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Effectiveness of a positive expiratory pressure device in conjunction with β_2-agonist nebulization therapy for bronchial asthma

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Patients with asthma often show increased airway hyperreactivity and mucus hypersecretion. Although β_2-agonist therapy is one of the most common and effective ways used to relieve airway obstruction, the use of a positive expiratory pressure device (PEPD) is also effective in mucus clearance. However, no previously reported study has examined the effectiveness of these two therapies used in combination. This study assessed the effectiveness of a PEPD on β_2-agonist nebulization therapy by measuring the pulmonary function before and after nebulization therapy in 54 asthmatic patients. The results show that the use of PEPD after β_2-agonist nebulization therapy improved pulmonary function compared with the use of β_2-agonist nebulization therapy alone, as shown by the increases in forced midexpiratory flow and forced vital capacity (FVC). Patients with forced expiratory volume in 1 sec (FEV_1) below 85% FVC obtained a significant improvement in FEV_1 and FVC after using PEPD. When PEPD was used before β_2-agonist nebulization therapy, there were no obvious direct bronchodilative effects. The use of PEPD after β_2-agonist therapy, however, significantly enhanced the bronchodilative effect of β_2-agonist therapy in patients with an FEV_1 below 85% FVC. The additional effect of PEPD use in improving pulmonary function after β_2-agonist nebulization therapy might be a result of an enhancement in mucus clearance.

Key words: Asthma, β_2-agonist, positive expiratory pressure device (PEPD)

The main pathological characteristics of bronchial asthma are chronic inflammatory changes in the airways associated with bronchial hyperresponsiveness. Asthmatic patients develop bronchoconstriction and episodic bronchial mucus plugging, which may have resulted from inflammation of the airway [1-3].

Both bronchodilator therapy and facilitation of the mucus expectoration are important in the management of bronchial asthma [4-7]. It has been identified that during an acute asthma attacks, enhancing the expectoration to remove excessive bronchial secretion is a crucial factor for the success of asthma therapy [8-10]. A number of positive expiratory pressure devices (PEPD) have been used to enhance expectoration. The flutter, a positive end pressure device that can create an oscillating positive pressure in the airway, has been reported to facilitate mucus elimination [11-13].

The effect of PEPD on lung function has been demonstrated in clinical trials [14,15]. However, little data is available on the use of PEPD in conjunction with β_2-agonist nebulization therapy.

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The aim of this study was to determine the effect of using PEPD in conjunction with β_2-agonists nebulization therapy in treating bronchial asthma. The effectiveness of the therapy was evaluated by comparing the pulmonary function of patients before and after therapy.

Materials and Methods

Patients

Fifty-four asthmatic patients (26 men and 28 women), with ages ranging from 7 to 81 years (mean, 39 years), were recruited for participation in this study. All patients had a diagnosis of asthma established symptomatically by findings of episodic wheezing, chest tightness, and/or dyspnea, and which was objectively confirmed by the methacholine airway hyperresponsiveness test. The criteria for selection of participants were based on the American Thoracic Society standards for diagnosis of asthma [16]. All patients were recruited from the Allergy Clinic of Cathay General Hospital-Taipei, and gave statements of informed consent. Pulmonary function tests were performed using Vitalography (Vitalograph Ltd., Buckingham, UK). All patients were asymptomatic before therapy, and pulmonary functions were recorded,

such as the forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC), forced expiratory flow rate between 25% and 75% of FVC (FMF). The PEPD was purchased from VarioRaw, SA, Switzerland. The β_2-agonists nebulization therapy was administered using a Pulmo Aid (Devilbiss, Sunrise Medical Somerset, PA, USA) with 2 mL Bricadyl (2.5 mg/mL) (AstraZeneca) diluted with 2 mL half saline.

Study design

All patients stopped receiving drug treatment at least 24 h before baseline pulmonary function tests were performed at the clinical laboratory unit of the hospital. Twenty-six patients received PEPD treatment followed by β_2-agonist nebulization therapy (Group A), and 28 received β_2-agonist nebulization therapy followed by PEPD treatment (Group B). Pulmonary function tests were performed before and after each kind of therapy. The duration of the therapy using PEPD was 10 min, and 15 min for β_2-agonist nebulization. These two procedures were performed 30 min apart. The severity of airway obstruction was defined as follows: an FEV_1 less than 85% FVC was considered as moderate to severe airway obstruction, an FEV_1 greater and equal to 85% of FVC was considered as mild airway obstruction. There was no significant difference in age and baseline pulmonary function between Group A and B (Table 1).

Statistical analysis

Pulmonary function before and after therapy in the same individuals was compared by using the paired Student's *t* test. A *p* valve less than 0.05 was considered statistically significant.

Table 1. Age, sex, and baseline pulmonary function among the two treatment groups

Category	Group A[a] (n = 26)	Group B[b] (n = 28)
Sex		
Female	11	17
Male	15	11
Age (yr)	40.3 ± 24.7	39.1 ± 24
FVC (L)	1.91 ± 24.7	1.58 ± 0.79
FEV_1 (L/sec)	1.48 ± 0.74	1.26 ± 0.57
FMF (L/min)	116.6 ± 81.8	113.8 ± 75.6

Abbreviations: FVC = forced vital capacity; FEV_1 = forced expiratory flow in one second; FMF = forced mid-expiratory flow
[a]Group A: patients received PEPD treatment followed by β_2-agonist therapy.
[b]Group B: patients received β_2-agonist therapy followed by PEPD treatment.

Results

When PEPD was used before the β_2-agonist nebulization therapy, no significant improvement in pulmonary function was found (Table 2, Group A). However, when PEPD was used after β_2-agonist nebulization therapy, a significant improvement in FEV_1, FVC and FMF was found in comparison with baseline (Table 2, Group B). The improvement of FMF and FVC were also significant when compared with values obtained after β_2-agonist nebulization therapy (Table 2, Group B).

Pulmonary function with PEPD use followed by β_2-agonist nebulization therapy in mild and moderate to severe asthmatic patients were compared. Patients with $FEV_1 \geq 85\%$ FVC (n = 8) showed no improvement in pulmonary function with this regimen. Although improvement in pulmonary function in these patients was obtained after β_2-agonist nebulization therapy, this

Table 2. Pulmonary function in the two treatment groups

	Baseline	PEPD	β_2-agonist
Group A (n = 26)			
FEV_1 (L/sec)	1.48 ± 0.74	1.47 ± 0.71	1.63 ± 0.74[a]
FVC (L)	1.91 ± 0.87	1.86 ± 0.84	1.47 ± 0.71
FMF (L/min)	116.8 ± 81.8	113.8 ± 75.6	116.8 ± 81.8[a]
Group B (n = 28)			
FEV_1 (L/sec)	1.26 ± 0.57	1.39 ± 0.65[a]	1.32 ± 0.61
FVC (L)	1.58 ± 0.79	1.73 ± 0.81[a,b]	1.53 ± 0.63
FMF (L/min)	104.5 ± 69.7	124.1 ± 99.3[a,b]	118.1 ± 98.3

Abbreviations: FVC = forced vital capacity; FEV_1 = forced expiratory flow in one second ; FMF = forced mid-expiratory ; PEPD = positive expiratory pressure device
[a]$p < 0.01$(compared with baseline).
[b]$p < 0.01$(compared with β_2-agonist).
Group A: patients received PEPD treatment followed by β_2-agonist therapy.
Group B: patients received β_2-agonist therapy followed by PEPD treatment.

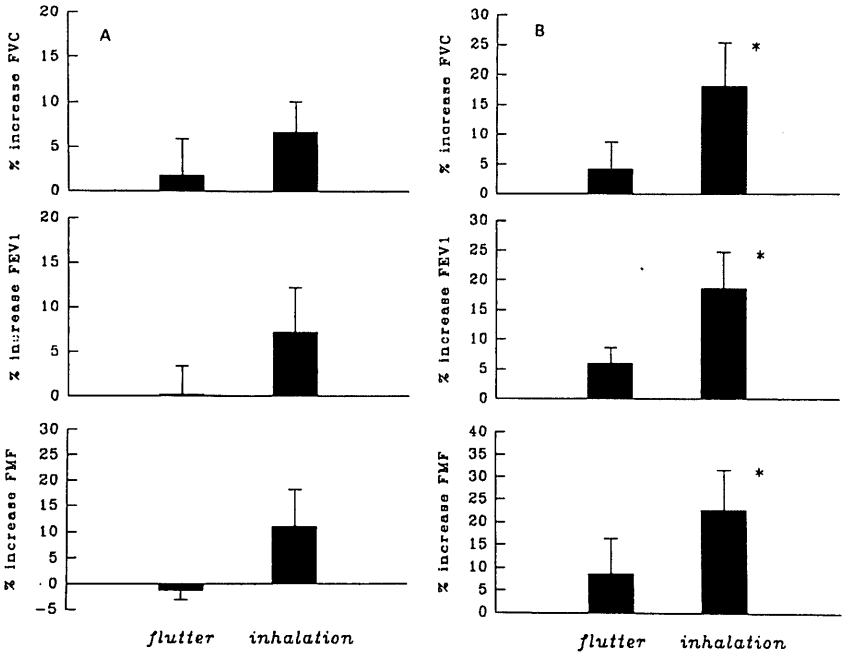

Fig. 1. Pulmonary function after PEPD use followed by β_2-agonist nebulization therapy in asthmatic patients with mild $FEV_1 \geq 85\%$ FVC (n = 8) **(A)** and moderate to severe $FEV_1 < 85\%$ (n = 18) **(B)** airway obstruction, ($^*p < 0.05$).

improvement did not reach a significant level (Fig. 1A). For patients with $FEV_1 < 85\%$ FVC (n = 18), the use of the PEPD followed by β_2-agonist nebulization therapy resulted in a significant improvement of pulmonary function, which includes FEV_1, FVC, and FMF (Fig. 1B).

In patients with $FEV_1 \geq 85\%$ FVC (n = 8), β_2-agonist nebulization therapy significantly improved pulmonary function, and further use of PEPD significantly improved FVC compared with baseline (Fig. 2A). For patients with $FEV_1 < 85\%$ FVC (n = 20), β_2-agonist nebulization therapy significantly improved FMF, and use of PEPD further improved FVC and FEV_1 compared with baseline (Fig. 2B).

Discussion

This study has demonstrated that the use of a PEPD alone for 10 min does not significantly improve pulmonary function in asthmatic patients. Patients with moderate to severe airway obstruction, however, obtained a significant improvement of FEV_1, FVC, and FMF when PEPD was used following nebulization therapy with β_2-agonist. These results indicate that PEPD therapy is a useful tool for the improvement of the bronchodilative effects of β_2-agonist therapy, and might have an important role in asthma therapy, especially for moderate to severe asthmatics when used prior to β_2-agonist nebulization therapy.

When patients received β_2-agonist nebulization therapy followed by PEPD therapy, there was a significant improvement of FVC in all patients. Further significant improvement of FEV_1 with PEPD, however, is observed only in patients with moderate to severe airway obstruction. These results indicate that there was still mucus plugging the airway even after β_2-agonist nebulization therapy. These patients may have obtained improvement of pulmonary function by the clearing of mucus using PEPD.

Little data is available about the use of PEPD in conjunction with β_2-agonist nebulization in patients with asthma. Although both treatments may have synergistic effects on improving pulmonary function, the efficacy of PEPD usage before and after β_2-agonist nebulization was different. The efficacy of β_2-agonist nebulization followed by PEPD therapy was better than PEPD therapy followed by β_2-agonist nebulization therapy, especially in patients with moderate to severe airway obstruction. The difference in efficacy may be because β_2-agonist nebulization does not only dilate the bronchi, but also produces a better environment for mucus clearance by PEPD usage, which means a better response of the bronchi to vibration and positive expiratory pressure. It has been reported that the main effect of β_2-agonist is to dilate the bronchi by a direct action on smooth muscle. A secondary action is to

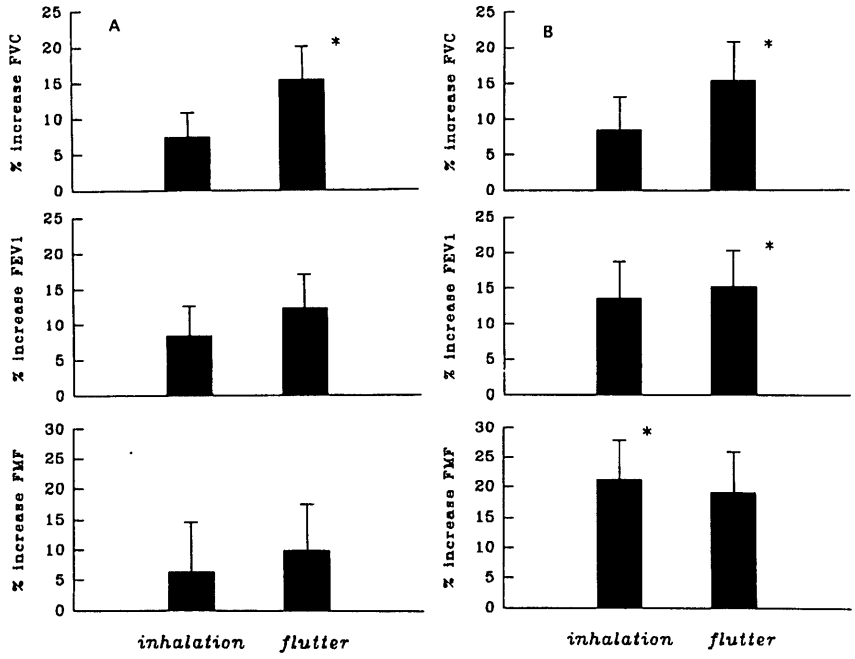

Fig. 2. Pulmonary function after β_2-agonist nebulization followed by PEPD therapy in asthmatic patients with mild FEV1 ≥ 85% (n = 8) (**A**) and moderate to severe FEV1 < 85% (n = 20) (**B**) asthmatic patients airway obstruction (*$p < 0.05$).

inhibit mediator release from mast cells. β_2-Agonist therapy may also inhibit vagal tone and increase mucus clearance by acting on cilia [1,17].

The improvement of FEV_1 and FVC by the nebulization therapy with β_2-agonist followed by PEPD usage indicates that this device can improve large airway obstruction. The effect of this device on lung function has also been demonstrated in other reports [13]. Girard *et al* [10] reported a significant improvement in FEV_1 and VC in asthmatics. Similar results were obtained in other studies in patients with chronic obstructive pulmonary diseases [14,15,18], and significantly improvement was observed in another group of patients with cystic fibrosis [12,19]. The positive effects of PEPD on lung function and dyspnea were secondary to an improvement in mucus clearance and prevention of bronchial collapse [21,22]. An oscillating positive expiratory pressure was generated right through the end of each exhalation, and the vibration caused an increasing liquefaction of the bronchial secretion [4,11,12,19], with the resulting improvement in peripheral ventilation [4].

This study has focused only on the immediate effects of PEPD use in conjunction with β_2-agonist therapy. Interpreting the effects of long-term therapy is more difficult, because the influence of variables such as infection exacerbation, patient's compliance, and changes in drug administration are more difficult to determine. No adverse effects occurred in the participants of this study. Most patients in this study claimed to have expectorated more abundantly and have experienced a decrease in their subjective dyspnea after using PEPD.

In conclusion, when asthmatic patients receive nebulization therapy with β_2-agonist, the use of a PEPD enhances its bronchodilative effect, especially in the patients with FEV_1 < 85% FVC. The additional effect of using a PEPD in conjunction with β_2-agonist therapy might be secondary to its enhancement in mucus clearance.

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