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SLEEP APNEA

Efficacy of Positive Airway Pressure on Brain Natriuretic Peptide in Patients with Heart Failure and Sleep-Disorder Breathing: A Meta-analysis of Randomized Controlled Trials

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Abstract

Objective Positive airway pressure (PAP) has been recognized as an effective therapeutic option for sleep-disordered breathing (SDB) in patients with heart failure (HF), and it can improve left ventricular function. Whether PAP can ameliorate serum brain natriuretic peptide (BNP) levels, a biomarker of HF, is controversial. The purpose of the present study was to quantitatively assess the efficacy of PAP on BNP in patients with HF and SDB.

Methods A systematic search of PubMed, Embase, Web of Science and Cochrane library identified six randomized controlled trials (RCTs), in which PAP was compared with medical therapy, subtherapeutic PAP or different types of PAP. The data of BNP were extracted and pooled into meta-analysis using STATA 12.0.

Results Totally 6 RCT studies (7 cohorts) with 222 patients were enrolled into analysis. The quality of each study was high and the heterogeneity ($I^2 = 58.1$ %) was noted between studies. A significant reduction of BNP was observed after PAP treatment in patients with HF and SDB (SMD −0.517, 95 % *CI* −0.764 to −0.270, $z = 4.11$, $p = 0.000$).

Conclusion Our meta-analysis of RCTs demonstrated that PAP elicits significant reduction of BNP in patients with HF and SDB.

Keywords Positive airway pressure · Adaptive servo-ventilation · Sleep-disordered breathing · Brain natriuretic peptide · Heart failure · Meta-analysis

All authors contributed equally to this work.

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Introduction

High prevalences of sleep-disordered breathing (SDB), including obstructive sleep apnea (OSA), central sleep apnea (CSA), and Cheyne–Stokes respiration (CSR) in patients with heart failure (HF) were observed [1–3]. SDB, particularly OSA, has been confirmed to be correlated with increased incidences of left ventricular (LV) dysfunction and hypertrophy [4, 5].

Natriuretic peptide, either B-type natriuretic peptide (BNP) or N-terminal part of the propeptide of BNP (NT-pro BNP) has been recommended as a novel biomarker for diagnosis and management of HF and can reflect left ventricular systolic/diastolic dysfunction [6]. Positive airway pressure (PAP) ventilation, including continuous PAP (CPAP), bilevel PAP (BiPAP), adaptive servo-ventilation (ASV), is a widely acceptable approach for treatment of patients with HF and SDB. PAP not only ameliorates SDB, improves LV function, but also alleviates the symptoms of HF [7, 8]. However, it has yielded conflicting results that whether PAP can ameliorate BNP or NT-pro BNP [9, 10].

The purpose of the present meta-analysis was to quantitatively evaluate the efficacy of PAP ventilation on BNP or NT-pro BNP in patients with HF and SDB.

Methods

This meta-analysis was conducted in accordance with the 'preferred reporting items for systematic reviews and meta-analyses' [11].

Literature Search

A systematic computerized search of PubMed, Embase, Web of Science and Cochrane library was undertaken from

inception to July 20, 2014 by two independent reviewers. All searches included the keywords and corresponding Mesh term: (sleep apnea or sleep-disordered breathing) and (positive airway pressure or non invasive ventilation) and (brain natriuretic peptide) and (heart failure) and (randomized controlled trial). Additionally, references in published studies were manual searched.

Study Selection Criterion

Studies were eligible if they met the following inclusion criteria: (1) study population was adult (age $\geq$ 18 years) with SDB (OSA, CSA or CSR); (2) HF was diagnosed according to the HF symptoms (New York Heart Association Class I-IV) and mean left ventricular ejection fraction (LVEF) less than 45 % in echocardiography. (3) study was RCT, with reasonable control group; (4) the mean duration of PAP was at least 1 week; (5) BNP levels were reported for both the experimental and control groups. Abstracts, reviews, case reports, editorials, conference articles, and non-English studies were excluded. If important data were ambiguous or lacked, the corresponding author was contacted by email, after twice non-response, the study was ruled out.

Data Extraction

The following variables were extracted from each included study by two reviewers: first author, year of publication, study population characteristics, study design, type of PAP, control type, and BNP levels in each group (experimental and control groups). If several therapeutic durations were reported in one study, the different duration was considered as a separate cohort and pooled into overall meta-analysis.

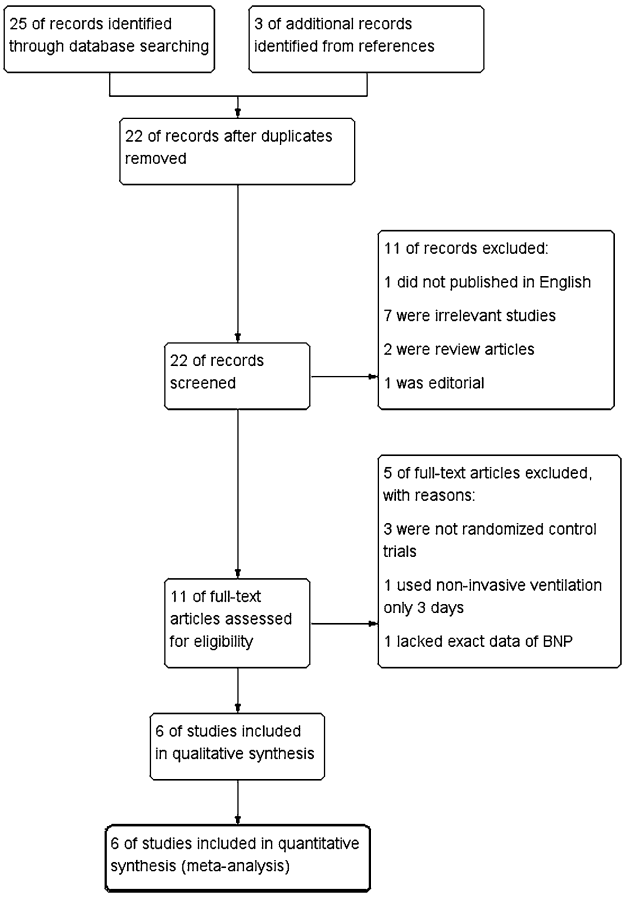

Fig. 1 Flow diagram

Quality Assessment

Study quality was evaluated using the Cochrane's tool for assessing RCTs risk of bias [12]. Six items were assessed: random sequence generation (selection bias), concealed allocation (selection bias), blinding of participants and

Table 1 Risk of bias

Study, year	Random sequence generation (selection bias)	Concealed allocation (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Pepperell 2003	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zhao 2006	Unclear	Unclear	High risk	Unclear	Low risk	Low risk	Low risk
Noda 2007	Unclear	Unclear	High risk	Low risk	Low risk	Low risk	Low risk
Campbell 2011	Unclear	Unclear	High risk	Unclear	Low risk	Low risk	Low risk
Randerath 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Arzt 2013	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	High risk

personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Two reviewers independently analyzed and assessed the quality of individual study, when discrepancy appeared, a third reviewer was consulted.

Statistical Analysis

All statistical analyses were performed with Review Manager Version 5.2 (The Cochrane Collaboration, Oxford, UK) and Stata Version 12.0 (Stata Corporation, College Station, Texas, USA). Standardized mean difference (SMD) with 95 % confidence interval (95 % *CI*) was calculated using post-intervention BNP value in each group. Random effect model was applied if high heterogeneity ($I^2 > 50$ %) presented, otherwise, fixed effect model was used. When data showed as median and range, mean and standard deviation was appropriately estimated [13]. Further subgroup analysis was performed after stratifying by PAP type and therapeutic duration. Analysis of publication bias was performed by Begg's test and Egger's test [14, 15]. Statistical significance was set at p value less than 0.05.

Results

Search Results

Figure 1 shows the flow diagram. A total of twenty-eight studies were initially found from the databases. Six studies were duplicate articles; 11 studies were excluded after browsing the titles and abstracts. The remaining 11 studies were enrolled for further full text scrutiny. Five studies were subsequently ruled out after reviewing of the full text: 3 were not RCTs [16–18], one lacked exact data of BNP [19], and one conducted PAP treatment less than 1 week [20]. Finally, 6 RCTs were pooled into the present meta-analysis [9, 10, 21–24].

The Quality of Included Studies

Assessment of the risk of bias of each study is outlined in Table 1. In general, the quality of included studies was moderate to high.

Characteristics of Eligible Studies

A total of 6 studies (7 cohorts) with 222 patients were included into meta-analysis. The mean age was 62.3 ± 7.2 years; mean BMI was 27.6 ± 3.0 kg/m^2. One study was crossover in design [10]; the remaining 5 were

Table 2 Characteristics of included studies

First author	Year	Sample size	Males (%)	Age (year)	BMI (kg/m^2)	SDB	SDB diagnostic criteria (events/hour)	RCT design	Detecting item	Duration	PAP type	Usage (hour/night)	Control treatment
Pepperell	2003	30	96.7	71.25 ± 8.1	26.2 ± 4.3	CSR	AHI ≥ 5	Parallel	BNP	1 month	ASV	5.0 ± 1.7	Subtherapeutic ASV
Zhao	2006	26	88.5	55.92 ± 14.29	NA	OSA/CSA	AHI ≥ 10	Parallel	NT-pro-BNP	7 ± 4 days	CPAP/ASV	7.3 ± 1	Drug therapy
Noda	2007	21	NA	51.6 ± 2	24.0 ± 1.1	CSA	AHI ≥ 20	Parallel	BNP	3 months	BIPAP	4.8 ± 0.3	Medical therapy
Campbell	2012	10	100.0	64.0 ± 6.8	26.5 ± 2.8	CSA-CSR	AHI ≥ 15	Crossover	NT-BNP	8 weeks	ASV	5.2 ± 2.0	Oxygen inhale
Randerath 3 months	2012	63	100.0	66.3 ± 9.1	31.3 ± 6.0	OSA and CSA	AHI ≥ 15	Parallel	NT-pro-BNP	3 months	ASV	5.2 ± 2.0	CPAP
Randerath 12 months	2012	63	100.0	66.3 ± 9.1	31.3 ± 6.0	OSA and CSA	AHI ≥ 15	Parallel	NT-pro-BNP	12 months	ASV	5.2 ± 2.0	CPAP
Arzt	2013	72	91.7	64.5 ± 9.5	30.2 ± 4.8	SDB	AHI ≥ 20	Parallel	NT-pro-BNP	12 weeks	ASV	4.5 ± 3.0	Medical management

BMI body mass index, *SDB* sleep-disordered breathing, *RCT* randomized controlled trial, *PAP* positive airway pressure, *CSR* Cheyne–Stokes respiration, *HF* heart failure, *BNP* brain natriuretic peptide, *ASV* adaptive servo-ventilation, *NA* no available, *OSA* obstructive sleep apnea, *CSA* central sleep apnea, *CHF* chronic heart failure, *NT-pro-BNP* N-terminal part of the propeptide of brain natriuretic peptide, *CPAP* continuous positive airway pressure, *BIPAP* bilevel positive airway pressure

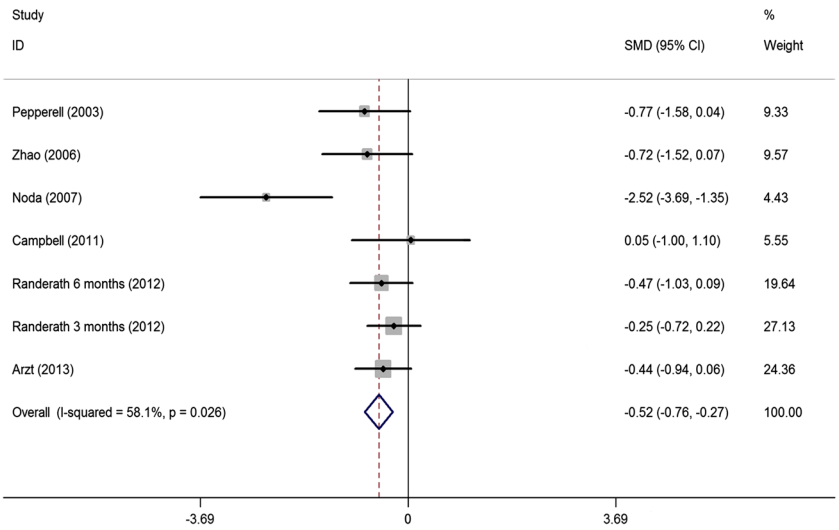

Fig. 2 Efficacy of PAP on BNP in patients with HF and SDB

Table 3 Subgroup analysis of the efficacy of PAP on BNP by different variables in patients with HF and SDB

Variables (number of cohorts)	SMD	95 % *CI*	*Z* value	*p* value
ASV				
ASV (6)	−0.424	−0.677 to −0.172	3.29	0.001
No ASV (1)	−2.520	−3.693 to −1.347	4.21	0.000
Therapeutic durations (weeks)				
< 12 (3)	−0.565	−1.064 to −0.066	2.22	0.026
≥12 (4)	−0.716	−1.336 to −0.096	2.26	0.024

PAP positive airway pressure, *BNP* brain natriuretic peptide, *HF* heart failure, *SDB* sleep-disordered breathing, *SMD* standard mean difference, *CI* confidence interval, *AHI* apnea-hypopnea index, *ASV* adaptive servo-ventilation

parallel. SDB of included studies patients varied from OSA, CSA to CSR. Patients in one study received BiPAP, and patients in the remaining 5 studies received ASV. The characteristics of the included studies are listed in Table 2.

Impact of PAP on BNP

Moderate heterogeneity ($I^2 = 58.1$ %) was noted, and random effect model was performed. When compared with control group, a significant reduction in BNP was observed in patients treated with PAP (SMD −0.517, 95 % *CI* −0.764 to −0.270, $z = 4.11$, $p = 0.000$), Fig. 2.

Further subgroup analysis showed that the significant reduction was not yet changed after stratifying by PAP type and therapeutic duration (Table 3).

Publication Bias

There was no statistical significance of publication bias in the present meta-analysis (Begg's funnel plots in Fig. 3, $p = 0.072$; Egger's test, $p = 0.157$).

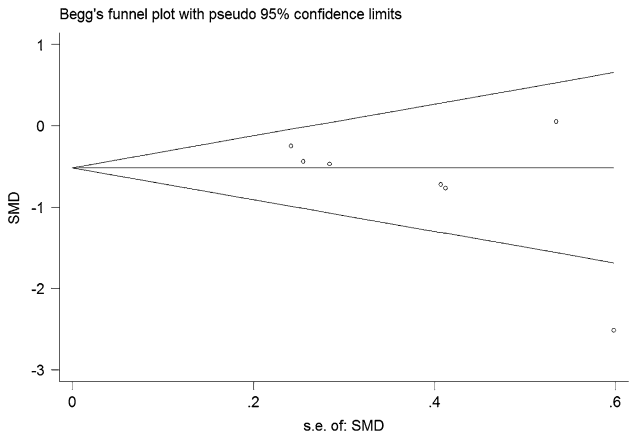

Fig. 3 Publication bias

Discussion

The present meta-analysis evaluated the efficacy of PAP on BNP in patients with HF and SDB. The results including 6

RCTs demonstrated that PAP can decrease BNP levels in patients with HF and SDB.

The prevalence of SDB, including OSA, CSA, and CSR, is up to 40 %, and SDB contributes to poor prognosis in HF patients [1, 3]. Accumulating evidence elucidates that PAP can improve LVEF and left ventricular hypertrophy in patients with HF and SDB [7, 8, 19]. The potential mechanism is multi-factors: reducing sympathetic nerve activity, increasing cardiac ejection, decreasing ventricular afterload, ameliorating pulmonary congestion, improving oxygen saturation, improving dyspneic symptom. BNP is released from ventricular in response to volume expansion and pressure overload and is associated with left ventricular function and prognosis in HF [25]. BNP has been studied as primary or secondary outcome in many interventional studies. PAP types vary from CPAP, BiPAP to ASV etc., whose efficacy on BNP is inconsistent. The PAP types enrolled in our meta-analysis were ASV and BiPAP, and the results proved that both ASV and BiPAP do ameliorate the BNP concentrations in subjects with HF and SDB.

Previous studies indicated that ASV is superior to CPAP in ameliorating CSA or CSR in patients with HF [26, 27]. One previous RCT showed that CPAP did not decrease BNP levels in SDB patients without HF [28], several studies, however, demonstrated an significant improvement of BNP in OSA patients without HF as a result of CPAP treatment [18, 29]. CPAP can only alleviate 50 % of CSA [7]. Study found that ASV can not only suppress all types of SDB, but also improve sleep quality [30]. Subjects in most studies of our meta-analysis suffered HF and CSA or CSR, and the BNP levels were improved in patients received ASV therapy. The reasons of why ASV is more effective than CPAP may be as follow: ASV modality generates fixed or automatic expiratory PAP to eliminate the obstruction of upper airway and provides flexible inspiratory PAP to relieve CSA or CSR [23, 31]. Therefore, ASV may stabilize respiration, eliminate hypoxia, alleviate ventricular afterload, and even decrease ventricular hypertrophy.

There are some strengths of the present meta-analysis. Firstly, all enrolled studies were RCTs, and all of them had a high quality. Secondly, there was a large sample size (Totally 222 patients) to strengthen our conclusion. Thirdly, no evidence showed any publication bias in the present meta-analysis. Lastly, all subjects had a good PAP compliance, the PAP usage time per night in all studies was more than 4 h.

Several limitations have to be mentioned in our analysis. Firstly, control type varied in accordance with different studies design, including medical therapy, CPAP, oral appliance, and subtherapeutic ASV. Secondly, the PAP therapeutic duration was various across each study, ranging from 7 days to 12 months; however, its efficacy did not change.

In conclusion, the present meta-analysis indicated that PAP can significantly lower BNP levels in patients with HF and SDB.

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Conflict of interest The authors declare that they have no conflict of interest.

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