Copeptin Reflects Thermal Strain during Exercise in a Hot Environment

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INTRODUCTION AND OBJECTIVES

Exertional Heat Illness (EHI) is an incapacitating and sometimes fatal phenomenon that affects both military and civilian populations. Elevated core temperature (Tc) is a defining criterion of EHI and preventive guidelines recommend maintaining Tc ≤38.0 °C during physical activity in the workplace. Tc=38 °C is an important thermal threshold, above which pronounced excursions in pituitary and adrenal hormones occur.[1]

Copeptin is the C-terminal component of the arginine vasopressin (AVP) precursor peptide. Copeptin is secreted in equimolar amounts to AVP in response to elevated plasma osmolality and also with non-osmotic stimuli such as release of noradrenaline. Copeptin is a valid and practical surrogate for AVP following extreme exertion[2] and also in pathological states involving physiological stress (sepsis, myocardial infarction), where it is may have prognostic value at Point Of Care. A relationship between copeptin and thermal strain has not been reported.

The primary aim of this study was to investigate for an interaction between plasma copeptin and Tc during physical exertion in the heat. The secondary aim was to explore concurrent plasma osmolality and normetadrenaline responses.

METHODS

The study was approved by the UK Ministry of Defence Research Ethics Committee and complied with the Declaration of Helsinki. Volunteers were British Army soldiers taking part in a military exercise in East Africa. Fifteen volunteers underwent study measures in relation to a training assault, which involved prolonged non-steady state exercise from 0700h to 1130h on day 6 in a hot field environment.

During the training assault, Tc was measured by ingested telemetric pill, which logged locally every 60 s. Volunteers were weighed by digital scale and provided blood samples (20 ml) before (PRE) and after (POST) the assault. These were stored in ice and centrifuged within 1 h of collection. Samples of plasma and sweat were immediately frozen to -20.0 ° C and remained frozen during transportation.

In the UK, plasma copeptin (BRAHMS Kryptor CT-proAVP sandwich immuno-fluorescent assay) plasma osmolality (suppression of freezing point method), and plasma free normetadrenaline (liquid chromatography/ tandem mass spectrometry) were measured.

Appropriate parametric or non-parametric statistical tests were applied after exploring the data for normality. Responses were compared by category, from PRE to POST and after a median split according to TcMax (> or ≤38.0 ° C).

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RESULTS AND CONCLUSIONS

Mean Tc was 37.1±0.2 ° C at the start of the assault, rising to a maximum (TcMax) of 38.1±0.4 ° C. From PRE to POST, body mass fell (77.1±8.2 kg vs 75.9±8.1 kg, P<0.001). A rise in plasma concentration was observed for copeptin (10.0±6.3 vs 16.7±9.6 pmol.L^{-1}, P<0.001, Figure 1) and normetadrenaline (350±157 vs 576±169 pmol.L^{-1}, P<0.0001) but not for plasma osmolality (291±4 vs 292±4 mosm.kg^{-1}).

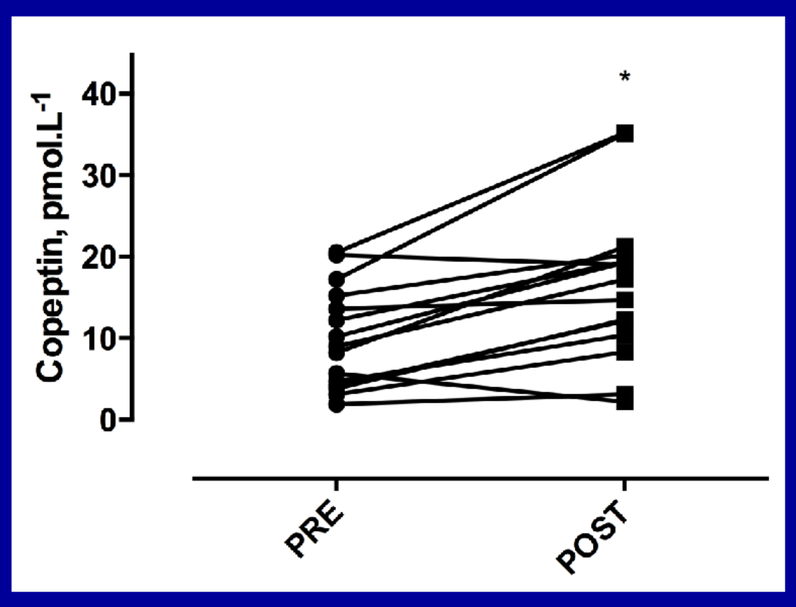

Figure 1: Plasma Copeptin in 15 volunteers, PRE vs POST training assault in a hot environment.*P<0.001, paired t-test.

In the eight volunteers with TcMax >38.0 ° C vs seven volunteers with TcMax ≤38.0 ° C, Δ copeptin (10.4±4.3 vs. 2.4±4.2 pmol.L^{-1}, P<0.01, Figure 2) and Δ normetadrenaline (275±150 pmol.L^{-1} vs 169±73, P<0.05) were greater, whereas Δ osmolality (2±5 vs -1±4 mosm.kg^{-1}) and % Δ body mass (-1.8±1.4 vs -1.2±1.1) did not differ.

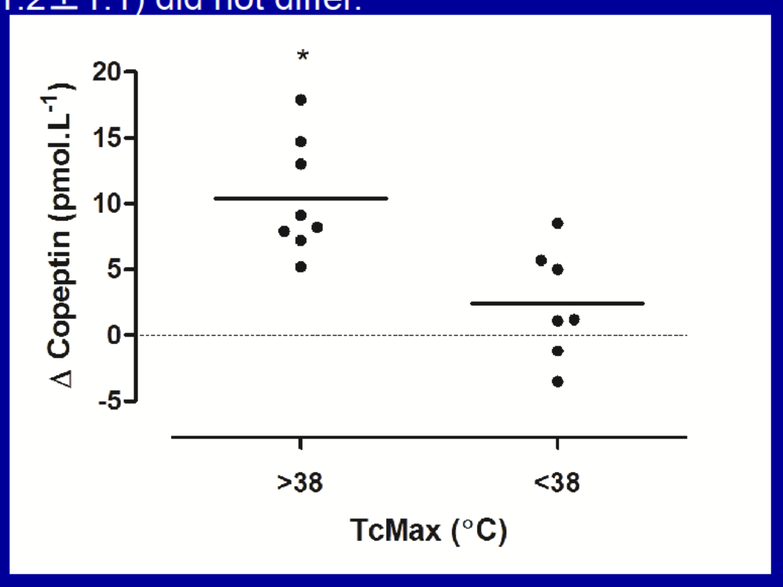

Figure 2: Change in plasma Copeptin in 15 volunteers according to TcMax > or ≤ 38 ° C. *P<0.01, Mann Whitney test.

Two-way ANOVA for repeated measures by time (PRE to POST) vs group (TcMax > or ≤38.0 ° C) showed an interaction for Δcopeptin (F=13.53, P<0.01). No interaction was demonstrated for Δosmolality or Δnormetadrenaline.

Copeptin and osmolality were weakly associated prior to exercise (PRE: Pearson r=0.46, P=0.08) and this relationship was strengthened following exercise (POST: Pearson r=0.70, P<0.01, Figure 3).

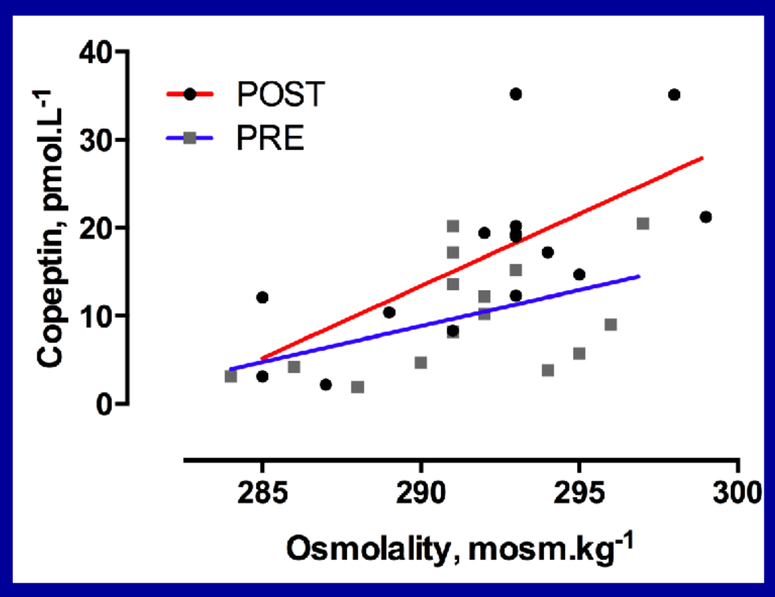

Figure 3: Correlation between Copeptin and Osmolality in 15 subjects, PRE (r=0.46, P=0.08) and POST (r=0.70, P<0.01).

The key finding of this study was that Δcopeptin differentiated thermal strain according to the EHI-preventive threshold of 38.0 ° C. There was a rise in normetadrenaline concurrent to the rise in copeptin, but no change in osmolality. These results could be compatible with non-osmotic secretion of AVP/copeptin, which is a recognised response to noradrenergic stimulation, or may indicate a change in the relationship between AVP/copeptin and osmolality during the training assault.

The osmotic sensitivity of AVP release is known to rise following passive heating.[3] The increase in copeptin per unit rise in osmolality from PRE to POST (Figure 3) shows that this may also occur in response to exercise in a hot environment. Under such conditions, Δcopeptin may be of utility in stratifying thermal exposures, particularly where continuous telemetric monitoring of Tc is not feasible. Further studies are required to determine the practical validity of copeptin as a biomarker for thermal strain. The potential for fever to confound the use of copeptin in clinical practice is also highlighted.

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