Pulmonary Effects of Oxygen Breathing

A 6-Hour Study in Normal Men

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The most constant early symptom of pulmonary oxygen toxicity in normal volunteers is substernal distress, which usually develops between the 12th and 16th hours. This suggests that oxygen breathing might produce an acute tracheobronchitis. The following measurements were done in 10 normal volunteers breathing 90% to 95% oxygen to detect this possibility: [1] bronchofiberscopic observations of the trachea, [2] estimation of tracheal mucous velocity, and [3] pulmonary function tests. Endoscopic evidence of tracheitis was present in all subjects at the end of 6 hours of breathing oxygen. Tracheal mucous velocity was depressed as early as 3 hours after oxygen breathing and was the most sensitive indicator of oxygen-induced tracheitis. Administration of terbutaline, a beta adrenergic stimulant, restored tracheal mucous velocity to control levels by increasing the proportion of faster moving mucous pathways.

THE COMMONEST COMPLAINT of normal humans breathing oxygen for prolonged periods is substernal distress. Generally it is the earliest symptom encountered; it occurs as early as 4 hours after the start of oxygen breathing but usually develops between the 12th and 16th hour. This suggests that oxygen breathing may produce an acute tracheobronchitis (1-4), but little or no increase of airway resistance occurs during this time (5, 6). Acute tracheobronchitis produces loss of ciliated epithelium and retention of secretions (7). Thus, depression of mucous transport might be a more sensitive indicator of tracheobronchial damage than an elevation of airway resistance. We tested this hypothesis in anesthetized dogs by measuring tracheal mucous velocity and found significant slowing of this function after 3 to 4 hours of oxygen breathing (8). If these animals were conscious, there might have been a different time course of this effect because mucous velocity is depressed by general anesthesia (9). In the present report, we discuss our study of 10 normal volunteers that confirmed the animal experiments showing that exposure to oxygen damages the tracheal mucosa as found by measurements of tracheal mucous velocity.

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Materials and Methods

SUBJECTS

Eight men and two women, ages 18 to 45 years (mean, 27 years), volunteered for the study. They gave informed consent and received financial remuneration.

PROCEDURE

The subjects came to the laboratory at 0800 after they had eaten. Their upper airway passages were anesthetized with 2% xylocaine solution, and a bronchofiberscope was introduced into the trachea through a nasopharyngeal airway (10). Tracheal mucous velocity was estimated by the cinebronchofiberscopic method (11). The bronchofiberscope was withdrawn and pulmonary function tests were obtained. Then the subject donned a full-plate face mask of the type used by scuba divers and breathed moistened oxygen through a demand valve. In preliminary experiments, it had been found that the oxygen content within this mask was 90% to 95%, with a relative humidity of 60% to 70%. Throughout the procedure the percentage of oxygen was monitored with a mass spectrometer (Model MGA-1100, Perkin Elmer, Pomona, California). Three hours after oxygen administration was begun, measurement of tracheal mucous velocity was repeated. During the run, which took about 15 minutes, the subject breathed 70% oxygen by means of a partial rebreathing mask. After removal of the bronchofiberscope, he again donned the full-plate mask and breathed 90% to 95% oxygen for an additional 3 hours. Tests of pulmonary function were repeated and then followed by a measurement of tracheal mucous velocity. The bronchofiberscope was left in situ, and 0.25 mg terbutaline (a beta adrenergic stimulant) was administered subcutaneously. Tracheal mucous velocity was measured 15 minutes after injection. After this procedure, pulmonary function was measured.

PULMONARY FUNCTION TESTS

Displaceable lung volumes were measured by spirometry. Total lung capacity was estimated by single breath helium dilution and residual volume calculated by subtracting the vital capacity. Forced expired volume delivered in one second ($FEV_{1.0}$) and flow-volume curves were measured with a high-frequency dry spirometer (Flow-Volume Converter Model 781, Ohio Medical Products, Houston, Texas). Total respiratory resistance was measured as a function of inspiratory vital capacity by using a modification of an analog computer method described by Hyatt and associates (12). Distribution of ventilation was estimated by a single breath nitrogen method (13).

TRACHEAL MUCOUS VELOCITY

Tracheal mucous velocity measurement has been fully

described in previous publications (11, 14). Only its principles and a new way of data reporting will be described here. If particles are placed on the mucosal surface, ciliary activity will carry them upwards on the mucous blanket toward the larynx. Their movement is filmed through a bronchofiberscope whose tip is located within the trachea; the particles appear larger as they approach the distal lens of the instrument. By standardizing the particle size and the film projection factor and knowing the filming speed, the velocities of the particles can be computed from their projected image size. The standard particles are obtained from Teflon® sheet by means of a punch that produces uniform discs measuring 0.68 mm in diameter, 0.13 mm in thickness, and 0.13 mg in weight. To establish the relation between the projected image size of the disc and its distance from the lens of the bronchofiberscope, measurements of the disc diameter with varying distance from the lens are made in Plexiglas® models of the trachea.

Because of variation in the velocity of particle transport by the mucous layer of the trachea, three measures of velocity are used: [1] V_{ave}, the mean velocity of all particles in a run (10 to 12) including those with zero motion, [2] V_3, the mean velocity of the three fastest particles in a given run, and [3] V_{max}, the velocity of the fastest particle in a given run. The paired variate of Student's t test was used to determine statistical significance. In addition to these measures obtained on an individual subject, a frequency histogram of all particle velocities from the 10 subjects was constructed for the following conditions: [1] control, [2] after 3 hours of oxygen breathing, [3] after 6 hours of oxygen breathing, and [4] after terbutaline administration. The pooled data at each time of measurement of tracheal mucous velocity were placed in 12 to 15 classes depending on the range of velocities. Each distribution was compared to the distribution from the base-line run. A chi-square test with K-3 (K is the number of classes) degrees of freedom was done between the observed frequencies and the expected frequencies that were calculated from the control distribution normalized for a population of the same size and variance. Degrees of skewness (displacement of the mode to the left or right of the mean) and kurtosis (peakedness or flatness of the curve) were obtained using Fisher's statistics calculated from the second, third, and fourth moments about the mean of each population. The moments 2 and 4 were corrected for grouping using Sheppard's corrections. The ratios of the squares of skewness and kurtosis to their variances, which depend only on population size, were used to compute a value of chi-square (two degrees of freedom). This value indicated the significance of the skewness and kurtosis combined (15).

Results

SYMPTOMS

None of the volunteers reported substernal distress during the 6 hours of 90% to 95% oxygen breathing. One subject had severe sinusitis and conjunctivitis. Two of the 10 subjects had symptoms of acute bronchitis several hours after the experiment ended. These two individuals and an additional one had fever the night of the study. Two other subjects became nauseated and vomited during the evening of the study. All of the subjects were extremely fatigued by the procedure.

ENDOSCOPIC OBSERVATIONS OF THE TRACHEA

After 6 hours of oxygen breathing, there were focal areas of redness, edema, and injection of small vessels in the trachea of all the subjects. Small erosions distal to the tip of the bronchofiberscopic placement were visualized in three subjects at the 6th hour of oxygen breathing. Excessive secretions were seen in 5 of the 10 subjects.

TRACHEAL MUCOUS VELOCITY

The control mean tracheal mucous velocity was 22.9 mm/min, SD 6.4 (Table 1). This fell to 17.8 mm/min, SD 6.4 ($P > 0.05$) after 3 hours of oxygen breathing and to 10.3 mm/min, SD 5.4 after 6 hours of oxygen breathing ($P < 0.01$). The other indexes of tracheal mucous velocity, V_3 and V_{max}, paralleled the change in V_{ave} with a similar degree of statistical significance. Subcutaneous administration of 0.25 mg of terbutaline restored mean tracheal mucous velocity to the control level.

Although the three indexes of tracheal mucous velocity failed to detect a significant difference at 3 hours of oxygen breathing, there was a significant difference ($P < 0.001$) in the 3-hour frequency histogram compared with the control, and significant kurtosis (flattening) was present ($P < 0.01$) (Figure 1). At 6 hours of oxygen breathing, an even greater difference was observed. In addition to the difference from the control ($P < 0.001$), the 6-hour curve was skewed to the right ($P < 0.01$), and significantly leptokurtic (high peaked curve [$P < 0.01$]). Although terbutaline administration restored mean velocity to control levels, the distribution of particle velocities was significantly different from the control distribution ($P < 0.01$) and was skewed to the right ($P < 0.01$). This skewness indicated that terbutaline restored average velocity mainly by increasing the proportion of faster moving particles.

PULMONARY FUNCTION TESTS

There were no significant changes in vital capacity, residual volume, total lung capacity, single breath nitrogen test, $FEV_{1.0}$, flow-volume curve, and total respiratory resistance as a function of vital capacity through the period of the study.

Discussion

In 1945, Kaunitz (16) described a tracheobronchitis in mice that were breathing oxygen. He found marked interstitial edema and complete denudation of tracheal epithelium. The walls of the bronchi were edematous, and the lumen was filled with epithelial cells, erythrocytes, and debris. Kaunitz further observed that, morphologically, the reaction in the tracheobronchial tree was identical to that associated with phosgene and other irritant gases. Recently, Boat and associates (17) exposed explants of tracheal epithelium from six human neonates to both

Table 1. Tracheal Mucous Velocity in 10 Normal Subjects Breathing Oxygen*

	Tracheal Mucous Velocity (SD)		
	V_{ave}	V_{max}	V_3
	← *mm/min* →		
Control	22.9 (6.4)	42.4 (12.5)	37.3 (8.6)
O_2 breathing, 3 hours	17.8 (6.4)	35.4 (6.5)	32.4 (7.1)
O_2 breathing, 6 hours	10.3 (5.4)	22.3 (9.9)	20.2 (9.5)
After terbutaline	20.8 (8.6)	38.9 (14.5)	33.9 (11.8)

* Values refer to mean and (SD); V_{ave} is the mean including particles with zero motion; V_{max}, the fastest single particle; and V_3, the mean of the three fastest particles.

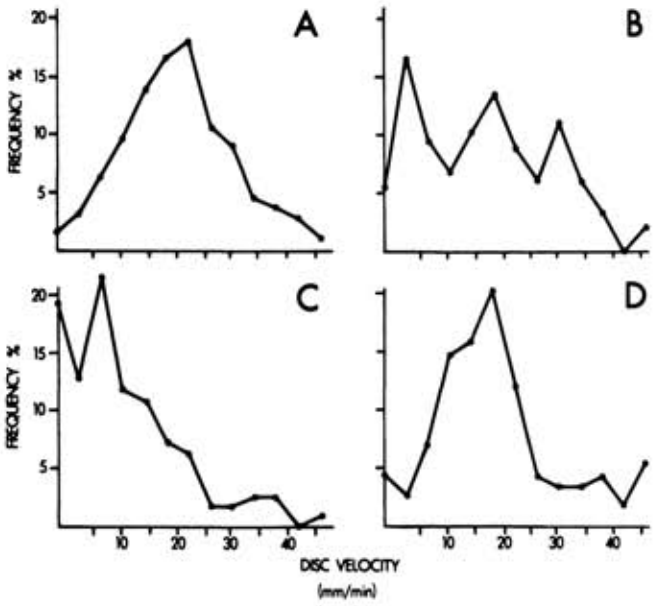

Figure 1. Frequency histograms of tracheal mucous velocity in 10 normal subjects. **A.** Control measurements. **B.** After 3 hours of oxygen breathing. **C.** After 6 hours of oxygen breathing. **D.** Fifteen minutes after subcutaneous administration of terbutaline immediately after run C.

80% and 20% oxygen. Cessation of ciliary movement and carbon particle transport occurred after 48 to 96 hours of exposure to 80% oxygen but not to 20% oxygen. The alteration of ciliary function seemed to be related to squamous metaplasia or to degeneration and sloughing of ciliated epithelium. In recent studies in our laboratory, we found widespread histologic signs of tracheobronchitis in anesthetized dogs breathing 100% oxygen for 6 hours and 75% oxygen for 12 hours*. Sloughing of ciliated epithelium, infiltration of ciliated epithelium by neutrophils, and dilation of submucosal capillaries were observed. Thus, there is ample evidence that oxygen causes a tracheobronchitis, but the time course varies according to the animal species.

The detection of acute tracheobronchitis caused by oxygen breathing has not been fully substantiated by tests measuring airway narrowing. Measurement of dynamic mechanics of breathing has been reported in normal subjects breathing oxygen at two atmospheres pressure for 5 to 11 hours. Although Fisher and associates (5) noted that most subjects developed respiratory symptoms, no change in airway resistance occurred 3 to 8 hours after termination of oxygen breathing. Dewar and associates (6) reported an increase in airway resistance of 30% but no change in $FEV_{1.0}$ immediately at the end of 5 hours oxygen breathing at 2 atmospheres. In the present study in which oxygen was breathed at ambient atmospheric pressure, no change in pulmonary mechanics was observed. Total respiratory resistance over the range of vital capacity did not change. It might be inferred that this finding excluded small airway constriction since an increase of respiratory resistance would be expected at low lung volumes. The normal maximal expiratory flow at low lung volumes also tended to exclude small airway obstruction.

Previous investigations of 100% breathing on mucociliary clearance in animals have produced conflicting results. Laurenzi, Yin, and Guarneri (18) found a significant slowing of mucous flow in the trachea of young cats after 20 minutes of oxygen breathing. These authors transilluminated the trachea to observe movement of a mixture of carbon and lycopodium spores. Marin and Morrow (19) found no change in tracheal mucous velocity by a radioisotopic scanning method after 10 minutes of oxygen breathing. Using tantalum bronchograms in artificially ventilated dogs, Wolfe, Ebert, and Sabiston (20) found that clearance over several hours from the conducting airways was twice as prolonged with oxygen compared with air breathing. Our previous studies using the cinebronchofiberscopic method in anesthetized dogs showed that tracheal mucous velocity is slowed after 3 to 4 hours of oxygen breathing (8).

The present study required repeated insertions of the bronchofiberscope and the application of topical anesthesia to the airway. It is doubtful that these factors influenced the results for the following reasons. Hourly bronchofiberscopic estimations of tracheal mucous velocity during a 4-hour period in anesthetized dogs as analyzed by indexes of velocity and frequency histograms did not change with time*. Topical anesthesia with xylocaine in conscious sheep did not affect tracheal mucous velocity compared to the unanesthetized state (9).

Cinebronchofiberscopic measurements in the present investigation indicate that as little as 3 hours of oxygen breathing might suppress tracheal mucous velocity in normal man. Even though there was no significant change in mean mucous velocity after 3 hours compared to the control level, analysis of the frequency histogram of particle velocities suggested a definite alteration in the distribution of particle velocity pathways. At this time period, we did not observe endoscopic evidence of tracheitis. By 6 hours, all indexes of tracheal mucous velocity and the frequency histogram of particle velocities showed suppression by oxygen. Endoscopic evidence of acute tracheitis was seen in areas distal to the placement of the bronchofiberscope. Thus, the lesions were probably related to oxygen breathing rather than the bronchofiberscopic procedure. The measurement of tracheal mucous velocity seems to be a more sensitive indicator of oxygen-induced tracheitis than endoscopy, subjective complaints, or pulmonary function tests. Furthermore, the slowing of tracheal mucous velocity might predispose to bacterial superinfection because of the loss of this vital host defense mechanism.

The decision to use terbutaline, a beta adrenergic stimulant, was based on previous observations that this drug increased mucous velocity when the velocity was slowed in chronic obstructive lung disease (14). Terbutaline restored mean tracheal mucous velocity to control levels after oxygen breathing by increasing the proportion of faster-moving mucous pathways. The mechanism for

* Sackner MA, Hirsch J, Epstein S, et al: Unpublished observations.

the improvement after terbutaline is uncertain; it could be related to an increase in frequency of ciliary beating, change in amount of composition and quantity of mucus, or both. Moreover, the improvement seemed to be related in part to the occurrence of a higher proportion of faster-moving particle pathways. Possibly, particles that remained slow after terbutaline might have been placed on regions that were structurally damaged. The effect of terbutaline is probably not specific; Isuprel®, an agent that is both an alpha and beta adrenergic stimulant, speeds up mucous velocity in the anesthetized dog when administered as an aerosol*. Despite the endoscopic evidence of tracheitis in humans and animal data indicating histopathologic changes in the tracheal mucosa*, restoration of mucociliary function by pharmacologic intervention can be achieved because of the great reserve of this system. This reserve was previously shown by Battista and associates (21) who compared tracheal histology and mucociliary clearance over time after producing damage to the trachea of chickens. Mucociliary clearance returned to control levels much earlier than the regeneration of ciliated epithelium. They proposed the existence of ciliary reserve capacity; with less than a full complement of ciliated cells in the normal mucosa, the trachea can effectively transport mucus. If this phenomenon operates during oxygen breathing, then histologic damage to the trachea might occur even earlier than after 3 hours of exposure. The damage and sloughing of ciliated epithelium creates a potential area of entry for pathogens that may in part explain the high incidence of fever and generalized fatigue found in normal subjects breathing oxygen for 6 hours or longer.

It should be cautioned that the interpretation of the present findings pertains only to normal subjects. The effect of oxygen on the tracheobronchial tree in patients with cardiopulmonary disorders may be quite different. Indeed, virtually nothing is known about pulmonary oxygen toxicity in this group. These patients could be resistant to oxygen-induced tracheobronchitis because, for the pulmonary parenchyma, prior lung injury protects against the development of pulmonary oxygen toxicity (4). Nevertheless, at the present stage of our knowledge, the experiments reported here suggest that inspired oxygen concentration even for brief periods should be carefully monitored according to need as estimated by blood gases to prevent tracheobronchitis. The role of beta adrenergic stimulants in restoring mucous velocity toward normal levels after suppression by oxygen breathing must be regarded as experimental. The duration of action of such agents and whether they are still effective after chronic administration requires further study.

* *See* footnote, p. 42.

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