension, hypothalamic osmoreceptors

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and angiotensin II, reflecting individual stress level (7). The AVP-induced vasoconstriction is mediated by the V_{1a} receptor on smooth muscle cells, the antidiuretic effect by the V_2 receptor on the distal kidney tubule, and the IP3 signal transduction pathway (8,9). Clinical relevance of AVP is given by its potential role in pathogenesis and its diagnostic value in congestive heart failure (10) and remodeling after AMI (11). As endocrine stress response, the AVP levels increase in shock and cardiac arrest (12–14). Routine measurement of AVP in clinical practice is prevented by various reasons, such as short half-life time (15), platelet binding (16), and assay variations. The glycosylated peptide copeptin is part of the uncleaved pro-AVP and emerges equimolar to AVP, because both are derived from the precursor prepro-AVP along with neurophysin II; therefore, it serves as an indirect marker for AVP. A recently developed assay for copeptin delivers the stability and reproducibility direct measurement of AVP is lacking (17).

The release pattern of copeptin in patients with AMI with immediate rise after onset of chest pain and decrease toward physiologic levels within 5 days (18) as well as the potential use of copeptin in rule-out of AMI (19) was described recently. Thus, the role of copeptin as diagnostic marker in suspected acute coronary syndrome (ACS) needs to be evaluated in large prospective cohorts.

The aim of the current investigation is to prospectively test whether copeptin adds diagnostic information to that provided by troponin and whether the combination of copeptin and troponin is superior to the combination of myoglobin and troponin in early evaluation of patients with suspected AMI.

Methods

Study population. All patients with suspected ACS presenting consecutively at the chest pain units of the University Medical Center of the Johannes Gutenberg-University Mainz, the Federal Armed Hospital Koblenz, or the University Hospital Hamburg-Eppendorf between January 2007 and July 2008 were enrolled in this study, to reflect an unbiased real world population.

Patients older than 18 years and younger than 85 years of age with angina pectoris or equivalent symptoms were eligible to participate. Exclusion criteria were trauma or major surgery within the last 4 weeks, pregnancy, intravenous drug abuse, and anemia (hemoglobin <10 g/dl).

Patients treated with antihypertensive drugs at enrollment or who had previous diagnosis of hypertension were classified as hypertensive. Patients were categorized as currently smoking, former smoking (if stopped 4 weeks to 40 years prior), and nonsmoker (if stopped smoking >40 years ago). Patients receiving dietary treatment or medication for diabetes were considered to have diabetes mellitus. We considered patients with previously diagnosed hyperlipidemia or with total cholesterol >200 mg/dl at admission as hyperlipidemic.

Blood was drawn at admission and after 3 and 6 h. A 12-lead ECG was obtained at the same time points.

Diagnosis of AMI was established according to the universal definition of MI (1). Patients with symptoms of myocardial ischemia together with ECG changes and/or elevated biomarkers of myocardial necrosis were categorized as having an AMI. Relevant ECG changes were defined as follows: ST-segment elevation ≥0.2 mV in at least 2 contiguous leads in V_2 to V_6 or ST-segment elevation ≥0.1 mV in other leads or with new left bundle branch block documented in ECG at admission or in outpatient clinic ECG were classified as AMI with ST-segment elevation; and ST-segment depression and T- or Q-wave changes were classified as ECG signs representative for acute ischemia. Necrosis of myocardium was noted if at least 1 determination of in-house troponin exceeded the predefined upper reference limit of the corresponding assay and if a typical kinetic with rise or fall ≥20% within 6 h after admission could be observed.

Abbreviations and Acronyms

ACS = acute coronary syndrome
AMI = acute myocardial infarction
AUC = area under the curve
AVP = arginin-vasopressin
CK-MB = creatine kinase-myocardial band
CPO = chest pain onset
CV = coefficient of variation
ECG = electrocardiogram/electrocardiographic
MI = myocardial infarction
NCCP = noncoronary chest pain
NPV = negative predictive value
NT-proBNP = N-terminal pro-brain natriuretic peptide
PPV = positive predictive value
ROC = receiver operating characteristic
TnI = troponin I
TnT = troponin T
UAP = unstable angina pectoris

Unstable angina pectoris (UAP) was diagnosed if ECG was nondiagnostic; in-house troponin was negative, but coronary angiography revealed a culprit lesion; or ischemia was proven in stress test with subsequent need of coronary intervention. All patients with excluded ACS were categorized as having noncoronary chest pain (NCCP). Final diagnosis was made by an expert committee of 2 cardiologists, blinded to copeptin values, on the basis of all available clinical, laboratory, and imaging findings.

The study was approved by the local ethics committees in Rheinland-Pfalz and Hamburg. Participation was voluntary; each patient gave written, informed consent.

Blood sampling and laboratory methods. Routine laboratory parameters, including C-reactive protein, creatinine, myoglobin, N-terminal pro-brain natriuretic peptide (NT-proBNP), and CK-MB, were measured immediately after blood withdrawal by standardized methods. Additionally, ethylenediaminetetraacetic acid plasma, citrate plasma, and serum samples were collected at each time point, centrifuged, and frozen at −80°C.

Cardiac troponin T (TnT) (Roche Diagnostics, Mannheim, Germany) representing in-house troponin at 2 study