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UNILATERAL PROVOKED BRONCHIAL ASTHMA IN MAN *

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Ventilatory and volumetric changes during provoked asthma have been studied by several authors, using a variety of methods such as spirometry, compliance measurements, and nitrogen washout with oxygen. During an asthmatic attack the effort necessary to maintain sufficient ventilation is greater than normal, owing to the increased bronchial resistance. This increase in resistance is apparently not uniform throughout the lungs, since the nitrogen-washout pattern indicates a very pronounced unevenness of inspired gas (1).

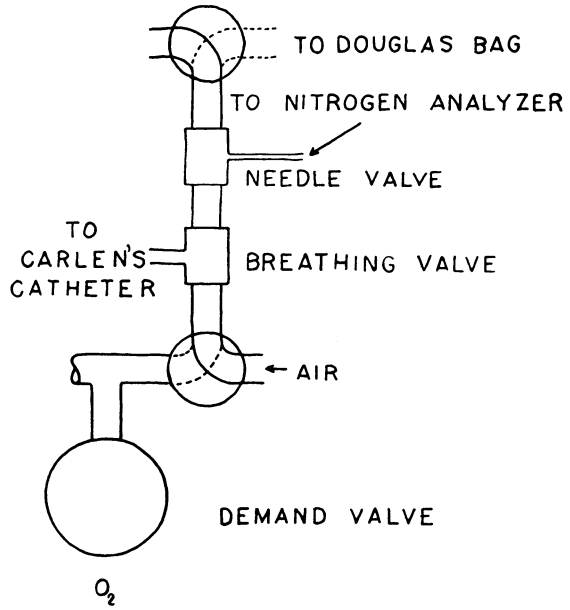

FIG. 1. DIAGRAM OF THE EXPERIMENTAL ARRANGEMENTS FOR SEPARATE LUNG FUNCTION STUDIES. The subject is connected to the system via a breathing valve with a negligible dead space. A rapid shift from air to oxygen breathing can be made, and at the same time the expired air will be directed toward Douglas bags. Air is sucked continuously from the needle valve to the nitrogen analyzer at a rate of about 20 ml per minute. Only one-half of the apparatus arrangement is shown; the demand valve is common to both sides.

In previous experiments on normal subjects we found it possible to provoke unilateral bronchoconstriction with histamine, using the same procedure as in the experiments to be described in this paper (unpublished results). The histamine effect, however, was not sufficiently long-lasting to enable us to carry out the intended measurements. For this reason asthmatic subjects were chosen for the following experiments to determine whether, by the use of allergens, an asthmatic attack could be provoked in one lung only. This attack should last long enough to allow the behavior of the affected lung to be studied and compared with that of the contralateral unprovoked lung when exposed to the same respiratory forces (of approximately normal values), and also to permit observation of the effects of epinephrine and theophyllamine on the asthmatic reaction.

EXPERIMENTAL

Case history. The experiments were made on two male volunteers, A and B, 34 and 29 years of age, with similar anamneses and allergic status. For several years they had had attacks of asthma after contact with horses. Intracutaneous skin tests with horse epidermal epithelium of 1:100 million were positive. Provocation tests with inhalation of horse epithelium were also positive. Chest X-rays were normal.

Method. Prior to the one-lung provocation experiments the sensitivity of the subjects to horse allergen was tested by causing them to inhale an aerosol, first of Coca's solution and then of increasing concentrations of horse epidermal epithelium dissolved in Coca's solution, until a slight asthmatic attack was provoked. (Composition of Coca's solution: KH_2PO_4, 3.64 g; $Na_2HPO_4 \cdot 2\ H_2O$, 14.3 g; NaCl, 50 g; 0.4 per cent solution of phenol, 1,000 ml; distilled water ad 10,000 g.) The solution to be inhaled was nebulized in an inhaler where the gas flow was pre-set at a fixed value of 8 L per minute. A side tube, containing about 1 L in the connection between the nebulizer and subject, stored the aerosol dur-

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ing expiration, and this arrangement ensured that a maximum of air containing aerosol reached the lungs. The amount of allergen inhaled could be varied by altering the allergen concentration or the inhalation time.

The premedication for the experiment was 7.5 mg morphine and 0.3 mg scopolamine for Subject A, and for subject B, 1.5 mg Dilaudid (dihydromorphinone) and 0.3 mg scopolamine administered subcutaneously.

Approximately 45 minutes after premedication, the throat was anesthetized with 3 ml 4 per cent lidocaine (Xylocaine) containing 2 drops of 1:1,000 epinephrine. Into the trachea and main bronchi, 4 to 5 ml 2 per cent lidocaine with epinephrine was introduced through a nasal catheter. In order to separate the two lungs, a no. 39 Carlen's double-lumen catheter was inserted, and its proper situation confirmed as described by Svanberg (2).

Before the allergen inhalation was started, a dummy experiment with Coca's solution was carried out. Since some of the drugs used to produce anesthesia counteract the allergic reaction, we found it necessary to expose the subject to allergen concentrations ten times larger than those needed to produce asthma in the sensitivity-test experiments when the subjects were not anesthetized. Two minutes was found to be suitable for inhalation of the allergen. The subject was allowed to inhale the aerosol of horse allergen nebulized by the inhaler in one lung only and room air in the other lung. Precautions were taken to protect the latter from inhalation of air contaminated with allergen.

After each inhalation period the subject was connected to two open-circuit oxygen systems, one for each lung. The nitrogen washout from the lungs was then followed breath-by-breath by means of nitrogen meters (3). The sampling needle valves to the nitrogen meters were inserted immediately distal to the expiratory side of the breathing valves; this made it possible to measure continuously the end-tidal nitrogen concentrations. During the washout period, the expired gases were collected in Douglas bags and the nitrogen accumulated was used to calculate the functional residual capacities (FRC) of the lungs. When the nitrogen content of the end-tidal air was down to 2 per cent, the washout procedure was stopped and the lung was switched to air breathing (Figure 1).

The lung clearance index or Becklake index (4)—i.e., the amount of oxygen needed to wash out 1 L of the FRC down to 2 per cent of nitrogen in end-tidal air—was calculated from the FRC and the total ventilation (in BTPS) during the washout. An increase in lung clearance index indicates a diminished ventilatory efficiency, but does not distinguish between the effect of nonuniform distribution or an unfavorable dead space/tidal volume ratio.

Semilogarithmic graphs of end-tidal nitrogen concentrations versus number of breaths (3) were plotted. This is a simplification of the original method of Fowler, Cornish and Kety, in which the amount of nitrogen given off per breath during oxygen breathing is plotted against the number of breaths (5). The curves obtained could usually be resolved into two straight lines; i.e., the lung ventilation behaved as if two exponential functions described the washout process. The nitrogen clearance delay percentage could also be calculated from the plotted curves. The delay percentage is the difference between the "average actual number of breaths" and "the average ideal number of breaths" during which a nitrogen molecule remains in the lungs before it is washed out by oxygen. These numbers can be calculated both for the actual experiment (average actual number of breaths) and for an ideal system having the same FRC, tidal volume, and dead space as the lungs of the subject, but ventilated uniformly (average ideal number of breaths). The difference between average actual and average ideal numbers of breaths indicates the delay in washout introduced by nonuniform ventilation and is expressed as a percentage of the ideal value (5). When the elimination rate of nitrogen from the asthmatic lung was very slow, the nitrogen remaining in the lung after washout was

TABLE I

Effect of unilateral provocation of bronchial asthma on lung function *

Subj.	Lung	N_2 elimination time†		FRC		Lung clearance index†		Delay percentage		Breaths per minute		Resp. minute volume				Oxygen uptake			
		b	a	b	a	b	a	b	a	b	a	b		a		b		a	
		min		*L*								*L*	%‡	*L*	%‡	*L*	%‡	*L*	%‡
	Right	2.0	1.8	2.1	2.0	7.2	5.9	45	34	10	11	7.3	54	6.0	78	0.17	55	0.22	71
A	Left	1.8	6.3§	1.7	1.8§	7.5	10.5§	83	165§			6.2	46	1.7§	22§	0.14	45	0.09§	29§
	Right	3.3	1.8§	1.8	1.9§	8.6	9.0§	47	24§	12	11	4.1	54	3.5§	40§	0.22	56	0.17§	49§
A	Left	2.6	1.2	1.8	1.7	6.7	6.9	32	0			3.5	46	5.2	60	0.17	44	0.18	51
	Right	7.7	4.2	2.8	2.8	7.9	6.4	127	0	13	13	3.6	51	3.9	66	0.20	59	0.21	64
B	Left	6.2	8.9§	2.3	2.4	9.1	13.1§	89	31§			3.4	49	2.0§	34§	0.14	41	0.12§	36§

* b = Before provocation; a = after provocation (when the unilateral "asthma" was most pronounced); FRC = functional residual capacity. All volumes in BTPS.
† See text for explanation of lung clearance index and N_2 elimination time.
‡ Per cent use of total respiratory minute volume and oxygen uptake.
§ Provoked lung.

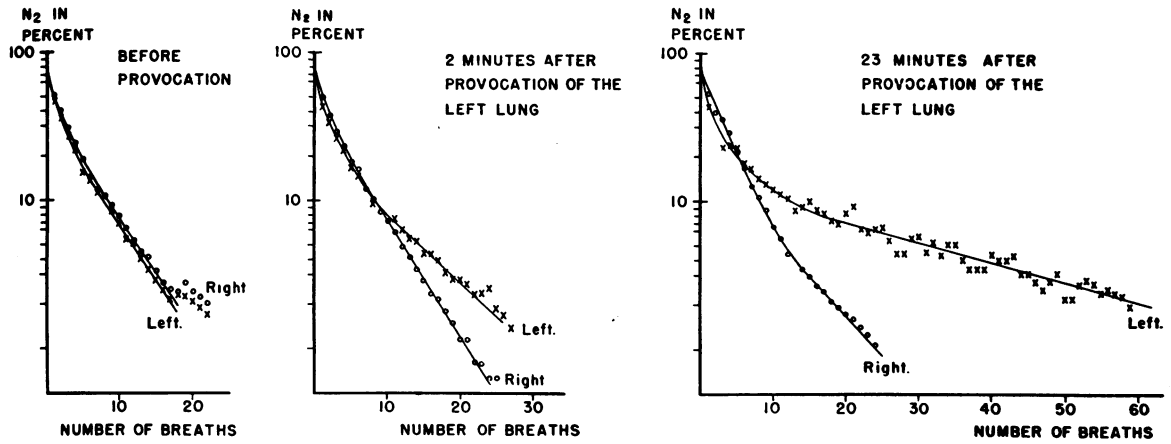

FIG. 2. NITROGEN ELIMINATION DURING OXYGEN BREATHING. Semilogarithmic graph showing how the unilateral reaction gradually increases in intensity after provocation. On the ordinate are the N_2 concentrations of the end-tidal air (Subject A).

estimated from the semilogarithmic plots of the end-tidal nitrogen concentrations and used to correct the FRC values. The usual corrections were made for nitrogen in cylinder oxygen and nitrogen eliminated from tissues (3).

When the nitrogen washout was finished for both lungs, the subject was connected to a double spirometer (Knipping type) filled with a gas mixture of about 30 per cent oxygen in nitrogen. Ventilation and oxygen uptake were then measured for a period of at least 5 minutes, and the vital capacity was determined. In two experiments on one subject the behavior of both lungs was studied when the subject held his breath after a normal expiration. On one occasion the forced expiratory volume (FEV) per second was recorded. The response to allergen was studied by repeating the nitrogen washout and bronchospirometry at suitable intervals, depending on the washout and "wash-in" time. While the asthmatic reaction was still pronounced, epinephrine or theophyllamine was given via the cubital vein, and the effect studied by means of bronchospirometry. Unilateral provocation was applied to both lungs on different occasions in Subject A, and on the left lung only in Subject B.

RESULTS

A marked effect of the allergen inhalation on the provoked lung, lasting for at least 1 hour, was noted in all experiments. The results are summarized in Table I. The values after provocation were obtained when the asthmatic reaction was most pronounced (15 to 30 minutes after provocation) (Figure 2). Nitrogen elimination time, FRC, lung clearance index, and delay percentage were derived from the nitrogen elimination curves and the amount of nitrogen eliminated. Breathing frequency, respiratory minute volume, and oxygen uptake were derived from the bronchospirometric curves. Spirometric measurements were made immediately after nitrogen elimination.

The nitrogen elimination time of the provoked lung was increased relative to the elimination time of the unprovoked lung in all experiments, and in most cases it was also prolonged relative to values obtained before provocation. The lung clearance index was moderately increased in the provoked

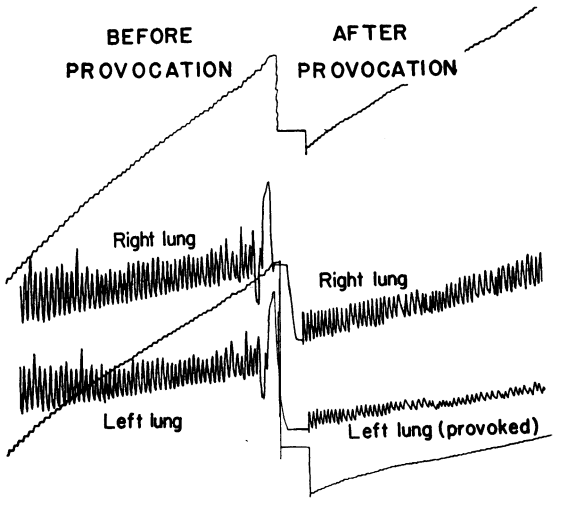

FIG. 3. BRONCHOSPIROGRAM AND VENTILOGRAM FROM SUBJECT A, BEFORE AND AFTER PROVOCATION OF THE LEFT LUNG. Ventilograms have been superimposed on the spirograms and have a common time axis. The ventilogram is the curve which increases stepwise. (Read from left to right.)

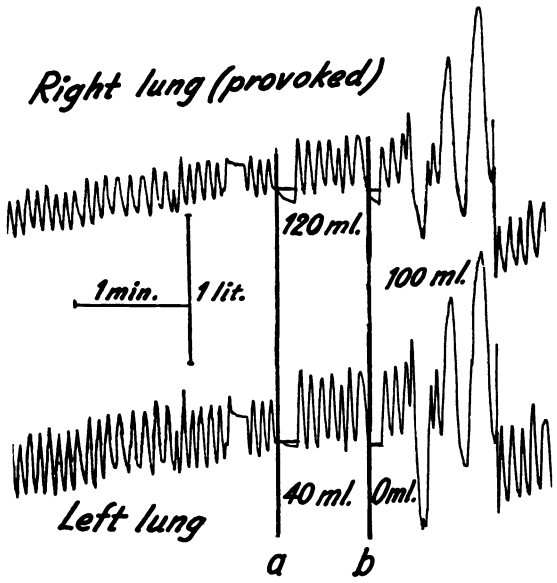

FIG. 4. BRONCHOSPIROGRAM FROM SUBJECT A, SHOWING HOW THE PROVOKED LUNG CONTINUED TO EXPEL AIR ON BREATH HOLDING AFTER A NORMAL EXPIRATION. Expiration downward. The subject was told to hold his breath at the time marked by the vertical lines a and b intercepting the spirograms. The 120 and 100 ml on the upper spirogram represent the amounts of air expelled from the provoked lung on breath holding; the 40 and 0 ml on the lower spirogram indicate air expelled from the unprovoked lung. (Read from left to right.)

lung in most measurements. In some instances no significant increase was noted but, on the other hand, the index never decreased after provocation.

Most of the nitrogen elimination curves could be resolved into two fractions, one slow and one fast. The distribution of inspired gas in the provoked lung did not show a general trend toward more pronounced unevenness, as judged from the delay percentage. No systematic changes in the magnitude of the slowly and quickly ventilated fractions could be seen.

In all experiments there was a definite decrease of oxygen uptake and tidal volume in the exposed lung, with correspondingly increased values in the control lung. The ventilation decreased relatively more than the oxygen uptake (Figure 3 and Table I). A slight increase in the FRC of the provoked lung in relation to that of the unprovoked lung was noted. A decrease was never seen (Table I).

During the bronchospirometry, two breath-holding experiments were carried out on Subject A at the end of a normal expiration. When the subject ceased to exhale, the airflow from the control lung stopped immediately, but the exposed lung continued to expel air for some seconds. The amount expelled after breath holding was about 100 cc, as can be seen from Figure 4.

When 0.1 mg epinephrine was rapidly injected intravenously during bronchospirometry, the normal distribution of the tidal volume between the two lungs was restored within 15 seconds from the end of the injection (Figure 5). The effect lasted only a few minutes, after which the asthma returned. Injection of theophyllamine gave within 30 seconds a clear but less pronounced effect, which, however, lasted considerably longer.

On Subject B a forced expiration was carried out after a maximal inspiration. The flow-rate relationship between the unprovoked and the provoked lung at an early part of the expiration was 1.4; in a later phase this relationship had increased to 3.8. In Figure 6 it can be seen that the unprovoked lung makes a small inhalation at the end of the FEV test, but no corresponding inhalation can be seen in the provoked lung.

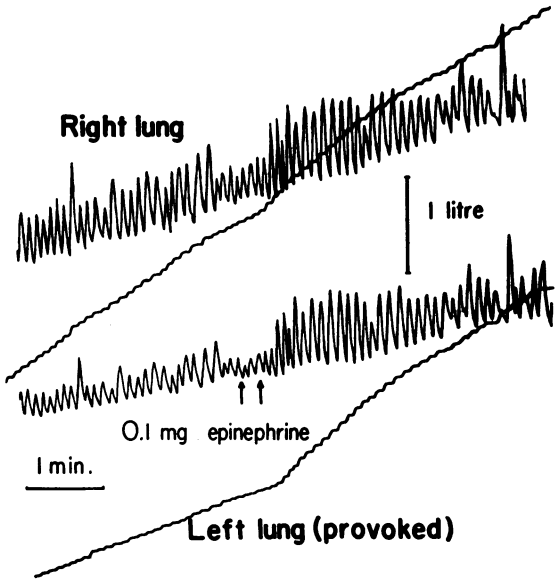

FIG. 5. BRONCHOSPIROGRAM AND VENTILOGRAM FROM SUBJECT A. Left lung provoked. Effect of epinephrine given intravenously. Injection was given between arrows. (During insertion of the needle and injection the subject involuntarily decreased his ventilation.) The effect is best seen on the ventilograms which, after injection, have almost the same slope. The volume pillar refers to spirograms. (Read from left to right.)

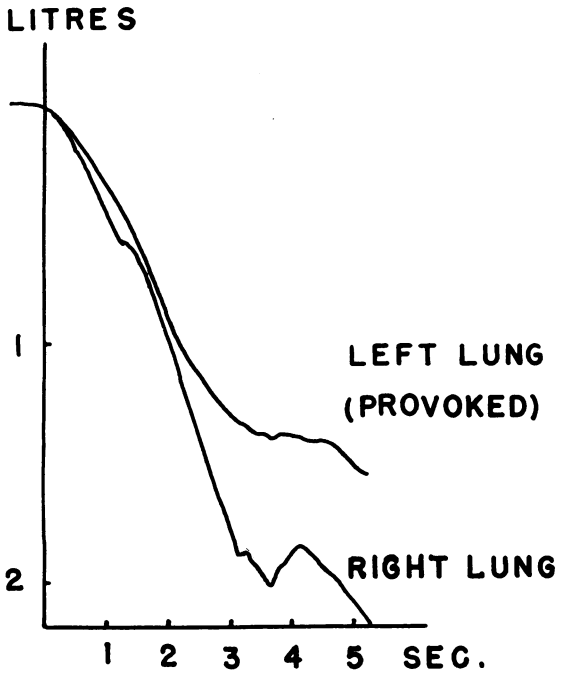

FIG. 6. DRAWING AFTER A BRONCHOSPIROGRAM FROM SUBJECT B DURING A FORCED EXPIRATORY VOLUME TEST. Immediately before the test the subject made a maximal inspiration. At time zero he began expiring with maximal force. The ordinate shows the volume of expired air, and the abscissa gives time in seconds. See text for further explanation. (The spirograms have been put into the same coordinate system to facilitate comparison.)

During the experiments Subject A was completely unaffected and no wheezing could be heard, but Subject B noted a slight feeling of oppression and a slight wheezing could be heard over the provoked lung. In all experiments the asthmatic attack ceased after about 1.5 hours, and did not recur that day or the following night.

DISCUSSION

The one-sided effect of unilateral provocation was clear and was established beyond all doubt. No signs of bronchial obstruction on the unprovoked side could be found. The possible effect of the unavoidable anesthesia on the results is very hard to judge. In any case, asthma can be provoked in a lung in spite of malfunction of its nervous elements. Nervous reflexes which spread the asthmatic attack from the provoked lung to the other either do not exist or are abolished by the surface anesthesia in the bronchial tree. Horse allergen is probably taken up by the fixed antibodies in the provoked lung and is apparently not removed by the blood stream in quantities large enough to give a measurable effect on the other lung under the experimental conditions.

The ventilatory efficiency of the provoked lung decreased, as indicated by the increase in lung clearance index. The delay percentage, however, did not increase significantly. This was unexpected, since after a bilateral provocation both delay percentage and lung clearance index usually increase. There is no reason why the effect of allergen on the bronchi should not be quite as evenly distributed during bilateral provocation. The great unevenness in distribution after bilateral provocation may be due to the large respiratory forces necessary to maintain a sufficient ventilation. It is suggested that this will dilate some of the bronchi more and thereby cause hyperventilation of some portions of the lung. The moderately increased lung clearance index in unilateral asthma would thus be an effect of an increased dead space/tidal volume ratio due to a decreased tidal volume.

The slight increase in FRC on the asthmatic side in relation to the normal side was probably caused by the increased bronchial resistance, with a slow and incomplete emptying of the exposed lung. If the breath was held at the end of a normal expiration, the asthmatic lung continued to expel gas for a few seconds, demonstrating an incomplete pressure equilization between the alveoli and the atmosphere. At the end of the breath-holding period the volume of the provoked lung had decreased by about 100 cc, canceling out the increase in FRC (Figure 4).

The resistance of the bronchi to gas flow seems to vary with the lung volume, as can be seen in the FEV experiment on Subject B, where the difference in flow rate increased with the decrease in lung volume. Further evidence of differences in bronchial resistance is seen in the same experiment, where at the end of a forced expiration the unprovoked lung makes a slight inspiration while the provoked lung is still exhaling (Figure 6).

As will be seen from Figures 3 and 4, the provoked lung apparently has a lower compliance than the unprovoked. This compliance change is only dynamic, however, since breath holding seems to restore a normal relationship between

tidal volumes. Since the gas flow from the provoked lung during breath holding had not completely stopped even after 10 seconds, it is difficult to measure the static compliance during asthma even at a very slow respiratory rate.

Subject B shows quite high FRC values that cannot be explained solely by the resistance in the Carlen's tube, which usually causes some increase in the FRC. There were probably emphysematous changes in the lungs of Subject B.

The somewhat larger decrease in ventilation relative to oxygen uptake in the provoked lung may be due to the high oxygen content of the spirometer (30 to 40 per cent oxygen in nitrogen). This would give a higher alveolar oxygen pressure than if air were breathed. Consequently, a vasoconstriction caused by low alveolar oxygen pressure will be more or less abolished, and the redistribution of blood from the hypoventilated to the unprovoked lung less pronounced. Such vasoconstriction has been shown to occur in many animals, and a few reports indicate that this mechanism is also present in human lungs (6).

It should be mentioned here that it is not theoretically correct to use the end-tidal N_2 concentrations for calculation of the delay percentage or the FRC correction. Properly, the amount of nitrogen given off per breath should be used instead. Lundin (3), and Bouhuys, Jönsson and Lundin (7) found no systematic changes between volume and percentage curves either in healthy or in emphysematous subjects; this seemed to justify the use of the much simpler percentage method in this case.

The rapid effect of epinephrine on the exposed lung (circulation time from the place of injection to the lungs plus a few seconds), indicates that under the experimental conditions the main effect of allergen is one of bronchospasm. It would seem unlikely that edema or mucous secretion could be so rapidly abolished. Arner, Wiholm and Öhnell have come to the same conclusion from the prompt abolition of hypoxia by epinephrine during a provoked asthmatic attack (8). The effect of theophylline is more gradual but it lasts longer. Thus, these findings seem to confirm the value of treating asthma with a combination of epinephrine and theophyllamine.

SUMMARY

One-sided "asthma" was provoked in two asthmatic subjects with a solution of horse epidermal epithelium inhaled as aerosol into one lung during bronchospirometry. The presence of asthma was demonstrated by a reduction of ventilation and oxygen uptake and a prolonged nitrogen elimination time during oxygen breathing. The uneveness of distribution of inspired gas did not increase significantly, but the ventilatory efficiency decreased, probably as a result of an increased dead space/tidal volume ratio in the provoked lung. No signs of asthma were noted in the unprovoked lung. Epinephrine abolished the asthmatic reaction within 15 seconds, suggesting that bronchospasm was the main causative factor for this kind of asthma. No evidence of a change in "static" compliance during asthma was found. The effect of the unavoidable anesthetic agents is discussed.

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