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Review

Continuous Positive Airway Pressure (CPAP) in Non-Apneic Asthma: A Clinical Review of Current Evidence

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Abstract

The use of continuous positive airway pressure (CPAP) in asthma has been a point of debate over the past several years. Various studies, including those on animals and humans have attempted to understand the role and pathophysiology of CPAP in patients with either well controlled or poorly controlled asthma. The aim of this manuscript is to review the currently available literature on the physiologic and clinical effects of CPAP in animal models of asthma and on humans with stable asthma.

KEYWORDS: Asthma, bronchoconstriction, continuous positive airway pressure

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INTRODUCTION

Bronchial asthma is a common chronic airway disorder with variable and recurring symptoms, including airway obstruction, bronchial hyperresponsiveness, and underlying inflammation. It is characterized by heterogeneity since the numerous phenotypes associated with it have been proposed recently [1].

Despite advances in medical treatment, the prevalence of patients with uncontrolled asthma continues to be relatively high in everyday clinical practice [1]. Asthma therapies, such as bronchodilator medications (typically in combination with inhaled corticosteroids) and a more recent technique called bronchial thermoplasty are focusing on airway smooth muscle (ASM), taking into consideration its importance in airflow obstruction [2]. Over the past years, the effect of positive airway pressure as a non-pharmacologic strategy to improve asthma control has become an object of scientific interest [3]. This review article aimed to summarize the available literature on such effects both in animal models of asthma and human subjects with stable asthma.

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Asthma Pathophysiology and Effect of Mechanical Ventilation

Our insight with regard to bronchial asthma has changed considering the advances in molecular phenotyping, which has revealed heterogeneous phenotypes within the asthmatic population. Exposure to various environmental factors such as viruses and inhaled antigens trigger an immune response directed at the T-helper type-2 (Th2) cells. Initial exposure to the allergens leads to sensitization; however, repeated exposure triggers a cascade of cellular and immune responses that culminates in airway hyperactivity and symptoms of asthma. The interaction between the dendritic cells and the antigen activate the Th0 and subsequently Th2 cells which release IL-4, IL-5, and IL-13. IL-4 and IL-13 stimulate B-cells to synthesize IgE, which causes the mast cells to release LTC4, PGD2, and histamine that result in goblet cell hyperplasia, edema, mucus secretions, and bronchial smooth muscle contraction. IL-5 stimulates eosinophils to release pro-inflammatory mediators causing an inflammatory process and thus bronchoconstriction.

Mechanical ventilation is reportedly associated with ventilation-induced lung injury and an augmented inflammatory response [4]. Tsangaris et al. [5] studied the inflammatory response triggered by the use of mechanical ventilation for extended durations in patients without acute lung injury. The study outcomes revealed that during mechanical ventilation the total bronchoalveolar lavage (BAL) protein increased but the BAL phospholipids decreased. Additionally, there was a reduction in the aggregation of surfactants. However, there was an increase in the inflammatory markers, including the platelet activating factor (PAF), PAF-acetylhydrolase and neutrophils after 1 week, despite being partially remitted after 2 weeks of mechanical ventilation. This study showed that prolonged mechanical ventilation in patients without acute lung injury is associated with the presence of inflammatory markers and alterations in surfactant.

Chiumello et al. [6] examined whether injurious ventilatory strategies would increase the release of inflammatory mediators including tumor necrosis factor-alpha (TNF-α) and macrophage inflammatory protein-2 (MIP-2) concentrations into the systemic circulation in a lung injury model. They concluded that the release of cytokines into the systemic circulation was influenced by the ventilatory modality, which may be eventually be relevant in developing multisystem organ failure.

Paone et al. [7] observed the effects of long-term noninvasive ventilation (NIV) on systemic inflammatory response in patients with COPD. Sputum analysis in the NIV versus oxygen therapy group showed similar levels of human neutrophil peptides (HNP), IL-6, IL-10, and TNF-α ($p>0.5$). However, the NIV group had higher HNP and IL-6 systemic levels and lower IL-10 concentrations ($p<0.001$). The authors concluded that the beneficial effects of NIV on lung mechanics in COPD patients may be negated by its potential effects on the inflammatory system.

Contrarily, Borel et al. [8] examined the effects of NIV on inflammatory markers in patients with mild obesity hypoventilation syndrome and reported no significant variations between the inflammatory and anti-inflammatory cytokines. NIV did not affect the inflammatory, metabolic, or cardiovascular markers in patients with mild obesity hypoventilation syndrome.

Overall, NIV may be essential in treating the acute exacerbations of bronchial asthma by avoiding invasive mechanical ventilation. This method has reportedly decreased the risk of triggering an acute inflammatory cascade that will potentiate lung injury.

Airway Smooth Muscle and Asthma Control

Asthma pathogenesis is influenced by the ASM function both directly by obstructing the airflow by contracting it and indirectly by airway remodeling and modulating airway inflammation. These processes interact with each other to ensure that the net contribution of ASM to asthma is manifold and complex [2]. In asthma, the contributing mechanisms of airway hyperresponsiveness (AHR) include increased dynamic muscle stiffness, increased vagal tone, and cytokine-potentiated increases in intracellular free calcium. Increased ASM mass has been identified as a hallmark of asthma and its abundance is particularly overt in cases of fatal or severe asthma. Moreover, excessive ASM mass and airway wall thickening is associated with AHR [2]. Several studies have reported that the mechanical stretch imposed on an isolated ASM may activate the signaling cascade of several cytoskeletal proteins that are implicated in actin dynamics, myosin light chain phosphorylation, and cytoskeletal organization [2, 3, 9-14].

Deep breathing has been reported to reverse bronchoconstriction in healthy individuals and a small proportion of asthma patients due to changes in the actin-myosin interaction [15]. However, most asthma patients can no longer take deep breaths. It is believed that the dynamic stretch of the ASM during an acute asthma exacerbation at decreased tidal volumes and high end-expiratory lung volumes prevail over the beneficial outcome of a mean stretch of ASM attained via deep inspiration (DI) [16].

Animal Studies

Animal studies have provided valuable information regarding the effects of lung volumes and CPAP on ASM. A study by McClean et al. [17] examined the in vitro contractility of ASM after being exposed to carbachol in a group of sheep whose tidal volume was restricted using a corset for 4 weeks. The corset was adjusted to reduce their functional residual capacity (FRC) by nearly 25%. They also measured the number of deep inspirations. ASM excision revealed higher and shorter contractile responses and discovered that ASM cells

MAIN POINTS

- Non-invasive ventilation is essential in the treatment of bronchial asthma.
- CPAP may be used to assist in inhaled therapy to ensure better bronchodilation.
- Short durations of CPAP may effectively treat chronic airway hyperresponsiveness which is a more aceptable modality than prolonged CPAP treatment.

can alter the organization of their contractile apparatus in response to changes in volume. The duration of maintaining this effect was not transient, since the results were obtained after excising the muscle. This study allowed for a potential explanation for the changes in airway responsiveness observed in obese subjects.

To understand the effects of CPAP on patients with asthma, it is imperative to understand the effect of CPAP on normal lung function. Xue et al. [18-21] designed four studies in rabbits, ferrets, and mice where CPAP versus sham CPAP was applied through a tracheostomy. The first study suggested that a 4-day application of mechanical strain to the lungs resulted in lower respiratory system responsiveness to acetylcholine *in vivo* [18]. The airways isolated from the lungs of animals subjected to CPAP were less responsive to acetylcholine *in vitro* than those of the control group. In the second study, the authors found that the ASM of ferrets subjected to CPAP for 14 days increased the luminal areas of the intrathoracic trachea and intraparenchymal airways and lower levels of myosin light chain phosphorylation, which accounted for the decreased AHR levels observed *in vivo* [19]. In the third study, the authors hypothesized that intermittently applying CPAP could reduce airway reactivity and that this effect could last for minimum 24 hours. They also reported that CPAP suppressed AHR caused by ovalbumin-induced airway inflammation [20]. In the last study, the same authors reported that only 2 hours of CPAP decreased airway resistance in vitro for the following 6 hours and that there were molecular changes including the IL-13-induced downregulation of Akt phosphorylation [21]. Therefore, considerably short durations of CPAP therapy may effectively treat chronic AHR, which would be considered as a more acceptable modality to several patients than prolonged CPAP treatment [22].

Human Studies

Similar to the study by McClean et al. [17], Ding et al. reported increased airway resistance in normal individuals subjected to the methacholine challenge when asked to breathe at 0.5 l below their FRC [23]. However, airway resistance decreased in normal subjects when they were instructed to breathe 0.5 l above their FRC. The authors concluded that low lung volumes may uncouple the airway and parenchyma, which was measured as a decreased elastic load leading to ASM shortening. Skloot et al. [24] compared ten asthmatics with ten healthy controls, and demonstrated that prohibiting deep breaths was associated with hyperresponsiveness to inhaled methacholine in normal subjects. This AHR persisted for some time even after permitting deep inspiration. These findings suggest that AHR is magnified at low lung volumes in response to inhaled irritants. Martin et al. [25] studied the effects of CPAP for a one minute when applied to eight asthmatic patients with aerosolized histamine induced bronchospasm. The outcomes indicated that CPAP resulted in a decreased work of breathing, trans-diaphragmatic, and pleural pressures and/or pressure time product despite an increased minute ventilation in seven out of eight subjects. Furthermore, the authors argued that despite increasing the end-expiratory lung volume, CPAP assists in inflating the chest to reduce the peak pleural pressure generated by the inspiratory muscles. Furthermore, they noticed a large decrease in pulmonary resistance during CPAP use, which increased after withdrawal. Consistent decrease in inspiratory work per liter of ventilation was caused both by the decrease in pulmonary resistance and by the assistance given to inspiratory muscles by CPAP.

In a later study, Martin et al. [26] evaluated seven non-apneic, non-snoring asthmatics to measure improvements in nocturnal asthma with the use of nasal CPAP. Two subjects demonstrated an increase in FEV_1 levels after CPAP, contrary to the other subjects. Lin et al. [27] studied the effects of nasal CPAP in fifteen patients. Eight subjects received nasal CPAP at 8 cm H_2O for 10 min while the remaining patients received a sham CPAP. The patients who underwent nasal CPAP demonstrated a significantly increased provocation dose causing a 20% decline in FEV_1 ($PD20FEV_1$) and better bronchodilator response to inhaled salbutamol.

Briefly using positive airway pressure by a computer-controlled syringe was applied in 24 asthma patients who were challenged with methacholine [28]. The patients were grouped according to their FEV_1 response to DI. This study aimed to evaluate respiratory resistance using forced oscillation. The change induced by the positive-pressure inflation in resistance was significantly greater than that induced by active DI only in the impaired DI response group. Additionally, those with impaired DI response had lower spontaneous inspiratory volume percentages. The authors concluded that positive-pressure inflation may open closed airways that could not be opened by active DI. Improvements associated with the reduction of airway obstruction by positive-pressure inflation over active DI was related to an increase in the percent inspired volume. The authors speculated that positive-pressure inflation may have increased the stretch of smooth muscles within the airway wall. They classified the asthmatics according to their response to DI as either responders or non-responders and measured airway resistance via force oscillation. The passive DI maneuver was set below 90% of inspiratory capacity and the reduction in resistance by positive-pressure inflation was significantly greater than that by active DI in the impaired DI response group. It has been stated that asthma leads to periodic airway closure and lung volume de-recruitment. However, deep breaths may not result in broncho-protection if they are trapped beyond a point of larger airway closure in such airways. Finally, Lin et al. [29] reported that patients with obstructive sleep apnea (OSA) without asthma, but with a positive methacholine challenge test, showed a decrease in their hyperreactivity to methacholine after two to three months of nasal CPAP therapy.

Busk et al. [30] observed the effects of nocturnal CPAP for 7 days, set at 8-10 cmH_2O versus sham CPAP in patients with clinically controlled mild asthma, to check for the presence of any decrease in airway reactivity. A methacoline challenge test was performed at baseline and 1 week after the use of nocturnal CPAP. The CPAP group (n=16 patients) showed a significant decrease in airway reactivity, while the sham group (n=9 patients) did not. Additionally, the CPAP group demonstrated a 15% increase in FEV_1 following an inhaled bronchodilator. Although this study demonstrated that using nocturnal CPAP reduced airway reactivity in asthma patients, it failed to exclude subjects with sleep apnea or provide data

regarding the their body weight, either of which could potentially influence airway strain [30].

D´Amato et al. [31] studied the efficacy of automatic CPAP as an adjunct therapy in patients with severe persistent asthma to ameliorate their symptoms, reduce PEF variability, and improve the patients' quality of life. This study included ten patients with more than a 25-year history of asthma. Subjects with sleep apnea were excluded after polysomnographic exam. CPAP, with a mean positive airway pressure of 5.3±1.3 cmH_2O, was applied for seven nights through a full-face mask. Lung function, asthma control, and quality of life were measured at baseline, during the treatment period, and within 1 month from baseline. The study showed a reduction in PEF variability during the 2 weeks on CPAP treatment, along with a significant improvement in the asthma control score.

Given the increasing number of asthmatic patients with OSA, it is important to understand the role of CPAP in these patients. Wenzel et al. [32] noted that after administering CPAP for in 41 subjects with OSA, a small number of patients demonstrated a mild to moderate AHR to histamine induction without any clinical relevance. Devouassoux et al. [33] studied 57 subjects with no history of smoking with OSA and without asthma and found that 1 and 4 weeks of CPAP treatment increased AHR in OSA patients despite no changes in FEV_1 or symptoms. AHR was not related to OSA severity and had no influence on CPAP compliance.

Korczynski et al. [34] randomized 101 non-asthmatics with OSA, of whom 40% were smokers, into the CPAP group and the no CPAP group for 3 weeks. The observed that increased AHR in those treated with CPAP, despite no changes in the symptoms. AHR was not related to OSA severity and had no influence on CPAP compliance. Furthermore, they found no relationship between AHR and smoking status. The authors speculated that positive pressure might have triggered a naso-bronchial reflex. In OSA, multiple pathways may be responsible to develop mucosal inflammation, including the desaturation-re-oxygenation sequence that generates oxidative stress and contributes to bronchial inflammation. Furthermore, IL-8 in induced sputum was significantly correlated with the severity of sleep apnea and oxygen desaturation. A major increase in bronchial neutrophils was accompanied by a high bronchial concentration of IL-8 [35].

In addition to the aforementioned studies, Davies et al. [36] conducted a systematic review to evaluate if CPAP treatment in asthmatic patients with co-existing OSA helped improve their quality of life and asthma-related symptoms. The study population was treated with CPAP for a mean duration of 19.5 weeks and although it showed that mean quality of life improved with CPAP, there was no significant improvement in FEV_1 ($p=0.84$). The authors concluded that the patients' quality of life can improve via CPAP; however, this effect was more notable in patients with either severe OSA or poorly controlled asthma.

Aerosol Deposition with the Use of Positive Airway Pressure

Nebulizer therapy is commonly used in patients with asthma to help reduce bronchial constriction and support breathing. In acute cases, nebulizer therapy is administered in conjunction with positive airway pressure. Furthermore, it is important to understand the effectiveness of these two therapies in conjunction and whether positive airway pressure has beneficial effects on aerosol deposition within the lungs.

In healthy individuals with no history of asthma, Franca et al. [37] performed a study in 13 patients and showed no differences in the aerosol deposition when using noninvasive positive airway pressure than when administering nebulization without pressure support. However, Tsai et al. [38] conducted a study in patients with stable asthma and showed that the administration of aerosolized beta2-agonists with positive end pressure appeared to improve the aerosol distribution in the patients. The study assessed the patients before and after nebulizer treatment and showed improvement in their FEV_1, PEF, FVC, as well as improvements in the mucociliary clearance.

To further understand the role of aerosol deposition in asthma patients, a study performed by Alcoforado et al. [39] focused on aerosol deposition in 28, stable, moderate-to-severe asthma patients with mean $FEV_1 < 60\%$ predicted, who were randomized into four groups: heliox + PEEP at 10 cmH_2O, oxygen + PEEP at 10 cmH_2O, heliox alone, and oxygen alone. The PEEP administration lasted for the time required to nebulize fenoterol and ipratropium. Inhaled bronchodilators were administered with PEEP along with heliox showed greater improvements in pulmonary function than by using heliox alone; however, these improvements were not significantly greater than those in the oxygen + PEEP group [39]. Although differences in pulmonary function tests between the heliox with PEEP and oxygen with PEEP group were small, they were attributed to the physical characteristics of the heliox. Heliox, unlike oxygen, has a lower density and higher viscosity, which allows for less turbulent flow and improved aerosol deposition within the pulmonary tract.

Although nebulizer therapy in conjunction with positive airway pressure reportedly improved lung function in patients with asthma, it is important to understand its effects on aerosol deposition in the pulmonary tract during oxygen therapy and not heliox. Galindo-Filho et al. [40] performed a study in which they randomized 21 patients and administered inhalation bronchodilators with and without NIV; particles on the lung were counted with a gamma camera to analyze pulmonary clearance at several times until one hour, despite better lung functions parameters such as FEV_1, FVC, peak expiratory flow and inspiratory capacity, no inter-group differences were observed with regard to aerosol deposition.

DISCUSSION

Therefore, bronchial asthma includes numerous phenotypes. The role of CPAP has been well studied in patients with asthma considering its effects on the inflammatory cascades, airway smooth muscle reactivity, and even its effects on bronchodilator therapy. Overall using CPAP may provide an effective therapy for certain patients with asthma [41]. In addition, studies have shown that obese asthmatics are much less responsive to current inhaled treatment options [42]. Obesity influences both inflammation and airway mechanics, which might be important parameters in obesity-related asthma due

to the effects such as smaller airways, muscle stiffness and hyperresponsiveness in the airway supine position [43]. CPAP could be used as a rescue therapy in partially controlled or uncontrolled asthmatics via intermittent daily and/or nightly use. CPAP may also be used to assist in the inhaled therapy to ensure better bronchodilatation.

However, there are several unresolved issues that need to be addressed. It is unclear whether applying CPAP induces reorganization of cytoskeletal and contractile proteins of ASM as well as extracellular matrix junctions as previously reported in animal studies. In addition, several factors significantly influence CPAP tolerance and compliance i.e. the adequacy of humidification, leak control, influence of different types of masks (nasal or full-face) [41]. These should be considered in future studies. Nasal intolerance is a frequent, but minor side effect occurring with CPAP, affecting as many as 50% of treated patients with OSA [41]. Furthermore, it is important to understand if peak expiratory flow monitoring or FEV_1 are the appropriate tools to assess the effect of CPAP on the airways.

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