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Reduced levels of vasopressin, an independent mechanism in the obesity paradox in patients with chronic heart failure: Insights from the DAMOCLES study

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ABSTRACT

Background: An "obesity paradox" has been described in patients with chronic heart failure (CHF), obese patients having a better survival. Vasopressin is elevated in patients with CHF, and higher levels are associated with worsening severity of the disease. We aimed at evaluating the relationship between body mass index (BMI), obesity (BMI ≥30 kg/m^2), and vasopressin in patients with CHF, as well as the prognostic implications of vasopressin across the full spectrum of BMI values.
Methods: We included 1132 consecutive CHF patients referred to a multidisciplinary CHF unit. BMI and vasopressin levels were measured at baseline, and their association was evaluated using multivariable linear and logistic regression models. Death was evaluated after a median follow-up of 2.93 years and using Cox regression analyses.
Results: Mean age was 73 years, 43% women, mean BMI 28 kg/m^2. Vasopressin levels were independently associated with all-cause death across the whole spectrum of BMI values, and were significantly lower in obese as compared to non-obese patients (median adjusted estimated levels of log-vasopressin in obese patients 2.57 [95% CI 1.5–3.67], in non-obese patients 3.16 [95% CI 2.11–4.23]; $p < 0.001$). Also, the higher the BMI, the lower the vasopressin levels, at least for patients with BMI <35 kg/m^2. Subgroup analyses stratifying by left ventricle ejection fraction and sensitivity analyses further adjusting for norepinephrin levels yielded similar findings.
Conclusions: Reduced levels of vasopressin may represent an independent mechanism in the survival paradox in obese patients with CHF. Studies including larger samples of patients BMI ≥35 kg/m^2 are needed.

1. Introduction

Obesity is a well-known risk factor for the development of a number of cardiovascular diseases, including chronic heart failure (CHF) [1–4]. Nevertheless, several studies have found obese patients with established CHF having a better survival than their normal weight counterparts [5,6]. This "obesity paradox" is also present in other chronic conditions, such as

Abbreviations: BMI, Body mass index; CHF, chronic heart failure; DAMOCLES, **D**efinition of the neuro-hormonal **A**ctivation, **M**yocardial function, gen**O**mic expression and **CL**inical outcomes in h**E**art fa**I**lure patient**S**; ESC, European Society of Cardiology; LVEF, left ventricular ejection fraction; NE, norepinephrin; NYHA, New York Heart Association.

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stroke [7] or chronic obstructive pulmonary disease (COPD) [8], and the underlying physiopathology is currently unclear.

The neurohormonal hypothesis claims that CHF is regulated by the sympathetic axis, the renin-angiotensin-aldosterone system, and vasopressin [9]. Their activation is related with poorer clinical outcomes [9], and consequently, inhibition of some of the components of the neurohormonal axis is currently the cornerstone of therapy in CHF, particularly in patients with reduced left ventricle ejection fraction (LVEF) [10,11]. In this context, recent studies have shown that obese patients with CHF have lower norepinephrine (NE) levels than non-obese individuals, and this has been hypothesized as a potential mechanism involved in the better survival observed in the former group [12].

On the other hand, as of now the relationship between obesity and levels of vasopressin has not been evaluated in patients with CHF. Vasopressin is released mainly after the stimuli of osmotic or non-osmotic drive, and through the V1a, V1b and V2 receptors contributes to arterial vasoconstriction, release of other hormones, and antidiuretic effects [13]. Vasopressin is found elevated in patients with CHF [14], and higher levels are associated with worsening severity of CHF [15].

The aims of this study were thus to evaluate the associations between the body mass index (BMI), obesity, and vasopressin levels in patients with CHF; as well as the prognostic implications of vasopressin in this patient population across the full spectrum of BMI levels.

2. Methods

2.1. Study design and ethics

The methodology used in the Definition of the neuro-hormonal Activation, Myocardial function, genOmic expression and CLinical outcomes in hEart failure patientS (DAMOCLES) study has been reported elsewhere [12]. Briefly, this was a prospective, single center cohort study of 1236 consecutive CHF patients referred to a multidisciplinary HF management program. The study was conducted in accordance with the Declaration of Helsinki, the study protocol was approved by the local ethics committee for clinical research, and all patients gave written informed consent before recruitment.

2.2. Study population

Patient recruitment took place between January 2004 and January 2013. For inclusion in DAMOCLES, patients had to be diagnosed with CHF according to the criteria defined by the European Society of Cardiology (ESC) [16], had to have had a recent episode of acute CHF decompensation requiring intravenous diuretic treatment (regardless of whether they were hospitalized, treated in the emergency department and discharged, or treated in the day care hospital), and had to be in stable condition. Diagnosis of CHF was confirmed by two independent cardiologists not involved in the study. Exclusion criteria of DAMOCLES were significant primary valvular disease, hypertrophic cardiomyopathy, hemoglobin levels <8.5 g/dL, active malignancy, and chronic liver disease.

For the present analysis, all DAMOCLES participants were considered for inclusion. Of them, we excluded patients with missing baseline information on vasopressin levels and/or on BMI.

2.3. Baseline examination

At recruitment, relevant clinical and demographic information, including the New York Heart Association (NYHA) functional class, the LVEF, and current medical therapy were recorded.

Peripheral blood samples were collected in all participants. Peripheral blood was drawn from a 22-gauge angiocatheter (Abbocath®) placed in an antecubital vein for blood samples and biological measurements. Patients were at rest in a supine condition in a quiet room for 30–60 min after venous cannulation and then 12 mL blood samples were drawn. All tubes were immersed in melting ice and frozen until they were processed. Levels of vasopressin were measured from 1.5 mL of plasma by high resolution liquid chromatography. Normal values of vasopressin were considered <7.6 pg/mL. Serum NT-proBNP (pg/mL) was measured using immunoassay based on a chemiluminescence using Elecys System (Roche®). Hemoglobin levels (g/dL) were measured by impedance laser colorimetry. Anemia was defined using the World Health Organization Criteria (cut-off values of 13 g/dL in men and 12 g/dL in women) [17]. The glomerular filtration rate was calculated from serum creatinine using the formula of Modification of Diet in Renal Disease Study Group (MDRD equation).

Weight and height were also measured upon inclusion. The BMI was estimated using the formula: BMI = weight (kg) / height (m^2). A BMI ≤21 kg/m^2 was considered "underweight", a BMI >21 and ≤25 kg/m^2 was considered "normal weight", a BMI >25 and <30 kg/m^2 was considered "overweight", and a BMI ≥30 kg/m^2 was considered "obesity".

2.4. Follow-up and event ascertainment

Follow-up in DAMOCLES lasted until November 2015, study participants being followed for a median of 2.93 years (mean 3.3 years). Follow-up was conducted by trained study personnel. Specifically, data on mortality and on cause of death were obtained from hospital and primary care electronic medical records, and/or by direct interview with the patients' relatives.

2.5. Statistical analyses

Baseline characteristics of the study participants were summarized for the whole cohort as well as by baseline absence/presence of obesity. For categorical variables, number and percentage were reported, and for continuous variables, mean (standard deviation) or median (interquartile range) were used, depending on the distribution of the variables. χ^2, Student's T, and non-parametric tests were used to compare characteristics across strata.

We used several approaches to assess the relationship between BMI and levels of vasopressin. First, we used smooth spline curves to display the unadjusted association between BMI, as a continuous exposure, and log-transformed vasopressin. We also used linear regression models to assess the crude and multivariable-adjusted associations between 1 kg/m^2 increases in BMI, as well as between obesity (defined as BMI ≥30 kg/m^2, compared to <30 kg/m^2), and log-transformed vasopressin. For the multivariable models, only predictors showing statistically significant associations with vasopressin in the crude analyses were included in the models (age, systolic blood pressure, etiology of CHF, NYHA functional class, log-transformed NT-ProBNP, pharmacological treatments, and sodium levels). We also estimated the adjusted marginal median vasopressin levels by BMI categories (as a dichotomous variable: non-obese vs. obese; and as a polychotomous variable: underweight, normal weight, overweight, and obese) after adjusting for potential confounders.

We also evaluated the associations between BMI, between obesity as compared to non-obesity, and between vasopressin levels, and all-cause death, using Cox proportional hazards regression models. Specifically, the analyses of vasopressin adjusted for potential confounders, which were incorporated into the model using a stepwise selection process. Smooth spline estimates were also created, displaying the unadjusted relationship between vasopressin and all-cause mortality.

To assess whether the association between vasopressin and all-cause death was modified by BMI, interaction tests were conducted, aimed at assessing the statistical significance of potential BMI * vasopressin and obesity * vasopressin interaction terms. Also, provided the clinical importance of LVEF subgroups, analyses were repeated stratifying by LVEF (<40% vs ≥40%).

Finally, to assess the independent associations between vasopressin and BMI, and between vasopressin and all-cause death, beyond its correlation with NE (which has been shown to be independently associated with both [12]), we conducted sensitivity analyses further adjusting for NE. This was done in the subset of patients in which NE levels were also available.

All statistical tests and confidence intervals (CI) were constructed with a type I error alpha level of 5%, with no adjustments for multiplicity. *P* values below 0.05 were considered statistically significant. R software (R Foundation for Statistical Computing, Vienna, Austria), version 3.0.1, was used for all statistical analyses.

3. Results

3.1. Study participants

Of the 1236 patients included in the DAMOCLES study, 104 had missing data on either vasopressin levels, BMI, or both, and were excluded from the present analysis. This defined a final study population of 1132 patients with CHF.

3.2. Baseline characteristics

The baseline characteristics of the study participants are presented in Table 1, overall and by absence/presence of obesity. Overall, mean age was 73 years, 43% participants were women, mean BMI was 28 kg/m^2, and almost half of the study population had LVEF ≥40%.

Obesity was present in 370 patients (33%). Obese CHF patients were slightly younger, more frequently female, had a higher mean LVEF than non-obese patients, and their levels of NTProBNP were significantly lower. Obese patients also had a significantly higher prevalence of coronary risk factors such as diabetes mellitus and hypertension, while the prevalence of anemia was lower than in the non-obese group. Other markers of severity such as NYHA functional class, hemoglobin, renal function and serum albumin did not differ between the two groups.

Table 1
Baseline characteristics of the study participants.

	Overall (*N* = 1132)	Non-obese (*N* = 762)	Obese (*N* = 370)	*P* value
Age, years	73 (11)	73 (11)	71 (11)	<0.001
Female	487 (43)	286 (38)	201 (54)	<0.001
BMI, kg/m^2	28 (6)	25 (3)	35 (5)	<0.001
SBP, mm Hg	124 (22)	122 (22)	128 (21)	<0.001
DBP, mm Hg	67 (13)	67 (13)	69 (13)	0.004
Heart rate, bmp	74 (15)	74 (14)	74 (16)	0.874
NYHA functional class				
I–II	663 (59)	450 (59)	213 (58)	0.969
III–IV	469 (41)	312 (41)	157 (43)	0.969
LVEF, %	45 (17)	43 (17)	49 (16)	<0.001
HFpEF[a]	547 (48)	325 (43)	222 (60)	<0.001
Ischemic cause	426 (38)	299 (39)	127 (34)	0.117
Comorbidities				
Hypertension	907 (80)	586 (77)	321 (87)	<0.001
Diabetes Mellitus	526 (47)	319 (42)	207 (56)	<0.001
CKD[b]	627 (56)	416 (55)	211 (57)	0.444
COPD	249 (22)	171 (22)	78 (21)	0.646
Anemia[c]	557 (49)	394 (52)	163 (44)	0.016
Treatments				
ACEI or ARBs	841 (74)	561 (74)	280 (76)	0.469
Betablockers	984 (87)	670 (88)	314 (85)	0.159
MRA	432 (38)	309 (41)	123 (33)	0.019
Loop diuretics	1029 (91)	699 (92)	330 (89)	0.186
Antiplatelet/anticoagulant	926 (82)	622 (82)	304 (82)	0.870
Laboratory measurements				
Hemoglobin, g/dL	12.6 (2)	12.5 (2)	12.7 (2)	0.302
eGFR-ml/min/1.73m^2	59 (25)	60 (24)	58 (25)	0.405
Vasopressin pg/mL	3 (1.4–5.1)	3.2 (1.4–5.3)	2.8 (1.2–4.6)	0.004
NT-pro BNP, pg/mL	1604 (685–3869)	1917 (802–4609)	1145 (497–2502)	<0.001

Data presented as number (%), mean (standard deviation), or median (IQR), as appropriate. Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HFpPEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralcorticoid receptors antagonists; NT-pro BNP = n-terminal pro-brain-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure.

[a] HFpEF was defined as LVEF ≥40%.

[b] CKD was defined as eGFR <60.

[c] Anemia was defined according to the World Health Organization criteria: hemoglobin level <12 g/dL in women, and <13 g/dL in men.

3.3. Unadjusted relationship between BMI and levels of vasopressin

Fig. 1 displays the crude association between BMI and vasopressin levels in the study population. The higher the BMI, the lower the levels of vasopressin (*p* value for linear trend 0.020). This was particularly true for BMI values below 35 kg/m^2. For BMI ≥35 kg/m^2, there was a trend towards rising levels of vasopressin with higher BMI values, nevertheless, the number of patients was small, the CIs were wide, and the non-linear component did not reach statistical significance.

3.4. Other clinical characteristics associated with vasopressin

Supplementary Table S1 presents the results of the bivariate analyses on the associations between other clinical characteristics and levels of vasopressin in the study population. Lower LVEF, worsened renal function, lower hemoglobin levels and higher levels of natriuretic peptides were significantly associated with higher levels of vasopressin.

Supplementary Table S2 presents the results of the multivariable-adjusted analyses. After including in the multivariable models all significant predictors identified in the bivariate analyses, only EGFR, hemoglobin and BMI (*Model 1*)/obesity (*Model 2*) remained independently associated with log-transformed vasopressin.

3.5. Adjusted association between BMI categories and Levels of Vasopressin

Fig. 2 presents the estimated marginal median vasopressin levels by BMI categories, after adjusting for potential confounders. Median estimated values of vasopressin were significantly lower in obese compared to non-obese patients (Fig. 2A: log-transformed vasopressin levels 2.57 [1.5–3.67] vs. 3.16 [2.11–4.23]; $p < 0.001$). Levels of vasopressin in obese CHF patients were also lower than those in underweight, normal weight and overweight CHF patients (Fig. 2B).

3.6. BMI and all-cause mortality

In unadjusted Cox regression analyses, higher BMI was associated with a lower risk of mortality (hazard ratio [HR] for a 1 kg/m^2 increase was 0.96 [95% CI 0.94–0.98], *p* value <0.001). Similarly, obesity (i.e., BMI ≥30 kg/m^2) as compared to non-obesity (i.e., BMI <30 kg/m^2) was associated with a reduced risk of all-cause death (HR 0.70 [95% CI 0.58–0.85], *p* value <0.001).

3.7. Vasopressin levels and all-cause mortality

Fig. 3 displays the relationship between log-transformed vasopressin levels and all-cause mortality. Rising levels of vasopressin were significantly associated with a higher risk of death (*p* value for the linear term 0.011). Interaction tests showed that this association did not differ by BMI (p value for the interaction term 0.218).

In multivariable Cox proportional hazards regression analyses adjusting for potential confounders, higher levels of vasopressin were also significantly associated with all-cause mortality (HR was 1.541 [95% CI 1.12–2.01], *p* value 0.001).

3.8. Sensitivity analyses: NE included in the models

For the analyses further adjusting for NE, the study population was restricted to 702 DAMOCLES patients, as in 430 patients levels of NE were not available. In these analyses, NE (HR was 1.633 [95% CI 1.05–2.54], p value 0.030) and vasopressin (HR was 1.533 [95% CI 1.12–2.09], p value 0.008) remained independently associated with all-cause mortality. In these adjusted models, the association between BMI and all-cause death lost the statistical significance after introducing NE in the model as described previously by our group [12].

3.9. Subgroup analyses: LVEF < 40% and LVEF ≥ 40%

In analyses stratified by LVEF, vasopressin levels remained lower in obese as compared to non-obese patients in both strata. In CHF with preserved LVEF, median estimated log-transformed vasopressin in obese patients was 2.40 (2.19–2.69) as compared to 3.16 (2.88–3.47) in non-obese patients; $p = 0.001$. In patients with CHF and reduced LVEF, median estimated log-transformed vasopressin in obese patients was 2.75 (2.45–3.16) as compared to 3.24 (3.02–3.55) in non-obese patients; $p = 0.046$. Vasopressin was an independent predictor of all-cause mortality in both groups.

4. Discussion

In a study of 1132 consecutive CHF patients managed in a multidisciplinary CHF unit, vasopressin levels, which were independently associated with all-cause death across the whole spectrum of BMI values, were significantly lower in obese as compared to non-obese patients. Also, the higher the BMI, the lower the serum vasopressin levels, at least for patients with BMI <35 kg/m^2. To our understanding, this is the first study to evaluate the relationship between BMI, vasopressin and mortality in patients with CHF, across the whole spectrum of BMI values. Our observations, particularly the independent associations

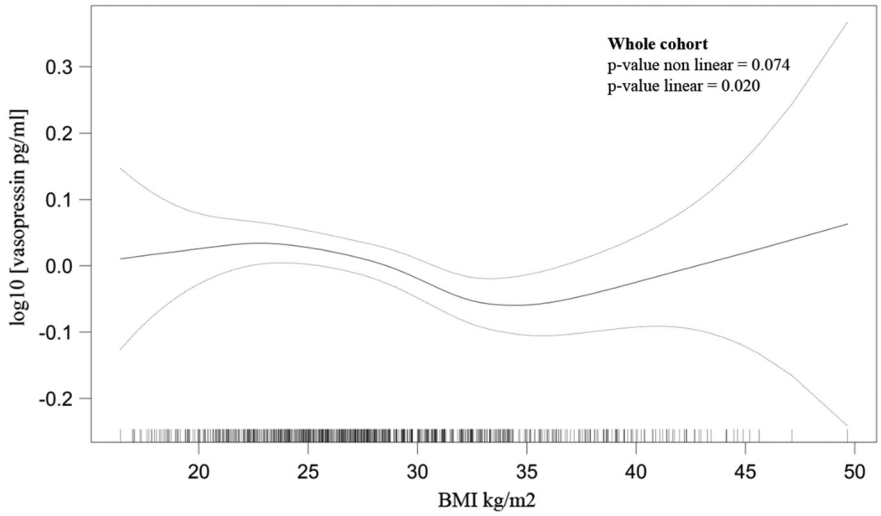

Fig. 1. Unadjusted relationship between BMI and vasopressin levels in the study population. General Additive Model (GAM) model showing the relationship between BMI (in kg/m^2) and levels of vasopressin (log transformed). Abbreviations: BMI = body mass index.

observed after adjusting for NE levels, suggest that reduced serum levels of vasopressin could represent an independent mechanism involved in the survival paradox observed in obese patients with CHF.

Our findings are consistent with those from previous studies, in which other markers of sympathethic activation such as NE were found to be lower in obese patients with CHF as compared to normal

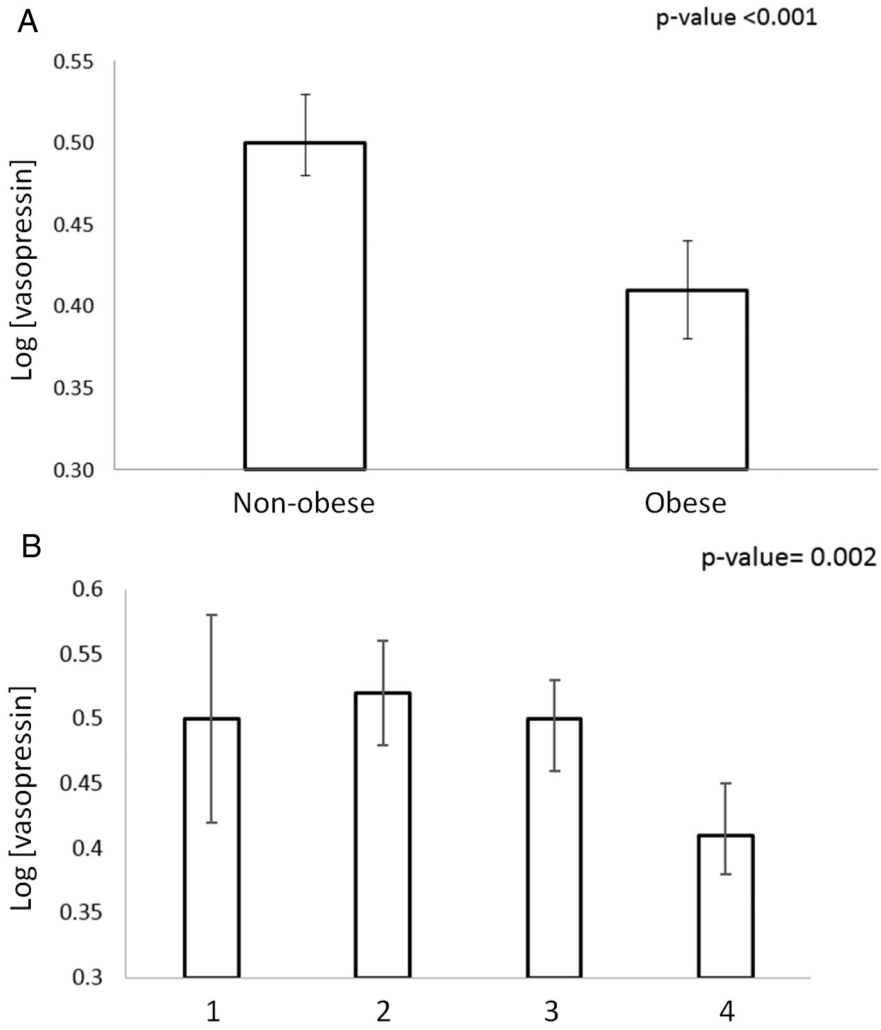

Fig. 2. Estimated marginal adjusted vasopressin levels by BMI categories. Fig. 2A compares obese (BMI ≥ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) CHF patients; and Fig. 2B further classified patients in 4 categories: BMI divided into 4 categories (1: underweight, BMI ≤ 21 kg/m^2; 2: normal weight, BMI >21 and ≤25 kg/m^2; overweight, BMI >25 and < 30 kg/m^2; and obese, BMI ≥ 30 kg/m^2). Levels of vasopressin (Y axis) are log transformed. Abbreviations: BMI = body mass index.

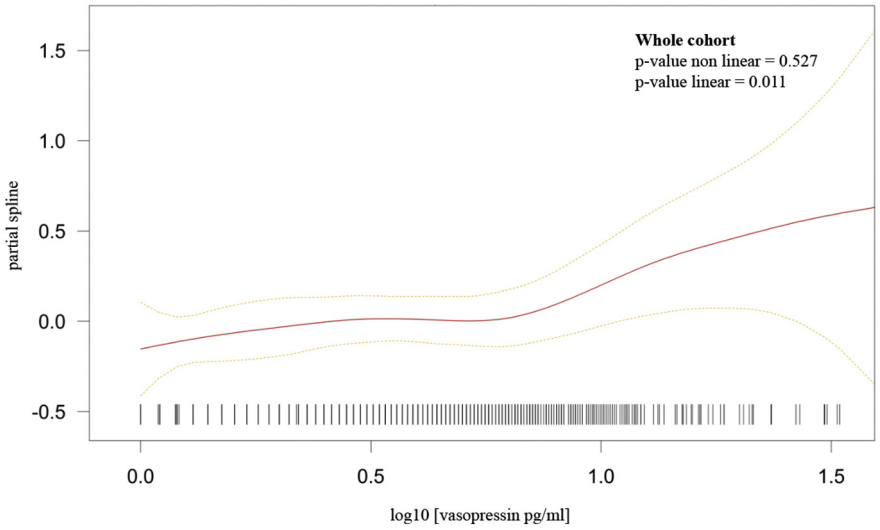

Fig. 3. Association between levels of vasopressin and all-cause mortality. Unadjusted smooth spline estimates of the association between levels of vasopressin and all-cause mortality. The Y axis presents the estimated beta coefficients of risk of all-cause death.

weight patients [12]. Also, in a study by Esler et al. [18], there were remarkable differences in the sympathetic activation between normal weight and obese patients with essential hypertension, the activation being lower in the latter. Our observation of a positive association between vasopressin levels and increased mortality is also consistent with the findings from other groups [19].

It is important to note that increased rather than decreased levels of vasopressin have been observed in obese patients in a number of studies, including obese children and teenagers, women with polycystic ovarium disease, or individuals with metabolic syndrome, among other patient subgroups [20–24]. In fact, increased levels of vasopressin are known to be one of the deleterious components of the metabolic syndrome [23,24]. Nonetheless, the physiopathology of vasopressin in patients with CHF seems to be different. In these patients, the classical stimuli that drives vasopressin release (osmotic pathway) is delayed and is erratic. In obese patients from the general population, hypoglycemia, metoclopramide and nicotine evoke a low vasopressin response, which are part of the non-osmotic drive [25]. On the other hand, in the presence of CHF, vasopressin mainly responds to the non-osmotic drive (mostly driven by reduced cardiac output and potentially hyponatremia and angiotensin II) [26]. Therefore, since the physiologic releasing stimuli vary in the presence of CHF, vasopressin levels, which are usually increased in obese individuals, paradoxically are decreased in obese patients with CHF.

Our findings shed light on the mechanisms potentially involved in the counterintuitive obesity paradox described in patients with CHF [5,6]. Our group had already proposed a role for NE, which is known to have deleterious effects and was found to be reduced in obese patients with CHF [12]. In this context, the present study provides further insight on the importance of other components of the sympathetic pathway as underlying mechanisms of the obesity paradox phenomenon. Importantly, the fact that vasopressin remained associated with mortality also in obese patients points to the fact that, despite lower levels of markers of sympathethic activation in this subgroup, neurohormonal blockade is still relevant in these patients. Nevertheless, such blockade may be even more relevant in their lean counterparts.

Of note, in our study the number of patients with BMI >35 kg/m^2 was very small. There seemed to be a trend towards higher vasopressin levels with higher BMI values for BMI values above 35 kg/m^2, nevertheless, the 95% CIs were wide, leading to great statistical uncertainty on the specific associations between BMI and vasopressin in this subgroup. Further studies including more patients with very high BMIs are needed to better understand whether the obesity paradox actually applies in this subgroup.

4.1. Study limitations

First, the associations between BMI and vasopressin levels were assessed cross-sectionally (both were measured at baseline), therefore, although we adjusted for a number potential confounders in the multivariable analyses, only association and not causality can be inferred.

Second, in our study we used BMI as the only anthropometric measure. Of note, BMI has been criticized as it does not discriminate between fat and lean mass [27]. However, whole-body dual-energy X-ray absorptiometry (DEXA) scans have demonstrated a clear relationship between BMI, fat mass and fat-free mass [14]. Still, assessing the association between measures of body composition and neurohormonal activation would have provided more insights on the features and mechanisms of the obesity paradox in CHF. Third, in our study, BMI was assessed once, i.e., we were not able to capture changes in BMI over time.

Fourth, it has been suggested that vasopressin may not be as reliable as a marker of the vasopressin axis as copeptin. Vasopressin is sometimes considered unreliable because >90% of the circulating hormone is bound to thrombocytes, it is a very unstable polypeptide, and it cannot be measured via sandwich immunoassays [28]. In this context, copeptin, the C-terminal portion of pro-vasopressin, has been proposed as an alternative, as it is structurally more stable and may remain stable for several days at room temperature ex vivo. A strong correlation between copeptin and vasopressin over a wide range of osmolalities has been found, therefore allowing it to become a surrogate marker of the vasopressin system [29]. However, the measurement of vasopressin by radioimmunoassay has been validated, and consequently, is used more often [30]. Finally, the number of patients with very high BMIs was very small. This may limit the generalizability of our findings to other environments where severe obesity is more prevalent, such as the US [31]. The fact that this was a single center study may have also limited the generalizability of our findings, and further, multicenter studies are needed to replicate these findings.

5. Conclusions

In a large population of CHF patients treated in a multidisciplinary CHF unit, BMI and obesity were independently, inversely associated with serum levels of vasopressin. Vasopressin, which was associated

with all-cause death across the entire spectrum of BMI values, may represent an independent mechanism involved in the survival paradox observed in obese patients with CHF. Further, larger studies are needed to better understand whether these findings also apply to patients with BMI >35 kg/m^2.

Declaration of conflicts of interest

The authors declare that they have no conflicts of interest relevant to the content of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.094.

References

[1] H.B. Hubert, M. Feinleib, P.M. McNamara, W.P. Castelli, Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study, Circulation 67 (5) (1983) 968–977.

[2] S.S. Anand, S. Islam, A. Rosengren, M.G. Franzosi, K. Steyn, A.H. Yusufali, M. Keltai, R. Diaz, S. Rangarajan, S. Yusuf, INTERHEART Investigators, Risk factors for myocardial infarction in women and men: insights from the INTERHEART study, Eur. Heart J. 29 (7) (2008) 932–940.

[3] A.B. Mitchell, J.W. Cole, P.F. McArdle, Y.C. Cheng, K.A. Ryan, M.J. Sparks, B.D. Mitchell, S.J. Kittner, Obesity increases risk of ischemic stroke in young adults, Stroke 46 (6) (2015) 1690–1692.

[4] S. Kenchaiah, J.C. Evans, D. Levy, P.W. Wilson, E.J. Benjamin, M.G. Larson, W.B. Kannel, R.S. Vasan, Obesity and the risk of heart failure, N. Engl. J. Med. 347 (5) (2002) 305–313.

[5] C.J. Lavie, A. Sharma, M.A. Alpert, A. De Schutter, F. Lopez-Jimenez, R.V. Milani, H.O. Ventura, Update on obesity and obesity paradox in heart failure, Prog. Cardiovasc. Dis. 58 (2016) 393–400.

[6] T.B. Horwich, G.C. Fonarow, A.L. Clark, Obesity and the obesity paradox in heart failure, Prog. Cardiovasc. Dis. 61 (2018) 151–156.

[7] P. Chittal, A.S. Babu, C.J. Lavie, Obesity paradox: does fat alter outcomes in chronic obstructive pulmonary disease? COPD. 12 (1) (2015) 14–18.

[8] K.K. Andersen, T.S. Olsen, The obesity paradox in stroke: lower mortality and lower risk of readmission for recurrent stroke in obese stroke patients, Int. J. Stroke 10 (1) (2015) 99–104.

[9] F. Triposkiadis, G. Karayannis, G. Giamouzis, J. Skoularigis, G. Louridas, J. Butler, The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications, J. Am. Coll. Cardiol. 54 (19) (2009) 1747–1762.

[10] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G.F. Cleland, A.J.S. Coats, V. Falk, J.R. González-Juanatey, V.P. Harjola, E.A. Jankowska, M. Jessup, C. Linde, P. Nihoyannopoulos, J.T. Parissis, B. Pieske, J.P. Riley, G.M.C. Rosano, L.M. Ruilope, F. Ruschitzka, F.H. Rutten, P. van der Meer, ESC Scientific Document Group, 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur. Heart J. 37 (27) (2016) 2129–2200.

[11] Writing Committee M, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey de Jr, Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: an update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2016; 134(13):e282–93.

[12] N. Farré, J. Aranyó, C. Enjuanes, J.M. Verdú-Rotellar, S. Ruiz, G. Gonzalez-Robledo, O. Meroño, M. de Ramon, P. Moliner, J. Bruguera, J. Comin-Colet, Differences in neurohormonal activity partially explain the obesity paradox in patients with heart failure: the role of sympathetic activation, Int. J. Cardiol. 181 (2015) 120–126.

[13] K. Yalta, T. Yalta, N. Sivri, E. Yetkin, Copeptin and cardiovascular disease: a review of a novel neurohormone, Int. J. Cardiol. 167 (5) (2013) 1750–1759.

[14] C.R. Lee, M.L. Watkins, J.H. Patterson, W. Gattis, C.M. O'Connor, M. Gheorghiade, K.F. Adams Jr., Vasopressin: a new target for the treatment of heart failure, Am. Heart J. 146 (1) (2003) 9–18.

[15] D.E. Lanfear, H.N. Sabbah, S.R. Goldsmith, S.J. Greene, A.P. Ambrosy, A.J. Fought, M.J. Kwasny, K. Swedberg, C.W. Yancy, M.A. Konstam, A.P. Maggioni, F. Zannad, M. Gheorghiade, EVEREST trial investigators, Association of arginine vasopressin levels with outcomes and the effect of V2 blockade in patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial, Circ Heart Fail. 6 (1) (2013) 47–52.

[16] K. Swedberg, J. Cleland, H. Dargie, H. Drexler, F. Follath, M. Komajda, et al., Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005), Eur. Heart J. 26 (11) (2005) 1115–1140.

[17] World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Available at: http://www.who.int/vmnis/indicators/haemoglobin/en/

[18] M. Esler, G. Lambert, M. Schlaich, J. Dixon, C.I. Sari, E. Lambert, Obesity paradox in hypertension: is this because sympathetic activation in obesity-hypertension takes a benign form? Hypertension 71 (1) (2018) 22–33.

[19] S. Zabarovskaja, C. Hage, A. Gabrielsen, L. Mellbin, L.H. Lund, Copeptin in heart failure, post-left ventricular assist device and post-heart transplantation, Heart Lung Circ. 26 (2) (2017) 143–149.

[20] J. Rothermel, A. Kulle, P.M. Holterhus, C. Toschke, N. Lass, T. Reinehr, Copeptin in obese children and adolescents: relationships to body mass index, cortisol and gender, Clin. Endocrinol. 85 (6) (2016) 868–873.

[21] M.I. Taskin, E. Bulbul, E. Adali, A.A. Hismiogulları, U. Inceboz, Circulating levels of obestatin and copeptin in obese and nonobese women with polycystic ovary syndrome, Eur. J. Obstet. Gynecol. Reprod. Biol. 189 (2015) 19–23.

[22] M. Vintila, M.L. Gheorhgiu, A. Caragheorgheopol, N. Baculescu, C. Lichiardopol, C. Badiu, et al., Increased copeptin levels in metabolic syndrome from a Romanian population, J Med Life. 9 (4) (2016) 353–357.

[23] C. Taveau, C. Chollet, L. Waeckel, D. Desposito, D.G. Bichet, M.F. Arthus, C. Magnan, E. Philippe, V. Paradis, F. Foufelle, I. Hainault, S. Enhorning, G. Velho, R. Roussel, L. Bankir, O. Melander, N. Bouby, Vasopressin and hydration play a major role in the development of glucose intolerance and hepatic steatosis in obese rats, Diabetologia 58 (5) (2015) 1081–1090.

[24] S. Enhörning, J. Struck, E. Wirfält, B. Hedblad, N.G. Morgenthaler, O. Melander, Plasma copeptin, a unifying factor behind the metabolic syndrome, J. Clin. Endocrinol. Metab. 96 (7) (2011) E1065–E1072.

[25] P. Chiodera, L. Capretti, C. Davoli, A. Caiazza, L. Bianconi, V. Coiro, Effect of obesity and weight loss on arginine vasopressin response to metoclopramide and nicotine from cigarette smoking, Metabolism 39 (8) (1990) 783–786.

[26] E. Łukaszyk, J. Małyszko, Copeptin: pathophysiology and potential clinical impact, Adv. Med. Sci. 60 (2) (2015) 335–341.

[27] A. Romero-Corral, V.K. Somers, J. Sierra-Johnson, R.J. Thomas, M.L. Collazo-Clavell, J. Korinek, T.G. Allison, J.A. Batsis, F.H. Sert-Kuniyoshi, F. Lopez-Jimenez, Accuracy of body mass index in diagnosing obesity in the adult general population, Int. J. Obes. 32 (6) (2008) 959–966.

[28] K. Yalta, T. Yalta, N. Sivri, E. Yetkin, Copeptin and cardiovascular disease: a review of a novel neurohormone, Int. J. Cardiol. 167 (5) (2013) 1750–1759.

[29] S. Balanescu, P. Kopp, M.B. Gaskill, N.G. Morgenthaler, C. Schindler, J. Rutishauser, Correlation of plasma copeptin and vasopressin concentrations in hypo-, iso-, and hyperosmolar states, J. Clin. Endocrinol. Metab. 96 (4) (2011) 1046–1052.

[30] P. Larose, H. Ong, P. Du Souich, Simple and rapid radioimmunoassay for the routine determination of vasopressin in plasma, Clin. Biochem. 18 (6) (1985) 357–361.

[31] C.M. Hales, C.D. Fryar, M.D. Carroll, D.S. Freedman, C.L. Ogden, Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007–2008 to 2015–2016, JAMA 319 (2018) 1723–1725.