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# Clinical Studies on Reversibility of Pulmonary Airway Dysfunctions in Asymptomatic Smokers: Role of Nervous Mechanism in Small Airway Disease

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## ABSTRACT

Pulmonary function tests were performed on twenty eight males, among whom eight were healthy nonsmokers and twenty were asymptomatic smokers. Pulmonary function tests such as spirometry, respiratory impedance ($Z_{3Hz}$), single breath nitrogen washout ($SBN_2$) and volume of isoflow ($Viso\dot{V}$) were done before and after inhalation of orciprenaline sulphate and atropine sulphate in all nonsmokers and smokers. Subdivisions of lung volume, diffusing capacity ($D_{Lco}$) and arterial blood gas analysis were conducted only before inhalation of drugs. Acute effects were studied after smoking a cigarette and effects of orciprenaline inhalation after smoking were also observed. Furthermore, effects of smoking on prior inhalation of orciprenaline, atropine or lidocaine were evaluated.

The results obtained were as follows:

1) There were no differences in the results of routine pulmonary function tests, between nonsmokers and smokers except $Z_{3Hz}$, which was significantly higher in smokers ($p < 0.01$) and there was a tendency to decrease in flow especially at low lung volumes in smokers. Smokers could be well differentiated from nonsmokers by $Viso\dot{V}/FVC$ ($p < 0.001$) and the difference in distribution of ventilation was greater ($p < 0.05$).

2) In nonsmokers, $Z_{3Hz}$ decreased and $\dot{V}_{50}$ increased significantly after inhalation of orciprenaline and atropine. $FEV_{1.0}$ increased significantly with atropine inhalation only. There were no changes in $Viso\dot{V}/FVC$ with inhalation of orciprenaline or atropine.

In smokers, $Z_{3Hz}$ and $Viso\dot{V}/FVC$ decreased significantly after inhalation of orciprenaline or atropine ($p < 0.001$). $FEV_{1.0}$ and flow rates improved significantly with both drugs.

3) After smoking a cigarette, $Z_{3Hz}$ and $Viso\dot{V}/FVC$ significantly increased ($p < 0.01$), but inhalation of orciprenaline or atropine prior to smoking significantly inhibited the acute effects of smoking and lidocaine completely inhibited the acute effects of smoking.

These results indicate that several parameters such as $Z_{3Hz}$, flow at low lung volume, $Viso\dot{V}/FVC$ could detect the airway dysfunctions in asymptomatic cigarette smokers. These airway dysfunctions might be due to increased vagal tone, leading to narrowing of the airways and these airway dysfunctions were reversible by bronchodilator drugs.

Lungs are the organ of respiration for continuous gaseous exchange. For gaseous exchange through the lungs, there should be proper ventilation and sufficient pulmonary blood flow. It is desirable that intact airway system should provide proper ventilation. Due to clinical convenience, pulmonary airways are divided into two components, central and peripheral. Airways less than 2 mm in internal diameter are called peripheral or small airways[25].

According to Woolcock and his associates[64], the peripheral airways are the silent zones in the lungs and clinical manifestations of early small airway obstructions are usually nonapparent or mild. Pulmonary function tests including airway resistance, forced expiratory volume in one second ($FEV_{1.0}$) and other flow rates at high lung volumes may be normal because they do not reflect the peripheral airways which are the sites of obstruction.

In healthy lungs, peripheral airway resistance is so small that it is difficult to measure in man. In 1967, Macklem and his associates[40] measured the resistance of the peripheral airways less than 2 mm in diameter in dogs and observed that there were large differences in resistance between large and small airways. In high lung volumes the airway resistance was due to large airways and even in low lung volumes the peripheral airways contributed only 15% of the total airway resistance.

In 1968, Hogg et al[25] have measured the central and peripheral airway resistances in excised lungs (at autopsy) of normal human and chronic obstructive pulmonary disease (COPD) patients by retrograde catheter technique. They have also suggested that in normal lung peripheral airways contributed only 25% of the total airway resistance, but in COPD patients this increased from 4 to 40 times because of narrowing, mucus plugging and obliteration of small airways. McLean[43] has concluded from his observation that the changes in the peripheral airways are the primary sites of COPD. Hence, it is likely that the clinical detection of COPD at an earlier stage is ordinarily delayed until more advanced obstruction becomes present.

If smoking is continued for many years, there is an increased prevalence of COPD. As the cigarette smokers at a high risk of developing COPD, there is great interest in identifying tests that can detect COPD in its early stage when changes in the peripheral airways may still be reversible. Since most advanced COPD patients have abnormal $FEV_{1.0}$ or the ratio of $FEV_{1.0}$ to FVC ($FEV_{1.0}$%) the disease may be irreversible[16]. For early detection of peripheral airway dysfunctions, sensitive lung function tests have been introduced. These tests include: 1) detection of abnormalities in gas exchange (diffusing capacity)[2,33], 2) frequency dependence of dynamic lung compliance (Cdyn)[28,64], 3) analysis of flow rates at low lung volumes utilizing maximum expiratory flow-volume curves (MEFV)[17,18,27,65], 4) closing volume[9,17,44,46] and 5) volume of isoflow ($Viso\dot{V}$) using MEFV curves with air and $He+O_2$[8,12,13,19–21,26,31,49].

Hutcheon and his associates[26] introduced the volume of isoflow ($Viso\dot{V}$) as a new test for the detection of small airway obstruction. Their report suggested that $Viso\dot{V}$ is more sensitive than the other tests as mentioned above.

Inhalation of various irritant particles and gases, such as dust, sulfur dioxide and ammonia, causes bronchoconstriction in man[50,56,62]. It has also been reported that inhalation of cigarette smoke induces bronchoconstriction in man[11,32,51] and animals[4–6,23,34,37,52]. Widdicombe[61] has established by experimental observations that airway smooth muscle tone is regulated by cholinergic vagal pathway. In quiet breathing, the airway smooth muscle is in tonic contraction and this muscle tone may be reduced by the administration of adrenergic receptors stimulant and atropine. Therefore, bronchoconstriction due to smoking may be mediated by vagal reflex by stimulating vagal airway sensory receptors, the so-called irritant receptors[5,23,52,56].

It has been observed that the acute effect of cigarette smoking can be demonstrated either with airway resistance[1,52] specific airway conductance[56] or Cdyn[41], but there has been no report of evaluating the acute effect of smoking by $Viso\dot{V}$.

Many studies have shown reversal effects with different beta adrenergic receptor agonists and anticholinergic drugs in different diseases such as chronic bronchitis, bronchial asthma and emphysema[10,30,38] but there are a very few reports on reversibility of pulmonary airway dysfunctions in asymptomatic smokers with beta adrenergic receptor agonists and anticholinergic bronchodilators.

This study was designed:

a. to make an early detection of pulmonary airway dysfunctions,
b. to evaluate the reversibility of pulmonary airway dysfunctions and
c. to investigate the role of cholinergic nerve in pulmonary airway dysfunctions in asymptomatic cigarette smokers.

Symbols and abbreviations used in this study are shown in Table 1.

**Table 1.** Symbols and Abbreviations

| Symbols and Abbreviations | Unit | |
|---|---|---|
| $A \overset{ass}{-} aD_{O_2}$ | mmHg | alveolar-arterial (assumption) oxygen pressure difference |
| B.I. | | Brinkman index (no. of cigarette smoking per day times year of smoking) |
| Cdyn | liter/cm$H_2O$ | dynamic compliance of the lung |
| COPD | | chronic obstructive pulmonary disease |
| $D_{Lco}$ | ml/min/mmHg | diffusing capacity of lung (single breath holding method) |
| $\%D_{Lco}$ | % | percentage of $D_{Lco}$ to predicted value |
| $FEV_{1.0}$ | liter | forced expiratory volume in 1.0 second |
| $FEV_{1.0}\%$ | % | percentage of $FEV_{1.0}$ to forced vital capacity |
| FVC | liter | forced vital capacity |
| %FVC | % | percentage of FVC to predicted value |
| FRC | liter | functional residual capacity |
| %FRC | % | percentage of FRC to predicted value |
| $FET_{He}$ | % | fractional end-tidal helium concentration |
| He | | helium gas |
| $He+O_2$ | | mixture of 80% helium and 20% oxygen gas |
| MEFV | | maximum expiratory flow volume curve |
| $\Delta N_2$ | %/liter | changes of nitrogen concentration from the slope of phase Ⅲ of $SBN_2$ |
| $O_2$ | | oxygen gas |
| $Pao_2$ | mmHg | partial pressure of arterial oxygen |
| $Paco_2$ | mmHg | partial pressure of arterial carbon dioxide |
| PF | liter/sec | peak flow |
| RV | liter | residual volume |
| %RV | % | percentage of RV to predicted value |
| RV/TLC | % | ratio of RV to TLC |
| $SBN_2$ | | single breath nitrogen washout |
| TLC | liter | total lung capacity |
| %TLC | % | percentage of TLC to predicted value |
| VC | liter | vital capacity |
| %VC | % | percentage of VC to predicted value |
| $\dot{V}_{75}$ | liter/sec | flow rate at 75% of MEFV |
| $\dot{V}_{50}$ | liter/sec | flow rate at 50% of MEFV |
| $\dot{V}_{25}$ | liter/sec | flow rate at 25% of MEFV |
| $\dot{V}_{50}/\dot{V}_{25}$ | | ratio of $\dot{V}_{50}$ and $\dot{V}_{25}$ |
| $\Delta\dot{V}_{50}$ | % | $\dot{V}_{50_{He}} - \dot{V}_{50_{air}} / \dot{V}_{50_{air}} \times 100$ |
| $\Delta\dot{V}_{25}$ | % | $\dot{V}_{25_{He}} - \dot{V}_{25_{air}} / \dot{V}_{25_{air}} \times 100$ |
| $Viso\dot{V}$ | liter | volume of isoflow |
| $Viso\dot{V}/FVC$ | % | percentage of volume of isoflow to FVC |
| $\dot{V}viso\dot{v}$ | liter/sec | flow at volume of isoflow |
| $Z_{3Hz}$ | cm$H_2O$/liter/sec | respiratory impedance |

## MATERIALS AND METHODS

Subjects:

Subjects of this work included twenty eight males, consisting of eight healthy nonsmokers and twenty asymptomatic smokers. Subjects were doctors, technicians, medical representatives and other employees of this hospital.

A nonsmoker was defined as an individual who had never smoked more than a few cigarettes during his life or had smoked absolutely none.

A smoker was defined as an individual who has smoked an average of more than 10 cigarettes per day for a period of more than five years and was smoking to the date of this experiment. Before inclusion in the study all the subjects were screened by personal interview to eliminate the possibility of any previous and current respiratory diseases. Presence of any lung disease excluded the subject from the study. The study was designed to isolate the effect of smoking as closely as possible.

Methods:

All the smoker subjects were requested to abstain from smoking at least 3 hr before the examination. Pulmonary function tests were performed which included the determination of vital capacity (VC), percentage of VC to predicted value (%VC) and forced expiratory volume in one second ($FEV_{1.0}$) with a box spirometer (OST-80, Chest Co. Ltd, Tokyo). Subdivisions of lung volume such as total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV) were determined by the closed circuit helium dilution method[22] and the pulmonary diffusing capacity ($D_{Lco}$) was measured by the single breathholding method. (P.K. Morgan Ltd., England). Predicted values for subdivisions of lung volume and diffusing capacity were obtained for adults by the prediction formula developed at the Second Department of Internal Medicine, Hiroshima University[53,54]. Respiratory impedance ($Z_{3Hz}$) was measured by 3Hz oscillation method (Nihon Koden Kogyo Ltd.).

Blood samples were drawn from the brachial artery and oxygen tension ($Pa_{O_2}$), carbon dioxide tension ($Pa_{CO_2}$) and pH were analyzed (ABL-3, Radiometer Co., Copenhagen, Denmark).

In all subjects MEFV curves were obtained while breathing air and repeated after three slow vital capacity maneuvers with low density gas of 80% He + 20% $O_2$ (Fig. 1)[18,21]. MEFV curves were recorded by displaying flow against volume on the X-Y coordinates of a recorder (Model WX 4401, Watanabe, Japan) during forced expiration from TLC level to RV level. Each MEFV curve was repeated until virtually indistinguisible values were obtained. The two MEFV curves (with air and He+$O_2$) were superimposed at the RV level if the volumes were

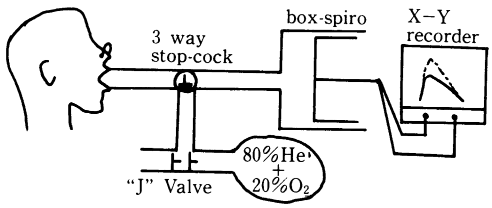


**Fig. 1.** Schematic outline of the method used to obtain MEFV curves with air and 80% helium + 20% $O_2$.

unequal. The volume at which the flow rates were identical on both air and He+$O_2$ curves called volume of isoflow (Viso$\dot{V}$), was expressed as percentage of FVC (Viso$\dot{V}$/FVC).

The responses to breathing He+$O_2$ at $\dot{V}_{50}$ and $\dot{V}_{25}$ were calculated as follows:

$$\frac{\text{flow with He} - \text{flow with air}}{\text{flow with air}} \times 100$$

and were expressed as $\Delta\dot{V}_{50}$ and $\Delta\dot{V}_{25}$, respectively. Fig. 2 shows the MEFV curves with air and He+$O_2$ and appearence of Viso$\dot{V}$.

To assess the distribution of ventilation, single breath nitrogen washout ($SBN_2$) was done in all nonsmokers and smokers (Fig. 3). After tidal breathing the subjects first exhaled to RV level and then inhaled 100% $O_2$ to TLC level and a slow exhalation to RV level was performed. Changes of $N_2$ concentration and volume were plotted on X-Y recorder (Hewlett-Packard, 7046 A) and $\Delta N_2$ was calculated from this $SBN_2$ curve[3].

To observe distribution of ventilation during three breaths of He+$O_2$ end-tidal helium concentration ($F_{ET_{He}}$) was measured. A Douglas bag containing 10% He, 20% $O_2$ and 70% $N_2$ was used as source of gas mixture[15]. Helium concentration was measured at the end of expiration following one, two and three slow vital capacity maneuver, inspired from the gas mixture. With the help of a mass-spectrometer (Perkin-Elmer, Model No. 1100) end tidal helium concentration was recorded in a unicorder (Nippon Denshi Kagaku, Model U-626 DS).

Following these baseline tests, the subjects inhaled aerosolized orciprenaline sulphate (Alotec®), 0.5 ml (10 mg) in 1 ml of normal saline with the help of intermittent positive pressure breathing (IPPB). Ten min after inhalation

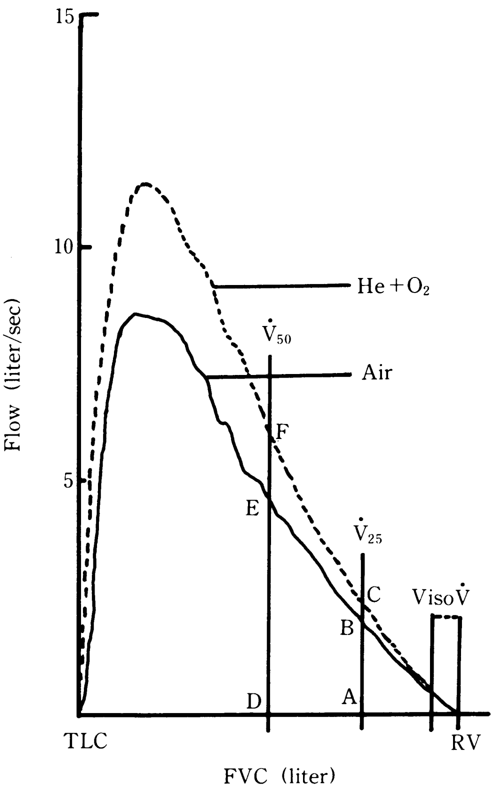


**Fig. 2.** MEFV curves with air (solid line) and after three breaths of 80%He+20%$O_2$ (dashed line). Figure shows the result in a 30 year-old nonsmoker. Iso$\dot{V}$ occured at low lung volume. AB = flow rate at 25% of MEFV curve with air, AC = flow rate at 25% of MEFV curve with He+$O_2$, DE = flow rate at 50% of MEFV curve with air, DF = flow rate at 50% of MEFV curve with He+$O_2$.

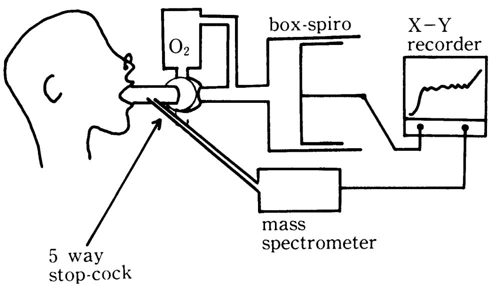


**Fig. 3.** Schematic view of the experimental set-up to perform single breath nitrogen washout.

of orciprenaline, the tests were repeated except subdivisions of lung volume, diffusing capacity and arterial blood gas analysis, which were done only before inhalation of the drugs.

On another day the same subjects were inhaled atropine sulphate, 0.05 mg/kg of the body weight, with a nebulizer (NE-U06, Omron, Japan) and the same pulmonary function tests were repeated 30 min after inhalation of atropine.

On a separate occasion, acute effects of cigarette smoking on pulmonary functions were measured in five asymptomatic smokers. The smokers abstained from cigarette smoking from the night before the day of experiment. Tests were performed in five different sets (Table 2).

**Table 2.** Sequences of study of acute effects of cigarette smoking

| Experiments | Time in min | | | | | | |
|---|---|---|---|---|---|---|---|
| | C | 0 | 5 | 10 | 15 | 30 | 60 |
| First set | T | S | T | T | | T | T |
| Second set | T | S | TO | | T | T | T |
| Third set | T | O | | TST | | | |
| Fourth set | T | A | | | | TST | |
| Fifth set | T | L | | TST | | | |

Note: C = control, T = tests was done, S = smoking a cigarette, O = orciprenaline inhalation, A = atropine inhalation, L = lidocaine inhalation. In the second set tests were repeated at 10, 30 and 60 min after inhalation of orciprenaline.

In the first set, after measurement of control parameters ($Z_{3Hz}$, $FEV_{1.0}$, Viso$\dot{V}$/FVC) the subjects smoked one cigarette in a usual way and tests were repeated immediately after smoking (within 5 min from starting of smoking) and at intervals of 10, 30 and 60 min after starting smoking.

In the second set, after control measurements subject smoked one cigarette. Tests were performed immediately after smoking and then inhaled orciprenaline. After orciprenaline inhalation, tests were repeated at intervals of 10, 30 and 60 min.

In the third, fourth and fifth sets after control measurements, the same subjects inhaled orciprenaline, atropine or lidocaine (4% lidocaine, 2 mg/kg) on different days. After inhalation of each drug, pulmonary function tests ($Z_{3Hz}$, $FEV_{1.0}$ and Viso$\dot{V}$/FVC) were done and immediately thereafter, the subject smoked one cigarette and tests were repeated again.

**Table 3.** Physical characteristics and pulmonary function tests of 8 nonsmokers and 20 asymptomatic smokers

| | | Nonsmokers | | Smokers | | p value |
|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | |
| Age | (year) | 27.6 | 4.4 | 31.2 | 7.3 | NS |
| Height | (cm) | 168.9 | 3.0 | 170.9 | 3.4 | NS |
| Weight | (kg) | 61.3 | 6.3 | 65.6 | 7.2 | NS |
| B.I. | | — | — | 285.20 | 275.80 | |
| VC | (liter) | 4.38 | 0.35 | 4.53 | 0.43 | NS |
| %VC | (%) | 106.1 | 7.2 | 109.6 | 9.6 | NS |
| FVC | (liter) | 4.41 | 0.41 | 4.54 | 0.44 | NS |
| %FVC | (%) | 106.9 | 8.5 | 109.8 | 8.9 | NS |
| $FEV_{1.0}$ | (liter) | 3.96 | 0.46 | 3.78 | 0.47 | NS |
| $FEV_{1.0}$% | (%) | 88.2 | 6.6 | 83.4 | 4.8 | NS |
| $Z_{3Hz}$ | ($cmH_2O$/liter/sec) | 2.35 | 0.39 | 3.30 | 0.70 | $<0.01$ |
| PF | (liter/sec) | 9.57 | 1.95 | 8.64 | 1.06 | NS |
| $\dot{V}_{75}$ | (liter/sec) | 7.97 | 1.74 | 7.15 | 0.97 | NS |
| $\dot{V}_{50}$ | (liter/sec) | 4.72 | 1.18 | 4.08 | 0.80 | NS |
| $\dot{V}_{25}$ | (liter/sec) | 2.03 | 0.66 | 1.47 | 0.46 | $<0.05$ |
| $\dot{V}_{50}/\dot{V}_{25}$ | | 2.41 | 0.43 | 2.95 | 0.83 | NS |
| $\Delta\dot{V}_{50}$ | (%) | 41.9 | 15.1 | 43.9 | 17.2 | NS |
| $\Delta\dot{V}_{25}$ | (%) | 26.9 | 13.9 | 19.1 | 11.5 | NS |
| Viso$\dot{V}$ | (liter) | 0.40 | 0.12 | 0.85 | 0.25 | $<0.001$ |
| Viso$\dot{V}$/FVC | (%) | 9.3 | 3.3 | 18.2 | 5.7 | $<0.001$ |
| $\dot{V}$viso$\dot{V}$ | (liter/sec) | 0.74 | 0.45 | 0.95 | 0.39 | NS |
| $\Delta N_2$ | (%/liter) | 1.47 | 0.50 | 1.69 | 0.46 | $<0.05$ |
| TLC | (liter) | 5.79 | 0.43 | 6.02 | 0.53 | NS |
| %TLC | (%) | 101.1 | 6.2 | 103.5 | 7.6 | NS |
| FRC | (liter) | 2.98 | 0.20 | 3.10 | 0.47 | NS |
| %FRC | (%) | 98.8 | 6.8 | 99.5 | 13.9 | NS |
| RV | (liter) | 1.43 | 0.14 | 1.48 | 0.29 | NS |
| %RV | (%) | 103.8 | 13.3 | 102.1 | 16.4 | NS |
| RV/TLC | (%) | 24.8 | 1.7 | 24.7 | 3.9 | NS |
| $D_{LCO}$ | (ml/min/mmHg) | 29.32 | 2.90 | 28.61 | 3.03 | NS |
| %$D_{LCO}$ | (%) | 94.1 | 8.5 | 91.8 | 9.2 | NS |
| $D_L/V_A$ | (ml/min/mmHg/liter) | 6.06 | 0.63 | 5.93 | 0.90 | NS |
| $Pao_2$ | (mmHg) | 100.0 | 10.3 | 95.6 | 7.1 | NS |
| $Paco_2$ | (mmHg) | 39.2 | 2.1 | 39.4 | 2.9 | NS |
| pH | | 7.413 | 0.03 | 7.418 | 0.02 | NS |
| $Sao_2$ | (%) | 97.7 | 0.91 | 97.3 | 0.62 | NS |
| $A\overset{ass}{-}aD_{O_2}$ | (mmHg) | 5.2 | 6.2 | 6.6 | 5.9 | NS |

Values are Mean ± SD. p value indicates significant difference between nonsmokers and smokers.

Data were analyzed statistically with paired or nonpaired students t test.

## RESULTS

Physical characteristics, smoking history and pulmonary function tests as control study are shown in Table 3. In this study, it was found that smokers had higher value in $Z_{3Hz}$ ($p<0.01$), Viso$\dot{V}$ ($p<0.001$), Viso$\dot{V}$/FVC ($p<0.001$) and $\Delta N_2$ ($p<0.05$) than nonsmokers. Although there was a significant difference in $\Delta N_2$ between nonsmokers and smokers, the mean values of $\Delta N_2$ in both groups were within normal limits as shown in Fig. 4. It was also observed that $\dot{V}_{25}$ was significantly lower in smokers than nonsmokers ($p<0.05$). In addition to these results, there were corelationships between Viso$\dot{V}$/FVC and Brinkman index (B.I.), between $\dot{V}_{25}$ and B.I. and also between Viso$\dot{V}$/FVC and $Z_{3Hz}$, shown in Figs. 5, 6 and 7 respectively.

Table 4 and 5 show the pulmonary function tests done before and after inhalation of orciprenaline and atropine in all subjects. Drugs were inhaled either with IPPB or nebulizer. But airway responsiveness was not influenced by the way of inhalation. The following results were obtained:

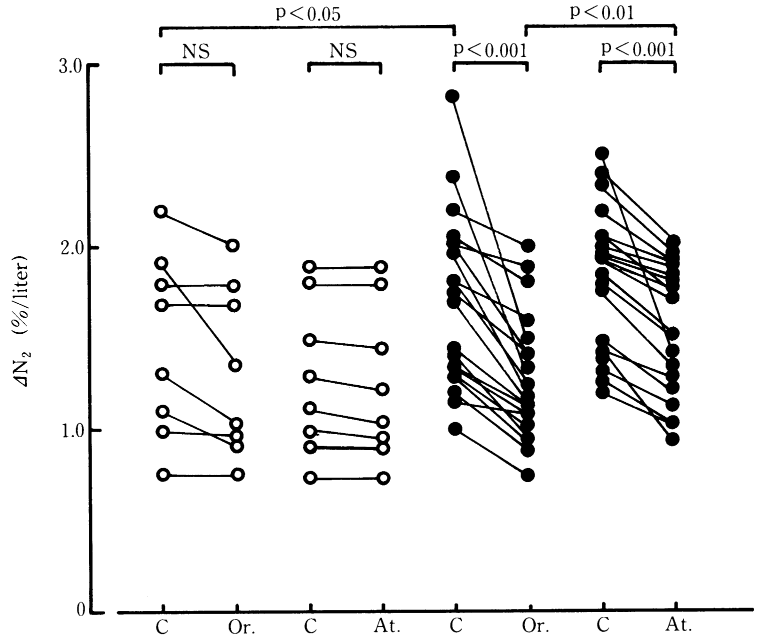


**Fig. 4.** Distribution of ventilation was measured by SBN2. Changes of nitrogen concentration was calculated from the slope of phase Ⅲ of SBN2 and expressed as $\Delta N_2$. $\Delta N_2$ was significantly higher in smokers (●——●) than nonsmokers (○——○). After inhalation of orciprenaline or atropine improved in smokers but no change was observed in nonsmokers. C = control, Or. = after orciprenaline inhalation, At. = after atropine inhalation. p value indicates significant difference.

1) Vital capacity (VC):

Orciprenaline inhalation: The mean values were 4.38 ± 0.35 liters and 4.53 ± 0.43 liters before orciprenaline inhalation in nonsmokers and smokers, respectively. After orciprenaline inhalation the values were 4.45 ± 0.44 liters in nonsmokers and 4.57 ± 0.48 liters in smokers and no significant changes were observed.

Atropine inhalation: Before atropine inhalation, VC were 4.40 ± 0.37 liters and 4.52 ± 0.44 liters in nonsmokers and smokers and after inhalation of atropine the values were 4.46 ± 0.40 liters and 4.58 ± 0.44 liters respectively. There were no significant changes after inhalation of atropine between nonsmokers and smokers.

2) Forced vital capacity (FVC):

Orciprenaline inhalation: The mean values were 4.41 ± 0.41 liters and 4.54 ± 0.44 liters before orciprenaline inhalation in nonsmokers and smokers, respectively. After orciprenaline inhalation, the values were 4.34 ± 0.48 liters and 4.55 ± 0.51 liters, respectively.

Atropine inhalation: Prior to atropine inhalation, FVC were 4.50 ± 0.35 liters and 4.54 ± 0.43 liters in nonsmokers and smokers, respectively. After atropine inhalation, the values were 4.41 ± 0.39 liters and 4.57 ± 0.43 liters, respectively. In both groups no significant changes were observed after inhalation of orciprenaline or atropine.

3) Forced expiratory volume in one second ($FEV_{1.0}$):

Orciprenaline inhalation: In nonsmokers the mean value was 3.96 ± 0.46 liters and a slight increase in mean value to 4.00 ± 0.39 liters occurred after orciprenaline inhalation, but it was not significant. In smokers this value was 3.78 ± 0.47 liters and increased significantly to 3.92 ± 0.48 liters ($p<0.01$).

Atropine inhalation: In nonsmokers, the mean value of $FEV_{1.0}$ was 3.94 ± 0.49 liters and after atropine inhalation it increased significantly to 4.05 ± 0.47 liters ($p<0.05$). In smokers it was 3.72 ± 0.43 liters and increased to 3.93 ± 0.45 liters ($p<0.001$). There was no significant difference in $FEV_{1.0}$ between nonsmok-

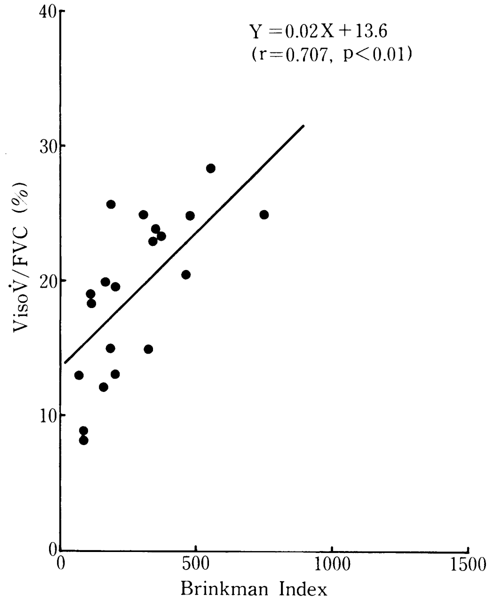


**Fig. 5.** Relationship between VisoV̇/FVC and B.I. VisoV̇/FVC increased with increasing value of B.I. ($r = 0.707$, $p<0.01$).

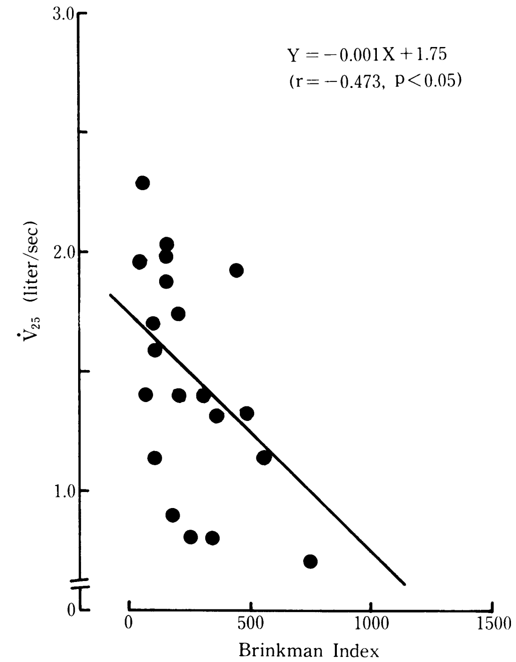


**Fig. 6.** Relationship between $\dot{V}_{25}$ and B.I. $\dot{V}_{25}$ decreased with the increasing value of B.I. ($r = -0.473$, $p<0.05$).

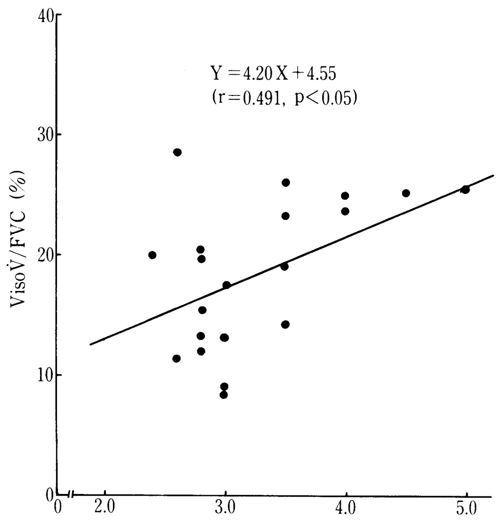


**Fig. 7.** Relationship between VisoV̇/FVC and $Z_{3Hz}$. VisoV̇/FVC increased with increasing value of $Z_{3Hz}$ ($r = 0.491$, $p<0.05$)

ers and smokers.

4) Respiratory impedance ($Z_{3Hz}$):

Orciprenaline inhalation: After inhalation of orciprenaline, $Z_{3Hz}$ significantly decreased from 2.35 ± 0.39 $cmH_2O$/liter/sec to 2.12 ± 0.39 $cmH_2O$/liter/sec ($p<0.01$) in nonsmokers and from 3.30 ± 0.70 $cmH_2O$/liter/sec to 2.68 ± 0.52 $cmH_2O$/liter/sec ($p<0.001$) in smokers.

Atropine inhalation: Again after inhalation of atropine, the value decreased from 2.35 ± 0.35 $cmH_2O$/liter/sec to 1.88 ± 0.32 $cmH_2O$/liter/sec ($p<0.001$) and from 3.30 ± 0.67 $cmH_2O$/liter/sec to 2.38 ± 0.38 $cmH_2O$/liter/sec ($p<0.001$) in nonsmokers and smokers, respectively.

Fig. 8 shows the changes of $Z_{3Hz}$ after inhalation of drugs with statistical analysis. Percentage decrease of $Z_{3Hz}$ after inhalation of orciprenaline and atropine were 9.7 ± 6.3% and 19.7 ± 6.1% in nonsmokers and 18.2 ± 6.6% and 26.0 ± 7.1% in smokers, respectively, shown in Fig. 9.

5) Flow rates:

Orciprenaline inhalation: After orciprenaline inhalation, PF and $\dot{V}_{75}$ did not increase significantly, but $\dot{V}_{50}$ increased significantly from 4.72 ± 1.18 liters/sec to 5.47 ± 1.51 liters/sec ($p<0.05$) and $\dot{V}_{25}$ increased from 2.03 ± 0.66

**Table 4.** Pulmonary function tests before and after inhalation of orciprenaline and atropine of 8 nonsmokers

| | | Orciprenaline | | | | | Atropine | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | before | | after | | p value | before | | after | | p value |
| | | Mean | SD | Mean | SD | | Mean | SD | Mean | SD | |
| VC | (liter) | 4.38 | 0.35 | 4.45 | 0.44 | NS | 4.40 | 0.37 | 4.46 | 0.40 | NS |
| %VC | (%) | 106.1 | 7.2 | 107.4 | 8.6 | NS | 106.5 | 7.7 | 107.8 | 8.4 | NS |
| FVC | (liter) | 4.41 | 0.41 | 4.34 | 0.48 | NS | 4.50 | 0.35 | 4.41 | 0.39 | NS |
| %FVC | (%) | 106.9 | 8.5 | 105.6 | 10.0 | NS | 108.8 | 8.0 | 106.6 | 8.5 | NS |
| $FEV_{1.0}$ | (liter) | 3.96 | 0.46 | 4.00 | 0.39 | NS | 3.94 | 0.49 | 4.05 | 0.47 | $<0.05$ |
| $FEV_{1.0}\%$ | (%) | 88.2 | 6.6 | 90.3 | 6.0 | $<0.01$ | 86.8 | 7.3 | 90.3 | 5.6 | $<0.001$ |
| $Z_{3Hz}$ | ($cmH_2O$/liter/sec) | 2.35 | 0.39 | 2.12 | 0.39 | $<0.01$ | 2.35 | 0.35 | 1.88 | 0.32 | $<0.001$ |
| PF | (liter/sec) | 9.57 | 1.95 | 9.94 | 2.85 | NS | 9.97 | 2.07 | 10.45 | 1.54 | NS |
| $\dot{V}_{75}$ | (liter/sec) | 7.97 | 1.74 | 8.15 | 1.29 | NS | 7.77 | 1.68 | 8.21 | 1.17 | NS |
| $\dot{V}_{50}$ | (liter/sec) | 4.72 | 1.18 | 5.47 | 1.51 | $<0.05$ | 4.75 | 1.20 | 5.69 | 1.43 | $<0.001$ |
| $\dot{V}_{25}$ | (liter/sec) | 2.03 | 0.66 | 2.26 | 0.59 | $<0.05$ | 2.09 | 0.76 | 2.18 | 0.68 | NS |
| $\dot{V}_{50}/\dot{V}_{25}$ | | 2.41 | 0.43 | 2.46 | 0.59 | NS | 2.37 | 0.40 | 2.46 | 0.50 | NS |
| $\Delta\dot{V}_{50}$ | (%) | 41.9 | 15.1 | 45.5 | 12.2 | NS | 51.8 | 19.1 | 48.9 | 14.7 | NS |
| $\Delta\dot{V}_{25}$ | (%) | 26.9 | 13.9 | 43.8 | 14.9 | $<0.01$ | 37.7 | 7.7 | 32.8 | 11.8 | NS |
| $Viso\dot{V}$ | (liter) | 0.40 | 0.12 | 0.37 | 0.14 | NS | 0.42 | 0.09 | 0.40 | 0.09 | NS |
| $Viso\dot{V}$/FVC | (%) | 9.3 | 3.3 | 8.6 | 3.6 | NS | 9.5 | 2.5 | 9.3 | 2.4 | NS |
| $\dot{V}viso\dot{V}$ | (liter/sec) | 0.74 | 0.45 | 0.73 | 0.47 | NS | 0.61 | 0.34 | 0.61 | 0.35 | NS |
| $\Delta N_2$ | (%/liter) | 1.47 | 0.50 | 1.30 | 0.47 | NS | 1.29 | 0.40 | 1.20 | 0.44 | NS |

Values are Mean ± SD. p value indicates significant difference from before inhalation values.

**Table 5.** Pulmonary function tests before and after inhalation of orciprenaline and atropine of 20 asymptomatic smokers

| | | Orciprenaline | | | | | Atropine | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | before | | after | | p value | before | | after | | p value |
| | | Mean | SD | Mean | SD | | Mean | SD | Mean | SD | |
| VC | (liter) | 4.53 | 0.43 | 4.57 | 0.48 | NS | 4.52 | 0.44 | 4.58 | 0.44 | NS |
| %VC | (%) | 109.6 | 9.6 | 110.9 | 10.7 | NS | 109.8 | 9.0 | 110.8 | 9.2 | NS |
| FVC | (liter) | 4.54 | 0.44 | 4.55 | 0.51 | NS | 4.54 | 0.43 | 4.57 | 0.43 | NS |
| %FVC | (%) | 109.8 | 8.9 | 110.9 | 11.5 | NS | 110.3 | 9.4 | 110.8 | 9.2 | NS |
| $FEV_{1.0}$ | (liter) | 3.78 | 0.47 | 3.92 | 0.48 | $<0.01$ | 3.72 | 0.43 | 3.93 | 0.45 | $<0.001$ |
| $FEV_{1.0}\%$ | (%) | 83.4 | 4.8 | 81.2 | 18.9 | NS | 81.8 | 5.1 | 82.4 | 19.0 | NS |
| $Z_{3Hz}$ | ($cmH_2O$/liter/sec) | 3.30 | 0.70 | 2.68 | 0.52 | $<0.001$ | 3.30 | 0.67 | 2.38 | 0.38 | $<0.001$ |
| PF | (liter/sec) | 8.64 | 1.06 | 9.16 | 0.93 | $<0.05$ | 8.91 | 1.20 | 9.50 | 1.10 | $<0.01$ |
| $\dot{V}_{75}$ | (liter/sec) | 7.15 | 0.97 | 7.80 | 1.02 | $<0.01$ | 6.99 | 0.75 | 8.11 | 1.05 | $<0.001$ |
| $\dot{V}_{50}$ | (liter/sec) | 4.08 | 0.80 | 4.68 | 0.85 | $<0.01$ | 3.98 | 0.77 | 4.93 | 0.96 | $<0.001$ |
| $\dot{V}_{25}$ | (liter/sec) | 1.47 | 0.47 | 1.74 | 0.54 | $<0.001$ | 1.45 | 0.46 | 1.64 | 0.46 | $<0.001$ |
| $\dot{V}_{50}/\dot{V}_{25}$ | | 2.95 | 0.83 | 2.89 | 0.81 | NS | 2.92 | 0.79 | 2.83 | 0.60 | NS |
| $\Delta\dot{V}_{50}$ | (%) | 43.9 | 17.2 | 45.1 | 17.4 | NS | 42.6 | 14.3 | 42.3 | 16.8 | NS |
| $\Delta\dot{V}_{25}$ | (%) | 19.1 | 11.5 | 28.2 | 13.8 | $<0.05$ | 22.6 | 13.2 | 24.9 | 16.5 | NS |
| $Viso\dot{V}$ | (liter) | 0.85 | 0.25 | 0.47 | 0.18 | $<0.001$ | 0.82 | 0.29 | 0.58 | 0.24 | $<0.001$ |
| $Viso\dot{V}$/FVC | (%) | 18.2 | 5.7 | 10.5 | 3.9 | $<0.001$ | 18.2 | 6.6 | 13.0 | 5.3 | $<0.001$ |
| $\dot{V}viso\dot{V}$ | (liter/sec) | 0.95 | 0.39 | 0.57 | 0.25 | $<0.001$ | 0.88 | 0.38 | 0.64 | 0.35 | $<0.001$ |
| $\Delta N_2$ | (%/liter) | 1.69 | 0.46 | 1.23 | 0.36 | $<0.001$ | 1.84 | 0.39 | 1.51 | 0.38 | $<0.001$ |

Values are Mean ± SD. p value indicates significant difference from before inhalation values.

liters/sec to 2.26 ± 0.59 liters/sec ($p<0.05$) in nonsmokers. In smokers all the flow rates (PF, $\dot{V}_{75}$, $\dot{V}_{50}$, $\dot{V}_{25}$) increased significantly as shown in Table 5.

Atropine inhalation: In nonsmokers no remarkable changes were observed in flow rates after atropine inhalation except $\dot{V}_{50}$ which increased from 4.75 ± 1.20 liters/sec to 5.69 ± 1.43 liters/sec ($p<0.001$), but in smokers PF increased from 8.91 ± 1.20 liters/sec to 9.50 ± 1.10 liters/sec ($p<0.01$), $\dot{V}_{75}$ from 6.99 ± 0.75 liters/sec to 8.11 ± 1.05 liters/sec ($p<0.001$),

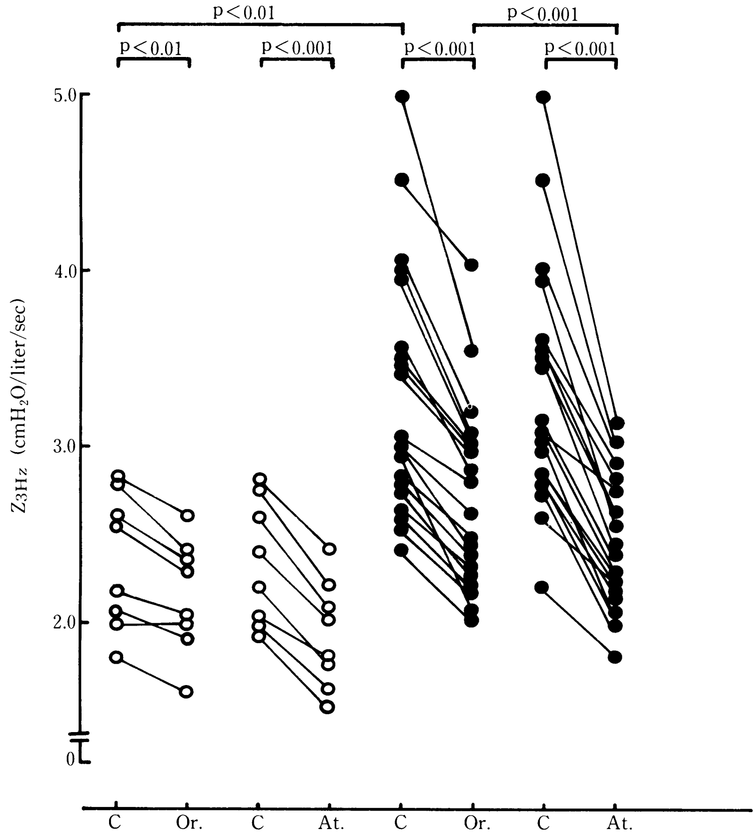


**Fig. 8.** Effects of orciprenaline or atropine on $Z_{3Hz}$ in nonsmokers (○——○) and smokers (●——●). $Z_{3Hz}$ decreased after inhalation of orciprenaline or atropine in both the groups. C = control, Or. = after orciprenaline inhalation, At. = after atropine inhalation. p values indicates significant difference.

$\dot{V}_{50}$ from 3.98 ± 0.77 liters/sec to 4.93 ± 0.96 liters/sec ($p<0.001$) and $\dot{V}_{25}$ from 1.45 ± 0.46 liters/sec to 1.64 ± 0.46 liters/sec ($p<0.001$). In nonsmokers $\dot{V}_{50}/\dot{V}_{25}$ was 2.41 ± 0.43 and 2.37 ± 0.40 before and 2.46 ± 0.59 and 2.46 ± 0.50 after inhalation of orciprenaline and atropine, respectively. In smokers the value was 2.95 ± 0.83 and 2.92 ± 0.79 before and 2.89 ± 0.81 and 2.83 ± 0.60 after inhalation of orciprenaline and atropine, respectively. No significant difference of $\dot{V}_{50}/\dot{V}_{25}$ was obtained between nonsmokers and smokers before and after inhalation of orciprenaline or atropine.

6) $\Delta\dot{V}_{50}$ and $\Delta\dot{V}_{25}$:

$\Delta\dot{V}_{50}$ and $\Delta\dot{V}_{25}$ represent the airway responsiveness while breathing air and helium. There was no significant change in $\Delta\dot{V}_{50}$ after inhalation of bronchodilators in both nonsmokers and smokers, but $\Delta\dot{V}_{25}$ increased significantly from 26.9 ± 13.9% to 43.8 ± 14.9% ($p<0.01$) in nonsmokers, and in smokers it increased from 19.1 ± 11.5% to 28.2 ± 13.8% ($p<0.05$) after orciprenaline inhalation. No change was observed after atropine inhalation.

7) Volume of isoflow (Iso$\dot{V}$):

Orciprenaline inhalation: Fig. 10 reveals the change of Iso$\dot{V}$/FVC after drug inhalations. After orciprenaline inhalation no significant change was observed in nonsmokers (it decreased from 9.3 ± 3.3% to 8.6 ± 3.6%) but it decreased significantly from 18.2 ± 5.7% to 10.5 ± 3.9% ($p<0.001$) in smokers.

Atropine inhalation: Fig. 10 shows that after atropine inhalation there was no significant change of Iso$\dot{V}$/FVC in nonsmokers (it decreased from 9.5 ± 2.5% to 9.3 ± 2.4 %). In smokers the value of Iso$\dot{V}$/FVC decreased significantly from 18.2 ± 6.6% to 13.0 ± 5.3%

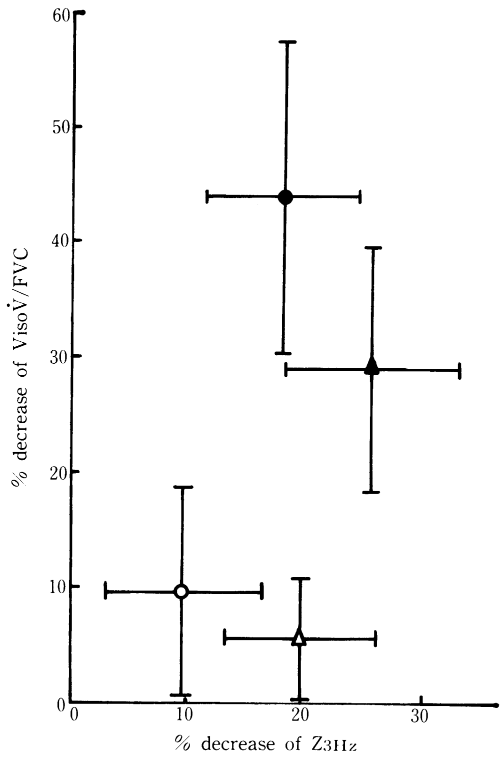


**Fig. 9.** Airway responsiveness with orciprenaline and atropine in nonsmokers and smokers. Results indicates that orciprenaline exerts its effect on both central and peripheral airways, and atropine exerts its effect predominantly on central airways.
○ = nonsmoker orciprenaline, △ = nonsmoker atropine,
● = smoker orciprenaline, ▲ = smoker atropine.

($p < 0.001$) after atropine inhalation. In comparison with the control value, percentage decrease of Viso$\dot{V}$/FVC in smokers was greater after orciprenaline inhalation (decreased 43.9% in orciprenaline and 28.9% in atropine inhalation, respectively) than atropine inhalation (Fig. 9).

8) $\Delta N_2$:

After inhalation of orciprenaline or atropine, no significant change of $\Delta N_2$ was observed in nonsmokers (it decreased from 1.47 ± 0.50%/liter to 1.30 ± 0.47%/liter after orciprenaline and from 1.29 ± 0.40%/liter to 1.20 ± 0.44%/liter after atropine inhalation). However, the value decreased in smokers significantly from 1.69 ± 0.46%/liter to 1.23 ± 0.36%/liter ($p < 0.001$) after orciprenaline and from 1.84 ± 0.39%/liter to 1.51 ± 0.38%/liter ($p < 0.001$) after atropine inhalation (Fig. 4).

9) End-tidal He concentration and distribution of ventilation ($FET_{He}$):

$FET_{He(1)}$, $FET_{He(2)}$ and $FET_{He(3)}$ were determined before and after orciprenaline inhalation in five nonsmokers and seven smokers as shown in Table 6. Tracings of one nonsmoker and one smoker are also shown in Fig. 11. $FET_{He}$ was lower in smokers especially at first $FET_{He}$, and after orciprenaline inhalation $FET_{He}$ improved in smokers. In nonsmokers, no change of $FET_{He}$ was observed after drug inhalation.

10) Acute effect of smoking on pulmonary functions:

Fig. 12 shows the mean ± SD values of $Z_{3Hz}$ before and after smoking a cigarette (above) and effect of orciprenaline inhalation after smoking (below). After smoking a cigarette $Z_{3Hz}$ increased significantly from 3.16 ± 0.35 $cmH_2O$/liter/sec to 4.14 ± 0.75 $cmH_2O$/liter/sec ($p < 0.01$) and returned to the pre-smoking level within 30 min but it did not decrease below the pre-smoking level. Inhalation of orciprenaline decreased $Z_{3Hz}$ significantly and below the control value (from 3.84 ± 0.32 $cmH_2O$/liter/sec to 2.92 ± 0.11 $cmH_2O$/liter/sec, $p < 0.01$).

Fig. 13 shows the mean ± SD values of Viso$\dot{V}$/FVC before and after smoking a cigarette (above) and the effect of orciprenaline after smoking was observed (below). Viso$\dot{V}$/FVC increased significantly after smoking (increased from 17.4 ± 6.6% to 20.6 ± 7.1%, $p < 0.01$). Then inhalation of orciprenaline decreased the value of Viso$\dot{V}$/FVC significantly from 20.6 ± 0.71% to 13.3 ± 4.9% ($p < 0.01$) and below the control value and action of orciprenaline was effective for one hr. No significant changes of $FEV_{1.0}$ were observed either after smoking (above) or after orciprenaline inhalation as shown in Fig. 14.

Furthermore, Fig. 15 shows that the mean ± SD values of $Z_{3Hz}$ reflect the acute effect of cigarette smoking with prior inhalation of orciprenaline, atropine or lidocaine. It shows that $Z_{3Hz}$ decreased significantly after inhalation of orciprenaline or atropine (decreased from 3.02 ± 0.29 $cmH_2O$/liter/sec to 2.52 ± 0.18 $cmH_2O$/liter/sec in orciprenaline, $p < 0.01$ and from 3.08 ± 0.41 $cmH_2O$/liter/sec to 2.36 ± 0.30 $cmH_2O$/liter/sec in atropine, $p < 0.01$) and after smoking a cigarette, there was a tendency for the value of $Z_{3Hz}$ to increase (increased

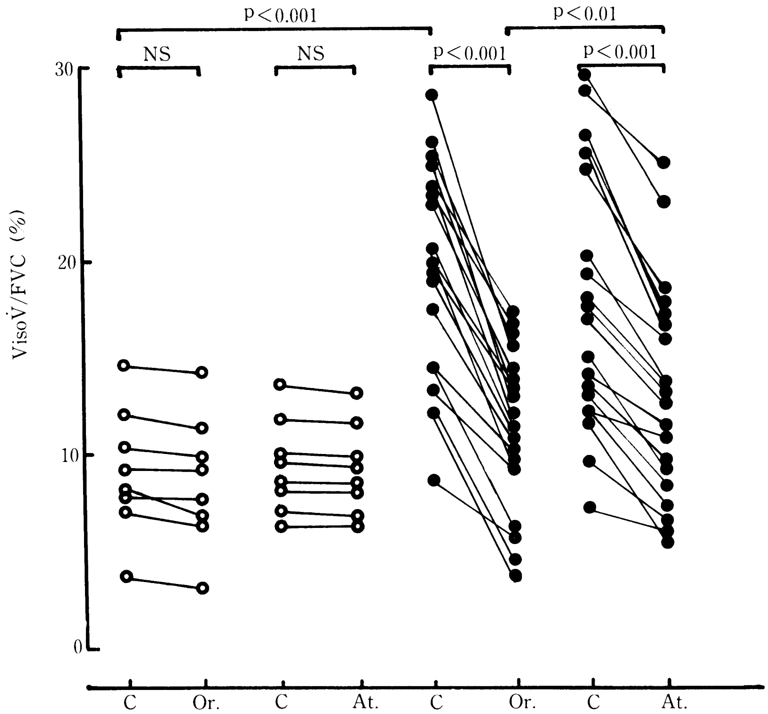


**Fig. 10.** Effects of orciprenaline or atropine on VisoV̇/FVC in nonsmokers (○——○) and smokers (●——●). VisoV̇/FVC was significantly higher in smokers and improved after inhalation of orciprenaline or atropine. No significant change was observed in nonsmokers. C = control, Or. = after orciprenaline inhalation, At. = after atropine inhalation. p value indicates significant difference.

**Table 6.** End-tidal helium concentration in nonsmokers and smokers before and after orciprenaline inhalation

| | Before orciprenaline inhalation | | | After orciprenaline inhalation | | |
|---|---|---|---|---|---|---|
| | $FET_{He(1)}$ | $FET_{He(2)}$ | $FET_{He(3)}$ | $FET_{He(1)}$ | $FET_{He(2)}$ | $FET_{He(3)}$ |
| Nonsmokers (n=5) | 7.16 ± 0.32 | 8.90 ± 0.23 | 9.68 ± 0.08 | 7.18 ± 0.31 | 8.98 ± 0.33 | 9.70 ± 0.17 |
| Smokers (n=7) | 6.38 ± 0.80 | 8.74 ± 0.56 | 9.52 ± 0.45 | 7.07 ± 0.92 | 9.00 ± 0.56 | 9.67 ± 0.36 |

Values are Mean ± SD. $FET_{He(1)}$, $FET_{He(2)}$ and $FET_{He(3)}$ = end-tidal helium concentration (%) obtained following one, two and three inhalations of a gas mixture containing 10% helium, 20% oxygen and 70% nitrogen.

from 2.52 ± 0.18 $cmH_2O$/liter/sec to 3.14 ± 0.26 $cmH_2O$/liter/sec in orciprenaline and from 2.36 ± 0.30 $cmH_2O$/liter/sec to 2.72 ± 0.41 $cmH_2O$/liter/sec in atropine). In spite of the increasing tendency, in comparison with the control value, orciprenaline or atropine significantly inhibited the acute effect of smoking on $Z_{3Hz}$. There were no changes of $Z_{3Hz}$ after inhalation of lidocaine and even after smoking.

Fig. 16 shows that VisoV̇/FVC was also decreased from 18.0 ± 6.9% to 10.3 ± 4.3% ($p<0.001$) after orciprenaline inhalation and from 17.8 ± 7.1% to 13.5 ± 5.6% ($p<0.02$) after atropine inhalation. After smoking a cigarette, there was a tendency for the value of VisoV̇/FVC to increase (increased from 10.3 ± 5.6% to 14.2 ± 6.1% in orciprenaline and from 13.5 ± 5.6% to 17.4 ± 5.7% in atropine). Although there was a tendency for the value of VisoV̇/FVC to increase after smoking with prior inhalation of orciprenaline or atropine, but in comparison with the control value, both drugs significantly inhibited the acute effect of smoking. There were no changes of VisoV̇/FVC af-

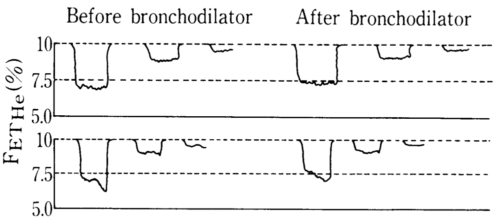


**Fig. 11.** Changes of helium concentrations during three slow vital capacity breathing maneuvers in a nonsmoker (above) and a cigarette smoker (below), before (left) and after (right) inhalation of orciprenaline. In each subject, three successive plateaus below the 10% $F_{ET_{He}}$ line represent expired concentration (%) after first, second and third breath of helium. In smoker $F_{ET_{He}}$ was lower than nonsmoker, especially at first $F_{ET_{He}}$.

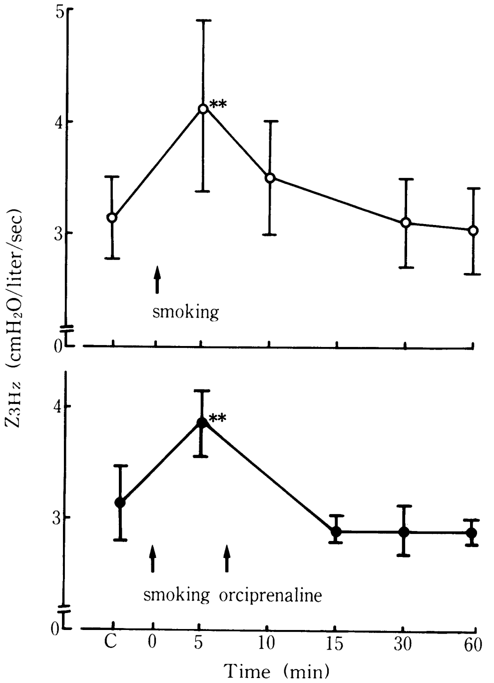


**Fig. 12.** Acute effect of smoking a cigarette on $Z_{3Hz}$ and effect of orciprenaline with time course was observed in five smokers. Changes of $Z_{3Hz}$ was significant immediately after smoking a cigarette only and the value returned to control level within 30 min (above). Inhalation of orciptrnaline after smoking decreased the value of respiratory impedance below the control rapidly (below).

** significant difference from control value. ($p < 0.01$)

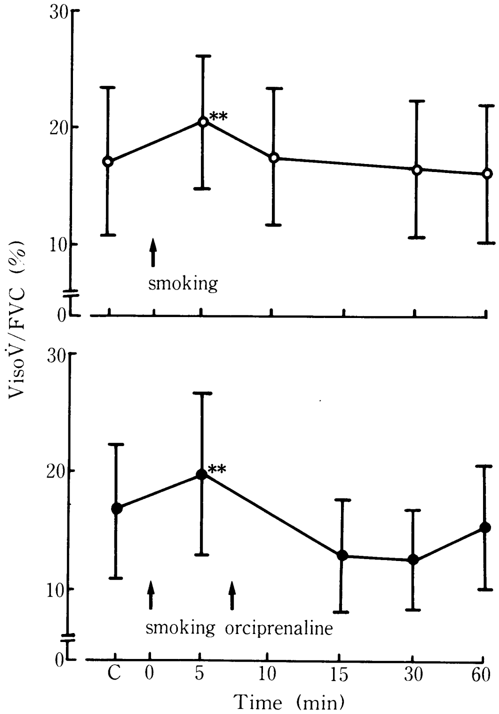


**Fig. 13.** Effect of smoking a cigarette on $Viso\dot{V}/FVC$ was significant (above). Inhalation of orciprenaline after smoking decreased the value below the control level quickly (below).

** significant difference from control value. ($p < 0.01$)

ter inhalation of lidocaine and even after smoking. Lidocaine completely prevented the acute effect of smoking in the present study.

There were no changes of $FEV_{1.0}$ after inhalation of orciprenaline or lidocaine, but inhalation of atropine significantly increased the value of $FEV_{1.0}$ from 3.73 ± 0.37 liters to 3.98 ± 0.28 liters ($p < 0.05$). No significant changes were observed after smoking (Fig. 17).

Fig. 18 shows that lidocaine inhalation neither induced bronchodilatation nor any change of pulmonary function tests followed by orciprenaline inhalation induced significant bronchodilatation.

## DISCUSSION

Mead and his associates[42] have shown that maximal expiratory flow ($\dot{V}_{max}$) at a given lung volume is determined by elastic recoil pressure (Pst) and upstream resistance (Rus). Airway resistance consists of two components, resistance due to convective acceleration (Rca) and friction-

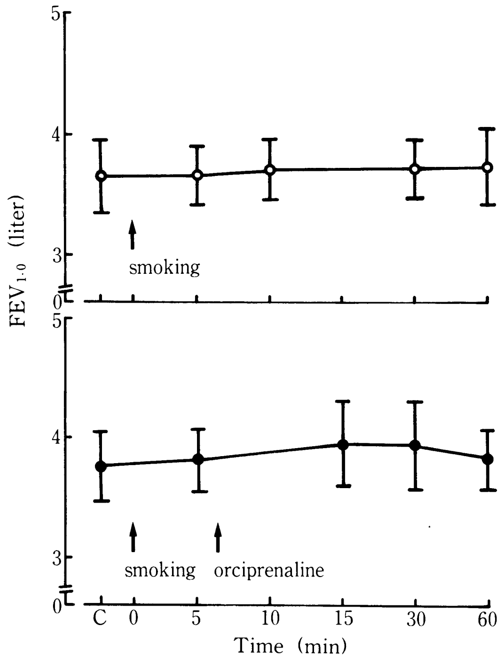


**Fig. 14.** Effect of smoking a cigarette on $FEV_{1.0}$. There was no significant change after smoking.

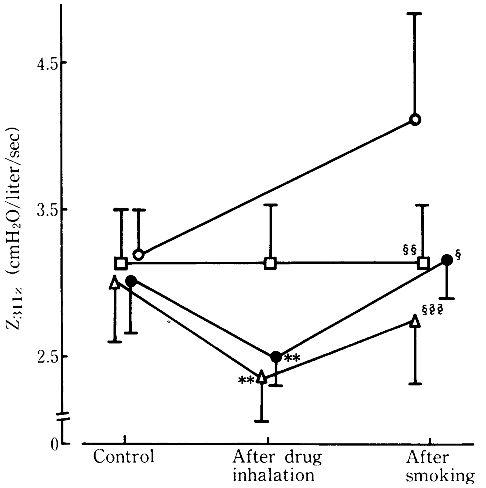


**Fig. 15.** Effect of cigarette smoking on $Z_{3Hz}$ in five smokers with prior inhalation of orciprenaline (●—●), atropine (△—△) or lidocaine (□—□). $Z_{3Hz}$ decreased significantly after orciprenaline or atropine inhalation. After that smoking a cigarette, there was a tendency to increase $Z_{3Hz}$ but in comparison with the control value (○—○) it was significantly inhibited. Lidocaine inhalation did not induce bronchodilatation and completely abolished the effect of smoking on $Z_{3Hz}$.
significantly difference from pre smoking control value (** $p<0.01$).
significantly difference from post smoking control value (§$p<0.05$, §§$p<0.01$, §§§$p<0.001$)

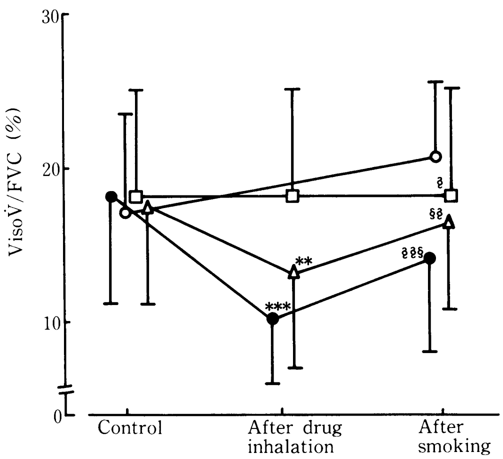


**Fig. 16.** Effect of smoking on VisoV̇/FVC in five smokers with prior inhalation of orciprenaline (●—●), atropine (△—△) or lidocaine (□—□). VisoV̇/FVC decreased significantly after inhalation of orciprenaline or atropine. After that smoking a cigarette, there was a tendency of increasing the VisoV̇/FVC value. But in comparison with the control value (○—○) inhalation of orciprenaline or atropine significantly inhibited the smoking effect. Lidocaine inhalation did not induce any change and completely abolished the effect of smoking.
significantly difference from pre smoking control value (** $p<0.02$, *** $p<0.001$).
significantly difference from post smoking control value (§$p<0.05$, §§$p<0.01$, §§§$p<0.001$).

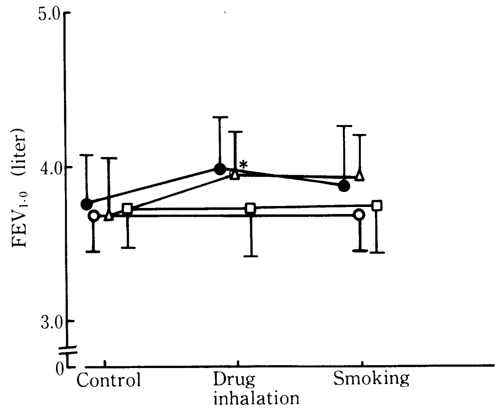


**Fig. 17.** Effect of smoking on $FEV_{1.0}$ in five smokers with prior inhalation of orciprenaline (●—●), atropine (△—△) or lidocaine (□—□). There were no significant changes after smoking in comparison with control (○—○) value but $FEV_{1.0}$ increased significantly after inhalation of atropine.
* reveals significant difference from control value ($p<0.05$)

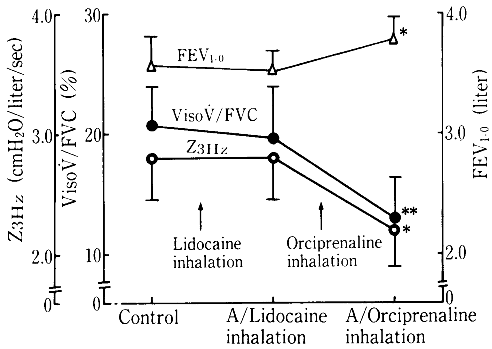


**Fig. 18.** Effect of orciprenaline inhalation on $Z_{3Hz}$, Viso$\dot{V}$/FVC and $FEV_{1.0}$ after inhalation of lidocaine in three smokers. Lidocaine did not induce bronchodilatation following inhalation of orciprenaline induced significant bronchodilatation, indicates that lidocaine inhalation did not affect bronchial smooth muscle.
significantly difference from control value (* $p<0.05$, ** $p<0.01$)

al resistance (Rfr) this relationship is represented by following equation:

$$\dot{V}max = Pst / (Rca + Rfr)...(1)$$

During forced vital capacity maneuver at higher lung volumes, equal pressure point (EPP), defines the point within the airways where intrabronchial pressure and pleural pressure becomes equal, remains predominantly in large airways and most of the resistance to airflow is due to convective acceleration and turbulence, both of which are density dependent[39,41,42,63].

Furthermore, it has been known that resistance due to laminar flow predominates over resistance due to Rca at low lung volumes. Since, resistance due to laminar flow is inversely proportional to the square of the cross-sectional area, Rus is markedly reduced in small airway because the cross-sectional area is considerably increased. Flow at the lower lung volumes should be paid attention as a marker of detecting lesion in small airway. Macklem and Wilson[41] have also demonstrated that the movement of EPP occured below 25% of VC in normal person. Following increase in resistance offered by upstream airways and loss of elastic recoil due to disease or aging, the EPP moves further towards the alveoli and may be located in small airways following the decrease of expiratory flow at a given lung volume[41,42].

As mentioned above, Rca and turbulence is density dependent and resistance due to laminar flow is viscosity dependent. Therefore, reduction of gas density after breathing helium decreases the Rus and turbulence and improves the flow as shown in Fig. 2. However, because Rfr tends to predominate at lower lung volumes and laminar component tends to increase, flow at lower lung volumes will become more viscosity dependent. $He+O_2$ mixture has lower density than air but viscosity of that is not so different. Therefore, flow at MEFV curve with air and $He+O_2$ becomes identical at lower lung volumes, that is the mechanism of occurring volume of isoflow. This study shows that $\dot{V}_{25}$ was significantly lower in smokers than in nonsmokers ($p<0.05$) and although Viso$\dot{V}$/FVC was less than 10% (mean) in nonsmokers, however, in smokers Viso$\dot{V}$/FVC was 18.2% (mean). It was significantly higher than nonsmokers ($p<0.001$). The higher value of Viso$\dot{V}$/FVC obtained in smokers may be due to two reasons, from equation (1), these are: 1) increased upstream resistance and 2) loss of elastic recoil pressure of the lung. However, the smokers of this study were young except one who was 53 years old. There was no past history of cough or sputum production and they were free from COPD because of their normal $FEV_{1.0}$ and $D_{Lco}$ and their response to bronchodilators[60]. In this study, peripheral airways dysfunction in smokers was detected by higher Viso$\dot{V}$/FVC value which was probably due to increased Rus rather than to loss of elastic recoil pressure[21].

Moreover, distribution of ventilation is also an important marker of airway dysfunction. It has been reported that there was impairment of distribution of ventilation in smokers[57]. Distribution of ventilation was measured by slope of phase III of $SBN_2$ washout ($\Delta N_2$) and it was significantly higher in smokers ($p<0.05$). $F_{ET_{He}}$ was also measured and it was lower in smokers than nonsmokers. There are three possible explanations for this observation: 1) a relatively larger residual volume (RV) in smokers leads to greater overall dilution of inhaled helium, 2) uneven ventilation results in lower helium concentration at late expiration and 3) disturbance of mixing in the lung. But RV did not differ between nonsmokers and smokers (Table 3). Therefore, difference and disturbance in distribution of ventilation might be due to increased Rus.

It has been established either by pulmonary function tests or pathological examinations that smoking causes changes in peripheral airways. Thus, airway dysfunctions detected in smokers seemed to be 1) narrowing of the peripheral airways and 2) disturbance in distribution of ventilation. Though there was a difference in distribution of ventilation between nonsmokers and smokers, no significant relationship was observed between $Viso\dot{V}/FVC$ and $N_2$. Moreover, Dosman et al[13] have suggested that distribution of ventilation might influence the response of maximal expiratory flow inhaling $He+O_2$. Fairshter and his associates[15] have observed that distribution of ventilation also influced $Viso\dot{V}$. Furthermore, $Z_{3Hz}$ was higher in smokers and there was a good relationship between $Viso\dot{V}/FVC$ and $Z_{3Hz}$ ($r = 0.491$, $p < 0.05$).

According to Bode and his associates[8], abnormalities in pulmonary function in smokers were reversible at least in part following cessation of smoking. McFadden and Linden[45] demonstrated an improvement of maximal mid-expiratory flow rates in 21 of 25 smokers treated with prolonged oral bronchodilator. In the present study it was also evaluated that the pulmonary airway dysfunctions in smokers were reversible after inhalation of a single dose of orciprenaline or atropine. Namely, $Viso\dot{V}/FVC$ was significantly decreased from the control value and flow-rates of MEFV curve were increased. Distribution of ventilation was also improved.

The data presented in Tables 4 and 5 suggest that there is a greater improvement in $FEV_{1.0}$ and $Z_{3Hz}$ in response to atropine than to orciprenaline and a moderately greater improvement of $Viso\dot{V}/FVC$ and flow-rates at low lung volumes after inhalation of orciprenaline. Thus, orciprenaline appears to exert its effect upon both large and small airways and atropine exerts its effect predominantly on large airways. Moreover, the acute response and reversibility of pulmonary airway abnormalities by orciprenaline may suggest that the narrowing of the peripheral airways is due to bronchospasm rather than to mucus plugging or mucosal edema[51].

Nakamura et al[52] measured the central and peripheral airway resistance simultaneously and reported that cigarette smoke inhalation in vagus intact dogs increased the peripheral resistance (Rp) to 239% of the control value and the central resistance (Rc) increased to 112%, but in bilateral vagotomized dogs, Rp increased to 143% and Rc increased to 104%. They concluded that cigarette smoking mainly increased Rp via vagal reflex. According to Sellick and Widdicombe[58,59], lung irritant receptors are complexes of nerve terminals that ramify beneath and between the cells of the airway epithelial lining.

Their histological structure and site are consistent with their sensitivity to intraluminal chemical and mechanical irritant stimuli. They are stimulated by a variety of conditions and cigarette smoke is one of them[47,48,58]. Stimulation of irritant receptors by dust and irritant gases such as ammonia, sulfur dioxide and smoke cause vagal reflex hyperpnea and vagal reflex bronchoconstriction in man and other experimental animals[47,48,50,51,55,59]. Nadel and Comroe[51] have found a decrease in sGaw within one minute after starting to smoke a cigarette and observed the response from 10 to 40 min and they have suggested that the response was due to vagal stimulus reflex by smoke particles similar to that initiated by dust particles rather than nicotine, because inhalation of the latter in aerosol form did not elicit bronchoconstriction[14].

In this study, the main cause of airway dysfunctions for smoking might be due to smoke particles rather than nicotine through vagal reflex. Hawkins et al[24] showed that guinea pig tracheal response to nicotine was unaffected by atropine.

Since, the changes of airway dysfunctions due to smoking seemed to be reversible, acute effect of cigarette smoking on pulmonary function tests was also investigated. According to Rees et al[56] reproducible changes of airway resistance occurred within 30 seconds of smoking. Subjects of the present study smoked a cigarette in a usual way and immediately thereafter a significant response on $Z_{3Hz}$ and $Viso\dot{V}/FVC$ was observed. The acute increase of $Z_{3Hz}$ and $Viso\dot{V}/FVC$ after smoking decreased to the control level within 10 to 30 min. Inhalation of orciprenaline after smoking decreased the values below the control level which was maintained for

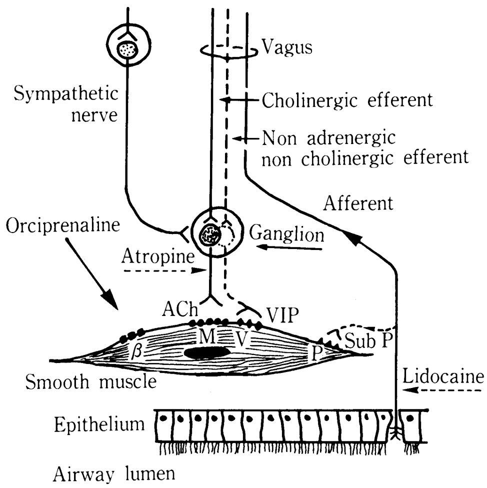


**Fig. 19.** Innervation of human airway smooth muscle: the three components of the autonomic nervous system. In addition to classical adrenergic and cholinergic nervous system, there is a third component to the autonomic nervous system shown by the dashed lines. The non-cholinergic, non-adrenergic pathways is inhibitory to airway smooth muscles, the neurotransmitter of which is likely to be an intestinal peptides (VIP). There may also be an excitatory non-cholinergic pathway, which may consists of collateral branches of afferent nerves which release substance P. Specific receptors for these neurotransmitters present on airway smooth muscle cells.

Figure drawn originally by Barnes, P.J.[7] was modified partially by the author.

β = adrenergic receptor, M = muscarinic cholinergic receptor, V = VIP receptor, Sub P = substance P, P = substance P receptor, ACh = acetylcholine. ------► = site of effect of drugs.

one hr. In addition, inhalation of orciprenaline or atropine prior to smoking significantly inhibited the acute effect of smoking. Why were there airway responses after smoking in subjects previously treated with orcipranaline or atropine? it is known that orciprenaline is a beta adrenergic agonist drug, activates adenyl cyclase, increases cAMP and produces smooth muscle relaxation. Since smoking causes further secretion of acetylcholine from post ganglionic nerve endings, it induces contraction of smooth muscles. Atropine is a competitive antagonist of acetylcholine which could not completely block the acute effects of smoking. The following reasons may be given: 1) The dose of atropine used in this study (0.05 mg/kg) was insufficient to completely antagonize acetylcholine secreted after smoking. 2) atropine is not a ganglion blocker. 3) The noncholinergic afferent stimulatory pathways are present in the airways. As shown in Fig. 19, it has been repoted that the noncholinergic afferent stimulatory pathway, so-called third nerve pathway, may run together with the afferent fibres of vagus nerve[7,35,36]. Stimulation of these afferent fibers releases substance P, which is a bronchial smooth muscle constrictor[7,35,36].

Lundberg[36] concluded that substance P induced contractions were resistant to atropine, suggesting a direct effect of substance P on the bronchial smooth muscle.

There are many reports on use of local anesthetics for the study of acute effects of smoke inhalation and nicotine in living animals and in bronchial smooth muscle strip preparations. It has been shown that drugs having a local anesthetic action abolishes the acute contraction of bronchial smooth muscle induced by nicotine and smoke[24,29].

In this study, lidocaine inhalation did not induce bronchodilatation and completely prevented the acute effects of smoking. There is evidence that intact vagus nerve pathways are supplied to the irritant receptors of the bronchial epithelial lining and that inhalation of lidocaine blocked the afferent pathways in vagus and prevented the reflex action of irritant receptors after smoking. There is a question of whether lidocaine inhalation also affects the bronchial smooth muscles. Although in the present study as shown in Fig. 18 lidocaine inhalation did not induce bronchodilatation, following inhalation of orciprenaline induced significant bronchodilatation. This indicates that lidocaine did not affect bronchial smooth muscles in the subjects of this study.

Based on the results of this study, the author have concluded that pulmonary airway dysfunctions in asymptomatic cigarette smokers were due to bronchospasm causing narrowing of the peripheral airways and difference in distribution of ventilation. All these abnormalities were reversible after inhalation of orciprenaline or atropine and cholinergic nerve plays an important role in peripheral airway dysfunctions in smokers.

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