**The copeptin response after physical activity is not associated with cardiac biomarkers or asymptomatic coronary artery disease**

**Running head:** Copeptin response after physical activity

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**Conflicts of Interest**

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## Abstract

**Background:** Copeptin concentrations increase both during acute coronary syndrome and following physical exercise. The relationship between copeptin increase following physical exercise and coronary artery disease (CAD) is uncertain. The aim of this study was to 1) describe the copeptin response following strenuous physical exercise, and 2) investigate the determinants of exercise induced copeptin concentrations, particularly in relation to cardiac biomarkers and CAD.

**Methods:** Serum samples were collected from 97 recreational cyclists 24 hours before, and immediately, 3 and 24 hours after a 91-km bike race. Three subjects were subsequently diagnosed with significant asymptomatic CAD. Delta copeptin concentrations were correlated to patient characteristics and to biomarker concentrations.

**Results:** Participants were 42.8 ± 9.6 years, and 76.3 % were male. Copeptin concentrations increased to maximal levels immediately after the race and were normalized in > 90% after 3 hours. A total of 53 % and 39 % exceeded the 95th and 99th percentile of the assay (10 and 19 pmol/L) respectively. In multivariate models, race time, serum sodium, creatinine and cortisol were significant predictors of copeptin levels. There was no correlation between changes in copeptin and changes in cardiac biomarkers (hs-cTnI, hs-cTnT and BNP). Copeptin concentrations were normal in the subjects with asymptomatic CAD.

**Conclusions:** The moderate, short-term, exercise induced copeptin increase observed in the present study was not related to hs-cTn or BNP levels. Copeptin was normal in three asymptomatic recreational athletes with significant CAD.

**Keywords:** endurance exercise, coronary artery disease, physiological response, antidiuretic hormone, cardiac pathophysiology, troponin

**Introduction**

Ischemic heart disease is the leading cause of sudden cardiac death during exercise among recreational athletes (1). An increase in circulating cardiac troponins (cTn) is the hallmark of myocardial necrosis and a part of the definition of myocardial infarction (MI) (2). However, cTn may also increase without evidence of necrosis; numerous studies have demonstrated significant increase in cTn following physical exercise in healthy athletes (3). The exercise induced cTn response represents a diagnostic challenge since it can mask cTn increase due to coronary artery disease (CAD) (4). It is therefore of major interest to develop diagnostic algorithms that can identify significant CAD in asymptomatic athletes and allow a better differentiation between a physiological and pathological cTn response following physical activity.

C-terminal pro-vasopressin (copeptin) is a part of the pre-pro hormone for vasopressin and an indirect marker of vasopressin. Copeptin reflects hemodynamic and endocrine stress level in several conditions including acute MI (5-7). Copeptin has been shown to increase 30 min following induced MI (8). Copeptin adds to conventional cTn assays in the early rule out of non-ST elevation acute coronary syndrome (NSTE-ACS) (9-13) and has been proposed as an additional biomarker of NSTE-ACS in the most recent (2015) European Society of Cardiology guidelines (14).

The primary purpose of the present study was to determine the potential role for copeptin in differentiating between a pathological and a physiological cardiac response following strenuous physical exercise in asymptomatic recreational athletes. First, we describe the physiological copeptin response in presumably healthy individuals after an endurance exercise competition. Secondly, we aimed to investigate the major determinants of the copeptin response, particularly with regards to the correlation with cardiac biomarkers. Finally, we have included a description of three subjects who were subsequently diagnosed with significant CAD, in order to understand the value of exercise induced copeptin concentrations in the setting of cardiac pathology.

## Methods

The current study is a part of the North Sea Race Endurance Exercise Study (NEEDED) conducted in 2013. Details regarding the study design and data collection have been described earlier (4, 15). Briefly, the NEEDED 2013 is a study of the biomarker response to strenuous physical exercise in presumably healthy, asymptomatic recreational athletes. A total of 97 cyclists provided written informed consent and were included in the study. Blood was sampled the day before and immediately (within 15 minutes), 3 and 24 hours after a 91-km mountain-bike race. Based on unexpected large increases in cTnI 13 subjects were investigated with coronary angiography and significant CAD was detected in three cyclists. Two of the three subjects were treated by revascularization (percutaneous coronary intervention). The third subject had a thrombotic infarction due to plaque rupture, and there was no need for further coronary intervention in this individual. The study was approved by the regional ethics committee (2013/550/REK vest).

### Biomarker analysis

Serum samples were frozen and stored at -80 degrees Celsius until being thawed and analysed utilizing a high sensitive copeptin assay at Kryptor Compact Plus (B.R.A.H.M.S GmbH, Thermo Fisher Scientific, Hennigsdorf, Germany), (lower limit of detection of 0.9 pmol/L and a 95th and 99th percentile of 10 and 19 pmol/L, respectively (10)). High sensitive cTnT was measured on Cobas e602 (Roche Diagnostics, Basel, Switzerland) (limit of blank 3 ng/L, 10% analytical CV at 13 ng/L and 99th percentile of 14 ng/L (16)). The other biomarkers including high sensitive cTnI (limit of detection > 1.6 ng/L, 10% analytical CV at 5 ng/L and 99th percentile of 26 ng/L (16)), cortisol and BNP were analyzed using Architect i2000SR (Abbott Diagnostics, Illinois, USA), while creatinine, sodium, albumin and CRP were analyzed using Architect c16000TM. Hematocrit was analyzed using XE-5000 (Sysmex, Kobe, Japan). Analytical performance, measuring range and reference intervals for the different biomarkers are specified in table 3, supplemental data.

The 97.5 percentile for the copeptin concentration after physical exercise was calculated to illustrate a normal copeptin response after physical activity. The concentrations were also was compared to the 95th and 99th percentile found in a healthy population at rest (i.e. 10 and 19 pmol/L), since these are commonly used as diagnostic threshold for signaling a possible acute ischemic myocardial event (2, 12, 17).

### Statistics

Continuous variables are reported as mean ± standard deviation (SD) or median with the interquartile range (IQR), if data distribution was non-normal. Normality was determined by Shapiro-Wilk test. The distributions of most variables were markedly skewed. We therefore chose to use non-parametric statistical tests. Differences in biomarker concentrations at the different sampling points were evaluated using the Friedman test. Significant differences between genders were evaluated by Mann-Whitney U test (continuous variables) or Pearson Chi-Square test (categorical variables). Bivariate correlations were assessed by Spearman rank correlation. Multiple regression analysis was performed when residuals were normally distributed, using an enter model. The change in copeptin concentrations from baseline to peak (immediately after the race) was used as the dependent variable. Independent variables included gender, obstructive CAD and variables that were bivariate correlated to the delta copeptin value (with a p-value <0.1). Independent fixed variables (age, sex, CAD, race time) are presented as is. For the biomarkers are delta values used as independent variables, representing changes from baseline to immediately after the race (peak values for albumin, creatinine, cortisol and hematocrit, minimum value for sodium). The residuals of the independent variables were normally distributed. A p-value of less than 0.05 was considered statistically significant. Statistical analysis was done using SPSS vs. 23.0 and 24.0.

## Results

Patient characteristics are outlined in Table1. In short, participants were 42.8±9.6 years, and 76.3 % were male.

### The copeptin profile following exercise

Copeptin concentration increased to maximal levels immediately after the race (Figure 1), with a median delta value of 9.8 (IQR 1.4-24.6) pmol/l. The upper 97.5 percentile of the copeptin concentrations at each time-point were: 13.0 pmol/L (baseline), 103.2 pmol/L (0 hours), 27.0 pmol/L (3 hours) and 17.1 pmol/L (24 hours). The response was highly variable amongst participants. Compared to the 95th and 99th percentile for the assay in healthy individuals at rest (i.e. 10 and 19 pmol/L) 53% and 39% of the cohort showed elevated copeptin concentrations immediately after the race, falling to 18% and 6 % after 3 respectively. After 24 hours did 14% have concentrations over 10 pmol/L and only one person (male) had a concentration above 19 pmol/L. Fewer women compared to men exceed the 95th percentile for the assay at all measurement points. Women had overall lower copeptin concentrations at all sampling time-points, see supplemental data, table 2.

### Profiles of other biomarkers following exercise

Serum cortisol, albumin, hematocrit, creatinine and cTnT reached maximum levels, whereas sodium reached minimum levels immediately following the race (table 2). cTnT concentrations exceeding the 99th percentile for the assay (i.e.14 ng/L) in 96 % of study subjects (n=93). cTnI reached maximum concentration 3 hours post-race exceeding the 99th percentile for the assay (i.e. 26 ng/L) in 82 % of study subjects (n=80). Serum BNP and CRP reached maximum levels 24 hours following the race.

### Predictors of copeptin levels following physical exercise

In the bivariate analysis the copeptin increase from baseline to immediately after the race was positively correlated with age (r=0.29, p=0.004), and negatively correlated with race duration (r= -0.29, p=0.004). The delta copeptin concentration was further significantly correlated with delta- sodium, creatinine, cortisol, haematocrit and albumin concentrations (Table 1, Supplemental data). Other relevant participant characteristics like body mass index, blood pressure measurements, training history, resting heart rate or mean heart rate during the race were not correlated to the increase in copeptin concentration. There was no correlation between the increase in copeptin and delta- cTnI, cTnT, BNP and CRP concentrations (Table 1, Supplemental data). In the multivariate model the following variables were independent predictors of increased copeptin concentrations immediately following the race: race time, delta- sodium, creatinine and cortisol concentrations (R2=0.48, p<0.001) (Table 2).

### Copeptin concentrations in study subjects with asymptomatic coronary artery disease

In the three study subjects with CAD, maximum cTnI values ranged from 380 to 2081 ng/L, and maximum cTnT from 75 to 240 ng/L. None of the three subjects had any signs or symptoms of CAD. The copeptin levels of the three participants with CAD were within the normal distribution of the cohort at all time-points (Figure 1). The copeptin concentrations were below the 95th percentile (10 pmol/L) of the assay at all time-points, with the exception of one measurement of 13 pmol/L, acquired immediately after the race.

**Discussion**

The copeptin increase following strenuous physical exercise in the present study was moderate, of short duration and related to race duration, increase in serum sodium, creatinine and cortisol concentration. There was no correlation between copeptin and cTn, BNP and CRP levels. Copeptin levels were low in three individuals with significant CAD. The present study does not support the use of copeptin to identify occult CAD in asymptomatic recreational athletes.

Copeptin concentrations are expected to increase shortly after physical activity (18-27). However, this is the first study reporting serial copeptin measurements for 24 hours following physical activity in a large cohort of presumably healthy subjects. Earlier studies included from 10 to 50 subjects (19, 21-23, 26) and blood was usually sampled once immediately after exercise (19, 21, 22, 27). The present study population differs from former studies that included a substantial number of patients with depression (24) or suspected coronary disease (18, 20, 24, 25). Our study also showed lower post-race increase in copeptin concentrations compared to some earlier studies. Lippi at al found that copeptin levels exceeded the upper reference limit in 13 of the 16 men participating in an ultramarathon (19). A study of 50 men participating in a 100 km ultramarathon showed post-race increases in copeptin of more than 1200% (22). Activity with lower physical load (e.g. cardiopulmonary exercise stress testing and participation in a footrace) lead to copeptin increases that were similar or lower compared to our findings (18, 20, 24, 25, 27).

The copeptin increase in our study was positively correlated with the increase in cortisol and the reduction in sodium (22, 27); underscoring that the copeptin response after exercise is driven by non-cardiac physiological mechanisms such as general stress and changes in the salt balance (28-30). This was expected since copeptin is part of the pre-pro hormone of vasopressin crucial for regulating the in vivo sodium concentration. The copeptin increase was also linked to increased creatinine concentration. There is a temporarily reduction in glomerular filtration during strenuous activity (31) which is closely linked to hydration status and copeptin secretion(32).

There were substantial changes in a large range of other biomarkers, including CRP and cTn and BNP. No evidence of a direct relationship between copeptin, cTn levels and CRP could be found. The dominating theory at present is that physical activity causes a reversible cardiomyocyte damage that temporarily increases the permeability of the cell membrane leading to release of soluble cTn molecules from the cytosol (3, 33). The lack of correlation between copeptin and cardiac biomarker responses underscores that there is no link between this process and the osmotic and stress mediated mechanisms causing the activity related copeptin increase.

The increase in copeptin during acute myocardial infarction is thought to relate to systemic stress induced by ischemic symptoms and the hemodynamic consequences of reduced myocardial function with subsequent neurohormonal activation (34). In the present study, the copeptin response was low and of short duration in the three subjects with asymptomatic CAD, even though these subjects probably had some degree of myocardial ischemia (4).This is in agreement with earlier findings that showed that the copeptin response after an exercise stress did not predict ischemia (20). Another recent publication did not find any trans-coronary copeptin gradient despite significantly elevated systemic copeptin levels supporting that there is no direct relationship between myocardial stress and systemic copeptin levels (35).

## *Limitations*

The current study was limited to three points of measurement during a post-race follow up of 24 hours. More frequent sampling within the first three hours post-race could have given additional information regarding the curve for decreasing copeptin concentrations. Another limitation is that we did not measure the plasma volume. Such measurements could have broadened our understanding of the copeptin release due to physical activity and should be undertaken in future studies. Only 13 subjects were investigated with cardiac imaging and only three athletes were diagnosed with CAD. The low number adds uncertainty to our conclusion, but the findings were consistent; they all had persistently low copeptin levels. This finding is also similar to earlier observations (20), and fits well with the theory that a general stress reaction (i.e. “endogenous stress”) is necessary to stimulate a copeptin response during cardiac ischemia.

## *Conclusions*

The present study indicates that the observed increase in copeptin during exercise relates to extra-cardial physiological mechanisms and that copeptin is unlikely to have a role in predicting significant CAD in asymptomatic recreational athletes.

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## Table 1

Baseline characteristics of the study participants (n=97), mean ± SD or median (IQR) for markedly skewed distributions..

|  |  |
| --- | --- |
| **Participant characteristic** |  |
| Gender (male, %) | 74 (76.3) |
| Age (years) | 42.8±9.6 |
| Weight (kg) | 83.4±14.0 |
| Body Mass Index (kg/m2) | 25.3 (23.4-28) |
| Smoker (n, %) |  |
|  Never | 49 (51) |
|  Stopped | 39 (40) |
|  Current | 4 (4) |
| No. of endurance competitions per year past 5 years | 7 (2-16) |
| Hours of training per week past 3 months | 7.0 (5-10) |
| Blood pressure (mmHg) before the race  |  |
|  Systolic | 138 (129-152) |
|  Diastolic | 77 (71-85) |
| Heart rate (beats per minute) |  |
|  Resting heart rate  | 63.0 (56.0-70.0) |
|  Mean heart rate during the race  | 158.0 (148-167.3) |
| Race time (hours) | 4.2 (3.8-4.9) |

**Table 2**

Changes in biomarkers from 24 hours pre-race (baseline) and until 24 hours post-race (mean ± SD, or median (IQR) if markedly skewed distributions). Maximal or minimal values in bold types (n=97).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|   | **Baseline** |  **+0h** |  **+3h** |  **+24h** | **P value\*** |
| Copeptin (pmol/L) | 3.6 (2.5-5.1) | **12.8 (4.6-28.9)** | 4.2 (2.5-9.5) | 5.4 (3.3-7.6) | < 0.001 |
| Cortisol (nmol/L) | 262.4 (215-328) | **645.9 (528-766)** | 220.8 (171-284) | 206.7 (153-244) | < 0.001 |
| Creatinine (µmol/L)  | 82.8 ± 12.7 | **100.7 ± 23.2** | 94.6 ± 18.1 | 83.9 ± 13.2 | < 0.001 |
| Sodium (mmol/L) | 141.0 ± 1.4 | **140.1 ± 2.1** | 140.6 ± 1.5 | 141.1 ± 1.4 | < 0.001 |
| Albumin (g/L) | 44.8 (43-46) | **46.9 (45-48)** | 44.6 (45-47) | 42.7 (41-44) | < 0.001 |
| Hematocrit | 42.6 ± 2.4 | **43.0 ± 2.4** | 41.7 ± 2.2 | 41.7 ± 2.5 | < 0.001 |
| cTnI (ng/L) | 3.3 (2.0-4.8) | 48.6 (27.2-72.0) | **65.8 (38.3-96.5)** | 12.8 (7.9-24.6) | < 0.001 |
| cTnT (ng/L) | 4.1 (3.0-5.5) | 40.9 (25.9-56.5) | **37.4 (24.1-48.3)** | 12.2 (8.3-18.0) | < 0.001 |
| BNP (pg/mL) | 13.7 (19.22) | 18.1 (10-26) | 22.3 (11-37) | **34.7 (21-51)** | < 0.001 |
| CRP (mg/L) | 0.9 (0.5-1.9) | 0.9 (0.5-1.8) | 1.8 (0.8-3.0) | **11.6 (6.0-17.5)** | < 0.001 |

## \*Significant differences between groups were evaluated using Friedman test.

## Table 3

The multiple liner regression analysis (n=97, enter model) with delta copeptin (changes from baseline to immediately after the race) as a dependent variable. Biomarkers used as independent variables are expressed as concentration change from baseline to immediately after the race (peak value for creatinine, cortisol, albumin and hematocrit, minimum value for sodium).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Unstandardized coefficients** | **Standardized coefficients** | **t** | **p-value** |
|  | B | Std. Error | Beta |  |  |
| Age | 0.39 | 0.21 | 0.14 | 1.89 | 0.063 |
| Sex | -9.00 | 5.19 | -0.15 | -1.73 | 0.088 |
| Race time | -5.9 | 2.50 | -0.20 | -2.36 | 0.021 |
| CAD | -12.2 | 11.17 | -0.08 | -1.09 | 0.277 |
| Delta sodium | 2.75 | 1.03 | 0.22 | 2.68 | 0.009 |
| Delta creatinine | 0.58 | 0.15 | 0.38 | 3.92 | <0.001 |
| Delta cortisol | 0.04 | 0.01 | 0.26 | 3.04 | 0.003 |
| Delta albumin | 0.24 | 1.27 | 0.02 | 0.19 | 0.851 |
| Delta hematocrit | 0.03 | 1.46 | 0.00 | 0.02 | 0.986 |

## Figure 1

Copeptin concentrations 24 hours before (BL), and 0, 3 and 24 hours following the race. Horizontal dotted lines represent the 95th and 99th percentile of the copeptin assay (10 and 19 pmol/l). The three participants with obstructive CAD are shown separately. Solid lines represents median (IQR).