and the “Duplicate/Update” label has been renamed “Update,” as some users expressed concern over the word “Duplicate.” With these changes in mind, we would like to emphasize that the ultimate purpose of the De`ja` Vu database is to maintain the integrity of biomedical literature, a goal that can be achieved only by a thorough and accurate interpretation of the information contained within. We therefore extend to both the editors and reviewers of Clinical Chemistry an invitation to explore the De`ja` Vu database and its accompanying text similarity tool, eTBLAST (http://etblast.org), to help identify future submissions of questionable manuscripts before they are published.

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References


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Copeptin Response to Clinical Maximal Exercise Tests

To the Editor:

Copeptin (the glycosylated 39–amino acid C-terminal fragment of the arginine vasopressin (AVP)1 precursor peptide), when measured with a novel assay (1), has emerged as a promising marker for the early diagnosis of acute myocardial infarction (MI) (2) and a powerful prognostic marker in a variety of settings. The underlying mechanism is thought to be the role of copeptin as a measure of a high individual stress level (3). Interestingly, exercise seems to elicit a significant increase in circulating copeptin concentrations within minutes (4). The aim of our study was to assess the copeptin response to exercise and its determinants.

We studied 414 consecutive patients undergoing myocardial perfusion scintigraphy (n = 253) or cardiopulmonary exercise testing (CPET) (n = 161) with upright symptom-limited cycle ergometer tests (increments of 10–25 W/min). In the CPET cohort, arterial samples for blood gas analysis were obtained at rest and peak exercise and

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We studied 414 consecutive patients undergoing myocardial perfusion scintigraphy (n = 253) or cardiopulmonary exercise testing (CPET) (n = 161) with upright symptom-limited cycle ergometer tests (increments of 10–25 W/min). In the CPET cohort, arterial samples for blood gas analysis were obtained at rest and peak exercise and
were analyzed immediately. In all patients, venous blood was drawn immediately from a catheter in an antecubital vein with the patient in the seated position (rest) before the test and immediately after test termination (peak exercise). These samples were collected in EDTA-containing tubes, placed on ice, and centrifuged at 3000g. Plasma samples were stored at −80 °C. Approximately 1 year after sample collection, a laboratory technician who had been blinded to the clinical data measured copeptin in the samples with a sandwich immunoluminometric assay (CT-proAVP LIA; BRAHMS, Hennigsdorf/Berlin, Germany) (1). A mean measured copeptin concentration of 97.6% of the original concentration after 14 days demonstrated the stability of the analyte in EDTA-containing plasma for at least 14 days at room temperature. Four cycles of freezing and thawing have been shown not to affect the analyte (1).

The mean age (SD) of the study population was 60 years (13 years). Of the study participants, 66% were male, 47% had known coronary artery disease, and 15% had chronic obstructive pulmonary disease. The mean exercise time was 6.3 min (2.0 min), the mean peak work rate was 1.72 W/kg (0.60 W/kg) body weight, and the mean percentage of the age-predicted peak heart rate was 90% (13%). The median resting copeptin concentration for the entire study population was 4.6 pmol/L (interquartile range, 3.1–7.8 pmol/L). The copeptin concentration increased significantly \( P < 0.001 \) from rest to peak exercise (Fig. 1), with a median percent increase of 59% (interquartile range, 14%–259%). Aspirin use \( \text{OR} = 2.71; 95\% \text{CI} = 1.54–4.79; P = 0.001 \), angiotensin-converting enzyme inhibitor use \( \text{OR} = 2.44; 95\% \text{CI} = 1.40–4.25; P = 0.002 \), nitrate use \( \text{OR} = 2.62; 95\% \text{CI} = 1.22–5.63; P = 0.014 \), a higher percentage of the age-predicted peak heart rate \( \text{OR} = 1.04 \text{per 1\% increase}; 95\% \text{CI}, 1.02–1.07; P = 0.001 \), and a higher body weight–indexed maximal work rate \( \text{OR} = 2.48 \text{per 1-W/kg increase}; 95\% \text{CI}, 1.60–3.83; P < 0.001 \) were independently associated with the percent change in copeptin in the highest quartile (quartile 4). In the CPET subgroup, a history of previous MI \( \text{OR} = 7.51; 95\% \text{CI}, 2.20–25.65; P = 0.001 \), a higher partial pressure of oxygen in arterial blood at rest \( \text{OR} = 1.07 \text{per 1-mmHg increase}; 95\% \text{CI}, 1.01–1.10; P < 0.001 \), and a higher increase in lactate \( \text{OR} = 1.43 \text{per 1-mmol/L increase}; 95\% \text{CI}, 1.22–1.67; P < 0.001 \) were independently associated with the percent change in copeptin concentration in quartile 4.

The mechanisms underlying the rapid increase in copeptin during exercise may include osmotic and nonosmotic AVP release and AVP release in the context of the stress response. In this study, several cardiac medications were independent predictors of a high percent change in copeptin, presumably by virtue of their surrogate status for the presence of coronary artery disease, previous MI, left ventricular dysfunction, and a higher (nonosmotic) AVP-release capacity. In addition, measures of both a higher absolute exercise capacity (work rate) and a higher exercise intensity (heart rate, lactate) were associated with a high percent change in copeptin concentration. The association between higher exercise intensity and copeptin release may be explained in 2 ways. First, longer and more-strenuous exercise is likely to be associated with higher stress and, presumably, AVP release. Second, the intensity-dependent increase in AVP during exercise has previously been attributed to changes in plasma osmolality occurring at higher exercise intensities due to hypotonic fluid movement from the intravascular to the extravascular space following metabolite accumulation in the muscle tissues (5). Given that changes in plasma osmolality, sodium, and lactate have been shown to occur in parallel in healthy people (5), we speculate that changes in lactate in this context reflect changes in osmolality. These data indicate that exercise before venipuncture has to be taken into account as a mechanism causing falsely high copeptin concentrations in patients with acute chest

![Fig. 1. Plasma copeptin concentrations at rest and at peak exercise.](image-url)

Box plots represent the median and interquartile range of copeptin concentrations (whiskers, 10th and 90th percentiles; circles, fifth and 95th percentiles). Note logarithmic scale.
Letters to the Editor

pain who are undergoing evaluation for MI.

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References


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Coprivalence of Autoantibodies to Cardiac Troponin I and T in Normal Blood Donors

To the Editor:

We recently reported the high frequency of plasma and serum samples with increased concentrations of IgG reactive to cardiac troponin I (cTnI1; 12.7%) (1) or T (9.9%) (2) in normal blood donor cohorts. Whereas the presence of autoantibodies to cardiac troponin I (α-cTnI) has been highlighted as a potential source of false-negative cTnI immunoassay results (3), the stabilizing effect of α-cTnI on the circulating half-life of cTnI has been much less explored (4). The former may result in delayed diagnosis of acute myocardial infarction (AMI) on presentation, while the latter may require additional diagnostic testing to reconcile the cTnI measurement with clinical observations, thus prolonging the duration of care, with its attendant cost. When such discordant results are noted, additional information from related biomarkers, particularly cTnT, is often used to clarify the findings. With the high prevalence of α-cTnT (2), however, one must question the significance of a negative or positive cTnT value that contradicts that of cTnI. With that in mind, we report here the coprivalence of autoantibodies to both cardiac troponin I and T in plasma and serum samples in a normal donor cohort.

We obtained frozen plasma or serum samples from normal blood donors (n = 345), all of which had been approved by an institutional review board for research use, from the Abbott Laboratories specimen bank and thawed them at 2–8 °C before use. We analyzed the samples using direct chemiluminescent microplate assays for α-cTnI (1) and α-cTnT (2).

The normal donor population could be categorized into 4 groups based on the signal-to-low control (S/LC) response of the α-cTnI and α-cTnT (Table 1). Samples were considered pos-

1 Nonstandard abbreviations: cTn, cardiac troponin; α-cTnI, autoantibody to cTnI; AMI, acute myocardial infarction; S/LC, signal to low control.