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SCIENTIFIC INVESTIGATIONS

The Clinical Value of N-Terminal Pro B-Type Natriuretic Peptide in Evaluating Obstructive Sleep Apnea in Patients With Coronary Artery Disease

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Study Objectives: Natriuretic peptides have been identified as biomarkers of increased myocardial wall stress in the context of obstructive sleep apnea (OSA) in the general population. However, the relationship between *N*-terminal pro B-type natriuretic peptide (NT-proBNP) and OSA remains unclear in patients with coronary artery disease (CAD). Hence, we aimed to investigate the clinical value of NT-proBNP in evaluating OSA in a large population of patients with CAD.
Methods: Consecutive patients with CAD were prospectively enrolled between February 2015 and March 2018. Portable respiratory monitoring was applied to facilitate the diagnosis of sleep apnea. Patients were as assigned to the non-OSA (when the respiratory events index [REI] or 3% oxygen desaturation index [ODI] < 15 events/h) and OSA (when the REI or 3% ODI ≥ 15 events/h) groups. Multivariate analyses were used to explore the independent association between NT-proBNP levels and OSA.
Results: A total of 1,292 consecutive patients were included with a mean NT-proBNP value of 826.57 μg/L. Patients with high levels of NT-proBNP experienced increasing severity of OSA in those with CAD (P = .0004). Univariate analysis demonstrated that NT-proBNP was a risk factor for OSA (odds ratio [OR] 1.10, 95% confidence interval [CI] 1.03–1.18, P = .005). In addition, multivariate analysis revealed that NT-proBNP was independently associated with the presence of OSA (OR 1.11, 95% CI 1.02–1.20, P = .012) even after adjusting for other cofounding factors.
Conclusions: Elevated levels of NT-proBNP were independently associated with a higher likelihood of OSA in patients with CAD. Periodically screening for NT-proBNP levels may provide early identification of OSA.

Keywords: coronary artery disease, *N*-terminal pro B-type natriuretic peptide, obstructive sleep apnea
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BRIEF SUMMARY
Current Knowledge/Study Rationale: Natriuretic peptides have been identified as biomarkers of increased myocardial wall stress in the context of obstructive sleep apnea (OSA) in the general population. However, the relationship between *N*-terminal pro B-type natriuretic peptide (NT-proBNP) and OSA remains unclear in patients with coronary artery disease (CAD).
Study Impact: Our study demonstrated that elevated levels of NT-proBNP were independently associated with a higher likelihood of OSA in patients with CAD. Periodically screening for NT-proBNP levels may provide early identification of OSA.

INTRODUCTION

Obstructive sleep apnea (OSA) is a pervasive sleep-related breathing disorder. The estimated prevalence of OSA in recent decades has increased dramatically, reaching an approximate maximal level of 38% in the general population.[1] OSA has been proven to be a significant risk factor for cardiovascular disease and increased cardiovascular mortality.[2–4] However, there are limited data on good biomarkers that would enable the identification of OSA among patients with coronary artery disease (CAD).

Intrathoracic pressure swings, intermittent hypoxia and elevated sympathetic activity in OSA are thought to exert detrimental impacts on cardiac structures and functions.[5] *N*-terminal pro B-type natriuretic peptide (NT-proBNP) is a cardiac hormone with vasodilatory and diuretic cardiac properties.[6] This peptide is secreted in response to increased ventricular preload and may reflect myocardial wall stress in the setting of OSA.[7] Increasing studies have attempted to evaluate the role of natriuretic peptides in OSA and concomitant CAD. However, the results remain conflicting because of the small sample size of the enrolled patients.[8–10]

Therefore, the current study aimed to analyze the potential association between the plasma levels of NT-proBNP and the presence of OSA in patients with CAD based on a large sample size.

METHODS

Participants

Consecutive patients with CAD were prospectively enrolled from February 2015 to March 2018. Patients were admitted to the hospital with suspected CAD and, if necessary, underwent

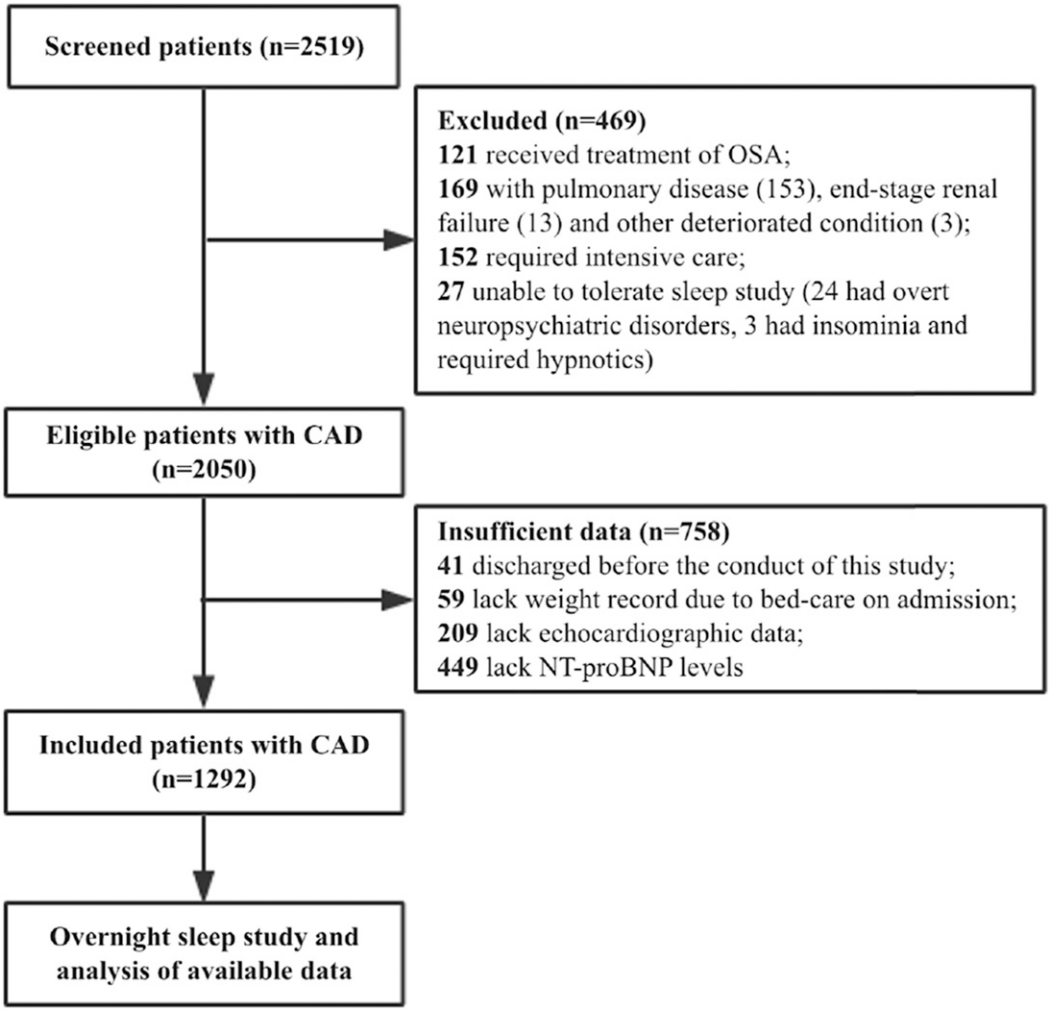
coronary intervention during hospitalization. Within an average duration of 7 days after admission, patients were evaluated for inclusion criteria. Inclusion criteria were as follows: (1) agreement to participate in this study; (2) confirmed diagnosis of CAD, meeting one or more of the following criteria: (a) proven history of myocardial infarction in the past; (b) coronary angiography or spiral computed tomography angiography showing ≥ 50% stenosis in at least one major coronary artery; and (c) at least one coronary artery that underwent percutaneous coronary intervention or percutaneous transluminary coronary angioplasty or coronary artery bypass graft treatment.[11] Patients were excluded if they fulfilled any of the following criteria: (1) previous diagnosis of OSA and received treatment with continuous positive airway pressure or other therapeutic modalities; (2) had pulmonary disease, end-stage renal failure, and any deteriorated conditions; (3) had disability, severe neurologic disorders, or memory, perceptual, and behavioral disorders; (4) received intensive care due to hemodynamic instability and susceptibility of malignant arrhythmia; (5) required supplementary oxygen during nocturnal respiratory study; and (6) used medications such as opiates, hypnotic agents, and muscle relaxants. The flow diagram of patient recruitment and study flow is illustrated in **Figure 1**.

The current research was approved by the Ethics Committee of Guangdong Provincial People's Hospital, and written informed consent was obtained from all enrolled patients.

Clinical and Laboratory Data Collection

Demographics, anthropometrics, previous medical history, laboratory data, sleep apnea parameters, Epworth Sleepiness Scale, and other baseline characteristics were recorded in electronic report form by two investigators and were rechecked by another two investigators. NT-proBNP was quantitively determined at the fasting morning of admission by an electrochemiluminescence immunoassay (ECLIA) using an automated analyzer (Cobas E601; Roche Diagnostics, Shanghai, China). Lipid profiles, glycosylated hemoglobin, uric acid, and D-dimer were also obtained. All laboratory tests were performed using standard methods of measurement in the Laboratory Department

Figure 1—Flow diagram of patient recruitment.



CAD = coronary artery disease, NT-proBNP = *N*-terminal pro B-type natriuretic peptide, OSA = obstructive sleep apnea.

(application of ISO 9000 Quality Management and Assurance Standards) of our hospital.

Nocturnal Respiratory Events Study

Portable monitor (PM), including level III PM (Alice PDx or NightOne; Philips China Investment Co., Ltd., Shanghai, China) and/or level IV PM (Morpheus Ox software; Dehaier Medical Systems, Beijing, China), was applied to facilitate the diagnosis of sleep apnea in addition to a thorough sleep history, clinical symptoms, and physical examination. Level III PM measures cardiopulmonary parameters, which include oxygen saturation at the fingertip, respiratory variables (eg, effect to breathe, nasal airflow), and a cardiac variable (eg, heart rate or electrocardiogram). Level IV PM measures one or two parameters, typically oxygen saturation and heart rate. All patients were assessed using level III PM within 7 days of study enrollment. Those who were immobile and/or unable to equip themselves with the recording device (n = 124) because of temporal disease instability were initially recorded using level IV PM. Thereafter, level III PM was used on another night to collect more comprehensive data for comparison and accurate interpretation of sleep respiratory events. A recorded time of at least 4 hours was considered effective for event interpretation.

We evaluated and scored nocturnal respiratory events by using the American Academy of Sleep Medicine rules.[12] Respiratory events include apnea and hypopnea events. Apnea events were recorded if there was a ≥ 90% reduction in respiratory airflow for more than 10 seconds. Hypopnea events were recorded if the following criteria were satisfied: (1) a ≥ 30% reduction in respiratory airflow for more than 10 seconds and (2) a 3% oxygen desaturation compared to the pre-event baseline. The respiratory event index (REI) is defined by the total number of apnea and hypopnea events per hour of recorded data. The oxygen desaturation index (ODI), another measure of OSA severity, was expressed as the sum of the average number of ≥ 3% oxygen desaturations per sleep hour. Both REI and 3% ODI were considered and were used to determine the presence and severity of OSA in the current study. Of note, for patients who underwent sleep tests more than twice, we used the maximum value of either REI or 3% ODI for the ultimate scoring of OSA severity. A cutoff REI or 3% ODI ≥ 15 events/h was used to define the existence of OSA,[13] and those with REI or 3% ODI < 15 events/h were considered without OSA.

Statistical Analysis

The positively skewed variable NT-proBNP was transformed by natural logarithm. Continuous variables were described as the mean ± standard deviation, and one-way ANOVA was used to compare differences between the NT-proBNP (Log-NT-proBNP) groups. Categorical variables were described by proportions, and Pearson chi-square test was used to compare differences between the NT-proBNP (Log-NT-proBNP) groups. To determine the risk of factors for OSA, univariate and multivariate logistic regression analyses were applied. The data were analyzed on the basis of available cases, whereas missing data were not incorporated. A two-sided value of $P < .05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Epidemiologic Characteristics

A total of 1,292 patients with CAD (1,070 males and 222 females) were recruited. The prevalence of OSA in CAD was 36.1% (n = 466) based on an REI or 3% ODI cutoff ≥ 15 events/h. A high prevalence of comorbidities of hypertension (58.6%), diabetes mellitus (25.8%), and hyperlipidemia (11.5%) was observed. In addition, the prevalence of a prior myocardial infarction and stroke was 6.6% and 5.3%, respectively.

Comparisons of Clinical Data Among Different NT-proBNP Groups

The detection levels of plasma NT-proBNP ranged from 5 pg/mL to 31,511 pg/mL. Based on this range of values, we classified patients with CAD into 4 groups by quartiles of logarithm. Details on the baseline characteristics within different NT-proBNP groups are shown in **Table 1**. Age, sex, low-density lipoprotein, hemoglobin A1c, serum creatinine, estimated glomerular filtration rate, and Epworth Sleepiness Scale were significantly different in the four groups with different levels of NT-proBNP. In particular, REI/3% ODI was also significantly different between groups with normal and elevated NT-proBNP levels. Nevertheless, no significant differences in height, weight, body mass index (BMI), triglycerides, and total cholesterol were identified.

Associations Between Plasma Levels of NT-proBNP and OSA Severity

The distribution of REI/3% ODI (ie, the severity of OSA) in the four consecutive groups of NT-proBNP levels is illustrated in **Figure 2**. Patients with high levels of NT-proBNP experienced increasing severity of OSA, and a significant linear trend was found ($P = .0004$). The multivariate logistic regression analysis revealed that NT-proBNP remained significantly and independently correlated with the presence of OSA (odds ratio [OR] 1.11, 95% confidence interval [CI] 1.03–1.20, $P = .012$), even after adjustment for many other confounding factors (**Table 2**). In addition, BMI (OR 1.24, 95% CI 1.19–1.30, $P < .001$) and age (OR 1.02, 95% CI 1.00–1.03, $P = .011$) were also found to be significant correlates of the severity of OSA. Notably, Spearman correlation analysis did not reveal a significant correlation between age and BMI with NT-proBNP levels ($r = .025$, $P = .786$; $r = .034$, $P = .711$, respectively). In addition, sex (female) had OR 0.59, 95% CI 0.41–0.85, $P = .004$.

DISCUSSION

The current study demonstrated that higher NT-proBNP levels were independently and positively associated with the presence and severity of OSA.

The prevalence of OSA varies widely, from 38% to 65% in patients with CAD,[14] mostly using AHI ≥ 15 events/h as a cutoff. A high prevalence of OSA with AHI ≥ 15 events/h (45.6%) was reported in a similar population,[15] which is partially in

Table 1—Baseline characteristics of patients with coronary artery disease in the four *N*-terminal pro B-type natriuretic peptide (Log-NT-proBNP) groups.

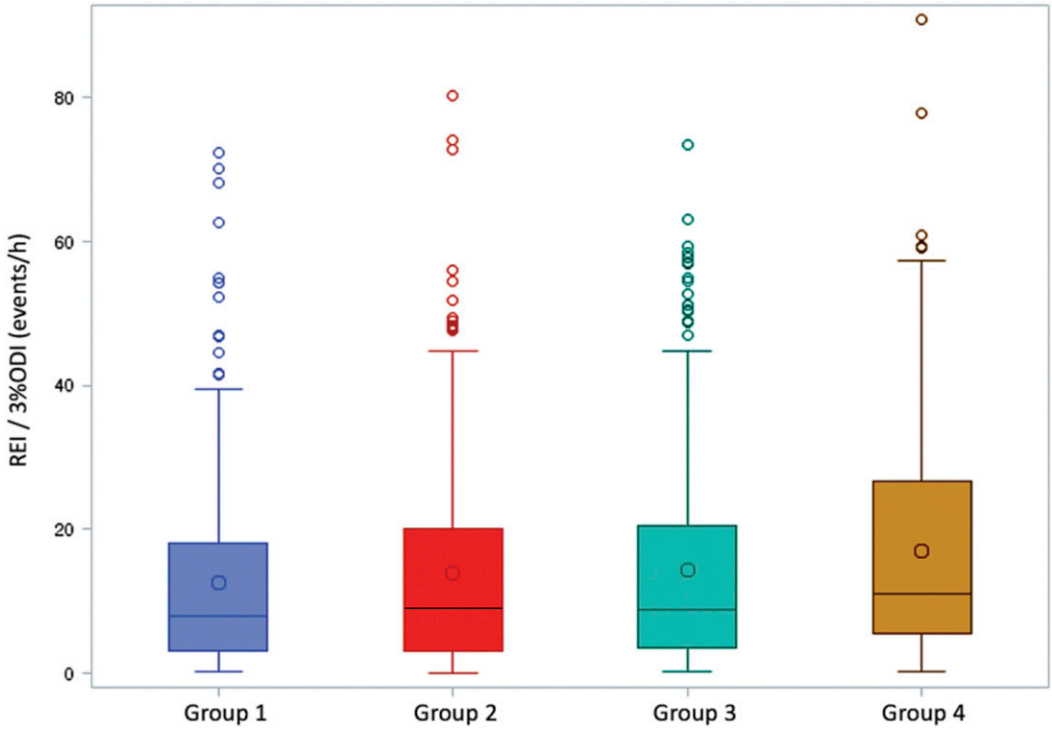
Variable	Group 1 (n = 323)	Group 2 (n = 323)	Group 3 (n = 324)	Group 4 (n = 322)	*P*
Age (year)	58.37 ± 9.37	60.95 ± 9.19	59.18 ± 9.97	59.86 ± 10.40	.007
Sex (M/F)	272/51	245/78	279/45	274/48	.002
Hypertension	186 (24.6)	189 (25.0)	195 (25.8)	187 (24.7)	.917
Diabetes mellitus	64 (19.2)	82 (24.6)	88 (26.4)	99 (29.7)	.015
Hyperlipidemia	53 (35.6)	30 (20.1)	33 (22.1)	33 (22.1)	.017
Prior myocardial infarction	9 (10.6)	13 (15.3)	27 (31.8)	36 (42.4)	< .001
Prior stroke	9 (13.2)	21 (30.9)	26 (38.2)	12 (17.6)	.010
Anemia	49 (13.9)	86 (24.4)	97 (27.6)	120 (34.1)	< .001
Weight (kg)	69.65 ± 10.44	68.85 ± 12.73	68.91 ± 11.20	67.87 ± 11.24	.287
Height (cm)	166.07 ± 7.23	165.54 ± 7.48	165.82 ± 7.51	165.16 ± 7.41	.458
BMI (kg/m^2)	25.19 ± 3.03	25.01 ± 3.64	25.00 ± 3.22	24.83 ± 3.41	.614
LDL (mmol/L)	2.96 ± 1.02	2.79 ± 0.91	2.86 ± 0.88	2.99 ± 1.02	.033
Total cholesterol (mmol/L)	4.63 ± 1.33	4.40 ± 1.21	4.50 ± 1.18	4.53 ± 1.29	.150
Triglycerides (mmol/L)	1.82 ± 1.23	1.74 ± 1.03	1.81 ± 1.33	1.64 ± 1.25	.229
HbA1c (%)	6.20 ± 1.08	6.38 ± 1.35	6.49 ± 1.44	6.54 ± 1.53	.008
Creatinine (μmol/L)	82.11 ± 17.81	82.09 ± 21.25	90.40 ± 24.07	126.72 ± 137.52	< .001
LVEF	0.66 ± 0.06	0.64 ± 0.08	0.60 ± 0.10	0.48 ± 0.14	< .001
eGFR (mL/min/1.73m^2)	89.49 ± 21.06	87.20 ± 20.07	81.85 ± 21.06	72.23 ± 28.24	< .001
ESS score	5.31 ± 4.65	4.28 ± 4.33	4.91 ± 4.45	4.05 ± 4.23	.009
REI/3%ODI (events/h)	12.70 ± 12.99	13.89 ± 14.02	14.44 ± 14.64	16.92 ± 15.39	.002
OSA severity					.056
Non-OSA	220 (26.6)	207 (25.1)	212 (25.7)	187 (22.6)	
OSA	103 (22.1)	116 (24.9)	112 (24.0)	135 (29.0)	

Data presented as mean ± standard deviation or n (%). The levels of NT-proBNP were classified into four groups by quartile. Group 1 = log-NT-proBNP ≤ Q1 (1.61–3.93). Group 2 = Q1 < log-NT-proBNP ≤ Q50 (3.94–5.03). Group 3 = Q50 < log-NT-proBNP ≤ Q75 (5.04–6.48). Group 4 = log-NT-proBNP > Q75 (6.49–10.36). BMI = body mass index, CAD = coronary artery disease, eGFR = estimated glomerular filtration rate, ESS = Epworth Sleepiness Scale, HbA1c = glycosylated hemoglobin, LDL= low-density lipoprotein cholesterol, Log-NT-proBNP = logarithmic transformation of NT-proBNP, LVEF = left ventricle ejection fraction, NT-proBNP = *N*-terminal pro B-type natriuretic peptide, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, REI = respiratory event index.

accordance with the current study. Furthermore, our findings are partially in accordance with a study by Valo et al,[10] who studied patients with OSA and concomitant CAD. In their study, elevated NT-proBNP levels in patients with an AHI > 15 events/h were observed and were significantly reduced after overnight continuous airway positive pressure therapy. However, the sample size was limited to only 21 patients. Another study[16] revealed an association between NT-proBNP and sleep-disordered breathing, but only young women were enrolled as opposed to our large number of patients with CAD. Meanwhile, the Berlin Questionnaire was used in that study[16] to define the severity of sleep-disordered breathing instead of adopting sleep monitors, which may impair the accuracy for the scoring of sleep apnea severity. Both REI and ODI were utilized in our study to explore the association between NT-proBNP and OSA. These parameters were significantly correlated with elevated natriuretic peptides. This finding may indicate that either the frequency of sleep apnea or oxygen desaturation may be an essential element that links NT-proBNP and OSA. Interestingly, a study by Gottlieb et al[17] showed that it is the sustained hypoxia (ie, the longer duration of oxygen desaturation) instead of the frequency of respiratory events (ie, 3% ODI or REI) that was related to the higher levels of natriuretic peptides. However, patients with heart failure with multiple etiologies apart from CAD were studied in their research, and this may explain the difference between our findings.

On the basis of a large community-dwelling sample, Patwardham et al[18] and Querejeta Rosa et al[19] found a lack of an independent association between circulating natriuretic peptides and OSA severity, even in the severe OSA group. Natriuretic peptide testing was not performed coincident with polysomnography (PSG) in these two studies. The length of time between the PSG and the measurement of natriuretic peptides were approximately 79 days and longer than 1 year, respectively. Indeed, this may have affected the results because the levels of natriuretic peptides could change over time in the potential setting of intercurrent cardiovascular or noncardiovascular events.[20] Overall, previous findings with respect to the role of NT-proBNP were not universal, and this could be predominantly explained by differences in population groups and size, as well

Figure 2—The severity of OSA in different NT-proBNP groups.



Patients with high levels of NT-proBNP experienced increasing severity of OSA in patients with CAD, and a significant linear trend was found (P = .0004). The levels of NT-proBNP were classified into four groups by quartile. Group 1 = log-NT-proBNP ≤ Q1 (1.61–3.93). Group 2 = Q1 < log-NT-proBNP ≤ Q50 (3.94–5.03). Group 3 = Q50 < log-NT-proBNP ≤ Q75 (5.04–6.48). Group 4 = log-NT-proBNP > Q75 (6.49–10.36). CAD = coronary artery disease, NT-proBNP = *N*-terminal pro B-type natriuretic peptide, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, REI = respiratory event index.

Table 2—The risk factors for OSA.

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Log-NT-proBNP	1.10	1.03–1.18	.005	1.11	1.02–1.20	.012
BMI	1.21	1.17–1.26	< .001	1.24	1.19–1.30	< .001
Diabetes mellitus	1.41	1.09–1.82	.009	1.03	0.72–1.49	.865
Hypertension	1.46	1.16–1.84	.002	1.17	0.90–1.53	.239
HbA1c	1.12	1.03–1.21	.010	1.06	0.95–1.19	.309
Anemia	1.18	0.92–1.52	.192	1.27	0.95–1.70	.114
Age	1.00	0.99–1.02	.470	1.02	1.01–1.04	.004
eGFR	0.99	0.99–0.10	.010	1.00	0.99–1.00	.585
Sex (female)	0.61	0.44–0.84	.002	0.59	0.41–0.85	.004

NT-proBNP remained significantly and independently correlated with the presence of OSA (OR 1.11, 95% CI 1.03–1.20, P = .008) even after adjustment for many other confounding factors (including BMI, diabetes mellitus, hypertension, HbA1c, anemia, age, eGFR, and sex). BMI = body mass index, CI = confidence interval, eGFR = estimated glomerular filtration rate, HbA1c = glycosylated hemoglobin, Log-NT-proBNP = logarithmic transformation of NT-proBNP, NT-proBNP = *N*-terminal pro B-type natriuretic peptide, OR= odds ratio, OSA = obstructive sleep apnea.

as various means used for estimating the presence and severity of OSA.[19,21,22]

Although our findings demonstrated that both age and BMI were also independent risk factors for OSA, we aimed to emphasize the role of NT-proBNP and concluded that it is a potential risk factor for OSA. Of note, an ideal biomarker should be related to OSA-induced end-organ dysfunction and involved in potential pathophysiological pathways; therefore, NT-proBNP is a good biomarker candidate. The circulating NT-proBNP reflects myocyte stretch and is considered a quantitative marker of hemodynamic cardiac stress.[23] There are several potential mechanisms that are thought to be of paramount importance in the pathophysiology of OSA and the levels of NT-proBNP. First, intrathoracic pressure swings resulting from inspiratory effort against the occluded airway during each apneic episode may increase ventricular transmural pressure,

left ventricular afterload, end-systolic volume, and end-diastolic volume. Overall, these perturbations lead to both ventricular pressure load and volume expansion.[24] Presumably, the more frequent apneic episodes in patients with severe OSA may result in a greater pressure gradient that persistently stretches the cardiac wall and thus leads to a surge in the amount of circulating natriuretic peptides. Second, rostral fluid shift in the supine position has been implicated as a causative mechanism for patients with OSA.[25] This phenomenon might be attributable to the negative intrathoracic pressure during obstructive events, which likely draws fluid from the peripheral tissue. With such a nocturnal volume shift, fluid accumulation around cardiopulmonary tissues may cause ventricular stretch and the release of NT-proBNP. Third, repetitive collapse of the upper airway can give rise to intermittent hypoxia. When combined with high transmural pressure, it may increase myocardial oxygen demand and reduce coronary blood flow. These changes could ultimately impair myocardial perfusion and reduce myocardial contractility,[26] which may in turn increase the ventricular vulnerability of being stretched and cause release of natriuretic peptides. Hypoxia was reported to induce the secretion of natriuretic peptides.[27] Meanwhile, oxidative stress through reactive oxygen species produced during nocturnal intermittent hypoxia is considered a risk factor for multiple cardiovascular consequences.[28] Finally, arousal-induced sympathetic activation may also contribute as a stimulus of NT-proBNP. The protective mechanism of airway reopening in response to apnea or hypopnea (ie, arousals) is associated with a great transient increase in blood pressure because of increased sympathetic vasoconstriction.[29] This change would eventually lead to increased afterload and possibly hemodynamic stress.

Elevated levels of NT-proBNP were found to significantly correlate with increased severity of OSA, suggesting a new phenotype of OSA with higher NT-proBNP levels. The presence of OSA in patients with high NT-proBNP might represent a more vulnerable population that may benefit from OSA treatment. In other words, changes in the biomarker levels in the context of OSA treatment reliably predict improvements in the specific end-organ outcomes.[10] Exploration of higher levels of NT-proBNP would enable the identification of the more "vulnerable" patients, who would more likely benefit from timely and targeted therapeutic interventions. However, the aforementioned assumptions need to be further confirmed by other large population-based studies.

Several limitations of our study are discussed as follows. First, only portable monitoring devices were used for the nocturnal respiration study. Overnight PSG is still the gold standard for the diagnosis and evaluation of OSA. However, this in-laboratory and time-consuming PSG is unsuitable for hospitalized patients with cardiovascular disease and often involves high costs as well as increased health care burdens. Additionally, the user-friendly and cost-effective PM (such as level III and IV) has similar accuracy for the diagnosis of OSA compared with PSG.[30] Second, only one recorded value of the baseline NT-proBNP levels might insufficiently reflect the long-term effect of OSA on plasma concentrations of natriuretic peptides. Third, a portable monitor has generally not been validated in acutely ill hospitalized patients; however, patients with hemodynamic instability received intensive care, and susceptibility to malignant arrhythmia was excluded in the current study. Finally, the nature of observational research would not allow us to determine causality between plasma concentrations of NT-proBNP and the severity of OSA. This relationship needs to be confirmed by future prospective cohort studies.

In conclusion, elevated levels of NT-proBNP were independently associated with a higher risk of having OSA in patients with CAD. Presumably, periodic screening for plasma levels of NT-proBNP may facilitate the early identification of OSA in patients with CAD, and further accurate diagnosis and possible individualized intervention of OSA could be performed.

ABBREVIATIONS

CAD, coronary artery disease
NT-proBNP, N-terminal pro B-type natriuretic peptide
ODI, oxygen desaturation index
OSA, obstructive sleep apnea
PM, portable monitor
PSG, polysomnography
REI, respiratory event index

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