

Effect of salmeterol/fluticasone combination on the dynamic changes of lung mechanics in mechanically ventilated COPD patients: a prospective pilot study

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Background: The combined therapy of inhaled corticosteroids and long-acting beta-2 agonists for mechanically ventilated patients with COPD has never been explored. Therefore, the aim of this study was to investigate their dynamic effects on lung mechanics and gas exchange.

Materials and methods: Ten mechanically ventilated patients with resolution of the causes of acute exacerbations of COPD were included. Four puffs of salmeterol 25 µg/fluticasone 125 µg combination therapy were administered. Lung mechanics, including maximum resistance of the respiratory system (Rrs), end-inspiratory static compliance, peak inspiratory pressure (PIP), plateau pressure, and mean airway pressure along with gas exchange function were measured and analyzed.

Results: Salmeterol/fluticasone produced a significant improvement in Rrs and PIP after 30 minutes. With regard to changes in baseline values, salmeterol/fluticasone inhalation had a greater effect on PIP than Rrs. However, the therapeutic effects seemed to lose significance after 3 hours of inhaled corticosteroid/long-acting beta-2 agonist administration.

Conclusion: The combination of salmeterol/fluticasone-inhaled therapy in mechanically ventilated patients with COPD had a significant benefit in reducing Rrs and PIP.

Keywords: COPD, inhaled corticosteroid, long-acting beta-2 agonist, mechanical ventilation, respiratory failure

Introduction

In patients with moderate-to-severe COPD, treatment with a combination of an inhaled long-acting beta-2 agonist (LABA), and an inhaled corticosteroid (ICS) has been shown to be more effective than the individual components in reducing exacerbations and improving lung function and health status.¹⁻⁴ In addition, the use of systemic corticosteroid treatment along with other therapies has been recommended for the management of hospitalized patients with acute exacerbations of COPD.⁴⁻⁶ A previous study demonstrated that in patients in a stable condition with severe COPD and chronic hypercapnic respiratory failure, a brief period of inhaled fluticasone treatment may produce a short-acting bronchodilator response, mainly related to a reduction in airway resistance, that is not detected by the usual pulmonary function tests.⁷ However, the combined therapy of an inhaled LABA and ICS is not yet recommended as a standard therapy for patients with COPD during acute exacerbations or for those with a chronic stable status requiring mechanical ventilatory support. Therefore, the aim of this study was to evaluate the short-term effect of inhaled salmeterol/fluticasone therapy on dynamic changes in lung mechanics and gas exchange in mechanically ventilated patients with acute exacerbations of COPD in whom the causes of acute

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respiratory failure are under control, but who are not yet ready to be weaned from mechanical ventilation.

Materials and methods

Study design and patients

This prospective cohort study was conducted at a 24-bed respiratory intensive care unit of Taipei Veterans General Hospital, a tertiary medical center in Taiwan. From August 2007 to November 2007, ten consecutive mechanically ventilated patients with an acute exacerbation of COPD as defined by the Global initiative for chronic Obstructive Lung Disease guidelines were enrolled. The inclusion criteria were subjects with a well-established diagnosis of COPD who were endotracheally intubated and mechanically ventilated. In addition, the causes of acute respiratory failure were under control in these patients, but they were not yet ready to have the mechanical ventilatory support withdrawn. Further, all of the included patients had stable vital signs, fraction concentration of inspired oxygen (FiO_2) less than 40%, and had not used long-acting bronchodilators, including oral, intravenous, or inhaled forms for at least 48 hours. None of the patients had received systemic corticosteroid therapy or a tapering of systemic corticosteroids to oral prednisolone less than 20 mg per day. The exclusion criteria included patients with persistent exacerbations, which required the use of intravenous or oral corticosteroid therapy of more than prednisolone 20 mg per day. In addition, patients with other severe clinically significant medical disorders besides COPD such as congestive heart failure, New York Heart Association Functional Classification III–V, liver cirrhosis, Child-Pugh score C, or chronic renal failure were also excluded, as were patients with a diagnosis of bronchial asthma, pneumonia, pulmonary edema, refractory hypoxemia, pneumothorax, or excessive airway secretions. The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their authorized representatives before enrollment.

Protocol

Oral systemic corticosteroids were withheld in the early morning before the study began, and the protocol was performed for all subjects at a similar time in the morning. Careful sputum suction using an open method and preoxygenation with 100% FiO_2 were performed before the initiation of the protocol and 5 minutes before each measurement. This time interval has been shown to be sufficient to avoid the effects of a transient bronchoconstrictive response to suction.⁸ The ventilator

was maintained in the volume-control mode during the whole study (3 hours) with tidal volume ≤ 8 mL/kg, flow rate 50–60 L/min, $FiO_2 \leq 40\%$, and positive end-expiratory pressure ≤ 5 cm H_2O . All of the subjects were sedated with intravenous short-acting anesthesia (midazolam), which was assessed by the absence of spontaneous breathing efforts. Before the use of hydrofluoroalkane pressurized metered-dose inhalers (HFA pMDIs) with a combination of salmeterol and fluticasone (Seretide[®] 125 Evohaler, containing salmeterol 25 μ g and fluticasone 125 μ g per puff, GlaxoSmithKline, Brentford, UK), six parameters were measured as baseline values, including maximum resistance of the respiratory system (Rrs), end-inspiratory static compliance of the respiratory system (Crs, st), peak inspiratory pressure (PIP), plateau pressure (Pplat), mean airway pressure (MAP), and gas exchange function (partial pressure of oxygen in arterial blood (PaO_2) versus FiO_2 , PaO_2/FiO_2 ratio). In the ventilator circuit, salmeterol/fluticasone inhalation was delivered via an AeroVent[®] (Monaghan Medical Corporation, Plattsburgh, NY, USA) device on the inspiratory limb with one puff per breath for four consecutive breaths during inspiration. The canister was shaken before each series of puffs.

Measurement of lung mechanics

All patients were examined in a semirecumbent position with the head of the bed up to 30°. During the protocol, a physician not involved in the study was always present to provide care for the patients. Lung mechanics were measured using the monitor and program setting of the mechanical ventilator (SERVO 300 ventilator, Siemens, Munich, Germany). Five parameters were measured to evaluate changes in lung mechanics, including Rrs, Crs, st, PIP, Pplat, and MAP, all of which were measured at the bedside, and the ratio of PaO_2/FiO_2 . We used the occlusion technique as previously described to measure lung mechanics.^{9,10}

All of the lung mechanics parameters were measured at baseline, and then 30 minutes, 1, 2, and 3 hours after salmeterol/fluticasone inhalation, at which times sputum suction was carefully performed. Arterial blood gas was analyzed at baseline, 1, and 3 hours after inhalation, and each sampling was performed before sputum suction. The setting of the ventilator was not changed during the whole course of the protocol, and all patients were kept in a ventilator-dependent state with the use of sedatives.

Statistical analysis

Measurements concerning the overall effects of salmeterol/fluticasone inhalation on lung mechanics and gas exchange

Table 1 Patient characteristics and baseline arterial blood gas

Age (years)	FEV ₁ (L)	FiO ₂	pH	PaCO ₂ (mmHg)	HCO ₃ ⁻ (mmHg)	PaO ₂ (mmHg)
81±4.1	1.16±0.18	0.33±0.07	7.44±0.06	27.9±5.4	18.8±5.9	104.2±19.6

Note: Data are presented as mean ± SD.

Abbreviations: FEV₁, force expiratory volume in 1 second; FiO₂, fractional concentration of inspired oxygen; PaCO₂, partial pressure of arterial carbon dioxide; PaO₂, partial pressure of arterial oxygen; SD, standard deviation.

function were analyzed using a nonparametric Wilcoxon signed rank test. Statistical analysis was performed using SPSS 19.0 software (Statistical Package for the Social Sciences, Chicago, IL, USA). The primary endpoints were changes in lung mechanics, including Rrs, Crs, st, PIP, Pplat, and MAP. The secondary endpoint was a change in gas exchange function. A *P*-value <0.05 was considered to be statistically significant for all tests.

Results

Patient characteristics and lung mechanics measured at different time points in ventilated COPD patients who received salmeterol/fluticasone inhalation

All of the enrolled patients completed the study, and their characteristics are shown in Table 1. The causes of acute respiratory failure were all due to COPD with secondary infections (ten cases). The COPD stages of the ten patients were moderate (three patients) to severe (seven patients), according to the Global initiative for chronic Obstructive Lung Disease guidelines. No specific side effects were noted during the combination therapy with salmeterol/fluticasone inhalation. Table 2 shows the mean values and standard deviations of respiratory mechanics recorded at the different time points. The changes in Rrs, PIP, and MAP are shown in Figure 1. Two patients showed no obvious bronchodilator responses to the combination therapy with salmeterol/fluticasone, and in the remaining eight patients, the mean Rrs change from baseline was 7.9%±8.7% at 30 minutes, reaching

a peak decrease of 16.5%±10.6% at 2 hours. Figure 2 shows individual values of Rrs during the study period.

Changes in maximum resistance of the Rrs in the ventilated COPD patients with salmeterol/fluticasone inhalation

As shown in Figure 3, a significant reduction in airway resistance was observed after 30 minutes of combination therapy with salmeterol/fluticasone (baseline, 17.4±7.6 cm H₂O/L/s; 30 minutes, 16.3±7.4 cm H₂O/L/s, *P*=0.043; 1 hour, 15.8±7.4 cm H₂O/L/s, *P*=0.018; 2 hours, 14.9±6.7 cm H₂O/L/s, *P*=0.011; 3 hours, 16.4±7.6 cm H₂O/L/s, *P*=0.116). The lowest value of airway resistance was noted at 2 hours, and at 3 hours airway, resistance was not significantly different from baseline, although a trend of a reduction was still observed.

Effect of salmeterol/fluticasone inhalation in PIP

As shown in Figure 4, a significant reduction in PIP was observed after 30 minutes of therapy (baseline, 29.8±7.6 cm H₂O; 30 minutes, 26.4±6.1 cm H₂O, *P*=0.018; 1 hour, 24.3±5.6 cm H₂O, *P*=0.005; 2 hours, 23.9±5.8 cm H₂O, *P*=0.005; 3 hours, 27.2±7.8 cm H₂O, *P*=0.028).

Gas exchange after salmeterol/fluticasone inhalation

As shown in Figure 5, no obvious improvement in the ratio of PaO₂ and FiO₂ was observed 1 or 3 hours after treatment

Table 2 Lung mechanics before and up to 3 hours after salmeterol/fluticasone inhalation

Parameters for lung mechanics	Baseline	30 minutes	1 hour	2 hours	3 hours
Rrs (cm H ₂ O/L/s)	17.4±7.6	16.3±7.4 ^a	15.8±7.4 ^a	14.9±6.7 ^a	16.4±7.6
Crs, st (mL/cm H ₂ O)	46.0±23.6	45.3±23.5	45.0±23.7	45.2±23.7	45.3±23.8
PIP (cm H ₂ O)	29.8±7.6	26.4±6.1 ^a	24.3±5.6 ^a	23.9±5.8 ^a	27.2±7.8 ^a
Pplat (cm H ₂ O)	23.1±10.2	21.2±7.1	19.9±5.0	21.7±5.5	23.5±9.9
MAP (cm H ₂ O)	12.3±3.4	12.2±3.5	11.3±3.2 ^a	10.9±3.2 ^a	11.4±3.5
PaO ₂ /FiO ₂	328.0±83.8	NA	374.7±97.8	NA	331.3±87.8

Notes: Values are presented as mean ± SD. ^aSignificantly different from baseline values (*P*<0.05, Wilcoxon signed rank test).

Abbreviations: Crs, st, end-inspiratory static compliance of the respiratory system; MAP, mean airway pressure; NA, not applicable; PaO₂/FiO₂, partial pressure of oxygen in arterial blood/fraction concentration of inspired oxygen; PIP, peak inspiratory pressure; Pplat, plateau pressure; Rrs, maximum resistance of the respiratory system; SD, standard deviation.

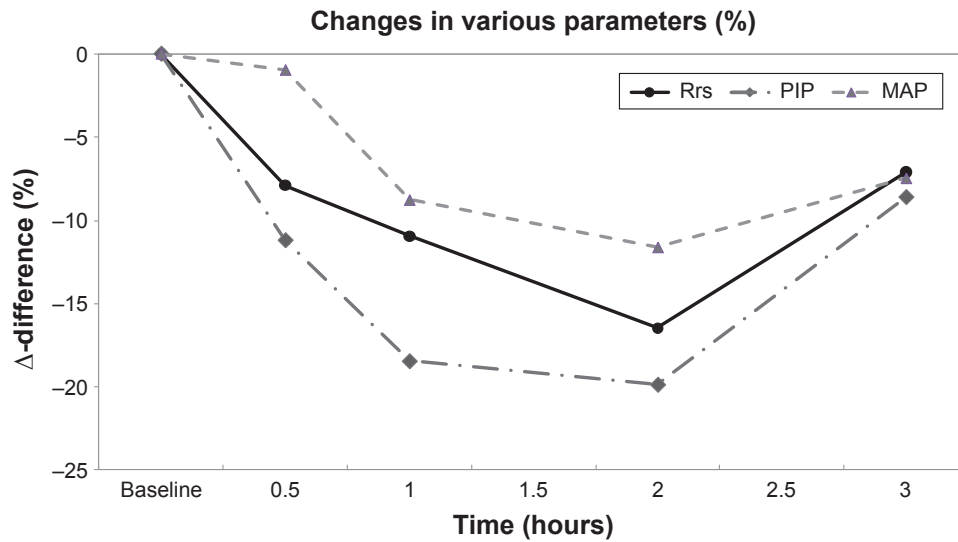


Figure 1 Percent changes (Δ -difference %) in peak inspiratory pressure (PIP), mean airway pressure (MAP), and maximum resistance of the respiratory system (Rrs). **Note:** Changes were observed after the use of combination therapy with salmeterol/fluticasone inhalation.

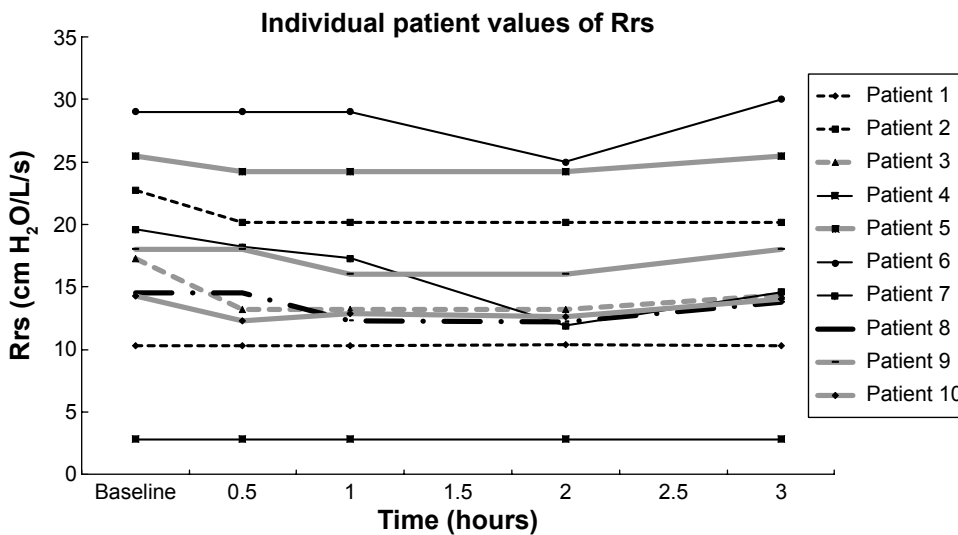


Figure 2 Individual patient values of maximum resistance of the respiratory system (Rrs). **Note:** Reduction in airway resistance was observed 30 minutes after salmeterol/fluticasone treatment.

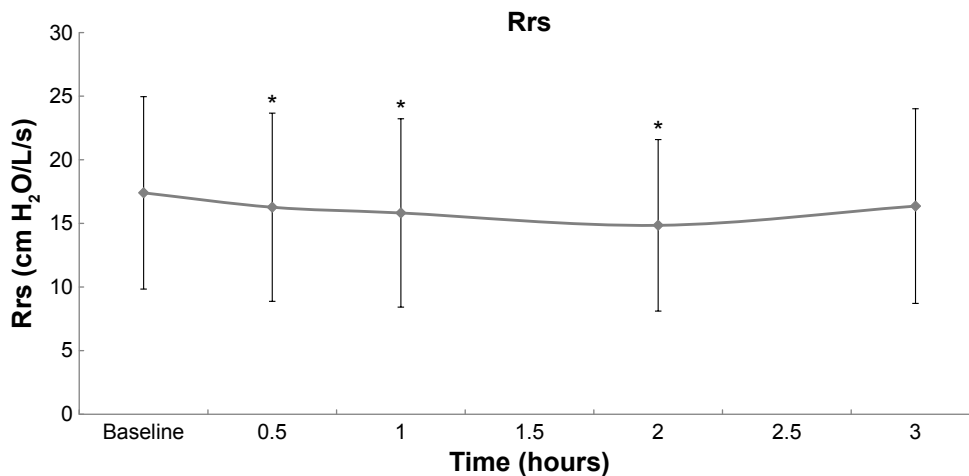


Figure 3 Effect of combination therapy with salmeterol/fluticasone inhalation on maximum resistance of the respiratory system (Rrs) mean values. **Notes:** Mean values \pm SD of airway resistance at baseline and up to 3 hours. *Significantly different from baseline values ($P < 0.05$, Wilcoxon signed rank test). **Abbreviation:** SD, standard deviation.

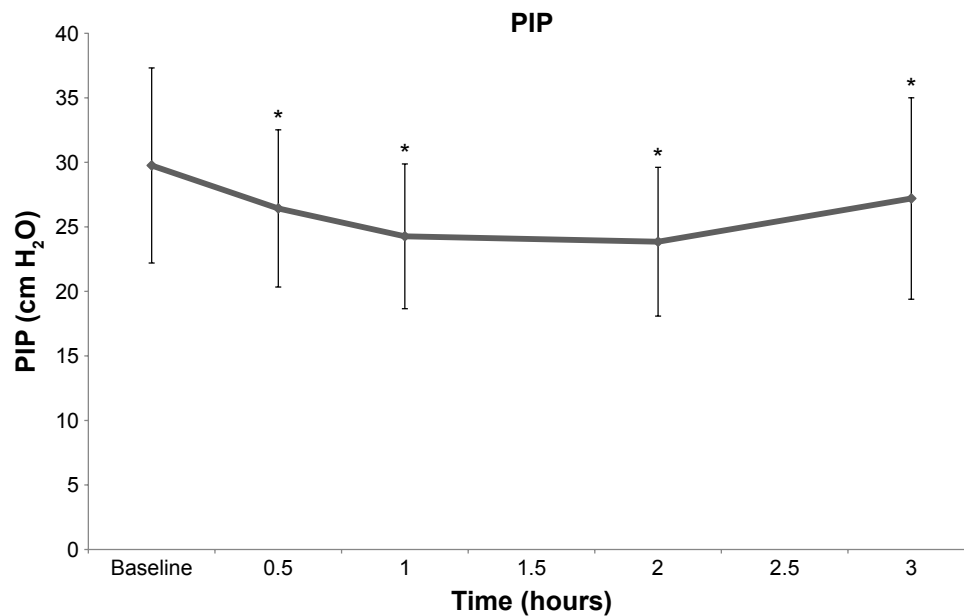


Figure 4 Effect of combination therapy with salmeterol/fluticasone inhalation on peak inspiratory pressure mean values.

Notes: Mean values \pm SD of peak inspiratory pressure at baseline and up to 3 hours. *Significantly different from baseline values ($P < 0.05$, Wilcoxon signed rank test).

Abbreviations: SD, standard deviation; PIP, peak inspiratory pressure.

(baseline, 328.0 ± 83.8 ; 1 hour, 374.7 ± 97.8 , $P = 0.114$; 3 hours, 331.3 ± 87.8 , $P = 0.847$).

Discussion

In this study, combination therapy using 100 μ g salmeterol and 500 μ g fluticasone inhalation delivered by MDIs with a spacer provided a significant improvement in lung mechanics, as expressed by a reduction in maximum resistance of the Rrs, PIP, and MAP in the short term. No obvious improvement in oxygenation after the combination therapy was noted. To the best of our knowledge, this is the first study to examine the effect of combination therapy with a

LABA and ICS on lung mechanics in mechanically ventilated COPD patients.

The use of bronchodilators with a MDI and spacer has been reported to have a similar effect and duration compared with nebulizers in mechanically ventilated COPD patients.^{11,12} Several studies have shown that short-acting beta-2 agonists cause a significant decrease in airway resistance in COPD patients under mechanical ventilation.^{13,14} However, only a few studies have reported the use of inhaled long-acting bronchodilators¹⁵ or ICSs⁷ in such patients. Malliotakis et al reported that salmeterol caused a significant decrease in dynamic and static airway pressure and also minimum and

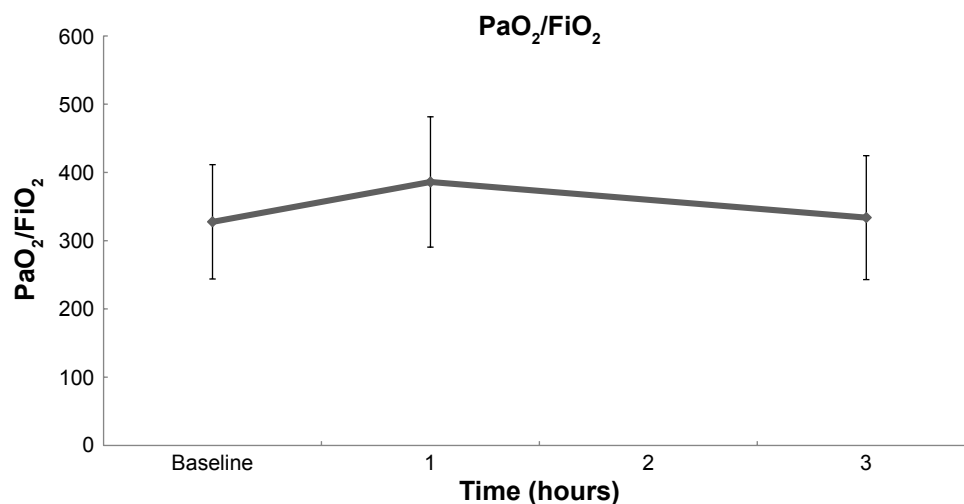


Figure 5 Effect of combination therapy with salmeterol/fluticasone inhalation on PaO₂/FiO₂ mean values.

Note: Mean values \pm SD of mean PaO₂/FiO₂ at baseline and up to 3 hours.

Abbreviations: PaO₂/FiO₂, partial pressure of oxygen in arterial blood/fraction concentration of inspired oxygen; SD, standard deviation.

maximum inspiratory resistance in mechanically ventilated patients with acute exacerbations of COPD.¹⁵ Similar to their results, we observed improvements in lung mechanics after 30 minutes of inhaled salmeterol/fluticasone treatment. However, the peak effect of this therapy appeared after 2 hours of drug administration. After 3 hours, except for a persistently significant reduction in PIP compared with baseline, there were no significant differences in other parameters including airway resistance and MAP from baseline.

Several factors may contribute to these differences in results. First, our cases were all Asians, not Caucasians. Second, the mean age of our patients was 81 years, which is much older than in the other study. Third, our patients were relatively stable in terms of underlying etiology of acute respiratory failure being controlled, as demonstrated by a lower dosage of systemic steroids (prednisolone less than 20 mg per day). As with lung mechanics, our patients had lower airway resistance and PIP at baseline.

Previous studies have reported that beta-2 adrenergic receptor agonists cause a transient decrease in PaO₂ in spite of concomitant bronchodilation^{16–20} through a pulmonary arterial vasodilation effect by activation of beta-adrenoceptors, which are present in pulmonary vessels, thereby causing an increase in pulmonary blood flow to poorly ventilated lung regions and worsening ventilation-perfusion inequality.^{21,22} Furthermore, adding an ICS with a LABA has been reported to improve oxygenation compared with a LABA alone as ICSs can acutely decrease bronchial blood flow.¹⁶ This effect may be caused by the capability of corticosteroids to interrupt the uptake of noradrenaline by smooth muscle cells of human bronchial arteries (extraneural uptake: uptake₂). This then increases the noradrenaline concentration at α -adrenergic receptor sites of bronchial vascular smooth muscle cells that explains corticosteroid-induced vasoconstriction.²³ This effect may change the blood flow from poorly ventilated alveoli to better ventilated areas, thereby improving the matching of ventilation and perfusion and maintaining an adequate PaO₂.²⁴ Interestingly, it has been shown that uptake₂ is inhibited by steroid hormones through a nongenomic action *in vitro*.²⁵ This nongenomic action occurs within seconds to a few minutes,²⁶ and this could explain why the protective action of fluticasone on the vascular effect of salmeterol is immediate. Our results also support this hypothesis.

The combination of an ICS and LABA is increasingly used as maintenance therapy in patients with moderate-to-severe COPD.^{27,28} The effect of ICSs is thought to be mediated through suppression of airway inflammation, while LABAs are thought to work by inducing bronchodilation. Increasing

evidence indicates that these two classes of drugs interact positively with each other, leading to added or perhaps synergistic benefits for patients. Corticosteroids enhance the expression of beta-2 adrenoceptors, thus providing protection against desensitization and the development of tolerance to beta-2 adrenoceptor agonists, which may occur with the prolonged use of these medications. LABAs, on the other hand, may amplify the anti-inflammatory effects of corticosteroids by accelerating nuclear translocation of the glucocorticoid receptor complex, and enhancing the transcription and expression of steroid-inducible genes in proinflammatory cells.

In previous clinical trials, inhaled salmeterol/fluticasone propionate 50/500 and 25/250 μ g treatment twice daily was shown to result in significant increases in pre- and postdose forced expiratory volume in 1 second and improvements from baseline compared to a placebo in patients with moderate-to-severe COPD.^{3,29,30} In addition, forced expiratory volume in 1 second 2 hours postdose was shown to improve significantly more with salmeterol/fluticasone propionate 50/500 or 50/250 μ g than with a placebo or fluticasone propionate in a 24-week trial.³⁰ Furthermore, another study reported an improvement in symptoms within 1 week with salmeterol/fluticasone propionate treatment twice daily.³¹

The major limitations of this study include the short study period and small sample size. Some methodological issues should also be discussed. First, only a single dose of combination therapy with salmeterol/fluticasone inhalation was given. Second, only ten patients were included in the study; however, several similar studies have also enrolled the same number of patient to investigate the effect of single dose inhalation.^{7,15} In addition, the lack of a placebo group may be another limitation; however, a placebo for a pMDI inhaler is difficult to find in Taiwan. Our enrolled cases were mechanically ventilated patients with acute exacerbations of COPD with the causes of acute respiratory failure under control. ICSs may be necessary to control airway inflammation in this population; however, having a comparison group with LABA therapy alone may raise ethical concerns. Therefore, further studies are needed to validate our results in patients with acute respiratory failure due to COPD who are receiving mechanical ventilation.

In this study, we used salmeterol/fluticasone combination therapy with a HFA pMDI instead of using a salmeterol HFA pMDI and fluticasone HFA pMDI separately. There are several reasons for this. First, only salmeterol chlorofluorocarbon (CFC) MDIs and fluticasone CFC MDIs are available in Taiwan. The ozone-depleting potential of CFCs has been well documented and they have mainly been replaced by

HFA products. Second, many studies have shown that HFA pMDIs are pharmacokinetically and clinically comparable to or even superior to traditional CFC MDIs.^{32–37}

Further studies are needed to evaluate the effects on lung mechanics in patients with COPD and respiratory failure requiring mechanical ventilation and multiple doses of combination therapy with salmeterol/fluticasone inhalation. In addition, a larger study population may also be necessary to confirm these findings with regard to the benefits of combination therapy.

Conclusion

Salmeterol/fluticasone inhalation therapy in patients with COPD and mechanical ventilation showed significant beneficial effects in reducing Rrs and PIP.

Acknowledgment

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Disclosure

The authors report no conflicts of interest in this work.

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