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Research Article

Correlation Between Serum Copeptin and NTproBNP Levels in Heart Failure

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Abstract

Introduction: Heart Failure is a leading cause of morbidity and mortality worldwide. It is associated with upregulation and dysfunction of the renin-angiotensin aldosterone system, the sympathetic nervous system and the vasopressin system. In heart failure, the levels of vasopressin are elevated and out of sync with the osmotic status. Arginine Vasopressin has a half-life of only 20 minutes and is bound to circulating platelets. Hence, it is not useful as a biomarker. Copeptin, a by-product of vasopressin metabolism has been used as a surrogate marker for Arginine Vasopressin in clinical practice. Thus, our study aims to find the use of copeptin in studying heart failure and its use in predicting severity. We also sought to correlate copeptin with NTproBNP the standard biomarker used in heart failure. Methods: Our study was a single-centre cross-sectional observational study involving 90 admitted heart failure patients over 18 months. NYHA Class was used to assess the severity of heart failure. Copeptin levels were measured using Human Copeptin ELISA Kit. Results: In these patients, elevated levels of copeptin and NTproBNP were found. In patients with higher NYHA Class, a greater rise in serum copeptin and NTproBNP levels was noted. Moreover, a strong positive correlation between NTproBNP and copeptin (rho = 0.7) was found in our study. Conclusion: Our study puts forward copeptin as a simple additional cost-effective biomarker for predicting the severity of heart failure.

Keywords

Heart Failure, Copeptin, NTproBNP, Severity, Arginine Vasopressin

1. Introduction

Heart failure is a leading cause of mortality and morbidity worldwide affecting up to 26 million people globally [1]. In India, it has an estimated prevalence between 1.3 – 4.6 million. The important causes of heart failure in India are coronary artery disease, hypertension, obesity and rheumatic heart disease [2]. Heart failure is a complex clinical syndrome resulting from structural or functional impairment of ventricular filling or ejection of blood. It is the end stage of all cardiac diseases ranging from myocardial infarction to cardiomyopathies [3]. The complex pathophysiology involves upregulation and dysfunction of the renin-angiotensin aldosterone system (RAAS), sympathetic nervous system and vasopressin system. This leads to salt and water retention, increased heart rate, pathological remodelling and fibrosis [4].

Arginine Vasopressin (AVP) is a nonapeptide produced by the hypothalamus that promotes renal water conversation and regulates osmolar status and cardiovascular homeostasis [5]. In heart failure, AVP is released in excess without regard for

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the osmotic status. This leads to chronically elevated levels of AVP. The exact mechanism behind this is not known, but is believed to be due to altered baroreceptor thresholds, and the simultaneous activation of the SNS RAAS axis. AVP is an unstable molecule with a half-life of only 20 minutes. Moreover, almost 90 % of AVP is bound to circulating platelets. Thus, AVP is not a useful biomarker in clinical practice [6, 7].

The AVP precursor molecule pre-provasopressin is secreted from the posterior pituitary in response to hypotension and hypoosmolality. Copeptin, derived from the cleavage of the c-terminal of pre-provasopressin is a relatively stable molecule and a surrogate marker of AVP in clinical practice [8, 9].

Copeptin has been previously studied in other conditions such as sepsis, chronic obstructive pulmonary disease, and cirrhosis [10, 11]. Various studies have explored the role of copeptin as a biomarker for heart failure. It has been shown to have a similar or even superior role as a biomarker in heart failure compared to the standard N- terminal pro-B type natriuretic peptide (NTproBNP) [12, 13]. Copeptin is an effective biomarker in both acute destabilized heart failure as well as chronic heart failure patients. Raised copeptin levels have been shown to be associated with increased mortality in these studies [14, 15]. There are lacunae in Indian literature regarding serum copeptin in heart failure and its correlation with NTproBNP. Our study aimed to address this.

2. Methods

The study was conducted at Safdarjung Hospital, a tertiary care hospital in New Delhi. It involved 90 heart failure patients over 18 months. It included patients over 18 years of age. Other conditions that can cause a rise in copeptin levels like hyponatremia, hypothalamic-pituitary axis dysfunction, sepsis, septic and haemorrhagic shock, ischaemic stroke, intracerebral haemorrhage, and chronic liver disease were excluded from the study. The study was conducted after approval from the institutional ethics committee and informed consent from the subjects. Blood samples were collected within 24 hours of admission and sent for relevant investigations. This was a cross-sectional study with no further follow-up.

Copeptin was measured using the human Copeptin Enzyme Linked Immunoassay (ELISA) kit. The kit was based on the principle of double antibody sandwich technology enzyme linked immunosorbent assay (ELISA). Collected samples were stored between 2-8 ℃ and used within five days.

NTproBNP was estimated using flouresence immunoassay using a standard kit.

The collected data was entered into a spreadsheet and analysed using Statistical Package for Social Services (SPSS) version 21.0

3. Results

90 patients were taken in this study. The median age was 60 years (52-67 IQR). 61 (67.8 %) were male and 29 (32.2 %) were females. Most patients were in NYHA Class 3 (49 patients – 54.4 %), 32 (35.6 %) and 9 (10.0 %) were in Class 4 and Class 2 respectively.

Table 1 demonstrates the correlation of different parameters with the New York Heart Association (NYHA) class. It was seen that a higher NYHA class had a significant association with higher NTproBNP and copeptin levels.

Our study also showed a statistically significant positive correlation ($p < 0.001$) between serum copeptin and NTproBNP levels (rho = 0.7). Figure 1 demonstrates correlation between NTproBNP and serum copeptin levels.

Figure 2 shows levels of NTproBNP and Serum copeptin stratified according to NYHA class. The levels of these cardiac biomarkers were much higher in patients in NYHA Class 4 than Class 3 and Class 2.

Table 1. *Correlation between NYHA and different parameters.*

Parameters	NYHA			p value
	Class 2 (n = 9)	Class 3 (n = 49)	Class 4 (n = 32)	
Age (years)	56.67 ±18.75	56.33 ±12.15	61.56 ±11.66	0.122[1]
Age				0.163[2]
21-30 Years	1 (11.1%)	2 (4.1%)	1 (3.1%)	
31-40 Years	1 (11.1%)	3 (6.1%)	1 (3.1%)	
41-50 Years	0 (0.0%)	9 (18.4%)	2 (6.2%)	
51-60 Years	3 (33.3%)	17 (34.7%)	7 (21.9%)	
61-70 Years	2 (22.2%)	12 (24.5%)	14 (43.8%)	

Parameters	NYHA			p value
	Class 2 (n = 9)	Class 3 (n = 49)	Class 4 (n = 32)	
71-80 Years	1 (11.1%)	6 (12.2%)	7 (21.9%)	
81-90 Years	1 (11.1%)	0 (0.0%)	0 (0.0%)	
Gender***				0.043[3]
Male	3 (33.3%)	37 (75.5%)	21 (65.6%)	
Female	6 (66.7%)	12 (24.5%)	11 (34.4%)	
NYHA Weighted Score***	2.00 ±0.00	3.00 ±0.00	4.00 ±0.00	<0.001[1]
NTProBNP (pg/mL)***	2039.89 ±1112.20	7211.98 ±3424.70	13662.00 ±6329.43	<0.001[1]
Serum Copeptin (pmol/L)***	18.72 ±9.88	22.28 ±7.93	33.01 ±15.61	<0.001[1]
Hemoglobin (mg/dL)	10.73 ±2.70	10.97 ±1.87	10.61 ±2.00	0.677[1]
Platelet Count (x10 ^{3}/mm ^{3})	153.22 ±73.83	205.23 ±80.99	203.03 ±85.74	0.152[1]
TLC (/mm ^{3})	6888.67 ±1482.01	6913.45 ±2321.54	6906.25 ±2527.90	0.975[1]
S. Sodium (mEq/L)	134.78 ±5.56	136.51 ±4.45	138.34 ±5.35	0.181[1]
S. Potassium (mEq/L)	4.06 ±0.61	4.30 ±0.51	4.47 ±0.63	0.228[1]
S. Urea (mg/dL)***	46.78 ±20.63	51.65 ±23.50	75.91 ±47.63	0.018[1]
S. Creatinine (mg/dL)	0.77 ±0.44	0.84 ±0.65	1.35 ±1.25	0.138[1]
S. Total Bilirubin (mg/dL)***	0.48 ±0.19	0.71 ±0.26	1.14 ±0.85	0.001[1]
SGOT (U/L)	56.11 ±34.40	67.80 ±63.75	316.62 ±751.76	0.267[1]
SGPT (U/L)	118.78 ±223.07	65.24 ±104.98	209.91 ±457.50	0.718[1]
ALP (U/L)	141.00 ±85.81	110.37 ±38.19	115.16 ±47.88	0.833[1]
Ejection Fraction (%)	36.50 ±9.19	33.18 ±10.06	25.38 ±10.89	0.069[1]

***Significant at p<0.05, 1: Kruskal Wallis Test, 2: Fisher's Exact Test, 3: Chi-Squared Test

Our study also showed a statistically significant positive correlation (p < 0.001) between serum copeptin and NTproBNP levels (rho = 0.7). Figure 1 demonstrates correlation between NTproBNP and serum copeptin levels.

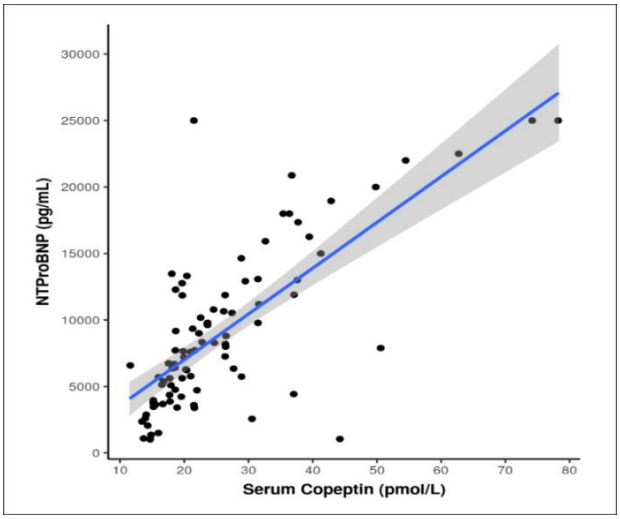

Figure 1. *Correlation between NTproBNP (pg/mL) and Serum Copeptin (pmol/L).*

Table 2. *Correlation between Serum Copeptin and NTproBNP.*

Correlation	Spearman Correlation Coefficient	P Value
Serum Copeptin (pmol/L) vs NTProBNP (pg/mL)	0.7	<0.001

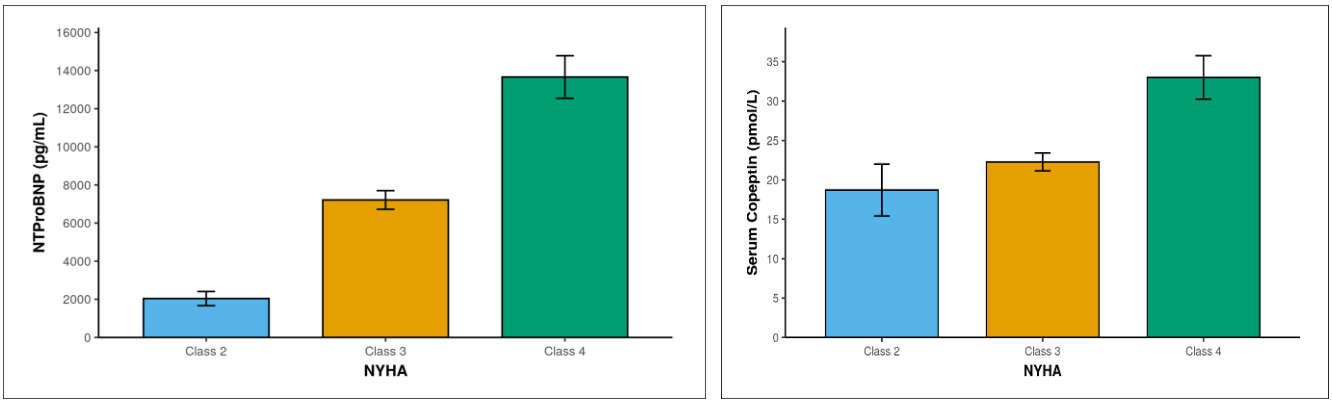

Figure 2. *Correlation between NYHA Class and NTproBNP (pg/mL) and Serum Copeptin (pmol/L).*

4. Discussion

Our study showed serum copeptin and NTproBNP as effective markers of heart failure.

The mean NTproBNP levels in our study were 8988 ± 5904.58 pg/mL. A higher NYHA Class was associated with higher NTproBNP levels. The mean NT proBNP levels in NYHA Class IV patients was 13662 ± 6329.43 pg/mL compared to Class III (7211.98 ± 3424.7) and Class II (2039.89 ± 1112.20).

In the PRIDE trial, it was seen that NTproBNP > 450 pg/mL for patients less than 50 years of age and > 900 pg/mL for patients over 50 years of age were strongly sensitive and specific for the diagnosis of heart failure [16].

The mean serum copeptin levels in our study were 25.74 ± 12.57 pmol/L. Similar to NTproBNP, higher levels of serum copeptin were seen in NYHA Class IV (33.01 ± 15.61) compared to Class III (22.28 ± 7.93) and Class II (18.72 ± 9.88).

The usual range of serum copeptin has been established in 2 large clinical trials. In the first study, plasma copeptin levels ranged from 1.0 – 13.8 pmol/L with a median concentration of 4.2 pmol/L [17]. The second evaluation in patients with over 700 randomly selected volunteers reported comparable results with plasma copeptin ranging from 1.0 to 13.0 pmol/L [18].

Other studies on copeptin in heart failure, like the study by Masson et al have demonstrated baseline copeptin levels of 13.8 pmol/L (7.6 – 24.2) [19]. Since our study included hospitalised patients with higher disease severity, the median copeptin levels were higher in our study.

Thus, higher levels of NTproBNP and Copeptin had a direct association with the severity of heart failure as indicated by a higher NYHA Class.

A strong positive correlation was demonstrated between NTproBNP and Serum copeptin in our study (rho = 0.7).

The limitation of our study was that it was a single-centre cross-sectional study with a small sample size. More studies with longitudinal design are needed to explore the possible involvement of the arginine vasopressin system in heart failure.

In conclusion, our study shows that serum copeptin can be used as an additional tool to assess heart failure and predict its severity.

Abbreviations

RAAS	Renin Angiotensin Aldosterone System
AVP	Arginine Vasopressin
NTproBNP	N-terminal Pro-B type Natriuretic Peptide
NYHA	New York Heart Association
ELISA	Enzyme Linked Immunoassay

Conflicts of Interest

The authors declare no conflicts of interest.

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