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References


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Circadian Secretion Pattern of Copeptin, the C-Terminal Vasopressin Precursor Fragment

To the Editor:

Copeptin, the C-terminal peptide of provasopressin, is stoichiometrically released with arginine vasopressin (AVP). In contrast to AVP, it is stable ex vivo (1) and reflects the AVP system, as shown in diabetes insipidus or the syndrome of inappropriate antidiuretic hormone secretion (2). Copeptin is a reliable marker of severe stress, with increased concentrations found in cases of critical illness, sepsis, hemorrhagic shock, and stroke (2). The serum copeptin concentration is profoundly and immediately stimulated after myocardial infarction (3). The absence of such stimulation within the first hours after the onset of symptoms has recently been proposed as an important negative predictor for excluding the likelihood of infarction in patients with unspecific chest pain (3).

Any further use of the peptide as a marker critically depends on clear cutoffs between health and disease. To better characterize the diagnostic accuracy of copeptin, we studied its physiological pulsatile and circadian variation in healthy individuals and compared copeptin rhythms with those of cortisol in these patients.

Blood for copeptin analysis was sampled every 20 min for 24 h (0900 to 0900) in 7 healthy individuals (1 female, 6 males; age range, 18–37 years; mean body mass index, 22.6 kg/m²). Sera were separated and immediately frozen at $-80\,^\circ\mathrm{C}$. The study was approved by the local research ethics committee.

Serum copeptin was measured with a chemiluminescence sandwich immunoassay [lower detection limit, 0.4 pmol/L; functional assay sensitivity at $<20\%$ interassay CV, $<1$ pmol/L; see (1)]. Cortisol was measured immunometrically (Bayer Immuno 1™ System, Bayer Corp.) according to manufacturer’s instructions. The maximal inter- and intraassay CVs were 6.5% at a copeptin concentration of 4.1 pmol/L and 7.9% at a cortisol concentration of 88 nmol/L (4).

We used a clustering algorithm to analyze attributes of the copeptin concentration profiles (fixed CV of 10%; $t$ statistic for an upstroke/downstroke $1$; cluster size for test peak/nadir $1$) provided optimal peak detection ($>90\%$ sensitivity and positive predictive accuracy) (5).

Copeptin concentrations showed no consistent circadian rhythm.

![Fig. 1. Individual 24-h copeptin rhythms for 7 healthy individuals.](image-url)
Peaks and troughs of the individual rhythms varied widely over the 24-h period with no evidence of synchronization among individuals or a clear relationship with the light–dark cycle [mean (SD) copeptin concentration, 4.3 (1.5) pmol/L; 11.4 (3.6) pulses/24-h period; mean pulse height, 5.1 (1.8) pmol/L] (Fig. 1). Interestingly, the expected large increase in cortisol during the second half of the night in these individuals [see (4)] is not related to copeptin. Because AVP is known to acutely stimulate cortisol via corticotropin release in stress situations, our present findings argue against both a role of AVP in the circadian release of cortisol and an important physiological role of AVP in the generation of cortisol pulses under nonstress conditions.

The highest copeptin concentration measured was 13.1 pmol/L; the mean maximum concentration for all individuals was 7.8 (2.9) pmol/L. Therefore, the variation in circadian copeptin concentration in healthy individuals remained well within the described reference interval (1). The timing of blood sampling did not appear as critical as for the interpretation of cortisol results. Our data will help to better define reference values for the use of copeptin measurements in predicting stress conditions. Reference values may be particularly important when a low copeptin concentration is used as a very early negative predictor in stress situations such as myocardial infarction (3), in which the physiological variation in copeptin has little influence on the interpretation of the results.

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Evaluation of the Quo-Test Hemoglobin A₁c Point-of-Care Instrument: Second Chance

**To the Editor:**

We previously reported the evaluation of 8 different hemoglobin A₁c (Hb A₁c) point-of-care instruments (1). Two of 8 manufacturers withdrew from that study after initial unpromising results. One of the 2 instruments withdrawn was the Quo-Test A₁c (Quotient Diagnostics), which was withdrawn because of a technical problem. The manufacturer claimed to have resolved the problem and asked us to reevaluate the instrument.

The Quo-Test method is based on affinity separation and the use of fluorescence quenching and gives results in 3 min. The instrument was certified by the National Glycohemoglobin Standardization Program (NGSP) as of September 2009 (2).

We used the same approach for evaluation as in the initial study, following the CLSI EP-5 protocol for imprecision and the CLSI EP-9 protocol for method comparison. Because the American Diabetes Association has recommended Hb A₁c as the preferred test for the diagnosis of diabetes (3), we added an additional sample of approximately 6.5% Hb A₁c in the EP-5 protocol. The EP-9 protocol was performed twice with 2 different lot numbers and compared