

Assessment of Human Natriuretic Peptides (B), Human N-Terminal Pro-BNP and Nor-epinephrine as Neurohumoral Markers in Sleep Disordered Breathing among Heart Failure Patients in Upper Egypt

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Abstract

Objective: The purposes of this study are to: (1) Measure neurohumoral activation in heart failure patients with and without sleep disordered breathing; (2) Assessment of neurohumoral markers with the severity of sleep apnea and severity of heart failure.

Patients and methods: In this case report study, we studied 100 patients with heart failure (64 male, 36 female). All patients underwent echocardiography and a full night-attended polysomnography, in addition to neurohumoral evaluation.

Results: Group (1) sleep Disordered Breathing (SDB) had significant increase in the plasma concentration level of BNP (591.50 ± 165.75 vs. 298.33 ± 86.63 pg/ml, $P=0.001^*$), NT-proBNP (1750.05 ± 773.15 vs. 686.98 ± 377.88 pg/ml, $P=0.001^*$) and nor epinephrine (NE) (616.12 ± 139.57 vs. 203.80 ± 64.30 pg/ml, $P=0.001^*$) when compared with No-SDB. A significant increase in plasma level of NT-proBNP and nor-epinephrine (NE) in OSA was observed when compared with central sleep apnea (CSA). Increased neurohumoral markers with different severity of apnea hypopnea index (AHI). Moreover, a significant increase was observed in neurohumoral markers with increased severity of left ventricular ejection fraction (LVEF). Based on echocardiographic etiology of heart failure, patients with dilated cardiomyopathy had a significant increase in plasma level of BNP and NT-pro BNP. On the other hand, plasma concentration level of nor-epinephrine (NE) was significantly increased in patients with hypertensive heart disease.

Conclusion: Heart failure patients with sleep disordered breathing were associated with higher levels of neurohumoral activation. Moreover N-TproBNP (<300 pg/ml) and nor epinephrine (NE) <300 pg/ml were predictors of OSA among heart failure.

Keywords: Human natriuretic peptides (B); Neurohumoral markers; Obstructive sleep apnea

Abbreviations: HF: Heart Failure; OSA: Obstructive Sleep Apnea; BNP: Human Natriuretic Peptides B; NT-proBNP: Human N-terminal proBNP; NE: Plasma Nor-epinephrine; CSA: Central Sleep Apnea; No SDB: No Sleep Disordered Breathing; AHI: Apnea Hypopnea Index; LVEF: Left Ventricular Ejection Fraction; OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; ESS: Epworth Sleepiness Scale; NYHA class: New York Heart Association Classification; PaCO₂: Arterial Carbon Dioxide Tension.

Introduction

Heart failure (HF) is an important and growing public health problem. It is a major cause of mortality and morbidity and is associated with progressively severe symptoms, chronic disability and impaired quality of life. Sleep-disordered breathing (SDB) is known to occur frequently in patients with stable but severe HF and may be a predictor of poor prognosis [1].

Neurohumoral activation starts early in the natural history of left ventricular dysfunction and levels of circulating hormones increase in proportion to the severity of HF. In HF patients with SDB, recurrent episodes of apnea and hypopnea are associated with dips in arterial oxygen saturation and excessive arousals from sleep, each of which is in turn associated with increased sympathetic nerve activity (SNA). Such increases in SNA are likely to contribute to increased neurohumoral activation and adversely affect prognosis [2].

The objectives of the present study are to: (A) Measure neurohumoral activation in HF patients with and without sleep disordered breathing;

(B) Assessment of neurohumoral markers with the severity of sleep apnea and severity of heart failure.

Patients and Methods

A total of 100 patients (64 male, 36 female) were enrolled in chest and cardiology outpatients' clinic at Assiut University hospital in a time period between June, 2015 and March, 2016. Patients were classified into two groups: Group (1): Sleep disordered breathing (85 patients) (SDB) and Group (2): No sleep disordered breathing (No SDB group) (15 patients). An informed written consent was obtained from all the patients. The study was approved by the Faculty of Medicine, Ethics Committee, Assiut University.

Exclusion criteria

Patients with recent unstable angina or myocardial infarction

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within 3 months of the study, history of chronic lung disease (i.e., obstructive pulmonary disease), pregnancy, history of stroke or clinical signs of peripheral or central nervous system disorders.

All patients were subjected to echocardiography and overnight attended polysomnogram, in addition to neurohumoral activation.

Echocardiography

All patients underwent echocardiography for assessment of LV function. (Vivid S5, GE). The main cause of HF was specified, i.e. Ischemic Heart Disease (IHD), Dilated Cardiomyopathy (DCM) and hypertensive heart disease. Left ventricular internal dimension (LV End-Diastolic Dimension (LVEDD), Left Ventricular End-systolic Dimension (LVESD), Interventricular Septal Thickness (IVST) and Posterior Wall Thickness (PWT) were determined from M-mode measurements. In addition, Left Ventricular Ejection Fraction (LVEF) was measured [3].

Polysomnography

All patients underwent full night attended polysomnography (Somnstar 4100, Sensor-Medics Co., Yorba Linda, CA, USA) in the sleep laboratory of the Assiut university hospital. The polysomnograms were all scored manually according to the American academy of sleep medicine [4]. The apnea hypopnea index (AHI) which is an index used to indicate the severity of sleep apnea. It is represented by the number of apnea and hypopnea events per hour of sleep. The apneas (pauses in breathing) must last for at least 10 s and be associated with a decrease in blood oxygenation. Combining AHI and oxygen desaturation gives an overall sleep apnea severity score that evaluates both the number of sleep disruptions and the degree of oxygen desaturation (low oxygen level in the blood).

The AHI is calculated by dividing the number of apnea events by the number of hours of sleep was calculated as the number of apnea and hypopnea events per hour of sleep. Severity of sleep apnea was measured based on the following frequencies: Mild (5 to 15 events/h); Moderate (15 to 30 events/h) and Severe (>30 events/h) [4].

Neurohumoral markers

Blood samples were drawn at the early morning from an antecubital vein using a serum separator tube (SST) and store samples at -20°C.

- Human Natriuretic peptides (B) (Catalog No: E0541h) and Human NT-pro BNP (Catalog No: E0485h): (Using ELISA Kit). A cut off value of <100 pg/mL for BNP and <300 pg/mL

Mean $\pm$ SD	Group (1) SDB (n=85)	Group (2) No SDB (n=15)	P-value
BNP (<100 pg/mL)	591.5 $\pm$ 165.7	298.3 $\pm$ 86.6	0.001*
NT pro BNP (<300 pg/mL)	1750.0 $\pm$ 773.1	686.9 $\pm$ 377.8	0.001*
NE (0-300 pg/ml)	616.1 $\pm$ 139.5	203.8 $\pm$ 64.3	0.001*

Table 1: Laboratory markers in heart failure patients with (SDB) and without sleep disordered breathing (SDB) (n=100). P-Value is done between both (SDB and NO SDB) groups. * =Significant difference

Mean $\pm$ SD	OSA (n=53)	CSA (n=32)	No SDB (n=15)	P1	P2	P3
BNP (<100 pg/mL)	515.8 $\pm$ 164.9	476.8 $\pm$ 166.0	298.3 $\pm$ 86.6	0.251	0.001*	0.001*
NT pro BNP (<300 pg/mL)	2489.3 $\pm$ 761.8	1303.7 $\pm$ 283.3	686.9 $\pm$ 377.8	0.001*	0.001*	0.001*
NE (0-300 pg/ml)	678.7 $\pm$ 143.7	395.1 $\pm$ 131.9	203.8 $\pm$ 64.3	0.001*	0.001*	0.001*

Values expressed as mean $\pm$ SD, P1 between (OSA vs. CSA), P2 (OSA vs. No SDB), P3 (CSA vs. No SDB). * =Significant difference.

Table 2: Laboratory markers in heart failure patients with obstructive (OSA) and central (CSA) sleep apnea and no sleep disordered breathing (n=100).

for NT-pro BNP makes the diagnosis of heart failure less likely regardless of age and sex [5].

- Norepinephrine: Using ELISA Kit (RE59261) the normal range: 0-300 pg/mL [6].

Statistical analysis

(SPSS-version 16) software was used for analysis of results. Results in this study were expressed as mean $\pm$ standard deviation or number and percentage. Comparison between 2 groups was done using t-test and one way ANOVA test for comparison between more than 2 groups. The difference was considered significant when $P < 0.05$. Logistic regression analysis was done to detect predictors of obstructive sleep apnea (OSA) in heart failure.

Results

Table 1 showed that group (1) patients with SDB had significant increase in the plasma concentration level of human natriuretic peptides B (BNP), N-terminal pro BNP (NT-pro BNP) and nor epinephrine (NE) when compared with (No-SDB).

On comparing laboratory markers between obstructive (OSA) and central (CSA) sleep apnea as shown in Table 2, our study revealed a significant increase in the plasma concentration level of both N-terminal pro BNP and nor epinephrine (NE) in patients with OSA when compared with CSA. No significant differences were demonstrated between both groups in human natriuretic peptides B (BNP). While, there was a significant increase in plasma concentration level of (BNP), (NT pro BNP) and nor epinephrine (NE) in both obstructive (OSA) and central (CSA) sleep apneas compared with No-SDB.

As shown in Figure 1, a significantly higher plasma concentrations of human natriuretic peptides B (BNP), N-terminal pro BNP (NT-pro BNP) and nor epinephrine (NE) were found in patients with OSA as compared with the other two groups. Table 3 shows, the concentration level of N-terminal pro BNP (NT-pro BNP) and nor epinephrine (NE)

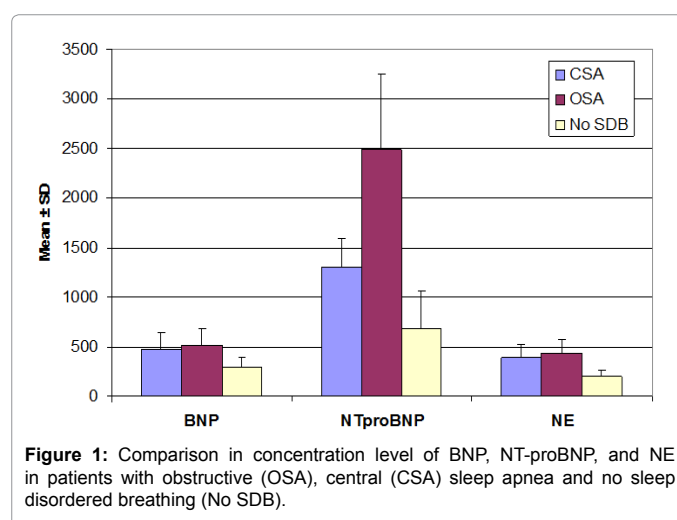


Figure 1: Comparison in concentration level of BNP, NT-proBNP, and NE in patients with obstructive (OSA), central (CSA) sleep apnea and no sleep disordered breathing (No SDB).

were significantly increased as apnea hypopnea index (AHI) severity increased. Table 4 shows that concentration level of BNP, N-terminal pro BNP (NT-pro BNP) and nor epinephrine (NE) was significantly increased in patients with different grades of left ventricular ejection fraction (LVEF).

Table 5 revealed that patients with dilated cardiomyopathy had a significant increase in plasma concentration level of BNP and N-terminal pro BNP (NT-pro BNP) as compared with the other two groups. On the other hand, plasma concentration level of nor epinephrine (NE) was significantly increased in patients with hypertensive heart disease.

Table 6 showed logistic regression analysis revealing the predictors of sleep disordered breathing (SDB) among heart failure patients.

The predictor factors were Body mass index (BMI ≥ 30), systemic hypertension, neck circumference <40 cm, waist circumference (<110 cm), left ventricular ejection fraction (LVEF) ($\leq 45\%$), N-terminal pro BNP (<300 pg/ml) and nor epinephrine (NE) (<300 pg/ml), in addition to, male sex and age <50 years.

Table 7 showed logistic regression analysis revealing the predictors of obstructive sleep apnea (OSA) in patients with heart failure. The most predictor factors for OSA were body mass index (BMI ≥ 30), neck circumference <40 cm, waist circumference (<110 cm), systemic hypertension, N-terminal pro BNP (<300 pg/ml) and nor-epinephrine (NE) <300 pg/ml, in addition to male sex and left ventricular ejection fraction (LVEF) ($\leq 45\%$).

	AHI index			P-value
	Mild (5-15 event/h) (n=6)	Moderate (15-30 event/h) (n=27)	Severe (>30 event/h) (n=52)	
BNP (<100 pg/ml)	390.3 $\pm$ 79.1	430.0 $\pm$ 87.0	570.8 $\pm$ 81.9	0.234
NTproBNP (300 pg/ml)	1417.5 $\pm$ 210.7	1836.5 $\pm$ 631.8	2819.2 $\pm$ 846.6	0.003 [*]
NE (0-300 pg/ml)	329.6 $\pm$ 81.5	441.3 $\pm$ 65.3	664.9 $\pm$ 151.6	0.001 [*]

P-Value is done between both (AHI & laboratory markers).^{*}=Significant difference.

Table 3: Laboratory markers in heart failure patients with different severity of apnea hypopnea index (AHI).

	LVEF (%)				P-value
	Normal range ($\geq 50\%$) n=6	Mildly abnormal (40–50%) n=12	Moderately abnormal (30–40%) n=14	Severely abnormal ($\leq 30\%$) n=21	
BNP (<100 pg/ml)	340.5 $\pm$ 192.2	412.1 $\pm$ 144.0	494.2 $\pm$ 156.2	567.7 $\pm$ 115.8	0.016 [*]
NTproBNP (<300 pg/ml)	609.0 $\pm$ 449.0	1197.5 $\pm$ 769.5	1913.7 $\pm$ 949.1	2289.0 $\pm$ 870.5	0.001 [*]
NE (0-300 pg/ml)	312.2 $\pm$ 150.6	340.2 $\pm$ 105.3	394.1 $\pm$ 164.7	445.6 $\pm$ 125.9	0.010 [*]

P-Value is done between both (LV EF & laboratory marker).^{*}=Significant difference.

Table 4: Laboratory markers in heart failure patients with different grades of left ventricular ejection fraction (LVEF).

	Ischemic heart disease (n=48)	Dilated cardiomyopathy (n=28)	Hypertensive heart disease (n=24)	P1	P2	P3
BNP (< 100 pg/ml)	482.9 $\pm$ 168.0	590.1 $\pm$ 156.9	440.6 $\pm$ 194.1	0.002 [*]	0.267	0.003 [*]
NTproBNP (<300 pg/ml)	2101.5 $\pm$ 847.4	3187.8 $\pm$ 941.7	1821.8 $\pm$ 371.5	0.002 [*]	0.232	0.010 [*]
NE (0-300 pg/ml)	374.8 $\pm$ 163.6	364.2 $\pm$ 129.0	582.8 $\pm$ 153.9	0.884	0.001 [*]	0.001 [*]

Values expressed as mean $\pm$ SD, P1 value (IHD vs. DCM), P2 value (IHD vs. HTN), P3 value (DCM vs. HTN).^{*}=significant difference.

Table 5: Laboratory markers according to different cause of heart failure.

	P-value	OR	95% C.I.	
			Lower	Upper
Age (<50 years)	0.001 [*]	1.421	1.342	2.342
Sex (male)	0.013 [*]	1.908	1.654	2.763
BMI ≥ 30 (Kg/m ²)	0.004 [*]	3.622	1.40	6.360
Neck circumference (<40 cm)	0.004 [*]	3.423	1.671	4.559
Waist circumference (<110 cm)	0.002 [*]	3.470	2.883	6.018
Hypertension	0.004 [*]	3.620	0.90	4.10
Atrial fibrillation	0.013 [*]	1.195	1.061	1.346
ESS Scale	0.121	1.251	0.890	2.871
NYHA class (III & IV)	0.002 [*]	1.320	0.895	5.675
PaCO ₂ (≤ 35 mmHg)	0.423	1.345	0.987	3.871
LV-EF ($\leq 45\%$)	0.003 [*]	3.100	1.06	4.140
BNP (<100 pg/ml)	0.657	0.928	0.340	3.206
NTproBNP (<300 pg/ml)	0.001 [*]	3.267	0.995	5.769
NE (<300 pg/ml)	0.003 [*]	2.234	1.012	4.053

^{*}=significance

Table 6: Logistic regression analysis revealing the predictor factors for sleep disordered breathing (SDB) in patients with heart failure.

	P-value	OR	95% C.I.	
			Lower	Upper
Age (<50 years)	0.159	0.880	0.736	1.051
Sex (male)	0.003*	1.782	1.472	3.242
BMI ≥ 30 (Kg/m ²)	0.002*	3.132	1.167	4.539
Neck circumference (<40 cm)	0.001*	2.923	0.671	3.559
Waist circumference (<110 cm)	0.005*	2.970	0.873	3.078
Hypertension	0.001*	2.604	0.987	4.542
Atrial fibrillation	0.871	3.195	2.761	5.346
ESS Scale	0.223	2.451	1.654	6.761
NYHA class (III & IV)	0.148	3.123	1.037	4.400
PaCO ₂ (≤ 35 mmHg)	0.209	1.220	0.895	1.665
LV-EF (≤ 45%)	0.013*	1.245	1.048	1.481
BNP (<100 pg/ml)	0.647	0.998	0.990	1.006
NTproBNP (<300 pg/ml)	0.011*	2.697	0.995	3.999
NE (<300 pg/ml)	0.009*	2.024	1.006	1.043

*=significance

Table 7: Logistic regression analysis revealing the predictor factors for obstructive sleep apnea in patients with heart failure.

	P-value	OR	95% C.I.	
			Lower	Upper
Age (<50 years)	0.135	1.349	0.911	1.997
Sex (male)	0.002*	2.791	1.472	4.252
BMI ≥ 30 (Kg/m ²)	0.456	1.032	0.127	3.839
Neck circumference (<40 cm)	0.747	1.023	0.651	3.239
Waist circumference (<110 cm)	0.340	1.970	0.873	2.048
Hypertension	0.234	1.204	0.987	6.112
Atrial fibrillation	0.001*	2.195	0.231	5.346
ESS Scale	0.423	3.451	2.654	5.461
NYHA class (III & IV)	0.002*	2.123	1.037	3.230
PaCO ₂ (≤ 35 mm Hg)	0.003*	2.330	0.895	3.435
LV-EF (≤ 45%)	0.010*	2.315	1.048	4.231
BNP (<100 pg/ml)	0.457	1.998	1.340	4.108
NTproBNP (<300 pg/ml)	0.987	1.347	0.975	2.239
NE (<300 pg/ml)	0.123	2.104	1.236	5.223

*=significance

Table 8: Logistic regression analysis revealing the predictor factors for central sleep apnea in patients with heart failure.

On the other hand, Table 8 revealed that the most predictors for CSA were male sex, atrial fibrillation, lower PaCO₂ (≤ 35 mmHg), NYHA functional class (III & IV) and left ventricular ejection fraction (LVEF) (≤ 45%).

Discussion

In the current study, we have studied the neurohumoral activation among heart failure patients with and without sleep disordered breathing, we demonstrated that heart failure patients with SDB had a significantly higher plasma level concentration in BNP (591.5 ± 165.7 vs. 298.3 ± 86.6 pg/ml), NT-pro BNP (1750.0 ± 773.1 vs. 686.9 ± 377.8 pg/ml) and nor-epinephrine (NE) (616.1 ± 139.5 vs. 203.8 ± 64.3 pg/ml) as compared with No-SDB. Also, there were significant increase in the plasma concentration level of both N-terminal pro BNP and nor epinephrine (NE) in patients with OSA when compared with CSA.

Our results are in agreement with Ferrari et al. who measured neurohumoral activation in 56 HF patients with and without SDB and found that HF patients with SDB had significantly higher levels of BNP (421.1 ± 78.1 vs. 318.3 ± 54.6 pg/ml) and noradrenaline (231.2 ± 87.2 vs. 120.5 ± 45.1 pg/ml) than those without SDB [6]. Also, Ferrier et

al. measured urinary catecholamines, and NT-BNP in 87 HF patients with left ventricular ejection fraction (LVEF<45%) and reported a significant increase in norepinephrine (NE) (P=0.013) and (NT-pro BNP) (P=0.001*) among HF with SDB [7]. Another study by Paulino et al. who evaluated the prevalence of sleep apnea and measured plasma concentration level of BNP among 316 French patients with stable heart failure and demonstrated a significant increase in plasma concentration level of BNP in OSA patients as compared with CSA and No-SDB (501 ± 244 vs. 406 ± 50 pg/ml in CSA) and (501 ± 244 vs. 205 ± 44 pg/ml in CSA) [8].

Also, Solin et al. demonstrated that mean overnight urinary norepinephrine excretion (UNE) level was significantly elevated in HF patients with OSA compared with CSA and No-SDB (43.9 ± 24.1 vs. 24.0 ± 10.8 vs. 22.4 ± 8.9 nmol/24 h, p<0.001), indicating increased overnight sympathetic activity [9].

The present study revealed that patients with CSA had a significant increase in concentration level of BNP, NT-pro BNP and nor-epinephrine (NE) when compared with No SDB group. Similarly, Carmona-Bernalet al. have studied BNP among 90 patients with HF due to systolic dysfunction (left ventricular ejection fraction ≤ 45%) with and without CSA and reported that a significant increase was observed among HF with CSA (366.44 ± 29.6 vs. 162.01 ± 13.6 pg/mL in No-SDB; p<0.001) [10].

Also, Calvin et al. reported that BNP concentration was significantly higher in those with CSA than in No-SDB (1,184 pg/mL vs. 346 pg/mL, P=0.001*) [11]. Moreover, Poletti et al. evaluated neurohormonal derangement among 147 HF patients with and without CSA and found a higher plasma norepinephrine (NE) in CSA (588 vs. 331 pg/mL, P=0.01) and natriuretic peptides B (BNP) (284 vs. 164 pg/ml) and NT-proBNP (2575 vs. 448 pg/mL, P=0.001) as compared with No SDB [12]. Cardiac natriuretic hormone production is elicited in response to ventricular volume expansion and pressure overload, which have been associated with presence of sleep-related central apneas, sympathetic activation, and hypoxia [12].

Possible explanation that HF patients with sleep apnea exhibit repeated bursts of sympathetic activity with each respiratory event cycle and subsequent arousal, in addition to the chronic upregulation in sympathetic activity which already present in HF. Such increase in sympathetic activity is likely contributed to the increased neurohumoral activation which adversely affect prognosis [9].

In the present study, it was observed that there was a significant increase in neurohumoral markers as the severity of sleep apnea increased, determined by apnea hypopnea index (AHI). Similarly, Rao et al. evaluated neurohumoral markers among heart failure with (SDB) using a cut-off value (AHI=15) and found that HF patients with AHI<15 had a significant increase in BNP (187 ± 119 vs. 73 ± 98 pg/ml) and urinary norepinephrine (NE) (309 ± 183 vs. 225 ± 148 nmol/24 h) as compared with HF patients with (AHI>15) [13].

Also our results revealed a significant increase was observed in neurohumoral markers with the increased severity of left ventricular ejection fraction (LVEF). Thus, an increase in the severity of left ventricular ejection fraction (LVEF) associated with an increase in neurohumoral markers. Our results are in agreement with Rao et al. who assessed BNP and plasma norepinephrine (NE) in grades of HF with SDB and found that patients with severe HF (LVEF>35) had a significant increase in BNP (172 ± 201 vs. 59 ± 46 pg/ml) and norepinephrine (284 ± 206 vs. 218 ± 118 pg/ml) as compared mild-to-moderate HF (EF>35%) [13].

In this study, we demonstrated that the possible predictors of sleep disordered breathing (SDB) among heart failure patients were body mass index (BMI ≥ 30), systemic hypertension, neck circumference < 40 cm, waist circumference (< 110 cm) and left ventricular ejection fraction (LVEF) ($\leq 45\%$). In addition to, higher level of (N-terminal proBNP < 300 pg/ml) and nor-epinephrine (NE < 300 pg/ml), similarly, Loo et al., studied 332 heart failure patients (mean age 62 ± 10 years) to determine possible predictors of sleep disordered breathing and demonstrated that neck circumference (OR=1.09; 95% (CI) 1.01-1.12, $P=0.002$ '), waist circumference (OR=1.06; 95% (CI) 1.01-1.13, $P=0.001$ '), BMI (OR=1.19; 95% (CI) 1.10-1.30, $P=0.001$ '), NT pro BNP (OR=2.03; 95% (CI) 1.12-3.10, $P=0.001$ ') were independent predictors of SDB [14].

Also, we demonstrated that NT pro BNP (< 300 pg/ml) (OR=2.697; 95% (CI) 0.99-3.99, $P=0.011$ ') and nor epinephrine (NE < 300 pg/ml) (OR=2.024; 95% (CI) 1.006-1.043; $P=0.009$ ') were possible predictors of obstructive sleep apnea (OSA) among heart failure patients. Similarly, Yumino et al. demonstrated the predictors of obstructive (OSA) and central sleep apnea (CSA) among 219 heart failure patients and reported that greater BMI and nor epinephrine were independent predictors of OSA, whereas older age, male sex, atrial fibrillation, hypocapnia were independent predictors of CSA among heart failure patients [15].

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