



Brief Communication

Early effects of continuous positive airway pressure in a rodent model of allergic rhinitis



I. Vilaseca ^{a, b, c, *}, E. Lehrer-Coriat ^d, M. Torres ^b, F. Aguilar ^e, I. Almendros ^f,
B.M. Martínez-Vidal ^g, R. Farré ^{b, d, h}, J.M. Montserrat ^{a, b, c, f, h}

^a Sleep Disorders Unit Hospital Clínic, Barcelona, Spain

^b Ciber Enfermedades Respiratorias (CIBERES), Bunyola, Spain

^c Faculty of Medicine, University of Barcelona, Barcelona, Spain

^d Otolaryngology Department, Hospital Esperit Sant, Santa Coloma de Gramanet, Spain

^e Otolaryngology Department, Hospital General de Granollers, Granollers, Spain

^f Biophysics and Bioengineering Unit, Medicine Faculty, University of Barcelona, Barcelona, Spain

^g Otolaryngology Department, Hospital del Sagrat Cor, Barcelona, Spain

^h Institut d' Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain

ARTICLE INFO

Article history:

Received 27 April 2016

Received in revised form

14 September 2016

Accepted 16 September 2016

Available online 5 November 2016

Keywords:

CPAP

Allergic rhinitis

CPAP-induced rhinitis

Nasal inflammation

ABSTRACT

Background: Continuous positive airway pressure (CPAP) is the most commonly used treatment in obstructive sleep apnea. In a previous rat model study, we demonstrated that nasal CPAP induces early rhinitis expressed by nasal neutrophil extravasation. Here we hypothesized that nasal CPAP would worsen nasal inflammation on a previously inflamed mucosa. The objective of this study was to evaluate the early nasal CPAP effects of allergic rhinitis (AR) in a rodent model.

Methods: Twenty Sprague-Dawley rats were sensitized with intraperitoneal ovalbumin (OVA). Nasal inflammation was induced by the administration of intranasal OVA during consecutive days. The same procedure was performed in 20 control rats treated with saline solution. The allergic (AR) and non-allergic (NAR) rats were then randomized to nasal CPAP at 10 cm H₂O for five hours or to sham CPAP. The degree of nasal inflammation was assessed by evaluating the percentage of neutrophils, eosinophils, basophils, and lymphocytes in the nasal mucosa. An unpaired Mann–Whitney test was used to analyze differences between groups.

Results: The greatest inflammation was observed in the group of AR without CPAP (1.24% ± 0.94%), followed by NAR with CPAP (0.64% ± 0.30%), AR with CPAP (0.64% ± 0.40%), and NAR without CPAP (0.21% ± 0.29%).

Conclusions: Administration of nasal CPAP or allergy sensitization can produce, individually, neutrophil extravasation on the nasal mucosa of a rat model. The application of both stimuli is not responsible for increased inflammation. Therefore, this study suggests that rhinitis is not a major limitation for CPAP administration.

© 2016 Elsevier B.V. All rights reserved.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a prevalent disorder characterized by recurrent partial or total upper airway closure during sleep. The most widespread treatment for OSAS is the nocturnal application of continuous positive airway pressure

(CPAP) through the nose. However, only 50–80% of patients initially accept nasal CPAP, and sufficient long-term compliance varies between 17% and 71% [1].

Some of the reasons that patients experience CPAP intolerance are nasal secondary effects. The mechanism could be due to a compression stimulus during the application of CPAP. Positive pressure triggers a biological response in a variety of cells in the nose as well as in the airways [2–4] and may cause nasal symptoms. It has also been suggested that pre-existing nasal obstruction or previous symptoms of nasal inflammation could be exacerbated

* Corresponding author. Otorhinolaryngology Department, Hospital Clínic, C/Villarroel, 170, 08036, Barcelona, Spain.

E-mail address: ivila@clinic.ub.es (I. Vilaseca).

by CPAP and therefore increase symptoms and contribute to poor patient compliance [5].

In a previous study, we demonstrated that nasal CPAP induces early local inflammation resulting in neutrophil extravasation in the nasal mucosa of healthy rats [6]. However, the impact of nasal CPAP on a previously inflamed mucosa has not yet been fully assessed. Our hypothesis was the following: When a previous nasal inflammation exists, a second source of injury (ie, CPAP) would worsen the nasal inflammation.

Therefore, the aim of our study was to evaluate early CPAP effects in a rat model of allergic rhinitis (AR).

2. Methods

The study was approved by the Ethics Committee for Animal Experimentation of the University of Barcelona. Twenty Sprague-Dawley rats were sensitized with intraperitoneal ovalbumin (OVA). Nasal inflammation was induced by the administration of OVA intranasal drops during 24 consecutive days (Fig. 1). The same procedure was performed in 20 control rats treated with saline solution. The allergic (AR) and non-allergic (NAR) rats were then anesthetized (urethane, 1 g/kg) and randomized to 5 h of nasal CPAP (10 cm H₂O pressure) or sham-CPAP [6]. Subsequently, a nasal scraping sample was obtained from the nostril. Two counts of each sample were performed in a blinded manner by two different evaluators. Counted cells were classified to compute the percentage of neutrophils over 1000 epithelial cells. The degree of nasal inflammation was assessed by directly evaluating the percentage of neutrophils, eosinophils, basophils, and lymphocytes in the nasal mucosa of the animals.

An unpaired Mann–Whitney test was used to analyze differences between groups. A *p* value < 0.05 was considered to be statistically significant.

3. Results

Nasal cytology showed that the cells most commonly detected in the nasal mucosa were neutrophils, which define a condition of minimal inflammation. The highest neutrophil extravasation rate

was observed in the group with allergic rhinitis without CPAP (AR/Sham-CPAP), followed by non-allergic rhinitis with CPAP (NAR/CPAP), allergic rhinitis with CPAP (AR/CPAP), and non-allergic rhinitis without CPAP (NAR/Sham-CPAP) (Fig. 2). There were significant differences between AR/Sham-CPAP and NAR/Sham-CPAP (1.24 ± 0.94 vs 0.21 ± 0.29 ; *p* = 0.006), AR/CPAP and NAR/Sham-CPAP (0.64 ± 0.40 vs 0.21 ± 0.29 ; *p* = 0.019), and NAR/Sham-CPAP and NAR/CPAP (0.21 ± 0.29 vs 0.64 ± 0.30 ; *p* = 0.007).

No significant differences in the percentage of eosinophils, basophils, or lymphocytes were observed between groups after the CPAP treatment, suggesting that the allergic rhinitis created in our model was mild.

4. Discussion

The results obtained in the present study confirmed our previous findings that the application of CPAP in the nasal mucosa in a rat model induces neutrophil extravasation [6,7]. Moreover, the induction of rhinitis by means of intraperitoneal nasal sensitization to OVA was also responsible for a significant increase in neutrophil

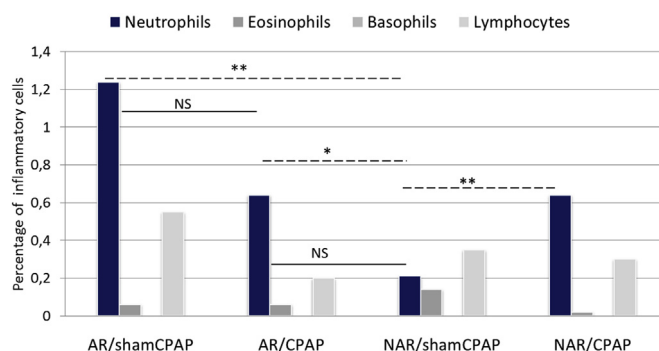


Fig. 2. Percentage of different types of inflammatory cells in nasal cytology. Neutrophil comparisons between groups. AR, allergic rhinitis; CPAP, continuous positive airway pressure; NAR, non-allergic rhinitis; NS, not statistically significant. **p* < 0.05; ***p* < 0.01.

Design setting

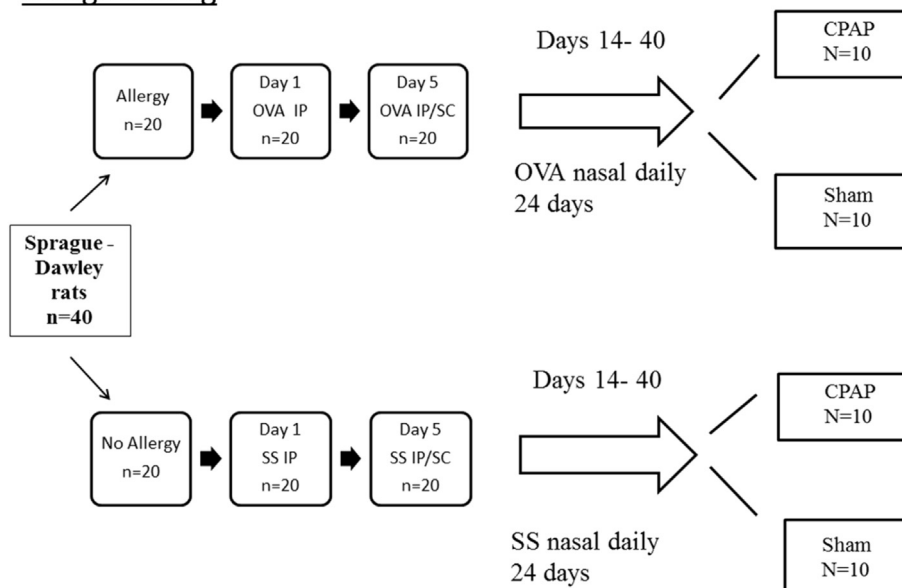


Fig. 1. Experimental setting. IP, intraperitoneal; OVA, ovalbumin; SC, subcutaneous; SS, saline solution.

extravasation in the nasal mucosa of the animals, whereas no significant eosinophil, basophil, or lymphocyte-related inflammation could be found. Contrary to initial expectations, the sequential application of two stimuli (ie, AR and CPAP) did not exacerbate nasal inflammation.

In a previous study, we demonstrated that the grade of nasal inflammation was dependent on the level of CPAP pressure [7]. In the present study, 10 cm H₂O was applied to the CPAP rat model. Although this value may seem high and difficult to tolerate by some patients, it mainly represents the mean pressure administered in our clinical practice [8–10].

Nasal cytology can be used to assess the consequence of IgE-mediated inflammation in the target organ of AR. Variations in the cellularity of nasal cytology are correlated with peaks of exposure to allergens, which are accompanied by increased symptoms. In our samples, a low number of eosinophils were found in the nasal cytology, suggesting that the IgE-mediated inflammation at the moment of CPAP application was mild [11]. Although it could be seen as a limitation, this is the most common clinical situation and is characteristic of a wide number of allergic patients. In fact, most allergic patients clinically present with mild inflammation with seasonal peaks, and most of them are prescribed antiallergenic drugs only for short periods of time.

In a previous study, Shadan et al. [12] could not identify the presence of pretreatment nasal symptoms as responsible for reduced compliance with CPAP, whereas the presence of subclinical inflammation before CPAP did. The authors found a greater increase in the neutrophil count after treatment in the compliant group compared to the non-compliant one, suggesting that CPAP exposure is directly responsible for nasal inflammation. In contrast, other authors have associated the presence of nasal symptoms with CPAP intolerance [13,14]. This disagreement may be caused by confounding factors, and therefore animal models may help to clarify this problem. In our second hit model study, the addition of a second source of inflammation in a sequential way was not responsible for an additional increased inflammation measured by nasal cytology. This finding, which has been suggested previously [15], agrees with clinical reports showing no differences in CPAP compliance between non-allergic and allergic patients [12].

The process of AR includes a wide spectrum of interleukin (IL) release, including those with inhibitory actions [16]. IL-10, for instance, is recognized for its ability to inhibit activation and effector function of T cells, monocytes, and macrophages. The principal function of IL-10 is to limit and ultimately to terminate inflammatory responses. A previous study in mice has shown that IL-10 is also produced by mast cells, counteracting the inflammatory effect that these cells have at the site of an allergic reaction [17]. From this point of view, the pre-existing allergic rhinitis in our rat model could protect in certain way against the effect of a second inflammatory hit by means of that inhibitory system.

One limitation of this study is the absence of information about inflammatory mediators, which could have provided more information about the mechanisms of nasal inflammation after CPAP. Another limitation is the acute evaluation of the CPAP effect. The study consisted of a chronic model of AR that was exposed to a second acute nasal stimulus, which represents the initial phase of adaptation to CPAP treatment. Therefore, the possibility of progressive adjustment was not evaluated. To our knowledge, a chronic model of rodent nasal CPAP has not previously been described. Such a model would be of great interest in evaluating CPAP side effects after a few days or weeks of nasal treatment. The

evaluation of nasal inflammation at different levels of CPAP pressure would also be of great interest for future research.

In conclusion, both the acute administration of nasal CPAP and allergic sensitization were found to be individually responsible for neutrophil extravasation in the nasal mucosa of rats. Application of a second challenge (nasal CPAP on a previously allergic mucosa) is not responsible for a significant increase in inflammation. The finding that the response to these two challenges is not synergistic, suggests that rhinitis is not a major limitation of CPAP administration in cases of mild inflammation.

Funding

This work was supported in part by FIS PI07/0318, co-financed by FEDER and CIBERES.

Conflict of interest

The authors have indicated no financial conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2016.09.016>.

References

- [1] Catcheside PG. Predictors of continuous positive airway pressure adherence. *F1000 Med Rep* 2010;2:70.
- [2] Lim LH, Wagner EM. Airway distension promotes leukocyte recruitment in rat tracheal circulation. *Am J Respir Crit Care Med* 2003;168:1068–74.
- [3] Skoczinski S, Ograbek-Król M, Tazbirek M, et al. Short-term CPAP treatment induces a mild increase in inflammatory cells in patients with sleep apnea syndrome. *Rhinology* 2008;46:144–50.
- [4] Tschumperlin DJ, Drazen JM. Chronic effects of mechanical force on airways. *Annu Rev Physiol* 2006;68:563–83.
- [5] Saka C, Vuralkan E, Firat IH, et al. The effects of CPAP treatment on nasal mucosa in patients with obstructive sleep apnea. *Eur Arch Otorhinolaryngol* 2012;269:2065–7.
- [6] Almendros I, Acerbi I, Vilaseca I, et al. Continuous positive airway pressure (CPAP) induces early nasal inflammation. *Sleep* 2008;31:127–31.
- [7] Martínez B, Farré R, Montserrat JM, et al. Effects of heated humidification on nasal inflammation in a rat model. *Sleep Med* 2010;11:413–6.
- [8] Campos-Rodríguez F, Queipo-Corona C, Carmona-Bernal C, et al. Continuous positive airway pressure improves quality of life in women with OSA: randomized controlled trial. *Am J Respir Crit Care Med* 2016 May 15 [Epub ahead of print].
- [9] Isetta V, Negrin MA, Monasterio C, et al. A Bayesian cost-effectiveness analysis of telemedicine-based strategy for the management of sleep apnea: a multicenter randomized controlled trial. *Thorax* 2015;70:1054–61.
- [10] Aguilar F, Cisternas A, Montserrat JM, et al. Effect of nasal continuous positive pressure on the nostrils of patients with sleep apnea syndrome and no previous nasal pathology. predictive factors for compliance. *Arch Bronconeumol* 2016;52:519–26.
- [11] Gelardi M, Incorvaia C, Passalacqua G, et al. The classification of allergic rhinitis and its cytological correlate. *Allergy* 2011;66:1615–25.
- [12] Shadan FF, Jalowayski AA, Fahrenholz J, et al. Nasal cytology: a marker of clinically silent inflammation in patients with obstructive sleep apnea and a predictor of noncompliance with nasal CPAP therapy. *J Clin Sleep Med* 2005;1:266–70.
- [13] Meurice JC, Dore P, Paquereau J, et al. Predictive factors of long term compliance with nasal continuous positive airway pressure treatment in sleep apnea syndrome. *Chest* 1994;105:429–33.
- [14] Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008;5:173–8.
- [15] Gelardi M, Carbonara G, Maffezzoni E, et al. Regular CPAP utilization reduces nasal inflammation assessed by nasal cytology in obstructive sleep apnea syndrome. *Sleep Med* 2012;13:859–63.
- [16] Pawankar R, Hayashi M, Yamanishi S, et al. The paradigm of cytokine networks in allergic airway inflammation. *Curr Opin Allergy Clin Immunol* 2015;15:41–8.
- [17] Grimbaldston MA, Nakae S, Kalesnikoff J, et al. Mast cell-derived interleukin 10 limits skin pathology in contact dermatitis and chronic irradiation with ultraviolet B. *Nat Immunol* 2007;8:1095–104.