Breathing 30 per cent oxygen attenuates bronchial responsiveness to methacholine in asthmatic patients

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ABSTRACT: The effect of breathing 30% oxygen on bronchial responsiveness to inhaled methacholine was studied in 30 asthmatic patients using a direct graphical recording method. An aerosol of methacholine solution was inhaled during tidal breathing by measuring respiratory resistance (Rrs) continuously, and dose-response curves were obtained on two separate days during air and 30% oxygen inhalation. Oxygen inhalations for 20 min caused no change in baseline Rrs. The threshold dose of methacholine, the dose which increased Rrs from the baseline value while breathing 30% oxygen, increased significantly compared with that while breathing air (P<0.01). No significant difference was found between the mean values of the slopes of the dose-response curves of the two groups. End-expiratory oxygen concentration (FETO) during air breathing decreased significantly from 13.7% to 12.0% at the point where methacholine dosage reached threshold. This study suggests that hyperoxia attenuates the bronchial responsiveness to methacholine in asthmatic patients.


It has been shown in dogs that inhalation of 10-15% O2 in N2 is followed by bronchoconstriction [1, 2]. The magnitude of the airway response depended on the degree of hypoxaemia. Astin et al. [3] have shown that administration of 30% oxygen in N2 to patients with chronic obstructive lung disease (COLD) decreases airway resistance in healthy subjects [4]. Lusby et al. [5] reported that breathing 30% O2 relieved hypoxia-induced bronchoconstriction in patients with COLD. In anaesthetized dogs, arterial O2 tension has been reported to decrease from 13.3±0.9 to 8.7±0.5, and from 12.9±0.9 to 7.6±0.3 kPa after inhalation of histamine aerosol (2% solution; 5 breath) in the control state and after ozone exposure, respectively [6].

There have been no reports as to whether administration of higher oxygen concentrations reduces bronchial responsiveness. Therefore, we undertook the present study, to examine the effect of higher concentrations of O2 on bronchial hyperresponsiveness in asthmatic patients by comparing dose-response curves during inhalation of air and 30% O2, obtained on two separate days in random sequence.

**Patients and methods**

We studied 30 mild asthmatic patients (15 males and 15 females) who had been diagnosed on the basis of the criteria of the American Thoracic Society [7]. All patients had a history of episodic dyspnoea with wheezing and a documented increase in forced expiratory volume in one second (FEV1) of more than 20%, either spontaneously or after medication. None had any other respiratory or cardiovascular disease. Clinical and pulmonary function profiles for the 30 patients studied are shown in table 1. Their ages ranged from 14 to 69 years (39.0±15.6 Mean±SD). Of these, 5 patients were ex-smokers (4.5-52 packs per year) who had stopped more than 1 year previously, 2 were light smokers (3-4 packs per year), and the remainder had never smoked. At the time of the study, asthma symptoms were either absent or well controlled with a minimum of medication. Thirteen subjects were taking small amounts of medication, but none were receiving steroid therapy. Theophylline type drugs, beta-stimulants, and xanthine-containing drinks were withheld for at least 12 hr (usually for 24 hr) prior to each visit, while other medications were continued. In these patients the same withdrawal of the drugs was repeated in the second study day. The study was approved by the Committee for Human Research of the Tohoku University School of Medicine. All subjects gave their fully-informed consent.

Direct graphical recordings of respiratory resistance (Rrs) to inhaled methacholine (Wako Pure Chemical Industries, Osaka, Japan) during air or 30% oxygen breathing were obtained using an automated system (TCK-6100H, Chest, Tokyo, Japan), as described...
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previously [8, 9]. The equipment consists of an aerosol delivery system, a loud speaker generating 3 Hz oscillatory pressure and an analog system for computing Rrs from mouth flow and mouth pressure (fig 1).

Twelve nebulizers for drug delivery (Bird, only 4 shown in fig 1) were connected to the main tube between the mouth and the flowmeter. The output of the nebulizers was maintained at 0.14-0.15 ml·min⁻¹. The aerosol particles were 9 µm in median diameter and 11 ± 6 µm (±sd) in mean diameter [8]. The nebulizers were switched on sequentially at constant time intervals of 1 min to provide increasing levels of drug concentration to the subject.

Table 1. - Clinical and pulmonary function data in subjects' in the main tube close to the mouthpiece were monitored continuously with a polarographic O₂ and an infrared CO₂ analyser (IH21A, Sanei, Tokyo, Japan).

The inspiratory O₂ concentration (FiO₂) was raised to 30% by mixing humidified 100% O₂ warmed to room temperature (24±2°C) in a 30 l flaccid balloon. The mixed gas was carried to the mouthpiece by a circulating pump producing a steady flow. To maintain FiO₂ at 30±2%, 100% O₂ was admitted manually into the balloon whenever a decrease in FiO₂ was noted.

Airflow at the mouth (V) was measured with a Fleisch pneumotachometer with a differential pressure transducer (MP 45 ± 0.5 kPa Validyne, Northridge, U.S.A.). This was calibrated using two different gas mixtures (air, 30% O₂-air) with the flow reference of the spirometer in the steady state. The degree of agreement between the two flow measuring systems was tested [10]. The flow difference between the two methods with air was y=0.03±0.03(±sd) l·s⁻¹, and with 30%O₂ y=0.01±0.03(±sd) l·s⁻¹; thus, these flow measuring methods can be interchanged.

Mouth pressure (Pao) was obtained from another

Table 1. - Clinical and pulmonary function data in subjects'
pressure transducer (Validyne, MP 45±49 kPa). Rrs was then calculated with an analog computer according to the method described by HYATT et al. [11]. Tidal volume and minute ventilation were obtained by integrating the flow signals of both air and 30% O₂.

On the first experimental day, baseline Rrs was measured. Forced vital capacity (FVC) and forced expiratory volume in one second per FVC (FEV/FVC, %) were then obtained using a dry sealed spirometer (OST80A, Chest, Tokyo, Japan). FVC was expressed as a percentage of the predicted value [12]. Ten minutes after spirometry, to avoid the effect of bronchoconstriction with deep inspiration [13], Rrs was remeasured in order to check the change in Rrs. Ten minutes after spirometry did not usually differ from that obtained before (within±0.1 kPa l·s⁻¹). Rrs was then measured for 20 min to ensure the stability of the control value of respiratory resistance (Rrs cont) during inhalation of saline, with the subjects breathing either air or 30% O₂. The methacholine challenge test was then performed during tidal breathing which was modified by the former method [14]. When Rrs had increased to about 200% of the control value, a bronchodilator aerosol, metaproterenol (2% solution) (Nippon Boehringer Ingelheim, Kawanishi, Japan), was administered to reverse the bronchoconstriction.

The same procedure was repeated within 5 days with the subject breathing the alternate Fio₂. Data from subjects, whose Rrs differed by more than 0.2 kPa l·s⁻¹, or whose FVC differed by more than 10% from the baseline of the previous study day, were excluded and restudied. The two separate test measurements were performed at the same time in the morning.

In another 5 asthmatic subjects the arterial blood gas tension was studied just before methacholine challenge and just after the start of Rrs increase by inhalation of methacholine during air breathing. The mean values of %FVC, FEV/FVC%, Pao₂, Paco₂, Rrs, Dmin and SGrs/Gr were not significantly different from those of the 30 patients in table 1. Arterial Pao₂, Pco₂, and pH were determined with a pH blood gas analyser (pH/Blood gas analyzer 213, Instrumentation Laboratory, Lexington, Mass. U.S.A), while subjects breathed room air.

After the dose-response curve was obtained, the following parameters were calculated: Dmin is the minimum cumulative dose of methacholine required to induce a steady fall in Grs (the reciprocal of Rrs) [8, 9]. Thus, Dmin was regarded as the threshold methacholine dose which initiated an increase in Rrs. The reciprocal of Dmin is defined as bronchial sensitivity. We calculated the cumulative methacholine dose using a unit defined to be one minute of inhalation of aerosol solution at 1.0 mg·m⁻³ during quiet tidal breathing.

The second parameter calculated was the slope of the decrease in Grs (SGrs), SGrs = Grs/t (in l·s⁻¹ kPa⁻¹ min⁻¹). The ratio of the mean decrease in Grs in one min to the baseline Grs, is defined as the bronchial reactivity.

Each dose-response curve was analysed graphically (by eye) by two observers; one who had participated in the experiments and another who had not. Occasionally, in cases where there was not good agreement between these observers (more than 6% difference), the tracings were analysed by a third observer who cast the deciding vote.

The values are expressed as mean±st, unless otherwise stated. In addition, values of Dmin are reported as geometric means and geometric standard deviations. Statistical comparisons were made using the Student's paired t test. One-way analysis of variance was performed to determine the reproducibility of bronchial responses to inhaled methacholine. Significance was accepted at p<0.05.

To examine repeatability we took repeated measurements in eight subjects. The difference between the first and the second measurements of log Dmin against the mean values was 0.07±0.13 (mean±2so) (n=8).

Fig. 1. - Direct graphical recording system consisting of an aerosol delivery system, a loud speaker oscillator, and an analog system. A CO₂ absorber, or O₂ and CO₂ analyser, and a 30 l meteorological balloon containing a mixture of O₂ and air were connected by polyethylene tubes with three way stopcocks.

Fig. 2. - Dose-response curves obtained in subject S.C. (no. 28) while breathing air, then 30% O₂ on the second day of the experiment. Note the clear shift toward the right of the rising phase of the curve for 30% O₂ while the slopes are not much different.
The experimental data from the subjects with bronchial asthma are presented in table 2. On the first day, FVC was 108±15% of predicted, and FEV/FVC was 70±14%. Mean Pao 2 and Paco 2 were 10.5±1.0 and 5.3±0.5 kPa, respectively.

Rrs obtained 20 minutes before the onset of methacholine inhalation during air breathing, arbitrarily defined as Rrs cont (air, 0'), was 0.45±0.14 kPa l·s⁻¹. Rrs just before starting 30% O₂ breathing, and 20 minutes before the onset of methacholine inhalation during 30% O₂ breathing, Rrs (O₂, 0'), was 0.43±0.13 kPa l·s⁻¹. These values did not differ significantly, so we assumed that the basal bronchomotor tone on these two days was similar.

Figure 2 shows one example of the dose-response curves obtained with subject 28 while breathing air and 30% O₂. The rising phase of the curve for 30% O₂ is clearly shifted toward the right without much change in the slope, suggesting that only Dmin had been increased by hyperoxia. Comparison between Rrs immediately before methacholine inhalation challenge during air breathing, Rrs (air, 20'), (0.44±0.13 kPa l·s⁻¹) and Rrs immediately before methacholine inhalation challenge during 30% O₂ breathing, Rrs (O₂, 20'), (0.42±0.16 kPa l·s⁻¹), showed no significant difference (table 2). As shown in fig. 3, the mean difference between the logDmin during 30% O₂ breathing and logDmin during air breathing was 0.36±0.59, which was statistically significant (0.001<p<0.01). We conclude that hyperoxia diminishes bronchial sensitivity in asthmatic patients. However, SGrs/Grs, the bronchial reactivity, did not change statistically during hyperoxia (table 2). LogDmin during air breathing correlated significantly with logDmin during 30% O₂ breathing (p<0.01). The correlation between the difference in logDmin with 30% O₂ and logDmin with air, and logDmin with air = y=−0.54x+0.302±0.505 (SEE) (r=0.56, p<0.001). Thus, there is a tendency toward greater reduction in bronchial sensitivity with 30% O₂ in the more sensitive patients.

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Mean (sd) 0.45 (0.15) 0.45 (0.13) -0.12 (0.614) 0.23 (0.12) 0.43 (0.13) 0.41 (0.13) 0.25* (0.57) 0.27 (0.17)

* Rrs = respiratory resistance, kPa l·s⁻¹; Rrs 0' = Rrs immediately after beginning of the experiment for air or 30% O₂ breathing; Rrs 20' = Rrs at the end of 20 min's air or 30% O₂ breathing and immediately before onset of methacholine inhalation test; Dmin: the reciprocal of bronchial sensitivity: the cumulative methacholine dose at the inflection point where reciprocal of Rrs (Grs) decreases linearly; SGrs = bronchial reactivity: linear slope of Grs decreased.
Neither FEV₁/FVC% or Paco₂, obtained on air breathing, nor SGRs/Grs, were significantly correlated with logDmin during 30% O₂ breathing. Ferco decreased significantly from 13.7±0.6% during methacholine challenge on air-breathing, to 12.0±0.9% at Dmin. In the additional 5 subjects, in whom arterial blood gas tension was directly measured, the Paco₂ decreased from 10.7±0.5 to 9.0±0.5 kPa. This change was significant. Paco₂ values were 5.2±0.6 and 5.3±0.5 kPa, respectively.

Neither minute ventilation nor tidal volume changed significantly during methacholine challenge.

Discusion

In this study we have demonstrated for the first time that 30% O₂ gas mixtures increase significantly the threshold dose of methacholine in asthmatic patients.

Astin et al. [3] reported that specific airway resistance decreased significantly during 30% O₂ administration in patients with COLD. Judging from the response to atropine, they suggested that the mechanism of hypoxemia causing an increase in airway resistance in patients with COLD would be similar to that described in dogs by Nadel et al. [1]. The latter authors suggested that changes in arterial oxygen tension might act through a reflex with the carotid body chemoreceptors and glossopharyngeal nerves as the afferent pathway, and that the magnitude of the airway response depends on the degree of hypoxemia. The mean Paco₂ and Pao₂ during air breathing in five subjects in Astin’s paper was 8.1±1.5 kPa and 6.8±1.1 kPa, respectively, the former increased to 13.7±3.1 kPa and the latter to 7.5±1.4 kPa when breathing 30% oxygen for 20 minutes. However, in our present study, mean Rrs did not significantly decrease on breathing 30% O₂ for 20 min. The mean Pao₂ before 30% O₂ breathing was 10.5±1.0 kPa which was almost normal compared with the 8.1±1.5 kPa of the patients with COLD in Astin’s study. Therefore, we believe that in our study the reflex was not great enough to cause significant bronchoconstriction during air breathing and that significant bronchoconstriction failed to occur during the 20 min administration of 30% O₂.

Many investigators, such as Ramsdale [15], have suggested that the degree of methacholine responsiveness may be misleading in subjects with underlying obstruction. In the present study, Rrs (air, O₂) and Rrs (O₂, O₂) were not statistically different; therefore the basal bronchomotor tone of the subjects at the time of measurement of bronchial response to inhaled methacholine should have been comparable on the two separate experimental days. In those 14 patients who had FEV₁/FVC ratios of more than 70%, the methacholine Dmin during 30% O₂ inhalation increased significantly (p<0.01). Furthermore, even in the 21 patients (No. 2, 6, 10, 12–20, 23, 24, 26–29) whose mean Rrs decreased by less than 15% on breathing 30% O₂ for 20 min, the methacholine Dmin increased after the 30% O₂ (p<0.05). This suggests that the change in Dmin is not caused by the change in the basal bronchomotor tone.

A change in the pattern of breathing could be thought to change the Dmin during the breathing of 30% O₂. However, as minute ventilation and tidal volume were unchanged during the breathing of either air or the 30% O₂ gas mixture, it is unlikely that the pattern of breathing was changed.

It is reported that acute isocapnic hypoxia increases lung volume in man [16, 17]. Usually, the dose response relationship to methacholine (MCh) is markedly lowered by increasing lung volume in both normal humans [18] and the cat [19]. However, in the present study Dmin was increased by higher oxygen inhalation. Thus, the increase in Dmin cannot be explained by the change in lung volume accompanied by hypoxemia.

A significant decrease in Ferco was observed during methacholine inhalation challenge and air breathing, from 13.7±0.6% at the onset of inhalation to 12.0±0.9% at the increase in Rrs (Dmin). This would correspond to a decrease of Pao₂ of about 1.6 kPa. Our direct measurement of blood gases in the additional asthmatic patients also proved that a significant decrease in Pao₂ (10.7±0.5 to 9.0±0.5 kPa) occurs at the increase in Rrs. Therefore, one may speculate that methacholine inhalation during air breathing would have decreased Pao₂ in the primary series of experiments and hypoxaemia would be relieved by 30% O₂ inhalation.

Several factors may have enhanced bronchoconstriction in the methacholine inhalation challenge during air breathing; first, the direct action of hypoxemia on bronchial smooth muscle, second, stimulation of irritant receptors by airway contraction or by histamine release from mast cells [20] to increase vagal tone, and third, the hypoxaemia mediated vagal reflex via carotid body.
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chemoreceptors [6, 21]. With respect to the first possible mechanism, Stephens et al. [22] reported that hypoxia impairs the contractile function of airway smooth muscle in the canine trachea. Impairment of power production as reflected in changes in the force-velocity relationship proved to be inversely related to oxygen tension. Further, Koosser et al. [23] hypothesized that in hypoxia, the endogeneous substrate and energy stored are depleted with a concomitant decrease in active processes such as tension development and calcium accumulation. These reports obviously cannot explain our observation of an augmentation of airway constriction in the hypoxic condition. The second possible explanation for our findings needs further study, for there have been few studies examining whether there is a change in the sensitivity of irritant receptors associated with hypoxia.

A more likely explanation of our findings relates to the third possibility, that is, a decrease in hypoxic reflex bronchoconstriction. It has been reported that hypoxaemia increases vagal tone via the carotid body chemoreceptor reflex, leading the bronchi to constriction [24]. It seems possible that administration of oxygen might reduce hypoxic activation of the carotid body reflex, causing a reduction of hypoxic reflex bronchoconstriction, which would reduce bronchial responsiveness to methacholine.

A recent report by Tam et al. [25] shows that isocapnic hypoxia has no effect on bronchomotor responsiveness to dry air-induced bronchoconstriction in subjects with mild asthma. Thus, the mechanism underlying the increase in airway resistance with hypoxia and, conversely, the decrease in resistance with hyperoxaemia remains uncertain, and further study is needed.

Our findings indicate that bronchial sensitivity in asthmatic patients is modified significantly by administration of 30% O2. In other words, bronchial sensitivity during air breathing, as estimated by methacholine challenge, may not reflect the true response of bronchial smooth muscle to methacholine alone.

We suggest that hypoxia induces a decrease in responsiveness by preventing hypoxia following methacholine challenge. However, further study should be made to confirm this conclusion. The suggested studies are as follows. Hypoxia following methacholine challenge should be demonstrated in the same patients as the main study population. It should be demonstrated that 30% oxygen relieves hypoxia following methacholine challenge. It should also be demonstrated that 30% oxygen modifies the bronchial responsiveness to other agents.

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References


L’inhalation d’oxygène à 30% atténue la réactivité bronchique à la méthacholine chez les patients asthmatiques. H. Inoue, C. Inoue, M. Okayama, K. Sekizawa, W. Hida, T. Takishima.

RÉSUMÉ: L’effet de l’inhalation d’oxygène à 30 % sur la réactivité bronchique à la méthacholine par inhalation, a été étudié chez 30 patients asthmatiques au moyen d’une méthode d’enregistrement graphique directe. Un aérosol d’une solution de méthacholine a été inhalé sous volume courant. L’on a mesuré de façon continue la résistance respiratoire (Rrs), et l’on a établi les courbes dose-réponse à deux jours différents, respectivement pendant l’inhalation d’air ou d’oxygène à 30%. L’inhalation d’oxygène pendant 20 minutes ne modifie pas la résistance respiratoire de base. La dose-seuil de méthacholine, c’est-à-dire la dose qui augmente la résistance à partir de la valeur basale, a augmenté significativement pendant l’inhalation d’oxygène par comparaison avec celle obtenue pendant l’inhalation d’air (p<0.01). Aucune différence significative n’a été trouvée entre les valeurs moyennes des pentes des courbes dose-réponse dans les deux groupes. La concentration d’oxygène en fin d’expiration (PETO) pendant la respiration d’air, décroît de manière significative de 13.7% à 12.0% au moment où le dosage de méthacholine atteint le seuil. Cette étude suggère que l’hyperoxie atténue la réactivité bronchique à la méthacholine chez les sujets asthmatiques.