Clinical Science (2009) **116**, 257–263 (Printed in Great Britain) doi:10.1042/CS20080140

Gender and renal function influence plasma levels of copeptin in healthy individuals

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ABSTRACT

The present study sought to identify confounding factors for the interpretation of copeptin levels in healthy individuals. The natriuretic peptides are recognized as diagnostic and prognostic tools in HF (heart failure). Interpretation of BNP (brain natriuretic peptide) and NTproBNP (N-terminal pro-BNP) levels is multifaceted as their secretion is influenced by many variables. A newly identified glycopeptide called copeptin is comparable with the natriuretic peptides in the diagnosis and prognosis of HF and as a prognostic biomarker after AMI (acute myocardial infarction). Copeptin, derived from the C-terminal portion of the precursor to AVP (arginine vasopressin), is secreted stoichiometrically with vasopressin, hence it can be used as a surrogate marker of the AVP system. In the present study, 706 healthy volunteers were recruited from a local HF screening study. Participants with a history of cardiovascular disease and those with echocardiographic abnormalities were excluded from the study. Copeptin and NTproBNP levels were assayed using in-house immunoluminometric assays. Median copeptin levels were significantly higher in the male volunteers compared with the females [median (range): 4.3 (0.4–44.3) compared with 3.2 (1.0–14.8) pmol/l; $P < 0.001$]. In males, copeptin was correlated with eGFR (estimated glomerular filtration rate; $r_s = -0.186$, $P < 0.001$). In females, the correlation of copeptin with eGFR was weak ($r_s = -0.097$, $P = 0.095$). DT (deceleration time) and left atrial size correlated with higher copeptin levels ($r_s = 0.085$, $P = 0.029$ and $r_s = 0.206$, $P < 0.001$ respectively). Only gender ($P < 0.001$), eGFR ($P < 0.001$), left atrial size ($P = 0.04$) and DT ($P = 0.02$) remained independently predictive of plasma copeptin. The present study suggests that gender and renal function specific partition values should be used to interpret copeptin values in future studies of this biomarker in HF or ischaemic heart disease.

INTRODUCTION

The morbidity and mortality of HF (heart failure) exerts a huge burden on industrialized societies. The patho-physiological mechanism responsible is the activation of the neurohormonal systems [1]. Therapies have been designed to antagonize these hormones and prevent the deleterious progression of the condition. For example, ACEi [ACE (angiotensin-converting enzyme) inhibitors] and β-blockers have transformed the management of HF. Novel peptides such as the natriuretic peptide systems have been increasingly recognized as diagnostic and prognostic tools in HF. Although BNP (brain natriuretic peptide) and NTproBNP (N-terminal pro-BNP) have

Key words: brain natriuretic peptide, copeptin, heart failure, renal function.

Abbreviations: A, transmitral peak flow during atrial filling phase; AVP, arginine vasopressin; BMI, body mass index; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; DT, deceleration time; E, transmitral peak flow during early filling phase; eGFR, estimated glomerular filtration rate; HF, heart failure; IVRT, isovolumetric relaxation time; LV, left ventricular; LVEF, LV ejection fraction; LVH, LV hypertrophy; LVWMI, LV wall motion index; MDRD, modification of diet in renal disease; MI, myocardial infarction; AMI, acute MI; NTproBNP, N-terminal pro-BNP; SBP, systolic blood pressure.

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a high sensitivity and negative predictive value for the detection of HF, specificity remains low and therefore positive predictive value of the test is not high [2]. The diagnostic accuracy of BNP and NTproBNP is influenced by many variables. BNP has been found to increase with age, independent of age-related alterations in renal function [3,4]. BNP levels are higher in females inferring a relationship with oestrogen status [5]. High natriuretic peptides levels are independently related to BMI (body mass index) and renal dysfunction [6]. Hence interpretation of BNP and NTproBNP levels is multifaceted.

New peptides are being identified to complement existing tools to improve the diagnostic and prognostic accuracy of clinical disease. A newly identified glycopeptide called copeptin has been shown to be comparable with the natriuretic peptides in the diagnosis and prognosis of HF [7]. In a study by Gegenhuber et al. [7] copeptin was found to be comparable with BNP for 1 year all-cause mortality in patients with acute destabilized HF. In addition, copeptin has also shown promise as a prognostic biomarker after AMI [acute MI (myocardial infarction)], with an accuracy equivalent to NTproBNP [8].

Copeptin is a glycoprotein derived from the C-terminal portion of the precursor to AVP (arginine vasopressin), which is of unknown physiological function [9]. AVP is a hormone synthesized in the paraventricular nuclei of the hypothalamus and stored in neurosecretory vesicles in the posterior pituitary gland. It is secreted in response to stimuli to promote water conservation, contributing to volume regulation and cardiovascular homoeostasis [10]. Concerns exist regarding the accuracy and reliability of AVP quantification largely in part due to its instability *ex vivo*, platelet binding and rapid plasma clearance [11,12]. In comparison with AVP, copeptin is stable *ex vivo* for up to 14 days in EDTA at room temperature [9]. The stoichiometric generation of copeptin allows it to be used as a surrogate marker for the AVP system.

With the introduction of copeptin as a potential diagnostic and prognostic factor in HF and acute coronary syndromes there is a need to understand variables which may affect copeptin levels in normal individuals, in order to derive a working normal range for diagnosis or prognosis of heart disease [7,8]. The objectives of the present population-based study was to identify these confounding factors for the interpretation of plasma copeptin levels, which may lead to improved utility of this marker.

MATERIALS AND METHODS

Study population

Healthy volunteers were derived from an HF screening study performed in the local community. From patient records, information regarding history of ischaemic heart disease (MI or angina), hypertension, diabetes mellitus, smoking and cardiovascular medication was sought. The present study complied with the Declaration of Helsinki and was approved by the local ethics committee. All volunteers gave written informed consent for physical examination, echocardiography and peripheral blood sampling. Participants with a history of ischaemic heart disease, hypertension, diabetes mellitus and those with echocardiographic abnormalities {including segmental wall motion abnormalities, valvular disease, LVH [LV (left ventricular) hypertrophy]} and those on cardiovascular medication were excluded from the present study. The eGFR (estimated glomerular filtration rate) of these subjects was derived using the MDRD (modification of diet in renal disease) formula [13].

Blood sampling

Venesection was performed in recumbent volunteers. Samples for measuring the plasma concentrations of the propeptides were collected in pre-chilled tubes containing EDTA and aprotinin. Plasma was stored at $-70\,^{\circ}C$ until assayed and all analyses were performed in a single batch. Samples for measuring plasma creatinine were collected in tubes containing lithium and heparin.

Echocardiography

Transthoracic echocardiography was performed in patients using a Sonos 5500 instrument (Philips Medical Systems). A 16-segment LVWMI (LV wall motion index) based on the American Society of Echocardiography model was derived by scoring each LV segment [1 = normal, 2 = hypokinesis, 3 = akinesis and 4 = dyskinesis (Paradoxical Motion)] and dividing the total by the number of segments scored. LVEF (LV ejection fraction) was calculated using the biplane method of discs formula [14]. All of the normal volunteers in the present study had a LVWMI = 1 (i.e. no segmental wall motion abnormalities), and no evidence of valvular disease or LVH. LV mass was calculated using the formula published by Devereux et al. [15] and indexed for body surface area to obtain the LV mass index. LVH is diagnosed when the LV mass index is greater than 134 g/m^2 or 110 g/m^2 in males and females respectively [16].

The transmitral peak-flow during the early (E) and the atrial (A) filling phase was determined using pulsed-wave Doppler examination at the tips of the mitral valve leaflets. The E/A ratio, LV IVRT (isovolumetric relaxation time) and DT (deceleration time) were calculated from these traces.

NTproBNP assay

Our NTproBNP assay was based on a non-competitive assay [17]. Sheep antibodies were raised against the N-terminal of human NTproBNP and monoclonal mouse antibodies were raised against the C-terminal. The N-terminal IgG was affinity-purified and biotinylated. Samples or NTproBNP standards were incubated in

Table 1 Baseline characteristics of study sample

Values are medians (range) or means (S.D.), except for age and eGFR which are means (range).

Baseline characteristic	Male ($n = 408$)	Female ($n = 298$)	Significance (P value)
Clinical characteristic			
Age (years)	59.7 (45.5–80.4)	64.0 (55.2–79.4)	< 0.001
eGFR (ml · min^{-1} · 1.73 m^{-2} surface area)	79.1 (42.5–113.8)	70.2 (39.9–99.4)	< 0.001
BMI (kg/m^2)	26.2 (3.9)	26.0 (4.3)	0.50
Heart rate (beats/min)	70.5 (11.5)	74.8 (11.4)	< 0.001
SBP (mmHg)	130.5 (17.4)	132.7 (18.1)	0.11
DBP (mmHg)	78.1 (12.2)	74.4 (11.7)	0.004
Biochemical measurement			
Plasma creatinine (μmol/l)	91.0 (67.0–156.0)	77.0 (56.0–122.0)	< 0.001
Plasma copeptin (pmol/l)	4.3 (0.4–44.3)	3.2 (1.0–14.8)	< 0.001
Plasma NTproBNP (pmol/l)	12.8 (5.7–932.8)	53.3 (5.7–991.9)	< 0.001
Echocardiographic characteristic			
Left atrium (cm)	3.4 (0.4)	3.1 (0.5)	< 0.001
E/A ratio	0.9 (0.2)	0.8 (0.2)	< 0.001
DT (ms)	234.2 (53.8)	236.4 (52.6)	0.48
IVRT (ms)	109.7 (26.3)	113.8 (54.4)	0.22
LV mass (g)	164.7 (44.4)	126.9 (45.4)	< 0.001
LV mass index (g/m^2)	88.4 (19.6)	74.5 (22.1)	< 0.001
LVEF (%)	62.4 (4.9)	62.7 (5.3)	0.78

C-terminal IgG-coated wells with the biotinylated antibody for 24 h at 4 °C. Detection was with methylacridinium-ester-labelled streptavidin. The lower limit of detection was 0.3 fmol/ml. There was no cross-reactivity with ANP (atrial natriuretic peptide), BNP or CNP (C-type natriuretic peptide).

Copeptin assay

The sandwich immunoluminometric assay which was used to determine copeptin levels has been reported previously [9]. Briefly, tubes were coated with sheep polyclonal antisera directed against amino acids 132–164 of preprovasopressin as a solid-phase antibody. Sheep antibody raised against the amino acids 149–164 of preprovasopressin was used as a tracer. Dilution of peptide representing amino acids 132–164 of preprovasopressin in normal horse serum was used as calibrators. The immunoassay was conducted by incubating 50 μl of sample/standard and 200 μl of tracer in the coated tubes for 2 h at room temperature (25 °C). Test tubes were washed with 1 ml of wash solution (1.5 mmol/l NaH_2PO_4, 8 mmol/l Na_2HPO_4, 140 mmol/l NaCl, 0.5 g/l Tween 20 and 0.1 g/l sodium azide) and bound chemiluminescence was measured on a LB952T luminometer (Berthold). The 95 % CI (confidence interval) for copeptin was 4.0–4.4 pmol/l [9].

Statistical analysis

Statistical analysis was performed using Statistics Package for Social Sciences version 12.0 (SPSS). Variables that did not follow a Gaussian distribution were log-transformed prior to statistical analysis to satisfy modelling assumptions. Concentrations of copeptin, NTproBNP and plasma creatinine had a non-Gaussian distribution and were log-transformed. For continuous variables in two independent groups the Mann–Whitney U test was used. Spearman's correlation coefficients were used to investigate the influence of patient characteristics on NTproBNP and copeptin levels in univariate analyses. Scatter diagrams were constructed to illustrate the general trend between the two variables. Boxplots were also constructed consisting of median boxes, which represent the interquartile ranges, and the whiskers representing the 2.5th and 97.5th percentiles. To analyse the interaction of multiple independent variables on NTproBNP and copeptin levels, the univariate general linear model was used. A P value below 0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics of the 706 healthy volunteers stratified according to gender are presented in Table 1. In the present study, 57.8 % of the healthy volunteers were male. The mean age of the male volunteers was significantly lower than in the females (59.7 compared with 64.0 years; $P < 0.001$). The BMI in the male group was comparable with that in the female group. Mean heart rate was higher in the female volunteers compared with the male cohort (74.8 compared with 70.5 beats/min; $P < 0.001$). The mean SBP (systolic blood pressure) in the male volunteers was comparable with the females.

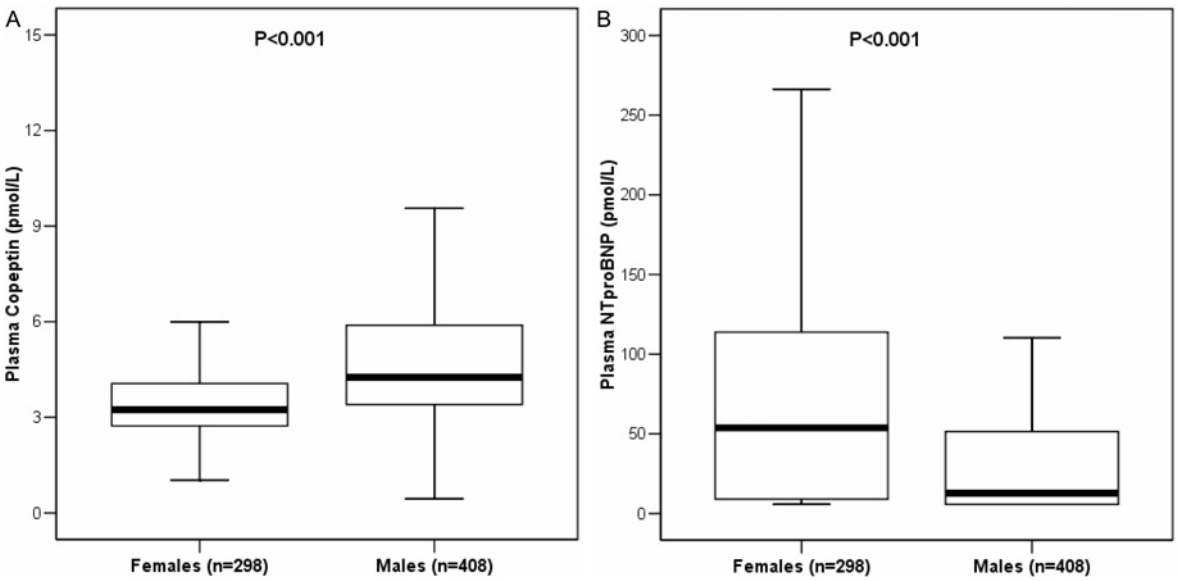

Figure 1 Gender differences in plasma copeptin and NTproBNP levels

(A) Boxplot demonstrating gender differences in copeptin levels. (B) Boxplot demonstrating gender differences in NTproBNP levels.

The DBP (diastolic blood pressure) was significantly higher in the males compared with the females [mean (S.D.), 78.1 (12.2) compared with 74.4 (11.7) mmHg; $P = 0.004$]. Mean eGFR was significantly higher in the males than in the females [mean (range), 79.1 (42.5–113.8) compared with 70.2 (39.9–99.4) $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$; $P < 0.001$). Median copeptin levels were higher in the male volunteers compared with the females [median (range), 4.3 (0.4–44.3) compared with 3.2 (1.0–14.8) pmol/l; $P < 0.001$] (Figure 1A). In contrast, median NTproBNP levels were higher in females compared with males [median (range), 53.3 (5.7–991.9) compared with 12.8 (5.7–932.8) pmol/l; $P < 0.001$] (Figure 1B). Left atrial size was significantly higher in the male cohort compared with the females [mean (S.D.), 3.4 (0.4) compared with 3.1 (0.5) cm; $P < 0.001$]. The E/A ratio was significantly higher in the males compared with the females [mean (S.D.), 0.9 (0.2) compared with 0.8 (0.2); $P < 0.001$]. Gender-specific definitions of LVH were used because of the significant differences in LV mass index between males and females [mean (S.D.), 88.4 (19.6) compared with 74.5 (22.1) g/m^2; $P < 0.001$ respectively].

Univariate analysis (cinical parameters)

In univariate analyses, copeptin was correlated positively with male gender ($r_s = 0.341$, $P < 0.001$; Table 2). Increasing BMI was significantly related to higher plasma copeptin concentrations ($r_s = 0.147$, $P < 0.001$). MDRD-derived eGFR, a measure of renal dysfunction, was not correlated with copeptin levels in the whole population ($r_s = -0.02$, $P = 0.678$). No significant relationships were observed between copeptin levels and age, heart rate, SBP, DBP or NTproBNP levels.

Table 2 Spearman Rho correlations

	Log copeptin		Log NTproBNP	
Clinical parameter	r_s	P value	r_s	P value
Age	−0.052	0.172	0.371	<0.001
Male gender	0.341	<0.001	−0.281	<0.001
BMI	0.147	<0.001	−0.049	0.193
Heart rate	0.018	0.640	−0.080	0.035
SBP	0.056	0.140	0.053	0.163
DBP	0.043	0.260	−0.093	0.015
Log creatinine	0.310	<0.001	−0.085	0.024
eGFR	−0.02	0.678	−0.293	<0.001
Left atrial size	0.206	<0.001	−0.015	0.710
DT	0.085	0.029	0.012	0.733
E/A ratio	0.18	0.638	−0.054	0.153
IVRT	0.007	0.856	−0.054	0.181
LV mass	0.183	<0.001	−0.089	0.034
LV mass index	0.091	0.033	−0.009	0.831

Owing to the very significant differences in copeptin between males and females, we examined these correlations in the two genders separately. In females, copeptin remained significantly correlated with BMI ($r_s = 0.185$, $P < 0.001$) and non-significantly with eGFR ($r_s = -0.097$, $P = 0.095$). In males, the correlation of copeptin with BMI was non-significant ($r_s = 0.091$, $P = 0.06$), but copeptin was very significantly correlated with eGFR ($r_s = -0.186$, $P < 0.001$) (Figure 2A). In the whole population, partial correlation analysis (controlling for gender) between copeptin and eGFR was significant ($r_s = -0.189$,

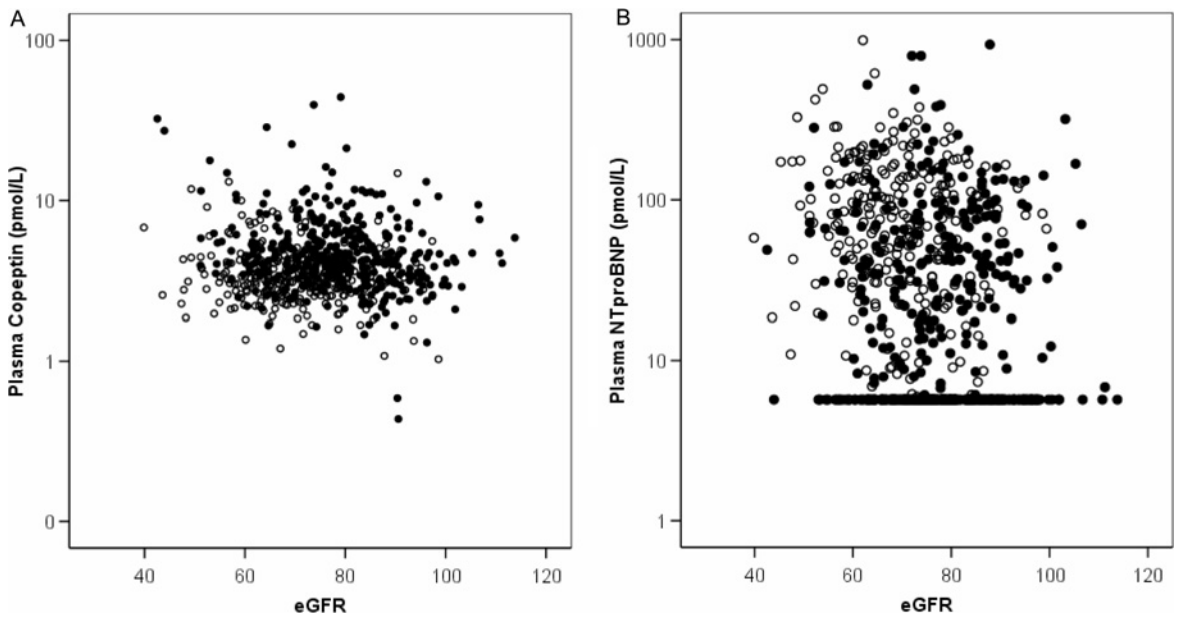

Figure 2 Relationship between plasma copeptin and NTproBNP with eGFR

(A) Relationship between copeptin and eGFR in males (●) and in females (○). $r_s = -0.186$, $P < 0.001$ and $r_s = -0.097$, $P = 0.095$ for males and females respectively. (B) Relationship between NTproBNP and eGFR in males (●) and females (○). $r_s = -0.293$, $P < 0.001$ for females.

$P < 0.001$), whereas the correlation between BMI and copeptin was non-significant ($r_s = 0.066$, $P = 0.08$).

In accordance with previous reports, NTproBNP was strongly correlated with female gender ($r_s = -0.281$, $P < 0.001$) and increasing age ($r_s = 0.371$, $P < 0.001$). We observed an inverse relationship between NTproBNP and heart rate ($r_s = -0.080$, $P = 0.035$). Plasma NTproBNP levels were inversely associated with DBP ($r_s = -0.093$, $P = 0.015$). NTproBNP was negatively correlated with eGFR ($r_s = -0.293$, $P < 0.001$) (Figure 2B).

Multivariate analysis (clinical parameters)

In multivariate analysis, male gender ($P < 0.001$) and eGFR ($P < 0.001$) were independent predictors of plasma copeptin levels.

Multivariate analysis, which included age, male gender, heart rate, DBP and eGFR, revealed that age ($P < 0.001$), female gender ($P < 0.001$), heart rate ($P < 0.001$) and eGFR ($P < 0.04$) were independent predictors of NTproBNP levels.

Univariate analysis (clinical parameters and echocardiographic parameters)

Copeptin was positively correlated with LV mass index ($r_s = 0.091$, $P = 0.033$). Variables that may reflect preload such as DT [18] and left atrial size correlated with higher copeptin levels ($r_s = 0.085$, $P = 0.029$ and $r_s = 0.206$, $P < 0.001$ respectively). Other indices of diastolic dysfunction such as E/A ratio and LV IVRT were not significantly correlated to copeptin levels.

Table 3 Independent predictors of plasma copeptin and NTproBNP

Independent predictor	*F*	Significance (*P* value)
Of plasma copeptin		
Gender	57.81	< 0.001
BMI	0.06	0.79
eGFR	14.50	< 0.001
Left atrial size	4.14	0.04
DT	5.67	0.02
LV mass index	1.01	0.31
Of plasma NTproBNP		
Age	45.59	< 0.001
Gender	23.69	< 0.001
Heart rate	11.16	< 0.001
DBP	0.49	0.48
eGFR	4.65	0.03
LV mass	1.81	0.18

NTproBNP was inversely correlated with LV mass ($r_s = -0.089$, $P = 0.034$). NTproBNP failed to correlate with any other echocardiographic variable.

Multivariate analysis (clinical parameters and echocardiographic parameters)

The significant clinical and echocardiographic variables in univariate analyses were used as covariates in multivariate analyses. Gender and eGFR remained strong independent predictors of copeptin levels (Table 3). DT and left

atrial size retained a weak independent relationship with copeptin levels.

In males, independent predictors of copeptin were eGFR ($P < 0.001$), left atrial size ($P < 0.03$) and DT ($P < 0.04$). In females, none of these variables were independent predictors of copeptin.

Age, female gender and heart rate remained strong independent predictors of plasma NTproBNP levels, whereas eGFR was a weak predictor.

DISCUSSION

NTproBNP is considered an established diagnostic and prognostic marker for HF. The significance of new prognostic markers is best established by comparing them with existing markers. A study by Gegenhuber et al. [7] showed that the prognostic utility of copeptin was comparable with that conferred by the natriuretic peptides for 1 year all-cause mortality in acute destabilized HF patients. Stoiser et al. [19] revealed that copeptin was an excellent predictor of composite end points in patients with advanced HF superior to that conferred by BNP. In the present study no correlation was observed between NTproBNP and copeptin inferring that these peptides mediate their effects via different pathways responsible for the progression of HF [20].

The normal range for copeptin in individuals without cardiovascular disease has not been established. The magnitude of effects of variables such as age and gender and their potential importance in the interpretation of copeptin levels remains unclear.

In the present study copeptin levels were found to be higher in male volunteers compared with females, which corroborates findings by Khan et al. [8]. This contrasts with NTproBNP, which is higher in females. Copeptin was correlated with BMI in univariate analyses; however, in the general linear model, including both clinical and echocardiographic parameters, BMI was displaced from the model and was not an independent predictor of copeptin levels. The MDRD-derived eGFR, a measure of renal function, was an independent predictor of copeptin levels. This may suggest that copeptin is mainly cleared from the kidneys or that the AVP system is activated in patients with renal impairment. We observed a lack of effect of age on plasma copeptin levels. The present study suggests that gender and renal function have to be taken into consideration when interpreting copeptin levels. In male subjects especially, there is a strong relationship between copeptin and eGFR. This is in contrast with NTproBNP, which is influenced by many factors, such as gender, age, renal function and BMI. In the present study NTproBNP levels were higher in females than males, which corroborates findings by Costello-Boerrigter et al. [21], who showed that NTproBNP was associated with higher BNP in females inferring that oestrogen status may be responsible.

Plasma copeptin was correlated significantly with left atrial size and DT, but not with other indices that may reflect diastolic dysfunction (E/A ratio and IVRT). The mitral valve E wave DT is dependent on many factors including LV relaxation and pressure, left atrial pressure and preload. It is likely that the correlation with copeptin may reflect preload, as this biomarker is released in stoichiometric amounts with AVP, which regulates fluid status. The preload is a known determinant of AVP release in normal homoeostatic physiology. The relationship with left atrial size and DT was especially noted in male subjects.

The present study confirmed previous research that NTproBNP is strongly related to age. A study by Raymond et al. [22] showed that NTproBNP levels doubled with each decade increase in age. They attributed this association to an increase in myocardial mass [23]. In our present study eGFR, a marker of renal dysfunction, was inversely correlated with NTproBNP levels; however, eGFR was a weak independent predictor of NTproBNP levels. Akiba et al. [24] reported that patients with renal failure had high levels of natriuretic peptides, which is consistent with our findings in the present study.

Investigating the interaction between the AVP system and clinical/echocardiographic variables in a healthy population as opposed to patients with cardiovascular disease is important in understanding how these neurohormonal systems behave in health. The present study demonstrates that relationships that exist in health may not follow through into disease. Copeptin in healthy individuals was related to gender and eGFR, but not with age. The relationship with eGFR was stronger in the male subjects. The normal range in female subjects was independent of eGFR and echocardiographic measurements. However Khan et al. [8] revealed that this was not the case in patients with AMI, as copeptin was correlated with age and eGFR and was higher in male patients. A burst of copeptin release following an AMI could show a relationship with age in disease, which may not show up if the normal range was narrow.

Interest has focussed on copeptin as a prognostic marker. Thorough understanding of the physiology as well as the pathophysiology of this marker in a large population-based study is required in order to derive normal reference ranges. Further studies will be needed to confirm these findings and to explore the associated mechanisms. In summary, gender and renal dysfunction were major factors influencing copeptin in normal volunteers, with other factors only minimally contributing. The interpretation of copeptin levels must take into account potential confounding factors such as male gender, renal impairment and the fluid status of the subject. Hence a single reference range for normal copeptin will not be valid considering the need to adjust

for the independent effects of gender and renal function. In summary, the reference range in male subjects has to take renal function into account. In females, the reference range may be independent of age and renal function.

A limitation of the present study is that the cohort consisted entirely of white Caucasians. Therefore these findings cannot be extrapolated to other ethnic groups without further studies. Furthermore, although a relationship of copeptin with creatinine and the MDRD-derived eGFR was documented, a relationship with renal function may necessitate direct measurement of GFR.

Conclusion

In conclusion, the present study suggests that gender and renal-function-specific partition values should be used to interpret copeptin values in future studies of this biomarker in HF or ischaemic heart disease.

FUNDING

This work was supported by the Brandenburg Ministry of Economics, Germany [grant number 80125434]; and the European Regional Development Fund [grant number 80125434].

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Received 1 May 2008/4 July 2008; accepted 22 July 2008
Published as Immediate Publication 22 July 2008, doi:10.1042/CS20080140