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Title: Continuous Positive Airway Pressure in Non-Apneic Asthma: A Clinical Review of the Current Evidence

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Abbreviations

AHR: airway hyperresponsiveness

ASM: airway smooth muscle

CPAP: continuous positive airway pressure

DI: deep inspiration

FEV_1: forced expiratory volume in first second

PEF: peak expiratory flow

PEEP: positive end-expiratory pressure

Abstract

The use of continuous positive airway pressure (CPAP) in the asthma has been a question of debate over the past several years. Various studies, including animal and human studies 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 current available literature on the physiologic and clinical effects of CPAP in animal models of asthma and humans with stable asthma.

Keywords: Asthma, bronchoconstriction, continuous positive airway pressure,

Introduction

Bronchial asthma is a common chronic airway disorder with variable and recurring symptoms, airway obstruction, bronchial hyperresponsiveness and underlying inflammation. It is characterized by heterogeneity as several phenotypes of asthma have been proposed recently [1].

Despite advances in medical treatment, the prevalence of patients with uncontrolled asthma is still high in everyday clinical practice [1]. Asthma therapies, such as bronchodilator medications (always in combination with inhaled corticosteroids) and, more recently, 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]. The aim of this review article is to summarize the available literature on such effects both in animal models of asthma and human subjects with stable asthma.

Asthma Pathophysiology and the Effect of Mechanical Ventilation

Our insight into bronchial asthma has changed as a result of the advances in molecular phenotyping which has revealed heterogeneous phenotypes within the asthmatic population. Exposure to various environmental factors that include viruses and inhaled antigens trigger an immune response directed at the T helper type-2 (Th2) cells. Initial exposure to the allergen leads to sensitization. Repeat exposure to the same allergen triggers a cascade of cellular and immune responses that leads to airway hyperactivity and symptoms of asthma. The interaction between the dendritic cells and the antigen lead to the activation of 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 lead to 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 known to be associated with ventilation-induced lung injury and an augmented inflammatory response [4]. Tsangaris et al. studied the inflammatory response

triggered by the use of mechanical ventilation in patients who were on prolonged mechanical ventilation without acute lung injury. This study showed that during mechanical ventilation the total bronchoalveolar lavage (BAL) protein increased but the BAL phospholipids decreased. In addition, the aggregation of surfactant was reduced and inflammatory markers, such as platelet activating factor (PAF), PAF-acetylhydrolase and neutrophils were increased after 1 week, however 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 [5].

Chiumello et al. examined whether injurious ventilatory strategies would increase the release of inflammatory mediators such as 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 is influenced by the ventilatory modality, which may be relevant for the development of multisystem organ failure [6].

Paone et al. looked at the effects of long term noninvasive ventilation (NIV) on the systemic inflammatory response in patients with COPD. Sputum analysis in the NIV versus oxygen therapy group showed similar human neutrophil peptides (HNP), IL-6, IL-10, and TNF-α levels ($P>0.5$). 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 patients with COPD may be negated by the potential effect on the inflammatory system [7].

In contrast, in a study by Borel et al. looked at the effect of NIV on inflammatory markers in patients with mild obesity hypoventilation syndrome. This study showed that the inflammatory and anti-inflammatory cytokines did not vary significantly. NIV had no effect on inflammatory, metabolic or cardiovascular markers in patients with mild obesity hypoventilation syndrome [8].

Overall, the use of NIV may play a role in the treatment of acute exacerbations of bronchial asthma in avoiding invasive mechanical ventilation and have been shown to decrease the risk of triggering an acute inflammatory cascade that will potentiate lung injury.

Airway Smooth Muscle and Asthma Control

The pathogenesis of asthma is affected by the function of the ASM both directly by airflow obstruction through its contraction and indirectly by airway remodeling and modulating airway inflammation. These processes interact with each other so that the net contribution of ASM to asthma is manifold and complex [2]. In asthma the contributing mechanisms to airway hyperresonsiveness (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 fatal or severe asthma. Moreover, excessive ASM mass and airway wall thickening is associated with AHR [2]. It has been found that mechanical stretch imposed on an isolated ASM can result in the activation and signaling cascade of several cytoskeletal proteins that are implicated in actin dynamics, myosin light chain phosphorylation and cytoskeletal organization [2, 3, 10-14].

In healthy individuals and a small proportion of asthmatics deep breathing has been shown to cause reversal of bronchoconstriction, due to changes in the actin-myosin interaction [15]. However, in a majory of asthmatics the ability of deep breaths to actually reverse bronchoconstriction seems blunted. It is believed that the dynamic stretch of ASM that occurs during an acute asthma exacerbation at decreased tidal volumes and high end-expiratory lung volumes prevails over the beneficial outcome of a mean stretch of ASM attained by 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. looked at the in vitro contractility of ASM after exposure to carbachol in a group of sheep whose tidal volume was restricted using a corset for four weeks [17]. The corset was adjusted to reduce their functional residual capacity (FRC) by nearly 25%. They also measured the number of deep inspirations. On excision of ASM, they found higher and shorter contractile responses and discovered that ASM cells can alter the organization of their contractile apparatus in response to changes in volume. The duration of maintenance of this effect was not transient, as the results were obtained after excision of

muscle. This study allowed for a potential explanation for the changes in airway responsiveness seen in obese subjects.

To understand the effects of CPAP on patients with asthma it is first important to understand the effect of CPAP on normal lung function. Xue et al. designed four different studies in rabbits, ferrets, and mice where CPAP versus sham CPAP was applied through a tracheostomy [18-21]. In the first study, it was shown that four-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 fourteen days had increased the luminal areas of the intrathoracic trachea and intraparenchymal airways and lower levels of myosin light chain phosphorylation. These accounted for the decreased AHR observed in vivo [19]. In the third study, the authors hypothesized that the intermittent application of CPAP could reduce airway reactivity and this effect could last for at least 24 hours. They also showed that CPAP suppressed AHR caused by ovalbumin-induced airway inflammation [20]. In the last study, the same authors reported that only two hours of CPAP decreased airway resistance in vitro for the following six hours and that there were molecular changes such as downregulation of Akt phosphorylation, induced by IL-13 [21]. This study suggested that a very short duration of CPAP therapy might be effective in treating chronic AHR and this would likely be much more acceptable to many patients than prolonged CPAP treatment [22].

Human Studies

In line with the study by McClean et al. [17] Ding et al. reported increased airway resistance in normal individuals subjected to methacholine challenge when asked to breathe at 0.5 L below their FRC [23]. On the contrary, airway resistance decreased in normal subjects when asked to breathe 0.5 L above their FRC. The authors concluded that at low lung volumes there may be an uncoupling between airway and parenchyma measured as a decreased elastic load leading to ASM shortening. In another small study, comparing ten asthmatics with ten healthy controls, Skloot et al. demonstrated that when deep breaths were prohibited, normal subjects became hyperresponsive to inhaled methacholine [24]. This AHR persisted for some time even

after deep inspiration was allowed. The combination of these findings points out that AHR to inhaled irritants is magnified at low lung volumes. A study by Martin et al. studied the effects of CPAP for a one minute period when applied to eight asthmatic patients with aerosolized histamine induced bronchospasm. This study showed that CPAP resulted in a decreased work of breathing, trans-diaphragmatic and pleural pressures and/or pressure time product despite an increaed minute ventilation in seven out of eight subjects [25]. Furthermore the authors argue that despite increasing end-expiratory lung volume, CPAP assists in inflation of the chest, so that the peak pleural pressure generated by the inspiratory muscles decreases. They also noticed a large decrease in pulmonary resistance during CPAP use, which increased after withdrawal. The 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 by Martin et al. seven nonapneic, nonsnoring asthmatics were evaluated to see if the use of nasal CPAP imporved nocturnal asthma [26]. In two of the subjects, FEV_1 improved after CPAP, however the remaining subjects were not found to have improvement in their FEV_1. Lin et al. went on to study the effects of nasal CPAP in fifteen patients. Eight subjects received nasal CPAP at 8cm H_20 for 10 minutes while the remaining patients received a sham CPAP. The patients who received the nasal CPAP were found to have a significantly increased provocation dose causing a 20% decline in FEV_1 ($PD20FEV_1$) and better bronchodilator response to inhaled salbutamol [27].

Brief use of positive airway pressure by a computer-controlled syringe was applied in 24 asthma patients challenged with methacholine [29]. Patients were grouped according to their FEV_1 response to DI. The aim of this study was to evaluate respiratory resistance measured by forced oscillation. The change induced by the positive-pressure inflation in resistance was significantly greater than the change induced by active DI only in the impaired DI response group. Additionally, those with impaired DI response had a lower spontaneous inspiratory volume percentage. The authors concluded that positive-pressure inflation may open closed airways that could not be opened by active DI. The improvement in 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 led

to an increase in the stretch of smooth muscle within the airway wall. They classified asthmatics according to their response to DI as either responders or non-responders. They also measured airway resistance through force oscillation. The passive DI maneuver was set below 90% of inspiratory capacity. 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 is associated with periodic airway closure and lung volume de-recruitment. Besides that, in such airways, trapped beyond a point of larger airway closure, deep breaths may not result in broncho-protection. Finally, Lin et al. showed that in patients with obstructive sleep apnea (OSA) without asthma but with a positive methacholine challenge test, two to three months of nasal CPAP therapy can decrease the hyperreactivity to methacholine [30].

A study performed by Bust et al. looked at the effects of nocturnal CPAP for seven days, set at 8-10 cmH2O versus sham CPAP in patients with clinically controlled mild asthma and if there was any decrease in airway reactivity [31]. A methacoline challenge test was performed at baseline and one week after the use of nocturlal CPAP. The CPAP group, which consisted of 16 patients, had a significant decrease in airway reactivity while the sham group, which consisted of 9 patients, had no significant change in airway reactivity. Additionaly, in the CPAP group there was a 15% increase in FEV_1 following an inhaled bronchodilator. Although this study did show that the use of nocturnal CPAP reduced airway reactivity in asthmatics it failed to exclude subjects with sleep apnea or provide data regarding the subjects body weight, either of which can potentially influence airway strain [31].

D´Amato et al. studied the efficacy of automatic CPAP as adjunct therapy in patients with severe persistent asthma to achieve control over symptoms, reduce PEF variability and improve quality of life [32]. 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. Measurements of lung function, asthma control and quality of life were performed at baseline, during the treatment period and within 1 month from baseline. The study showed that the variability of PEF was reduced during the two weeks on CPAP treatment and that the asthma control score was also improved significantly after the use of CPAP.

Given the increasing number of asthmatic patients with OSA it is important to understand the role of CPAP in these patients. Wenzel et al. noted that after six weeks of CPAP in 41 subjects with OSA, a mild to moderate AHR to histamine was induced in a minority of treated patients without any clinical relevance [33]. Devouassoux et al. studied 57 never smokers with OSA and without asthma and found that after 1 and 4 weeks of CPAP treatment, AHR was increased in OSA patients despite no changes in FEV_1 or symptoms [34]. AHR was not related to OSA severity and had no influence on CPAP compliance.

Korczynski et al. randomized one hundred one non-asthmatics with OSA, of whom 40% were smokers, to CPAP versus no CPAP for 3 weeks [35]. The authors found increased AHR in those treated with CPAP, albeit there were no changes in symptoms. AHR was not related to OSA severity and had no influence on CPAP compliance. Furthermore, they found no relation between AHR and smoking status. The authors speculated that positive pressure might have triggered the naso-bronchial reflex. In OSA multiple pathways may be responsible for the development of mucosal inflammation, such as the desaturation-re-oxygenation sequence that leads to oxidative stress and contributes to bronchial inflammation. Furthermore, a significant relationship between IL-8 in induced sputum and the severity of sleep apnea and oxygen desaturation was found. A major increase in bronchial neutrophils was accompanied by a high bronchial concentration of IL-8 [36].

In addition to the aformentiones studies, Davies et al. conducted a systematic review to evaluate if CPAP treatment in asthmatic patients with co-existing OSA helped improve quality of life and asthma-related symptoms. The study population was treated with CPAP for a mean duration of 19.5 weeks. 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 quality of life can improve with the use of CPAP in patiehts with asthma however this effect was more notable in patients with either severe OSA or poorly controlled asthma [37].

Aerosol Deposition with the Use of Positive Airway Pressure

Nebulizer therapy is a common therapeutic approach in patients with asthma to help reduce bronchial constriction and reduce work of breathing. In the acute setting nebulizer therapy is administered in conjuction with positive airway pressure and it is important to understand the

effectiveness of these two therapies in conjuction and if positive airway pressure improves the aerosol deposition within the lungs.

In healthy individuals with no history of asthma, Franca et al. performed a study in thirteen patients and showed that there was no difference in the aerosol deposition when using noninvasive positive airway pressure compared to nebulization without pressure support [38]. However, Tsai et al. conducted a study in patients with stable asthma and showed that the administration of aerosolized beta2-agonists with positive end pressure appears to improve the distribution of aerosol in these patients. The study assessed the patients before and after nebulizer treatment and showed improvement in their FEV_1, PEF, FVC, as well as improvement in mucociliary clearance [39].

To further understand the role of aerosol deposition in asthmatics a study performed by Alcoforado et al. looked at aerosol deposition in twenty-eight stable moderate to severe asthmatics 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 the time required for nebulization of fenoterol and ipratropium. The administration of inhaled bronchodilators with PEEP along with heliox showed greater improvement in pulmonary function than the use of heliox alone and not significantly greater than in the group of oxygen with PEEP [40]. Although the difference in pulmonary function tests between the heliox with PEEP and oxygen with PEEP group is small, this difference is attributed to the physical attributes of the heliox. Heliox unlike oxygen has a lower density and higher viscosity which allows for less turbulent flow and thus improved aerosol depositon within the pulmonary tract.

Although its been shown that nebulizer therapy in conjuction with positive airway pressure improves lung function in patients with asthma, its important to understand its effects on aerosol deposition in the pulmonary tract while on oxygen therapy and not heliox. Galindo-Filho et al. carried out a study where they randomized twenty-one patients to receive inhaled 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 differences were observed between groups in regards to aerosol deposition [41].

Discussion

In conclusion, bronchial asthma consists of various different phenotypes. The role of CPAP has been well studied in patients with asthma in regards to its effects on the inflammatory cascade, airway smooth muscle reactivity and even its effects on bronchodilator therapy. Overall the use of CPAP may provide an effective therapy for certain patients with asthma [42]. In addition studies have shown that obese asthmatics are much less responsive to current inhaled treatment options [43]. Obesity has an effect both on inflammation and on airway mechanics, which might be important in obesity-related asthma through the effects on smaller airways, muscle stiffness and hyperresponsiveness in the airway supine position [44]. CPAP could in this case be used as a rescue therapy in partially controlled or uncontrolled asthmatics through intermittent daily and/or nightly use. There may be also a role for CPAP to assist in the inhaled therapy for achieving better bronchodilatation.

However, there are several unresolved issues that need to be addressed such that it remains unknown in humans whether the application of 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 have a great impact on CPAP tolerance and compliance i.e. the adequacy of humidification, leak control, influence of different types of masks (nasal or full-face). These should be considered in future studies. Nasal intolerance is a frequent minor side effect occurring with CPAP, affecting as many as 50% of treated patients with OSA. 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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