Clinical research protocol

A Cohort Study on Increasing Blood Pressure Benefits in Sleep Apnea Patients After CPAP Treatment

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I. Research Background and Scientific Basis

Over the past few decades, the prevalence of hypertension among Chinese citizens has risen significantly, with approximately 27.9% of adults currently affected by the condition[1]. Timely intervention targeting factors that elevate blood pressure is crucial for delaying the progression of hypertension and preventing cardiovascular and cerebrovascular diseases. Some patients with early blood pressure abnormalities (130-139/80-89 mmHg) may prioritize lifestyle interventions. Following effective non-pharmacological treatment, some patients achieve normal blood pressure (below 120/80 mmHg), while others fail to normalize or even experience further increases. Persistent elevated blood pressure may indicate that contributing factors remain unaddressed, potentially rendering non-pharmacological approaches ineffective.

（1）The Therapeutic Effects of CPAP on Blood Pressure Abnormalities

Obstructive sleep apnea (OSA) is a highly prevalent respiratory disorder. Current estimates indicate that approximately 176 million people in China suffer from OSA, with 67 million classified as having moderate to severe OSA[2]. Numerous studies indicate that OSA is a significant risk factor for hypertension[3–5]. Patients with OSA experience recurrent upper airway obstruction during the night, which not only leads to intermittent hypoxemia but also causes autonomic nervous system dysfunction. Excessive sympathetic nervous system activation at night results in significant fluctuations in blood pressure within a short period[6], even accompanied by a blunted baroreflex response[7]. Simultaneously, OSA causes fragmented sleep and sleep deprivation at night, leading to poor daytime alertness and mood in patients. This results in elevated sympathetic activity throughout the day, causing a significant increase in daytime blood pressure[8].

Continuous positive airway pressure (CPAP) is the primary treatment for moderate-to-severe obstructive sleep apnea (OSA). It maintains upper airway patency through an “airway support” mechanism, thereby eliminating respiratory events. Although numerous studies indicate that OSA patients experience blood pressure benefits following CPAP therapy[9–12], However, results from

numerous studies collectively indicate that the degree of blood pressure improvement following CPAP therapy is not entirely satisfactory. For example, in a meta-analysis involving 1,904 patients[12], Following CPAP therapy, daytime systolic and diastolic blood pressure decreased by 3.55 mmHg and 2.97 mmHg, respectively; nighttime systolic and diastolic blood pressure decreased by 3.67 mmHg and 2.33 mmHg, respectively. Although the downward trend in blood pressure was statistically significant, the magnitude of improvement was disappointing. Even in a study published by Ou in 2024, blood pressure did not show significant improvement after 6 months of CPAP treatment[13]. Evidently, some hypertensive patients with combined OSA do not experience blood pressure benefits following effective CPAP therapy. Investigating factors influencing CPAP treatment outcomes is crucial for selecting suitable hypertensive patients for CPAP therapy and tailoring individualized intervention approaches.

（2）Patients with OSA-related blood pressure fluctuations may be candidates for blood pressure benefits from CPAP therapy

Patients with OSA often exhibit non-dipping blood pressure and elevated morning blood pressure. Studies indicate that patients with OSA-induced blood pressure rhythm abnormalities are more likely to benefit from CPAP therapy[14,15]. For example, studies by Pengo et al. confirm that OSA patients with non-spoon-shaped blood pressure profiles experience significant blood pressure reduction following CPAP therapy, whereas those with spoon-shaped blood pressure profiles show minimal improvement in blood pressure after CPAP treatment[14]. Domestic scholars have found that patients with significantly elevated pulse transit time (PTT)-blood pressure due to OSA experience marked improvement in office blood pressure following CPAP therapy[15]. However, while PPT-BP can reflect trends in blood pressure changes, its readings exhibit significant fluctuations and may differ from actual blood pressure levels. This discrepancy is particularly noticeable in the measurement of blood pressure troughs and peaks, where errors frequently occur[16]; Conventional ambulatory blood pressure monitoring can only measure blood pressure intermittently, clearly failing to capture the transient effects of respiratory events on blood pressure. Considering that

blood pressure may fluctuate dramatically within a short timeframe during sleep-related respiratory events[17], Developing reliable technology capable of continuously recording noninvasive blood pressure holds significant value for identifying patients with OSA-related hypertension and screening individuals who may benefit from CPAP therapy.

Our research group will employ novel volumetric clamping technology to precisely measure beat-by-beat blood pressure[18], Furthermore, by precisely integrating it with sleep parameters, we developed a sleep-blood pressure index that accurately reflects blood pressure fluctuations during respiratory events and explored its predictive value for CPAP treatment outcomes.

（3）Sleep aids may improve sleep quality and enhance CPAP compliance, potentially increasing blood pressure benefits

Numerous studies indicate that CPAP usage duration is one of the most critical factors determining cardiovascular benefits in patients with obstructive sleep apnea[11,19]. However, many OSA patients also suffer from severe insomnia, making it difficult for them to tolerate CPAP therapy. At the same time, some OSA patients experience a lowered arousal threshold after CPAP treatment[20], Difficulty falling asleep and early morning awakenings significantly impair CPAP treatment adherence. Therefore, insomnia and awakenings may be factors affecting CPAP treatment compliance, thereby reducing blood pressure benefits in OSA patients. Recent studies indicate that trazodone reduces post-CPAP awakenings and improves CPAP treatment adherence[21], Therefore, we hypothesize that administering sleep aids to OSA patients experiencing insomnia and wakefulness may improve sleep quality following CPAP therapy, enhance CPAP compliance, and potentially increase blood pressure benefits.

This study will conduct a cohort analysis involving patients with early-stage blood pressure abnormalities who have not received drug therapy, as well as hypertensive patients requesting non-pharmacological blood pressure management.

The objectives are: ① to identify OSA patients likely to benefit from blood pressure control using

an innovative sleep-blood pressure index; ② to examine the impact of insomnia and arousal following CPAP therapy on blood pressure; ③ to enhance sleep quality with sleep aids, thereby improving CPAP treatment adherence and blood pressure outcomes. This study will provide novel insights and solutions to address the challenge of uncontrolled blood pressure following CPAP therapy for OSA.

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II. Research Objectives and Content

1. Research Objectives

1.1 Validate innovative sleep-blood pressure parameters for screening OSA patients who benefit from blood pressure improvement after CPAP therapy.

1.2 Identify reasons for suboptimal blood pressure improvement in OSA patients after CPAP therapy through analysis of treated patients.

1.3 Improve CPAP treatment compliance and enhance blood pressure benefits by administering trazodone or zopiclone for insomnia and post-CPAP arousals (including micro-arousals).

2. Research Content

2.1 Screen OSA patients likely to benefit using an innovative sleep-blood pressure index: Develop the sleep-blood pressure index by precisely measuring continuous blood pressure via novel volumetric clamping technology and synchronizing it with PSG through engineering techniques. Conduct a cohort study to analyze characteristics of patients with blood pressure improvement after CPAP therapy, obtaining a sleep-blood pressure index and its cutoff value for predicting CPAP treatment benefits.

2.2 Exploring Factors Influencing Blood Pressure Improvement After CPAP Therapy: Compare differences in sleep-related parameters—including insomnia indices, arousal-related indices, and autonomic function—between patients with and without blood pressure improvement after 3 months of CPAP therapy. Analyze residual sleep factors affecting CPAP efficacy.

2.3 Enhancing CPAP Compliance and Blood Pressure Benefits in OSA Patients: Select patients with pre-CPAP insomnia or frequent post-CPAP arousals. Administer trazodone or zopiclone for 4 weeks alongside CPAP therapy. Demonstrate how sleep aids improve sleep quality in OSA patients, thereby increasing CPAP compliance and enhancing blood pressure outcomes.

3. Distinctive Features and Innovations

3.1 Theoretical Innovation: Identifies and corrects reasons for unimproved blood pressure after CPAP therapy, thereby increasing benefits for OSA patients.

3.2 Technical Innovation: Develops a sleep-blood pressure index through synchronized continuous blood pressure and sleep monitoring, providing a new indicator for cardiovascular risk assessment in OSA patients.

4. Key Scientific Questions:

Scientific Question 1: How can we predict which individuals are likely to benefit from CPAP therapy before treatment initiation?

Solution: Administer an innovative sleep-blood pressure index to patients with moderate-to-severe OSA and initiate CPAP therapy, demonstrating that the sleep-blood pressure index can predict blood pressure improvement following CPAP treatment.

Scientific Question 2: Why is blood pressure improvement limited in OSA patients after CPAP therapy?

Solution: Investigate the relationship between sleep parameters and clinical improvements post-CPAP therapy, identifying insomnia and arousal as key factors limiting treatment benefits in OSA patients.

Scientific Question 3: How can we enhance blood pressure benefits in OSA patients following CPAP therapy?

Solution: Improve CPAP adherence by administering sleep aids to specific patient groups, thereby increasing blood pressure benefits in OSA patients.

III. Research Protocol and Technical Approach

1. Study Design: Through a cohort study, this research aims to: ① explore innovative sleep-blood pressure indices; ② elucidate factors influencing suboptimal blood pressure improvement following CPAP therapy in OSA patients; ③ determine whether sleep aids alleviate insomnia and awakenings, thereby enhancing CPAP compliance and improving blood pressure.

2. Study Population: Participants will be recruited from the Sleep Medicine Center and Hypertension Department of Anzhen Hospital.

(1) Inclusion Criteria:

- Aged 18–70 years;
- Diagnosed with obstructive sleep apnea (OSA) via overnight polysomnography (PSG), meeting either: (a) AHI ≥ 5 events/hour with at least one of the following: (1) patient-reported daytime sleepiness, unrefreshing sleep, fatigue, or insomnia; (2) sleep arousal due to gasping or choking; (3) Reports from bed partners or witnesses of habitual snoring, breathing interruptions, or both during sleep. Or (b) AHI ≥ 15 events/hour.
- Blood pressure meeting any of the following criteria: (1) Office BP 120-139/80-89 mmHg with ≤2 cardiovascular risk factors; (2) Newly diagnosed blood pressure 140-159/90-99 mmHg without cardiovascular risk factors; (3) Hypertensive patients with low cardiovascular risk who are currently on stable antihypertensive medication but whose office blood pressure does not meet normal blood pressure standards (120/80 mmHg); (4) Any non-high cardiovascular risk patient who voluntarily requests three months of non-antihypertensive medication therapy;
- Able to tolerate 24-hour ambulatory blood pressure monitoring and continuous blood pressure monitoring;
- Understands and signs the informed consent form, voluntarily agrees to undergo 3 months of

CPAP therapy and participate in follow-up visits.

(2) Exclusion Criteria:

- Previously diagnosed OSA currently undergoing treatment (CPAP, orthodontic appliances, surgery, etc.);
- Secondary hypertension caused by factors other than OSA, such as renal artery stenosis, nephropathy, Cushing's syndrome, or primary aldosteronism;
- Unstable medical condition (cardiovascular or cerebrovascular events or major surgery within the past 3 months, severe hypersomnia [ESS ≥ 16 points] or cognitive impairment preventing cooperation, active psychiatric illness, or substance/alcohol abuse);
- Rheumatic/autoimmune diseases and malignancies;
- Aortic diseases (e.g., giant cell arteritis, aortic dissection, aneurysms);
- Conditions preventing accurate blood pressure measurement (e.g., atrial fibrillation, upper limb vascular disease);
- Familial early-onset hypertension;
- Use of any prescription or over-the-counter sleep aids within 4 weeks prior to enrollment (e.g., benzodiazepines, non-benzodiazepine hypnotics, melatonin receptor agonists, trazodone, sedative antidepressants/antipsychotics, sedative-containing OTC products);
- Allergy or contraindication to potential study drugs (trazodone, zopiclone);
- Pregnancy, lactation, or planned pregnancy;
- Frequent night shift work (≥3 nights/week) or diagnosed circadian rhythm disorder;
- Participation in other interventional clinical trials.

3. CPAP Intervention: Subjects undergo CPAP therapy in fixed pressure mode, with ≥4 hours of use

per night and ≥21 days of use per month. Prior to treatment initiation, subjects undergo overnight automatic (or manual) pressure titration under PSG or overnight automatic pressure titration without PSG, based on clinical condition, to select the optimal pressure achieving “optimal/good” therapeutic effect (referencing the American Academy of Sleep Medicine's CPAP Treatment and Titration Standards for Adult Obstructive Sleep Apnea). Investigators enhance subjects' understanding of CPAP through educational outreach to overcome psychological barriers. During follow-up, respiratory and otolaryngology specialists addressed specialty-related issues affecting CPAP use, promptly resolving CPAP-related discomforts to enhance CPAP adherence.

4. Pharmacological Intervention: For patients with OSA and insomnia selected in Study Component 3, or those experiencing frequent awakenings despite CPAP therapy, combined CPAP and trazodone (or zopiclone) treatment was recommended. The treatment regimen involves taking trazodone at an initial dose of 25-50 mg/night before bedtime. Based on patient tolerance and efficacy, the dose may be increased by 25 mg every 3-5 days, not exceeding a maximum of 150 mg/night. Zopiclone should start at 3.75-7.5 mg/night, adjustable to 7.5 mg/night as appropriate. The total treatment period was 4 weeks. Changes in subjective and objective sleep quality before and after medication were recorded using questionnaires, actigraphs, and polysomnography. During follow-up, patients were naturally grouped based on treatment choice and adherence: CPAP alone, CPAP plus trazodone, trazodone alone, and untreated. Compare baseline-to-endpoint blood pressure changes across groups, including intra-group comparisons and inter-group comparisons of rate of change.

5. Sample Size Estimation: Based on the research team's preliminary findings, this project will enroll 120 OSA patients receiving CPAP therapy (Research Content 1-2) and 80 patients with insomnia combined with OSA or frequent awakenings during CPAP use (Research Content 3).

IV. Expected Outcomes and Evaluation Metrics

(1) Expected Results

1. The Sleep-Blood Pressure Index can predict the efficacy of blood pressure improvement following CPAP therapy, identifying OSA patients likely to benefit from CPAP treatment.

2. Insomnia and awakenings (including micro-awakenings), along with the resulting sympathetic overactivation, are key factors contributing to suboptimal blood pressure improvement after CPAP. Trazodone and zopiclone improve sleep quality, reduce awakenings and blood pressure fluctuations during CPAP therapy, thereby lowering daytime blood pressure values.

(2) Evaluation Metrics

1. Propose and validate an innovative sleep-blood pressure metric.

2. Publish two SCI papers (Q1 and Q2 journals).

This protocol strictly adheres to the Good Clinical Practice (GCP) guidelines and Anzhen Hospital's Special Management Measures for High-Level Research. It integrates all technical details of the application and has mitigated common risks of ethical rejection (funding disclosure, vulnerable subject protection, and intervention rationale).