Serum copeptin and copeptin/NT-proBNP ratio — new tools to differentiate takotsubo syndrome from acute myocardial infarction

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Abstract: Background: Today no established biomarkers are available for the early diagnosis of takotsubo syndrome and its differentiation from ST-segment elevation myocardial infarction. We hypothesized that copeptin and copeptin/NT-proBNP ratio may serve a routine marker combination for non-invasive differentiation. Methods: The study compared the serum concentrations of copeptin, troponin I (TnI) and NT-proBNP in 19 consecutive women diagnosed with takotsubo syndrome according to the Mayo Clinic criteria and 10 consecutive women diagnosed with ST-segment elevation myocardial infarction. Results: Copeptin concentrations were significantly lower in patients with takotsubo syndrome than in patients with ST-segment elevation myocardial infarction. The diagnostic accuracy to distinguish takotsubo syndrome from ST-segment elevation myocardial infarction is highest for copeptin/NTproBNP ratio, copeptin/TnI at admission ratio and copeptin alone (AUC 0.8713, 0.8538, 0.8480, respectively). Conclusions: The serum copeptin to NTproBNP ratio could be an additional tool in the non-invasive differentiation between takotsubo syndrome and ST-segment elevation myocardial infarction. However, further researches are needed.

Keywords: copeptin, takotsubo syndrome, acute myocardial infarction.
Introduction

Takotsubo syndrome (TTS) usually occurs in postmenopausal women and is characterised by a transient left ventricular wall motion abnormalities after emotional or physical stress [1]. The most widely known diagnostic criteria are Mayo Clinic Diagnostic Criteria which include transient hypokinesis, akinesis or dyskinesis of the left ventricle, absence of obstructive coronary artery disease, new abnormalities in ECG and absence of pheochromocytoma and myocarditis [2]. The most common symptoms of TTS are acute chest pain, dyspnoea, palpitation or syncope [3]. However, patients may present with symptoms of TTS complication: pulmonary oedema, cardiogenic shock or even cardiac arrest. Clinical manifestation of TTS induced by severe physical stress may be dominated by the manifestation of the underlying acute illness [4]. Most common findings in ECG is ST-segment elevation followed by progressive T-wave inversion and QT interval prolongation over several days [5]. In the clinical setting, TTS should be promptly differentiated from acute myocardial infarction (AMI) in order to avoid misdiagnosis and institute appropriate management. TTS and ST-segment elevation myocardial infarction (STEMI) share many clinical and laboratory diagnostic features, and their differentiation is currently based on invasive coronary arteriography, revealing normal vessels or no obstructive coronary artery disease in the former and culprit coronary stenosis, coronary thrombosis or destabilised coronary plaques in the latter [2]. Differentiation between these two clinical entities, based on routine laboratory parameters, would be a considerable step forward in the prompt diagnosis on admission to the hospital. Today no established biomarkers are available for the early diagnosis of TTS and its differentiation from STEMI. On admission troponin values are usually equally elevated compared to STEMI whereas peak values are lower. Previously, we examined the ratios of NT-proBNP/troponin I and we found that the value of N-terminal pro-brain natriuretic peptide (NT-proBNP) is significantly higher in TTS than in STEMI and concluded that early NT-proBNP/TnI ratio may help to differentiate TTS from STEMI with a greater accuracy than that yielded by NT-proBNP alone [6]. In another study, Fröhlich et al. [7] found that NT-proBNP/myoglobin of 3.8 distinguished TTS from STEMI while a NT-proBNP/myoglobin ratio of 14 separated well between TTS and non-ST-elevation myocardial infarction.

We decided to investigate the usefulness of other known biomarker — copeptin which is now used for an early diagnosis of acute coronary syndromes (ACS) [8–11]. The activation of neuroendocrine pathways, in particular the hypothalamic-pituitary-adrenal axis and vasopressin release, is a characteristic response to biological stress [12]. Vasopressin is secreted from the pituitary gland in response to hypovolemia, hypoxia, acidosis, and changes in plasma osmolality [13, 14]. However, it has a short half-life in blood. Copeptin, the C-terminal part of the pre-provasopressin (pre-proAVP)
secreted stoichiometrically with arginin-vasopressin from the neurohypophysis is an important early modulator of the individual endogenous stress response [15]. Moreover, copeptin is a stable protein in the circulation. Therefore, we assumed that copeptin in addition to NT-proBNP may serve a routine marker combination for non-invasive differentiation between TTS and STEMI. In order to test this hypothesis, the release of copeptin and NT-proBNP was investigated in women with TTS and in women with STEMI for further comparison.

**Materials and Methods**

The study conforms to the principles outlined in the Declaration of Helsinki. The study protocol was approved by an institutional ethics committee. All patients gave informed consent.

**Study design and population**

The study compared the baseline serum concentrations of copeptin, troponin I (TnI) and NT-proBNP in 19 consecutive women diagnosed with TTS according to the Mayo Clinic criteria and 10 consecutive women diagnosed with STEMI at the 1st Department of Cardiology, Medical University of Warsaw. In all cases the final diagnosis was adjudicated by independent cardiologists blinded to copeptin concentrations.

**Biochemical analysis**

Blood samples for TnI, NT-proBNP were obtained and analysed within 12 hours from symptoms onset. The serum concentrations of TnI were determined using commercially available tests on an Dimension® EXL™ integrated chemistry system LOCI® Module (Siemens Healthcare Diagnostics, Erlangen, Germany). Serum NT-proBNP concentration was determined by quantitative chemiluminescent method in the integrated clinical biochemistry system Dimension. Assay range of NTproBNP 5 — 35 000 pg/ml, analytical sensitivity is 5 pg/ml and detection limit 2.3 pg/ml. The upper limit of normal in the non-acute setting of heart failure is 125 pg/mL whereas in the acute setting, higher values should be used (<300 pg/mL). Serum for copeptin measurements were collected on admission and were stored at –70°C immediately after centrifugation. Copeptin was measured by using a commercially available enzyme immunoassay (Phoenix Pharmaceuticals, Inc, Burlingame, USA). The minimum detection limit was 0.1 ng/mL.
Imaging studies

Each patient underwent a complete echocardiographic examination using an Epiq 7 or iE33 Philips ultrasound system. Left ventricular ejection fraction (LVEF) was assessed with the biplane Simpson’s method. Also, coronary angiography was performed in each patient. In all patients with TTS coronary artery diseases were excluded. In all patients with STEMI coronary angiography revealed significant changes and angioplasty was performed.

Statistical analysis

Continuous variables are presented as median with interquartile range (IQR). Differences between continuous variables are assessed with U-Mann–Whitney test. Categorical variables are shown as number and percentages and analysed using the Fisher’s exact test. Receiver operating characteristic (ROC) curve analysis was performed for baselinecopeptin and copeptin/NTproBNP ratio as diagnostic parameters using the deLong test. The area under the curve (AUC) and optimal cut-off values as the value providing the optimal test accuracy from the ROC curve were also calculated. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using the PQStat software.

Results

Baseline clinical characteristics

Baseline characteristics of the study group are summarised in Table 1.

Table 1. Baseline characteristic of the study groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>TTS (n = 19)</th>
<th>STEMI (n = 10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>75.0 (65.5–78.0)</td>
<td>59.5 (58.0–60)</td>
<td>0.0058</td>
</tr>
<tr>
<td>Female sex (n, %)</td>
<td>19 (100)</td>
<td>10 (100)</td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>41 (35–47)</td>
<td>51 (45–54)</td>
<td>0.1122</td>
</tr>
<tr>
<td>Copeptin (ng/mL)</td>
<td>0.49 (0.45–1.21)</td>
<td>1.55 (1.34–1.65)</td>
<td>0.002</td>
</tr>
<tr>
<td>TnI at admission (mg/dL)</td>
<td>1.46 (0.40–2.93)</td>
<td>0.18 (0.04–0.38)</td>
<td>0.034</td>
</tr>
<tr>
<td>peak TnI (mg/dL)</td>
<td>1.33 (0.51–3.24)</td>
<td>30.10 (25.25–36.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>4538 (1798–9205)</td>
<td>1491 (1329–1690)</td>
<td>0.013</td>
</tr>
<tr>
<td>Copeptin/NT-proBNP ratio</td>
<td>1.28·10^{-4} (4.94·10^{-5}–4.98·10^{-4})</td>
<td>1.05·10^{-3} (795·10^{-4}–1.36·10^{-2})</td>
<td>0.002</td>
</tr>
</tbody>
</table>
All patients were postmenopausal females. The median age was 75 years in the TTS group and 59.5 years in the STEMI group. There were not differences in estimated glomerular filtration rate (eGFR) between patients with STEMI and TTS. eGFR was normal in all patients.

All patients with TTS were found to suffer from its typical form (apical ballooning). Laboratory analysis in the TTS group, revealed significantly lower levels of peak TnI and higher levels of NT-proBNP compared to patients with STEMI.

Copeptin release

As shown in Table 1, the copeptin concentrations were significantly lower in the TTS patients than in the STEMI patients. Serum copeptin concentrations at presentation effectively identified patients with STEMI (AUC = 0.85, 95% CI: 0.71–1.00). Serum copeptin concentration >1.306 mg/mL was the best cut-off value to identify patients with STEMI (a sensitivity of 90% and specificity of 79%) (Fig. 1).

The ratio of copeptin to NT-proBNP and TnI

The data on incremental ability of biomarkers and their ratios to distinguish TTS from STEMI are presented in Fig. 2. The diagnostic accuracy in that case is highest for copeptin/NT-proBNP ratio, copeptin/TnI at admission ratio and copeptin alone (AUC 0.8713, 0.8538, 0.8480, respectively).

<table>
<thead>
<tr>
<th>Variable</th>
<th>TTS (n = 19)</th>
<th>STEMI (n = 10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copeptin/TnI at admission ratio</td>
<td>0.50 (0.21–1.13)</td>
<td>8.51 (5.78–39.00)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms (h)</td>
<td>8 (6–21)</td>
<td>2 (2–4)</td>
<td>0.8459</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>13 (68)</td>
<td>5 (50)</td>
<td>0.3312</td>
</tr>
<tr>
<td>Hyperlipidemia (n, %)</td>
<td>13 (68)</td>
<td>4 (40)</td>
<td>0.1396</td>
</tr>
<tr>
<td>Tobacco use (n, %)</td>
<td>4 (21)</td>
<td>8 (80)</td>
<td>0.0022</td>
</tr>
<tr>
<td>Diabetes mellitus (n, %)</td>
<td>4 (21)</td>
<td>2 (20)</td>
<td>0.9469</td>
</tr>
<tr>
<td>Obesity (n, %)</td>
<td>3 (16)</td>
<td>2 (20)</td>
<td>0.7754</td>
</tr>
<tr>
<td>Family history (n, %)</td>
<td>3 (16)</td>
<td>3 (30)</td>
<td>0.3692</td>
</tr>
</tbody>
</table>

Continuous variables are presented as median with interquartile range (IQR). Categorical variables are shown as number and percentages and analysed using the Fisher’s exact test. A p-value <0.05 was considered statistically significant.
Fig. 1. Receiver operator characteristic (ROC) curve for copeptin for the differential diagnosis of STEMI.

Discussion

Copeptin was investigated as a novel marker for non-invasive differentiation between TTS and STEMI. The results clearly indicate that the serum copeptin concentrations were significantly lower in the patients with TTS compared to the patients with STEMI. Burgdorf et al. [16] reported elevated serum copeptin levels only in approximately 50% of patients with TTS. In patients with a typical (apical) ballooning pattern significantly lower levels of copeptin were found. These conflicting results and low copeptin levels in the TTS patients investigated in the present study suggest that the arginine vasopressin (AVP) system (and copeptin) is not responsible for the development of TTS. The pathogenic mechanism of TTS is still not fully understood.
Sympathetic hyperactivity, as well as coronary vasospasm, microcirculatory disorder, and oestrogen deficiency have been considered as the most likely pathogenic mechanisms of TTS [17, 18].

TTS is a distinctive reversible cardiomyopathy that mimics AMI and a differential diagnosis is required in patients with an apparent ACS. Serum levels of a variety of biomarkers including copeptin [19, 20], ratios of serum NT-proBNP/myoglobin, NT-proBNP/TnI have been recently proposed for the differentiation between these two conditions [6, 7]. Both TTS and STEMI are characterised by elevated cardiac troponin I and T and creatinine kinase — MB (CKMB), but the mechanisms leading to the release of these markers are different. In TTS, the elevation in cardiac markers is usually mild and not associated with ischaemia and subsequent necrosis of cardiomyocytes.
On the other hand, copeptin levels are significantly higher in patients with STEMI than in patients with TTS presenting early to the emergency department. There are several hypotheses to explain the release of copeptin after AMI. The most possible explanation is that myocardial injury triggers neuroendocrine changes that result in the rapid release of copeptin into the circulation [13]. Also, inadequate filling of the left ventricle caused by AMI stimulates cardiac baroreceptors or causes direct damage to baroreceptors which subsequently leads to AVP and copeptin secretion from the posterior pituitary gland [21].

Summing up, it seems that the combination of NT proBNP and copeptin levels may provide additional information improving the diagnostic accuracy in both TTS and STEMI.

**Conclusions**

Copeptin is released into the circulation in STEMI but not during an early phase of TTS. Copeptin seems to be a good marker partner for NTproBNP to use in combination for prompt differentiating between TTS and STEMI. The serum copeptin to NTproBNP ratio seems to be an additional, useful tool in the non-invasive differentiation between TTS and STEMI.

**Limitations**

This is a single-centre study with a relatively small sample size. However, in this preliminary study we have obtained interesting results and further research will be continued.

**Conflict of interest**

None declared.

**References**


