Release Kinetics of Copeptin in Patients Undergoing Transcoronary Ablation of Septal Hypertrophy

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BACKGROUND: The release kinetics of copeptin in patients with acute myocardial infarction (AMI) have been difficult to establish.

METHODS: We analyzed the release kinetics of copeptin in patients with hypertrophic obstructive cardiomyopathy undergoing transcoronary ablation of septal hypertrophy (TASH) as a model of AMI. We included 21 consecutive patients who underwent TASH. Blood samples were collected before and at 15, 30, 45, 60, 75, 90, and 105 min, and at 2, 4, 8, and 24 h after TASH. Serum copeptin was quantified by a sandwich immunoluminometric assay.

RESULTS: All patients had copeptin concentrations below the 99th percentile at baseline. The median copeptin concentration was significantly increased at 30 min (16.0 pmol/L; interquartile range (IQR), 13.4–20.2 pmol/L), compared with the median baseline concentration (6.6 pmol/L; IQR, 5.3–8.3 pmol/L; P = 0.002). The copeptin concentration peaked 90 min after induction of myocardial infarction and returned to baseline concentrations (median, 8.2 pmol/L; IQR, 6.3–10.1) after 24 h, compared with the above baseline values (P = 0.06). Serum creatine kinase (CK) activities were significantly increased above baseline values by 1 day after TASH [median maximal postprocedural CK activity, 935.0 U/L (IQR, 545.5–1115.0 U/L); median baseline CK activity, 80.0 U/L (IQR, 63.5–109.0 U/L); P < 0.001].

CONCLUSIONS: Our results provide additional evidence that early rule-out of suspected AMI is possible by using the copeptin concentration in combination with cardiac troponin T.

The majority of patients with chest pain and suspected acute coronary syndrome are diagnosed with other cardiac or extracardiac conditions (1). Accordingly, many patients are hospitalized unnecessarily (2). Cardiac troponins play a key role in differentiating patients with non-ST-elevation myocardial infarction from the large proportion of patients with acute chest pain (3–6); however, multiple other biomarkers have been evaluated for their diagnostic capability (7–10). The main problem with most biomarkers is the diagnostic gap in the first hours after the onset of myocardial ischemia, and a second blood draw is needed to detect an increase or decrease in the biomarker concentration. For this purpose, the evaluation of new biomarkers capable of excluding acute myocardial infarction (AMI) at an earlier time is a major scientific target.

Copeptin, a glycoprotein from the C-terminal fragment of the arginine vasopressin prohormone, is cosecreted with arginine vasopressin from the neurohypophysis. Previously published data have shown the diagnostic and prognostic impact of copeptin used in combination with cardiac troponins for patients with AMI (11–13). Because defining the exact time when myocardial ischemia begins has been inaccurate and because of the patient-related delay before presentation to the hospital, the early release kinetics of copeptin have not been well described. Given that several studies have focused on the release of copeptin in different pathologies (AMI, tako-tsubo cardiomyopathy, stroke, sepsis), the use of copeptin has become well established as a suitable marker for reflecting individual stress levels (14–17). The exact release kinetics of copeptin in the presence of AMI have not yet been evaluated, however, because it has not been possible to exactly define the onset of myocardial ischemia in routine clinical practice.

The objective of our study was to characterize the exact time course of copeptin increase in patients undergoing transcoronary ablation of septal hypertrophy (TASH) as a surrogate for patients with AMI.

From January 2010 until June 2011, 21 patients with hypertrophic obstructive cardiomyopathy who underwent TASH were included in the study. TASH was performed according to routine clinical practice. A description of the pre- and postprocedural management of the patients has recently been published (18). All patients received analgesic and anxiolytic pretreatment. All patients enrolled in the study provided informed consent, which included consent for bio-

3 Nonstandard abbreviations: AMI, acute myocardial infarction; TASH, transcoronary ablation of septal hypertrophy; IQR, interquartile range; CK, creatine kinase.
were processed immediately and frozen at induction of myocardial infarction. The serum samples were assayed at 15, 30, 45, 60, 75, 90, and 105 min, and at 2, 4, 8, and 24 h after tubes to measure the copeptin concentration at 15, 30, 60, and 120 min. The functional assay sensitivity, defined as the lowest concentration with an interassay CV of <20%, was 2.25 pmol/L. The median copeptin concentration for 359 healthy individuals (age, 18–80 years) was 4.2 pmol/L (range, 1.0–13.8 pmol/L; 95% CI, 4.0–4.4 pmol/L). The 99th percentile value was 13.5 pmol/L, and that for the 97.5 percentile was 11.25 pmol/L.

All data for continuous variables are expressed as the mean (SD) or as the median and interquartile range (IQR), as appropriate. Categorical variables are reported as a number and a percentage. Continuous variables were compared with the Wilcoxon signed rank test. The data were distributed parametrically according to the Kolmogorov–Smirnov test. All statistical tests were performed with SPSS software (version 15.0; SPSS/IBM). A 2-tailed P value <0.05 was considered statistically significant.

Table 1 summarizes the clinical and procedural characteristics of all the patients [13 men, 8 women; mean (SD) age, 59.0 (13.3) years] enrolled in the study; these data have been described in detail elsewhere (18). All TASH procedures were performed with a single septal branch occlusion in a single-session procedure. During the procedure, the mean administered ethanol volume was 1.77 (0.59) mL. The median occlusion time was 20.0 min (IQR, 14.5–31.0 min).

All patients had copeptin concentrations below the 99th percentile at baseline. Copeptin concentrations were significantly increased at 30 min (16.0 pmol/L; IQR, 13.4–20.2 pmol/L), compared with the median baseline concentration (6.6 pmol/L; IQR, 5.3–8.3 pmol/L; P = 0.002). The copeptin concentration peaked 90 min after induction of myocardial infarction (31.9 pmol/L; IQR, 16.4–117.1 pmol/L), compared with the median copeptin concentration at baseline (6.6 pmol/L; IQR, 5.3–8.3 pmol/L; P < 0.001), and it returned to baseline values after 24 h (8.2 pmol/L; IQR, 6.3–10.1 pmol/L), compared with the median baseline concentration presented above (P = 0.06; Fig. 1). We observed increases in copeptin concentrations in every patient during the first 2 h after induction of myocardial infarction. The copeptin concentrations and minimum/maximum concentrations for each time point are presented in Table 2 in the Data Supplement that accompanies the online version of this brief communication at http://www.clinchem.org/content/vol59/issue3. Serum creatine kinase (CK) activities were increased significantly (maximal postprocedural CK activity; 1 mg/dL = 88.4 µmol/L).

<table>
<thead>
<tr>
<th>Variable (n = 21)</th>
<th>Data are presented as the mean (SD).</th>
<th>Data are presented as the median (IQR).</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.0 (13.3)*</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>13 (61.9)</td>
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</tr>
<tr>
<td>Body mass index, kg/m²</td>
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<tr>
<td>Cardiovascular risk factors, n (%)</td>
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<td>Hypertension</td>
<td>13 (61.9)</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>6 (28.6)</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Family history</td>
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<tr>
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<tr>
<td>Creatinine, mg/dLb</td>
<td>0.78 (0.76–0.93)c</td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate, ml · min⁻¹ · (1.73 m²)⁻¹</td>
<td>90.53 (79.04–113.73)c</td>
<td></td>
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</tbody>
</table>

* Data are presented as the mean (SD).

**Table 1. Baseline characteristics of the patients.**
have been unknown. Our study precisely documented the early release kinetics of copeptin after the induction of myocardial infarction in patients undergoing TASH as a surrogate for AMI.

Our data clearly show that copeptin is released quickly, within the first 30 min after the induction of myocardial infarction. It reaches a maximum after 90 min and returns to baseline concentrations after 24 h. We used the TASH procedure as a model of AMI because it closely mimics the pathophysiology of AMI and permits a well-defined chronological assignment of biomarker release in response to the initiation of myocardial infarction (18). We cannot entirely exclude the possibility that this early increase in copeptin is partly related to the pain and stress caused by the TASH procedure itself; however, all patients received analgesic and anxiolytic pretreatment to lower their stress levels. Furthermore, the baseline copeptin concentrations were below the 99th percentile in all patients, indicating they all had low individual stress levels. The copeptin concentration increased in every patient during the first 2 h after induction of myocardial infarction.

Characterizing the kinetics of the appearance of detectable copeptin concentration changes in patients with AMI is of major clinical and socioeconomic importance, because chest pain is one of the most frequent causes of emergency department admissions. Understanding both the different time courses of troponin and copeptin and their correlation with the patient’s symptoms, electrocardiograms, and imaging study results is important for early diagnosis, individual risk stratification, and individualized therapy, especially in the early hours after symptom onset.

If additional validation of cardiac troponin in patients with initial cardiac troponin and copeptin concentrations below the 99th percentile is unnecessary, a shorter observation period would be possible and therefore have major implications on the use of resources. This validation, however, needs to be performed in a large-scale real-world scenario to establish fast-track workup protocols in the chest pain unit.

We believe that this study is the first to serially measure copeptin concentrations in patients with hypertrophic obstructive cardiomyopathy undergoing TASH. Some limitations of our study must be considered, however. The patients we studied had no coronary artery disease and therefore had no possibility of ischemic preconditioning, which can influence the effect of ischemia-related copeptin release. Furthermore,
the kinetics of copeptin release after alcohol ablation might be different from that arising from the stuttering thrombotic occlusion of an epicardial coronary artery, in which the vessel dynamically opens and closes during the early period of myocardial infarction. The total occlusion of a small septal artery during the TASH procedure may not have much influence on the systemic hemodynamics leading to vasopressin and copeptin release from the neurohypophysis. We speculate that myocardial necrosis in humans might lead to vasopressin release independently of neurohypophysis release. Nevertheless, our data clearly demonstrate a significant increase in the copeptin concentration by 30 min, with a peak occurring 90 min after induction of myocardial infarction.

In conclusion, our results provide valuable additional evidence that early rule-out of suspected AMI is possible via the use of the copeptin concentration in combination with cardiac troponin.

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References


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