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Body Mass Index and Heart Failure: Paradox or Mistaken Identity?

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Abstract
Background: Obesity paradox is a clinical situation where obesity confers benefit. This is anachronistic considering that obesity increases the risk of cardiovascular diseases like heart failure (HF). This raises the question of whether obese patients with clinically diagnosed HF were actually in HF.
Methods: This was a secondary analysis of data generated in a larger study on Prevalence of Dysnatraemia in HF patients admitted on our service. History, physical and 2D echocardiographic examinations were done for the study patients. Blood was taken for point of care NT- pro BNP assay. Echo and BNP data were divided along weight group lines and compared
Results: There were 120 patients; 69 males and 51 females aged between 18 to 92 years with a mean of 51.9 $\pm$ 16.67 (SD) years. The NT-pro BNP levels ranged from 301.0 to 950.0 pg/ml with a mean of 509.7 $\pm$ 161.9 (SD) pg/ml. Applying the appropriate age specific cut off values, 25/120 (20.8%) were accurately identified as HF; while 95/120 (79.2%) were misclassified. Of the 120, 13 were obese, 29 overweight and 78 normal. 11/13 of the obese (84.6%) were misclassified. 22/29 overweight (75.9%) were misclassified and 62/78 with normal weight (79.5%) were misclassified. The proportion misclassified was high across board but highest for the obese category. Mean ejection fraction (EF) rose significantly ($p = 0.037$) with BMI; more for males ($p=0.019$) than females ($p = 0.54$). Using EF $\geq$ 50% to define heart failure with preserved ejection fraction (HFpEF) BMI was higher in HFpEF compared with HFrEF to a statistically significant level, p = 0 001 again more in males than females.
Conclusion: Using BNP as a marker of HF in the obese gives inconsistent results; and should be reserved for prognostication and follow- up. Most obese people are likely to present with clinical features of HF without actually being in HF.

Keywords: *Obesity; Heart failure; Paradox; Mistaken identity*

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Abstrait
Contexte: Le paradoxe de l'obésité est une situation clinique où l'obésité confère un bénéfice. Ceci est anachronique étant donné que l'obésité augmente le risque de maladies cardiovasculaires comme l'insuffisance cardiaque (IC). Cela soulève la question de savoir si les patients obèses atteints d'IC cliniquement diagnostiquée étaient réellement en IC.
Méthodes: Il s'agissait d'une analyse secondaire des données générées dans une étude plus vaste sur la prévalence de la dysnatrémie chez les patients atteints d'insuffisance cardiaque admis dans notre service. Des examens antécédents, physiques et échocardiographiques 2D ont été effectués pour les patients de l'étude. Le sang a été prélevé pour le test NT-pro BNP au point de service. Les données Echo et BNP ont été divisées selon les groupes de poids et comparées
Résultats: Il y avait 120 patients; 69 hommes et 51 femmes âgés de 18 à 92 ans avec une moyenne de 51.9 + 16.67 (ET) ans. Les niveaux de NT-pro BNP variaient de 301.0 à 950.0 pg/ml avec une moyenne de 509.7 + 161.9 (SD) pg/ml. En appliquant les valeurs seuils spécifiques à l'âge appropriées, 25/120 (20.8 %) ont été identifiés avec précision comme IC ; tandis que 95/120 (79.2 %) ont été mal classés. Sur les 120, 13 étaient obèses, 29 en surpoids et 78 normaux. 11/13 des obèses (84.6%) ont été mal classés. 22/29 en surpoids (75.9 %) ont été mal classés et 62/78 avec un poids normal (79.5 %) ont été mal classés. La proportion de personnes mal classées était élevée dans tous les domaines, mais la plus élevée pour la catégorie des obèses. La fraction d'éjection moyenne (FE) augmentait significativement ($p = 0.037$) avec l'IMC; plus pour les hommes ($p = 0.019$) que pour les femmes ($p = 0.54$). En utilisant EF> 50% pour définir l'insuffisance cardiaque avec fraction d'éjection préservée (HFpEF), l'IMC était plus élevé dans HFpEF par rapport à HFrEF à un niveau statistiquement significatif, p = 0 001 encore plus chez les hommes que chez les femmes.
Conclusion: L'utilisation du BNP comme marqueur de l'IC chez l'obèse donne des résultats incohérents; et doit être réservé au pronostic et au suivi. La plupart des personnes obèses sont susceptibles de présenter des caractéristiques cliniques d'IC sans être réellement atteintes d'IC.

Introduction

Over the years, the term obesity paradox has become acceptable in medical literature [1]. This is a clinical situation where obesity as it were confers some clinical benefit or protection [2]. That body mass index (BMI) could confer any benefit in cardiovascular disease (CVD) is anachronistic, considering that obesity increases the risk of CVD. Kenchaiah et al [3] showed that for every 1kg/m^2 increase in BMI, heart failure (HF) risk over 14 years rose by 5% in men and 7% in women; and that the HF risk rose across all categories of BMI. Curiously, despite robust evidence of adverse consequences of obesity on cardiac haemodynamics, structure and function, obese patients with established CVD seem to fare better than their leaner counterparts in similar clinical situations [4]. In HF, cachexia strongly predicts reduced survival independently [5]. If this is true having been re-inforced by the description of reverse epidemiology in HF [6], could it also be true that most obese people with a clinical diagnosis of HF do not actually have HF. This is relevant considering that in HF studies, its diagnosis is arrived at largely clinically with Framingham criteria. This set of clinical criteria may exist in various combinations in obesity without HF. For instance, an obese patient with obstructive sleep apnoea syndrome (OSAS) may present with features similar to paroxysmal nocturnal dyspnea, and be dyspnoeic on exertion because of restrictive lung disease as well as physical de-conditioning. Peripheral oedema could result in them due to venous insufficiency that they usually have.

We therefore came up with a hypothesis that the obese patients satisfying clinical criteria for HF, actually do not have HF; and that it may be why they appear to fare better in supposedly HF situations. We sought to test this in our HF cohort by assaying brain natriuretic peptide (BNP) which is a biochemical marker of HF and relating it with BMI. The only Nigerian study encountered in literature [7] did not include BNP assay.

Methodology

One hundred and twenty patients presenting with heart failure irrespective of cause and requiring in-patient care were consecutively recruited between May 2015 and May 2016 in a large study titled "Prevalence of dysnatraemia and its effects on outcome in hospitalized patients with heart failure in Jos University Teaching Hospital". The study was approved by the hospital Research and Ethics Committee. The patients were 18 years and above. Written informed consent was obtained from each participant before recruitment; after which they were interviewed and examined by one of the authors (SUU). Findings on physical examination were recorded. Weight was measured in kilograms on admission with an analogue weighing scale; with only light clothing. Height was measured using a stadiometer in metres without shoes or head gear. From these BMI was derived as quotient of weight and square of height. As part of blood investigations, 3 ml of blood was collected from each patient in sodium heparin vacutainers and sent to the Chemical Pathology laboratory within 1 hour of collection for NT-pro BNP analysis using Cobas h 23.2 point of care equipment (KQ 0135167); by immunoassay using the gold labelling technique. All known biosafety methods and universal precautions were observed. They also underwent echocardiography, with measurements taken in standard fashion [8]; utilizing the Aloka SSD-3500 equipment fitted with a 2.5 MHz transducer

STATISTICS: The Epi-Info version 7.2 software (Centre for Disease Control and Prevention, Atlanta Georgia, USA) was used for data analysis. Quantitative variables were summarized using mean and standard deviation. Categorical variables were expressed using percentages. The student t-test was used to compare means of groups. In all cases, $p < 0.05$ was considered statistically significant.

Results

The size of the cohort was 120 made up of 69 males and 51 females. Their ages ranged from 18 to 92 years with a mean of 51.9 $\pm$ 16.67 (SD) years.

The NT-pro BNP levels ranged from 301.0 to 950.0 pg/ml with a mean of 509.7 $\pm$ 161.9 (SD) pg/ml. Applying the cut off value of 450 pg/ml for patients < 50 years, 900 pg/ml for patients 50 to 75 years and 1800 for patients > 75 years [9], 25 out of 120 (20.8%) were accurately identified as being in HF; while though qualifying for the diagnosis of HF using the Framingham criteria, 95 out of 120 (79.2%) were misclassified. Of the 120, 13 were obese, 29 were overweight and 78 normal.

Out of the 13 that were obese, 11 (84.6%) were misclassified. Among the 29 that were overweight, 22 (75.9%) were misclassified and out of the 78 with normal weight, 62 (79.5%) were misclassified. The implication is that the proportion misclassified was high across board but highest for the obese category. Stratifying the patients into weight categories and comparing their mean ejection fraction (EF), it showed that the EF rose significantly ($p = 0.037$) with BMI (See Table 1). Based on gender, it became obvious that this was a male gender effect; as the trend in females did not attain statistical significance ($p = 0.54$) while it did with males, $p = 0.019$. (See Table 2).

Ejection fraction ranged from 21.6 % to 55.5% and increased as weight category increased.

Using EF ≥ 50% to define heart failure with preserved ejection fraction (HFpEF) and EF < 50% for HFrEF and correlating with weight strata, it showed that mean BMI was higher in HFpEF compared with HFrEF to a statistically significant level, p = 0 001(See Table 3). This again was more of a male than female effect (See Table 4).

Table 1: Comparison of BMI with EF

BMI Category (kg/m²)	Mean EF + SD (%)	P
<20	32.78+11.65	0.037
20 - 24.9	37.47+14.03	
25 - 29.9	41.31+17.12	
≥ 30	45.62+14.29	

Table 2: Comparison of BMI with EF by Gender

BMI (kg/m²)	Mean EF + SD (%)		P	
	Male	Female	Male	Female
<20	30.23+8.05	35.14+14.10	0.019	0.55
20 - 24.9	36.39+14.25	40.07+13.59		
25 - 29.9	45.86+20.07	37.07+13.13		
≥ 30	47.83+14.02	43.71+15.35		

Table 3: Comparison of BMI with HF Category

HF Category	BMI kg/m²	p
HFpEF	26.41 + 4.92	0.001
HFrEF	23.12 + 4.78	
Data are mean + SD		

Key: HFpEF – Heart Failure with preserved Ejection Fraction
HFrEF – Heart Failure with reduced Ejection Fraction

Table 4: Comparison of BMI with HF Category by Gender

HF Category	BMI kg/m²		P	
	Male	Female	Male	Female
HFpEF	27.56+4.37	24.86+5.35	0.000	0.62
HFrEF	22.47+4.09	23.99+5.52		
Data are mean + SD				

Key: HFpEF – Heart Failure with preserved Ejection Fraction
HFrEF – Heart Failure with reduced Ejection Fraction

Discussion

BNP is a biomarker used to diagnose and treat HF [10]. They are secreted from the ventricles exposed to elevation in stress be it volume or pressure overload; and in acute presentation are useful in identifying those at increased risk for complications [11]. They are also useful from the perspective of their negative predictive value which helps in ruling out HF [12].

The result here showed that using BNP as a biomarker for CCF, most of our patients would be said not to be in heart failure; though by the Framingham criteria they would be diagnosed as such. This should however be taken with some circumspection as they were mostly chronic heart failure patients previously on treatment. Many drugs used in the treatment of CCF affect BNP levels; with blockers of renin angiotensin aldosterone system reducing [13] while digitalis and beta blockers increase [14]. Interestingly, the proportion of the misclassified was highest among the obese. This is borne out by the fact that with increase in BMI, the EF an objective measure of left ventricular function rose (See Table 1). Looking at BMI from the perspective of HFpEF or HFrEF, it also turned out that the higher the BMI, the higher the proportion with preserved EF. In all of these, it emerged to be a gender driven effect. This is because when dichotomized by gender, the trend was not significant for females; only for males (See Table 4).

This is not surprising. Factors that influence BNP values in women are different from those of the men [15]. These inconsistencies have led many researchers to suggest that rather than being used to diagnose CCF, BNP assay is better suited for predicting outcome in heart failure [16] as it reflects severity of HF in individual cases [17]. Elevated levels of BNP apart from the obese have also been found in renal failure, pulmonary embolism as well as pulmonary hypertension [18]; conditions that could clinically mimic HF. These suggest that BNP as a biochemical marker for diagnosing HF may be of high sensitivity, but certainly low on specificity. In such instances it should be reserved for following up and prognostication in individual cases. BNP levels measured after starting treatment as was the case in our cohort have been found to be more predictive of poor outcome than those taken at first presentation and initiation of treatment [19]. BNP levels in patients chronically in HF and on treatment should therefore not be a biomarker of HF.

In support of the mistaken relationship between BMI and BNP as a biomarker of HF is the fact that the obese were the most likely to be misclassified as shown in this study. Therefore the concept of obesity paradox in HF may be faulty as it has shown in a meta-analysis to be inconsistent [20], and may actually be flawed. As an accurate diagnostic marker in HF patients older than 80 years it has been scored very low leading to a suggestion that the threshold value should be revised [21]. Another point in support of the mistaken identity relationship is the position that the diagnostic class of HFpEF is particularly susceptible to misdiagnosis using BNP [22]. Most of the obese HF patients were misclassified using BNP in our study, as well as being largely in the HFpEF category. Clinicians should therefore not be misled by this so called paradox to become complacent in dealing with obesity and overweight. Studies have shown that the obese express circulating natriuretic peptides poorly and become symptomatic with earlier stages of HF.

Study Limitations: This study is limited by the fact that this was a single centre study enlisting a relatively small sample size. Moreover, many of the patients were already diagnosed cases of HF on treatment for a variable period with drugs many of which affect BNP assay. BMI classification of obesity was lumped together without considering sarcopenic obesity, when there is high BMI and reduced muscle mass. This is the type that is adverse to outcome in cardiovascular diseases [23].

Conclusion

Using BNP as a marker of HF in the obese gives inconsistent results; and should be reserved for prognostication and follow up in individual cases. Most obese people are likely to present with clinical features of HF without actually being in that state; and when they fare better a wrong impression is created that obesity is protective in HF.

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