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# Efficacy Analysis of Inhaled Nitric Oxide Combined with Continuous Positive Airway Pressure Ventilation in the Treatment of Refractory OSA

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**Abstract:** Refractory obstructive sleep apnea (OSA), as a difficult subtype in the field of sleep breathing disorders, has always been a key and difficult issue in the clinical management of respiratory and sleep medicine. The limitations of conventional continuous positive airway pressure (CPAP) treatment for this type of patient are becoming increasingly prominent, and there is an urgent need to explore more optimized combination therapy options in clinical practice. This article focuses on the treatment pathway of inhaled nitric oxide (iNO) combined with CPAP, and conducts a systematic analysis from four aspects: pathological and physiological mechanism compatibility, clinical efficacy, safety performance, and clinical application value. The aim is to clarify the logic and application prospects of the combined treatment plan for refractory OSA, provide theoretical reference for optimizing clinical treatment decisions, and provide ideological support for the improvement of relevant diagnosis and treatment standards in the future.

**Keywords:** Sexual Sleep Apnea; Inhalation of Nitric Oxide; Continuous Positive Airway Pressure Ventilation; Combination Therapy.

## 1. Clinical Characteristics and Limitations of Conventional Treatment for Refractory OSA

The core clinical feature of refractory OSA is that patients with standardized CPAP treatment and compliance meet clinical requirements, but the sleep apnea hypopnea index (AHI) cannot be reduced to clinical control standards. At the same time, symptoms such as nocturnal hypoxemia, sleep structure disorders, and daytime sleepiness persist, and some patients may even experience the progression of cardiovascular, metabolic, and other systemic complications.

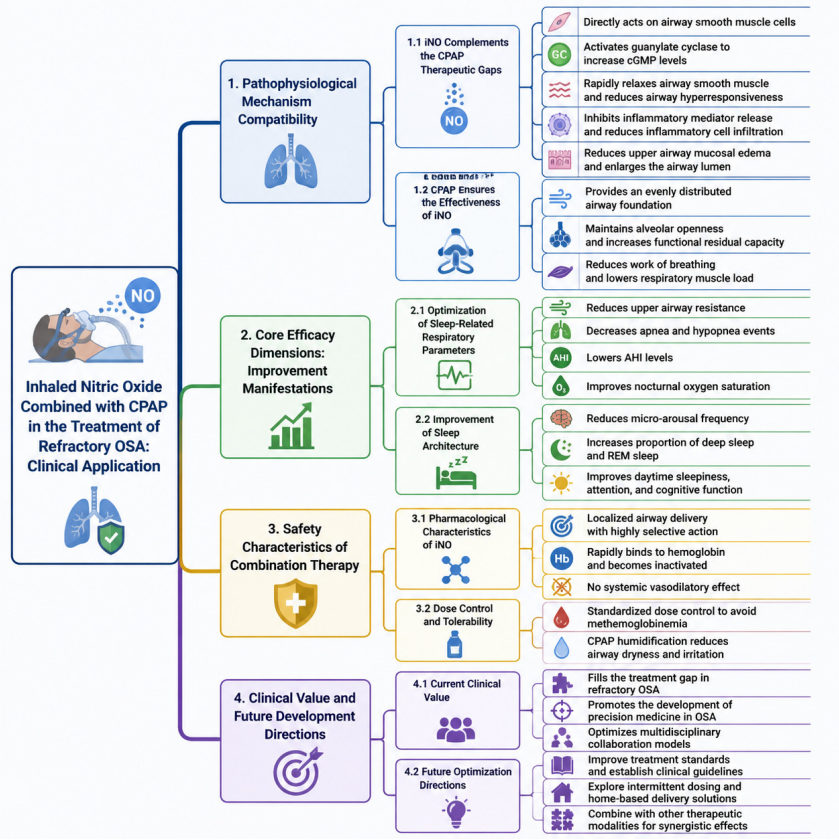



**Figure 1.** Framework of the mechanism of action and clinical value of inhaled nitric oxide combined with CPAP in the treatment of refractory OSA

The pathogenesis of this type of patient is more complex compared to the general OSA population, and is not caused by a single stenosis of the upper airway anatomical structure. It is often accompanied by multiple pathological and physiological changes such as upper airway mucosal edema, airway smooth muscle tension abnormalities, pulmonary vascular regulation dysfunction, and decreased sensitivity of respiratory center regulation. Conventional CPAP can only support the upper airway through mechanical pressure and cannot improve the above-mentioned pathological abnormalities in a targeted manner, which is also the core reason for its limited efficacy.The conceptual framework of this study is illustrated in Figure 1. [1-2]

# 2. Pathophysiological Compatibility of Inhaled Nitric Oxide Combined with CPAP Therapy

## 2.1. Supplementing the Blind Spots of iNO on CPAP

After entering the airway, the core pharmacological effect of iNO (inhaled nitric oxide) is to directly act on airway smooth muscle cells. Specifically, iNO molecules rapidly diffuse into cells and activate the intracellular guanylate cyclase with precision, thereby significantly increasing the level of the second messenger in cells - cyclic guanosine monophosphate (cGMP). The increase in cGMP levels triggers a series of cascade reactions, ultimately leading to a decrease in intracellular calcium ion concentration in smooth muscle cells, thereby rapidly and effectively relaxing airway smooth muscle. This direct biochemical relaxation effect can significantly reduce airway hyperresponsiveness and alleviate smooth muscle spasms caused by inflammation, stimulation, or neural regulation abnormalities. From the perspective of its mechanism of action, this pharmacological pathway can effectively compensate for the fundamental deficiency of CPAP (Continuous Positive Airway Pressure), which can only mechanically open the airway through physical pressure but cannot regulate smooth muscle tension at the cellular and molecular levels. By reducing smooth muscle tension from the source, iNO can synergize with mechanical support from CPAP, further reducing the total resistance of the upper airway, thereby improving the overall ventilation efficiency and tidal volume of patients. Meanwhile, iNO also exhibits various regulatory functions in anti-inflammatory and edema reducing effects. It can alleviate the inflammatory edema state of the upper airway mucosa from pathological and physiological aspects by inhibiting the release of key inflammatory factors such as tumor necrosis factor alpha and interleukin, and reducing the aggregation and infiltration of inflammatory cells such as neutrophils in the airway mucosa. The decrease in airway mucosal thickness directly expands the effective ventilation cross-sectional area of the upper airway in the coronal and sagittal planes. This enables the mechanical support force applied by CPAP to act on a relatively optimized structure after volume reduction, improving its spreading efficiency. This means that achieving the same ventilation effect may not require excessive treatment pressure. This not only optimizes the treatment effect, but more importantly, improves the comfort and tolerance of patients' long-term use of CPAP, reducing treatment interruptions caused by stress discomfort. [3]

## 2.2. The Guarantee of CPAP's Effect on iNO

The continuous and constant positive airway pressure provided by CPAP first creates ideal conditions for the delivery and distribution of iNO in physical space. It provides a uniform and open "duct" system for the passage of iNO airflow by maintaining the patency of the entire upper airway, especially the easily collapsed areas such as the pharynx. This effectively avoids uneven flow velocity, vortex formation, or local accumulation of iNO in narrow and tortuous airways caused by collapse, ensuring that iNO can effectively and uniformly act on the target area at a stable concentration, including the mucosal epithelium of the upper airway, deep smooth muscle bundles, and even the more distal alveoli and pulmonary vascular beds, thereby maximizing the coverage and efficacy of its pharmacological effects. Secondly, at the alveolar level, the sustained positive pressure of CPAP can effectively prevent alveolar collapse at the end of expiration and maintain the open state of alveoli. This not only increases functional residual gas and improves gas exchange reserves, but more importantly, provides a huge and effective exchange area for iNO gas to come into contact with alveolar epithelial cells and pulmonary vascular endothelial cells. The increase in contact area directly enhances the efficiency of iNO molecules being absorbed and utilized locally in the lungs, which may reduce the inhaled dose of iNO when achieving the same physiological effects. This helps to reduce the potential risk of adverse reactions, such as methemoglobinemia or direct lung injury, that may arise from high concentrations of iNO or its metabolites (such as nitrogen dioxide). Finally, in terms of stabilizing respiratory mechanics, CPAP significantly reduces the respiratory work produced by patients during sleep, especially during inhalation, to counteract upper airway resistance through its "pneumatic split" effect. The reduction of load on respiratory muscles (mainly diaphragm and intercostal muscles) effectively avoids respiratory muscle fatigue and its resulting secondary hypoventilation and hypercapnia. This provides a more stable and reliable respiratory physiology basis for iNO to improve ventilation, regulate vascular tone, optimize ventilation/blood flow ratio (V/Q), and even enhance systemic oxygenation. In summary, the combined application of CPAP and iNO is not simply a superposition, but forms a deep complementary synergistic mode: CPAP provides the basic "structural support" to maintain the opening of the airway and alveoli; INO performs fine "functional regulation" on this basis, targeting the relief of spasms and inflammation; The combined effect of the two ultimately leads to "circulatory improvement" in the oxygenation status of the pulmonary and systemic circulation. This complete intervention chain can intervene from multiple pathological and physiological links such as anatomical structural abnormalities, neuromuscular control disorders, and local inflammatory reactions, thus more comprehensively targeting the complex etiology of refractory obstructive sleep apnea.

# 3. Analysis of Therapeutic Efficacy and Safety of Inhaled Nitric Oxide Combined with CPAP Therapy

## 3.1. Improvement Performance in Core Efficacy Dimensions

The improvement effect of combination therapy on the core

indicators of refractory OSA is first reflected in the optimization of sleep respiratory parameters. The mechanical support provided by CPAP and the pharmacological regulation of airway smooth muscle tension by iNO can produce a synergistic effect, effectively reducing the resistance of the entire upper airway from both physical and functional perspectives. The reduction of resistance directly translates into a more coordinated match between respiratory drive and airflow, thereby significantly reducing the frequency and duration of respiratory pauses and hypoventilation events during sleep, resulting in a significant decrease in the core indicator of disease severity - the apnea hypopnea index (AHI). The reduction of ventilation events and the improvement of ventilation efficiency directly improve gas exchange, resulting in an increase in the average and baseline levels of nocturnal oxygen saturation ($SpO_2$) and a significant reduction in the duration and depth of hypoxemia (usually $SpO_2$<90%), fundamentally helping to alleviate the damage burden of intermittent hypoxia on the cardiovascular and cerebrovascular systems. Secondly, combination therapy can effectively and deeply improve the sleep structure of patients. Frequent respiratory events and their resulting reflexive micro awakenings are the culprits that disrupt the continuity and fragmentation of sleep structure. By stabilizing nighttime breathing, combined therapy can significantly reduce the number of micro awakenings related to respiratory effort. A more stable and continuous sleep process enables the brain to smoothly organize and complete a complete sleep cycle, which is directly reflected in the effective increase and recovery of the proportion of deep sleep (N3 phase) and rapid eye movement (REM) sleep, which is crucial for memory consolidation and emotional regulation. This fundamental improvement in sleep quality is the physiological basis for alleviating core clinical symptoms such as excessive daytime sleepiness, cognitive decline (such as lack of concentration and memory), fatigue, and weakness in patients, thereby improving their overall quality of life, daytime functional status, and work ability. [4]

### 3.2. Safety Characteristics of Combination Therapy

Under the standardized application dosage and rigorous operation and monitoring procedures, the safety performance of inhaled nitric oxide (iNO) combined with CPAP treatment is good, which provides an important basis for its clinical application. The safety advantage of iNO primarily stems from its unique pharmacokinetic properties: its administration is through local inhalation via the airway, and its action is highly selective. INO mainly acts on the pulmonary blood vessels and airways in well ventilated areas, rapidly producing local effects; Once it enters the bloodstream, it immediately binds with heme iron in hemoglobin with high affinity, generating inactive methemoglobin (MetHb) and nitrate/nitrite, which are quickly "cleared" and inactivated. This characteristic determines that iNO does not produce significant systemic vasodilation effects like systemic vasodilators, thus avoiding adverse reactions such as systemic hypotension commonly seen in systemic medication. Secondly, by regulating and typically controlling low doses (usually at the ppm level), supplemented by routine monitoring of methemoglobin levels in the blood, potential adverse reactions such as methemoglobinemia can be effectively prevented and avoided, and their risks can be controlled at extremely low levels. In addition, the active humidification function integrated into CPAP devices can provide sufficient heating and humidification airflow while delivering therapeutic gases. This not only improves patient comfort, but also effectively reduces or avoids local discomfort symptoms such as dryness and irritation that may be directly caused by iNO dry and cold gases on the airway mucosa, thereby further enhancing the tolerance and patient acceptance of the entire combination therapy at the instrument level. Overall, this combination therapy not only demonstrates synergistic efficacy, but also has a controllable and good short-term safety and tolerability foundation. [5]

## 4. The Clinical Application Value and Future Direction of Combination Therapy

### 4.1. Current Clinical Application Value

The clinical application of combination therapy (iNO combined with CPAP) has the core value of filling the current gap in the treatment of refractory OSA. For the "refractory" patient population where the residual index of respiratory events (AHI) remains high after standard CPAP treatment, or subjective tolerance and symptom improvement are poor, there has traditionally been a lack of efficient and tolerable escalation plans. This joint strategy provides a novel intervention approach from the perspective of pathological and physiological mechanisms, offering practical and effective treatment options for patients who are "ineffective" or "unresponsive" to conventional CPAP treatment. By effectively controlling the condition of such severe and complex patients, the need for frequent emergency visits, repeated hospitalizations, and various complications (such as uncontrollable hypertension, refractory atrial fibrillation, and acute exacerbation of heart failure) caused by long-term disease control can be significantly reduced, thereby reducing the long-term medical resource consumption and economic burden on individuals and society as a whole. This has important public health significance. Secondly, the introduction and application of combination therapy can actively promote the evolution of OSA diagnosis and treatment mode from "one size fits all" to "precision". It will guide clinical doctors and researchers to go beyond the simple AHI values and pay more attention to and distinguish the heterogeneous mechanisms behind refractory OSA - for example, whether the "structural" factors dominated by airway collapse, the "functional" factors dominated by airway inflammation and abnormal tension, or both. This mechanism based segmentation enables treatment selection to shift from relying solely on CPAP to matching more suitable targeted regimens based on the patient's specific pathophysiological characteristics, thereby improving the accuracy and scientific level of overall diagnosis and treatment of OSA. In addition, the evaluation and implementation of combination therapy regimens, especially those involving inhalation management of iNO, naturally require and can promote the deepening and improvement of multidisciplinary collaboration (MDT) models. It will promote closer collaboration among respiratory and critical care medicine departments, sleep medicine centers, cardiovascular medicine, otolaryngology and neck surgery, as well as clinical pharmacy and respiratory therapy teams. Various disciplines can jointly participate in the entire process from patient screening, mechanism evaluation, plan formulation, treatment implementation to long-term follow-up and complication management,

providing patients with comprehensive and integrated diagnosis and treatment services that integrate diagnosis, treatment, rehabilitation, and chronic disease management. This represents the advanced direction of modern medicine in dealing with complex chronic diseases.

### 4.2. Future Optimization Directions

The future development of combination therapy will inevitably focus on the standardization and refinement of treatment standards as its primary optimization direction. There is an urgent need to design rigorous prospective clinical studies to clarify the specific indications, optimal treatment dose window (such as ppm concentration of iNO), administration mode (such as continuous inhalation or intermittent inhalation at night), treatment duration (short-term induction therapy or long-term maintenance therapy), and efficacy evaluation criteria for different pathological and physiological subtypes (such as high inflammation phenotype, high smooth muscle response phenotype, etc.) of refractory OSA patients. Based on high-level evidence, the ultimate formation of authoritative clinical practice guidelines or expert consensus is the cornerstone to ensure the safe, effective, and standardized promotion and application of this therapy. Secondly, it is necessary to actively explore more accessible and convenient treatment models. For example, studying the feasibility of "intermittent" or "on-demand" dosing regimens, which only initiate iNO inhalation during sleep or when respiratory events are monitored, may reduce total drug exposure and costs while ensuring efficacy. At the same time, developing integrated and intelligent portable iNO generation and delivery devices suitable for home use, seamlessly integrating with home CPAP treatment, is a key step in reducing treatment barriers, achieving long-term community and family management, and ultimately improving patient treatment accessibility and long-term compliance. In addition, it is necessary to broaden our horizons and further explore combination therapy as a cornerstone, combining it with other existing treatment methods in a "cocktail" style comprehensive strategy. For example, for patients with significantly elevated inflammatory markers, combination therapy with local or systemic anti-inflammatory drugs; For patients with clear anatomical problems such as mandibular retrognathia, use in combination with oral orthodontic treatment; Evaluate the potential of sequential or combined treatment with upper airway surgery for patients with specific upper airway structural obstruction, such as severe tonsillar hypertrophy. By constructing this multi-level and personalized comprehensive treatment plan network, it is expected to continuously improve the overall control rate of refractory OSA, provide patients with a more diverse and personalized treatment selection sequence, and ultimately overcome this clinical challenge. [6]

## 5. Conclusion

The combination of inhaled nitric oxide and continuous positive airway pressure ventilation for the treatment of refractory OSA has a sufficient pathological and physiological mechanism basis. The combined application of the two can achieve complementary mechanisms of action, comprehensively covering multiple pathological and physiological abnormalities of refractory OSA. It has shown clear efficacy in improving sleep respiratory parameters, enhancing oxygenation levels, improving sleep quality, and delaying the progression of complications in multiple dimensions. At the same time, it has good safety and personalized adaptability under the premise of standardized application. This combination therapy provides an effective new pathway for the clinical management of refractory OSA and has high clinical application value. With the improvement of subsequent treatment standards and optimization of application models, its application prospects in the diagnosis and treatment of refractory OSA will be even broader, and it is expected to become one of the mainstream treatment options for refractory OSA, promoting the overall diagnosis and treatment level of OSA.

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