CPAP as a novel treatment for bronchial asthma?

Riccardo Pellegrino, Giulia Michela Pellegrino, and Vito Brusasco
Allergologia e Fisiopatologia Respiratoria, Azienda Ospedaliera S. Croce e Carle, Cuneo; and Dipartimento di Medicina Interna, Università di Genova, Genova, Italy

Airway hyperresponsiveness in bronchial asthma is deemed to be sustained by airway wall inflammation, which ultimately triggers the airway smooth muscle (ASM) to contract. Yet the magnitude of the resulting airway narrowing in vivo depends on several factors, including the ASM mass, its contractility, and the loads on it (3).

One of the key mechanisms regulating airway caliber is provided by the changes in lung volume imposed by the respiratory pump. During lung inflation, airway caliber increases because airways and lung parenchyma are mechanically interdependent. In 1961 a seminal study by Nadel and Tierney (17) first reported that a single large breath could ablate induced airway narrowing in healthy subjects, suggesting that the contractile properties of ASM can be altered by stretching. Subsequent studies showed that the bronchodilator effect of a single large inflation may be reduced or even lost during natural asthma attacks (10, 18). By contrast, the sustained increment of tidal volume during exercise was able to produce an effective bronchodilation (5), comparable to that obtainable pharmacologically (16).

Studies at micromechanic and molecular levels have repeatedly shown that stretching reduces the tone of ASM by decreasing the number and cycling rate of cross bridges between actin and myosin filaments (7) and/or preventing their plastic adaptation within the internal cell scaffold (8). However, neither theory can explain why a series of increased tidal volumes is able to alter ASM contractility in asthma whereas a single lung inflation does not.

Now we come to learn from a study published in this issue of the Journal of Applied Physiology (25) that also increasing end-expiratory lung volume can affect airway narrowing in an animal model of asthma. Rabbits treated with a continuous positive airway pressure (CPAP) of 6 cmH₂O for 4 consecutive days or just 4 nights exhibited a remarkable and consistent decrease in bronchoconstrictor response 1 day after the suspension of the CPAP. The same occurred in ovalbumin-sensitized rabbits. As no major changes were observed in the amount of ASM, the authors conclude that the persistent effects of CPAP were the result of a reduction in ASM contractility. Whatever the underlying mechanisms, which were not specifically addressed, this study has two major merits. First, it documents the crucial role of the operational lung volumes in determining the response to constrictor agents. In a way, the study reaches the same conclusions of previous studies conducted in humans showing that bronchoconstrictor response was significantly increased in subjects breathing at low lung volume either voluntarily (6) or under different conditions, namely, chest wall strapping (24), supine posture (15), and obesity (23). Assuming a constant tidal volume, these data suggest that end-expiratory and end-inspiratory lung volumes, or both, are critical determinants in the control of bronchial tone. Second and perhaps more important, the study tells us that the reduction in airway responsiveness with CPAP appears to persist over 24 h, thus opening the question whether CPAP could also be used to treat bronchial asthma. Because length adaptation of isolated ASM in vitro is rather short (13) and the bronchodilator effect of a series of deep breaths lasts only minutes (20), the mechanisms of such a long-lasting effect of CPAP remain to be investigated in humans.

Studies reporting results on this question in the literature are quite scanty, limited, and not always univocal. The few trials conducted in status asthmaticus reported that CPAP via a face mask is highly effective in improving gas exchange, unloading the inspiratory muscles, reducing breathing frequency (14), reducing dyspnea (21), and preventing mechanical ventilation (11). Other studies examining the effects of CPAP in patients with nocturnal asthma in addition to sleep apnea concluded that nasal CPAP could improve asthma symptom score (4, 9) but not airway hyperresponsiveness nor the main spirometric parameters (9). One study conducted in nonapneic nocturnal asthma reported a significant improvement in the forced expiratory volume in 1 s and symptoms only in two of the seven participants in the trial (12). It is therefore somewhat striking that in the face of such strong physiological evidence that functional residual capacity (FRC) is able to regulate bronchial tone and the response to constrictor stimuli, clinical studies are noticeable by their absence. One possible answer is that the CPAP treatment has been used so far only at night and this would not be easily accepted by nonapneic patients because it disrupts the normal sleep architecture (12). Therefore, prescribing nocturnal CPAP in mild-to-moderate asthma patients in whom current medications are easy to take and very effective in controlling the disease would not be a reasonable solution. Neither would the treatment seem to play an important therapeutic role in severe asthma, as CPAP is expected to modify airway contractility rather than the irreversible fibrotic remodeling processes. Now, if it is the nocturnal application what makes the CPAP unacceptable by the nonapneic asthmatic patients, why not test whether its intermittent use during the day improves lung function and symptoms? If this were feasible and effective, then the CPAP could find a role in any kind of asthma where the contribution of ASM to airway narrowing is little controlled by regular therapy, which makes quality of life miserable and poor. Finally, there might be a role for the CPAP to assist in the inhalation therapy. As ventilation inhomogeneities are minimized at maximum lung inflation in both asthma (2, 22) and chronic obstructive pulmonary disease (1), the CPAP could be used to improve the deposition of bronchoactive agents within the lung regions that receive little medications with the conventional inhalation techniques because of severe narrowing of the subtending airways.
In conclusion, if the study by Xue et al. (25) suggests that CPAP can modulate the degree of airway responsiveness in an animal model of asthma, further studies need to be designed in humans to assess the efficacy of the technique in treating asthma.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES