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Differences in neurohormonal activity partially explain the obesity paradox in patients with heart failure: The role of sympathetic activation ☆

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ABSTRACT

Background: Obese patients with chronic Heart Failure (HF) have better outcome than their lean counterparts, although little is known about the pathophysiology of this obesity paradox. Our aim was to evaluate the hypothesis that patients with chronic HF and obesity (defined as body mass index (BMI) ≥ 30 kg / m^2), may have an attenuated neurohormonal activation in comparison with non-obese patients.

Methods and results: The present study is the post-hoc analysis of a cohort of 742 chronic HF patients from a single-center study evaluating sympathetic activation by measuring baseline levels of norepinephrine (NE). Obesity was present in 33% of patients. Higher BMI and obesity were significantly associated with lower NE levels in multivariable linear regression models adjusted for covariates ($p < 0.001$). Addition to NE in multivariate Cox proportional hazard models attenuated the prognostic impact of BMI in terms of outcomes. Finally, when we explored the prognosis impact of raised NE levels (>70th percentile) carrying out a separate analysis in obese and non-obese patients we found that in both groups NE remained a significant independent predictor of poorer outcomes, despite the lower NE levels in patients with chronic HF and obesity: all-cause mortality hazard ratio = 2.37 (95% confidence interval, 1.14–4.94) and hazard ratio = 1.59 (95% confidence interval, 1.05–2.4) in obese and non-obese respectively; and cardiovascular mortality hazard ratio = 3.08 (95% confidence interval, 1.05–9.01) in obese patients and hazard ratio = 2.08 (95% confidence interval, 1.42–3.05) in non-obese patients.

Conclusion: Patients with chronic HF and obesity have significantly lower sympathetic activation. This finding may partially explain the obesity paradox described in chronic HF patients.

1. Introduction

Obesity is a major public health problem due to its high incidence, increasing prevalence and its role in causing cardiovascular disorders such as coronary artery disease and hypertension, which are, in turn, involved in the development of heart failure (HF) [1]. However, several studies in the last decade have shown that obese patients with chronic HF have better outcomes compared to overweight, normal weight and underweight patients: the so-called obesity paradox [2]. Despite these observations and various hypotheses trying to explain this paradox, there is still no clear understanding of the mechanisms involved [3].

Chronic HF is characterized by an increased activation of the sympathetic, renin–angiotensin–aldosterone systems and the vasopressin axis [4]. These increased levels of neurohormones have been associated with poorer outcomes in patients with HF and reduced ejection fraction (HFrEF) [5]. Research in this field has led to the development of the neurohormonal hypothesis, a key concept to understand the pathophysiology of the HF syndrome in patients with HFrEF and to develop effective drugs in the management of these patients in terms of mortality and morbidity [6]. Although this concept has not been fully studied

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in patients with HF and preserved ejection fraction (HFpEF), the neurohormonal hypothesis and treatment using neurohormonal blockers have also been extrapolated into this specific subgroup of patients [6].

Given the impact of neurohormonal activity on progression and outcomes in patients with chronic HF, it would be interesting to evaluate whether differences in the preferential activation of neurohormonal sympathetic pathway may partially explain the inverse relationship between obesity and mortality. However, no studies to date have evaluated the link between obesity and cardiac endocrine function in order to explain the pathophysiological mechanisms of the obesity paradox in chronic HF.

The hypothesis of this study was that obese patients would have a differential sympathetic activation compared to non-obese patients, and that this difference could partially explain the obesity paradox. Therefore, the aims of our study were, first, to evaluate possible differences in terms of sympathetic activation, measured as circulating levels of norepinephrine (NE), according to body weight; and, second, to explore the contribution of sympathetic activation in the reported protective role of obesity in patients with chronic HF.

2. Methods

2.1. Study population and recruitment

The data presented were obtained by a post-hoc analysis of a prospective single center study to evaluate the sympathetic activation in patients with chronic HF and obesity. The study population consisted in 1072 consecutive chronic HF patients followed in a multidisciplinary HF program. The study was conducted in accordance with the Declaration of Helsinki, the study protocol was approved by the local committee of ethics for clinical research, and all patients gave written informed consent before recruitment.

For inclusion in the study, patients had to be in a stable condition and diagnosed with chronic HF with either reduced or preserved ejection fraction, according to the European Society of Cardiology diagnostic criteria [6]. Patients were only included if they had had a previous episode of acute HF requiring intravenous diuretic treatment either during hospital admission, emergency room visit or in a HF-day care hospital. Diagnosis of chronic HF was confirmed by two independent cardiologists not involved in the study. Exclusion criteria for the study were: significant primary valvular disease, hemoglobin (Hb) levels < 8.5 g/dL, clinical signs of fluid overload, pericardial disease, restrictive cardiomyopathy, hypertrophic cardiomyopathy, active malignancy, and chronic liver disease. Patients without measurements of NE available at screening were also excluded. At recruitment, peripheral blood samples were collected and relevant clinical and demographic information, including NYHA functional class, current medical therapy, and the most recent left ventricular ejection fraction (LVEF) evaluation was recorded.

2.2. Blood collection and biological measurements

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 position 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. The levels of NE were measured from 1.5 mL of plasma by high resolution liquid chromatography. Normal values considered <— 420 pg/mL. Norepinephrine analysis had a coefficient of variation of 8.7%. Serum NT-ProBNP (pg/mL) was measured using immunoassay based on chemiluminescence using Elecsys System (Roche®).

2.3. Body mass index measurement and other clinical parameters

Weight and height were prospectively measured upon inclusion. Body mass index (BMI) was estimated using the formula: BMI = weight (kg) / [height (m)]^2. Obesity was

Table 1
Demographics and baseline characteristics of the overall study population of patients with chronic heart failure and according to obesity group. Obesity was defined as BMI ≥ 30 kg / m^2.

Variables	Total (n = 742)	Obese (n = 247)	Non-obese (n = 495)	p-value
Age, years	72 ± 11	70 ± 10	73 ± 11	0.002
Gender (female), No. (%)	324(43)	134(54)	190(38)	<0.001
BMI, kg/m^2	28 ± 6	35 ± 3	25 ± 3	<0.001
Blood pressure, mm Hg				
Systolic	125 ± 23	130 ± 22	122 ± 23	<0.001
Diastolic	68 ± 14	69 ± 14	67 ± 13	0.19
Heart rate, bpm	74 ± 15	74 ± 16	74 ± 14	0.921
NYHA functional class, No. (%)				
I–II	412(55.5)	136(55)	276(56)	0.876
III–IV	330(44.5)	111(45)	219(44)	0.876
LVEF, %	44 ± 17	48 ± 17	42 ± 17	<0.001
HFpPEF[a], No. (%)	329(44)	134(54)	195(40)	<0.001
Ischemic cause of HF, No. (%)	303(41)	94(38)	209(42)	0.303
Comorbidities, No. (%)				
Hypertension	582 (78)	209(85)	373(75)	0.002
AFib	234(31.5)	84(34)	150(30)	0.174
Diabetes Mellitus	345(46,5)	139(56)	206(42)	<0.001
CKD[b]	418(56)	140(57)	278(56)	0.478
COPD	163(22)	60(24)	103(21)	0.162
Anemia[c]	298(40)	99(40)	199(40)	0.520
Treatment, No. (%)				
ACEI or ARBs	578(78)	199(80)	379(77)	0.126
Betablockers	656(88)	210(85)	446(90)	0.051
MRA	308(41)	96(39)	212(43)	0.306
Digoxine	96(13)	30(12)	66(13)	0.728
Loop diuretics	655(88)	215(87)	440(89)	0.469
Antiplatelet/anticoagulant	610(82)	203(82)	407(82)	1
Laboratory measurements				
Hemoglobin, g/dL	12.5 ± 2	12.6 ± 2	12.5 ± 2	0.294
eGFR-ml/min/1.73 m^2	58.5 ± 24	59 ± 25	58 ± 24	0.906
Serum albumin, g/dL	3.7 ± 0.5	3.8 ± 0.4	3.75 ± 0.5	0.462
Norepinephrine, pg/mL	522(351–730)	466(324–657)	561(372–769)	<0.001
NT-pro BNP, pg/mL	1547(685–4044)	1145(487–2446)	1922(799–4760)	<0.001

Abbreviations: BMI, Body Mass Index; NYHA, New York Heart Association; LVEF, Left Ventricular Ejection Fraction; HFpPEF, Heart Failure with preserved Ejection Fraction; AFib, Atrial Fibrillation; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; ACEI, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; MRA, Mineralocorticoid Receptors Antagonists; eGFR, estimated Glomerular Filtration Rate; NT-proBNP, N-Terminal pro-Brain-type Natriuretic Peptide. Data are presented as arithmetic means ± SD (standard deviation) or numbers (with percentages). Data on norepinephrine and NT-proBNP are presented as median (Q_1–Q_3).

[a] HFpPEF was defined as LVEF ≥ 45%.

[b] CKD was defined as eGFR < 60 mL/min/1.73.

[c] Anemia was defined using the World Health Organization criteria (hemoglobin level < 12 g/dL in women and <13 g/dL in men).