Effects of prolonged oxygen exposure at 1.5, 2.0, or 2.5 ATA on pulmonary function in men (Predictive Studies V)

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Clark, J. M., C. J. Lambertsen, R. Gelfand, N. D. Flores, J. B. Pisarello, M. D. Rossman, and J. A. Elias. Effects of prolonged oxygen exposure at 1.5, 2.0, or 2.5 ATA on pulmonary function in men (Predictive Studies V). *J. Appl. Physiol.* 86(1): 243–259, 1999.—As part of a study of human organ O_2 tolerance, lung flow-volume and spirometric measurements were performed repeatedly before, during, and after continuous O_2 exposures at 1.5, 2.0, and 2.5 ATA for average durations of 17.7, 9.0, and 5.7 h, respectively (effects of O_2 breathing at 3.0 ATA for 3.5 h were reported previously; J. M. Clark, R. M. Jackson, C. J. Lambertsen, R. Gelfand, W. D. B. Hiller, and M. Unger. *J. Appl. Physiol.* 71: 878–885, 1991). Additional measurements of pulmonary mechanical function, gas exchange, and alveolar inflammatory cells were obtained before and after O_2 exposure. Rates of pulmonary symptom development and lung volume reduction increased progressively with elevation of O_2 pressure. Average rates of vital capacity reduction over a useful range of O_2 pressures provided a valuable general description of pulmonary O_2 tolerance in humans. However, the existence of multiple pulmonary effects of O_2 toxicity and the complexity of their interactions require awareness that deviations from the average relationships may occur in different individuals or under varying conditions of O_2 exposure and subsequent recovery. The associated pulmonary function deficits may represent responses to a composite of direct and indirect effects of O_2 poisoning, along with related consequences and subsequent reactions to those effects.

pulmonary oxygen toxicity; oxygen limits; human oxygen tolerance; hyperbaric oxygen; oxygen poisoning

THIS PAPER IS ONE OF THE PULMONARY components of correlated, comprehensive investigations of specific organ O_2 tolerance in humans, referred to collectively as Predictive Studies V (24). The objectives of the overall investigation included the identification of neurological, pulmonary, cardiovascular, and other manifestations of O_2 toxicity caused by continuous exposures that approach the limits of human tolerance, over the range of O_2 pressures that are most relevant to diving and decompression (20), the therapy of decompression sickness and gas embolism (27), and general hyperbaric medicine (19). In addition to providing guidelines for safe and effective applications of hyperoxia, the results of these studies provide the required baselines for subsequent investigation of modifying influences that either increase or decrease inherent O_2 tolerance (e.g., interrupted O_2 exposure, exercise, CO_2 inhalation or retention) (5, 21, 22).

Optimal use of hyperoxia in any operational or therapeutic application requires awareness of the fact that the beneficial properties of O_2 coexist with toxic properties that, at sufficient pressure and duration of exposure, can have ultimately lethal effects on any living cell (5, 9, 21). Before the start of Predictive Studies V, pulmonary effects of O_2 toxicity had been investigated at 2.0 ATA in this laboratory (10, 16, 30) and at 1.0 ATA or less in several other laboratories (4, 5, 9, 11, 28). A study of human pulmonary tolerance to air breathing at 5.0 ATA (1.05 ATA P_{O_2}) (14) was performed concurrently with the present investigations. Although the results of these previous studies generally confirmed the expected increase in the rate of development of pulmonary O_2 poisoning with elevation of inspired P_{O_2}, they did not provide the quantitative information that is needed for the increasing applications of hyperoxia throughout the operational and therapeutic range of O_2 pressures (19, 20, 27). The pulmonary components of Predictive Studies V greatly expanded the database that is now available for improving the reliability and accuracy of an earlier predictive analysis of pulmonary O_2 tolerance in humans (5, 9). Potential gains from broad and detailed investigations of human pulmonary O_2 tolerance were further enhanced by recognition that patterns and degrees of pulmonary function effects were likely to vary with different combinations of inspired P_{O_2} and exposure duration (9).

The previous studies were complemented and extended by an overall design that included continuous exposures to O_2 pressures of 3.0, 2.5, 2.0, and 1.5 ATA for maximum durations of 3.5, 6.0, 11.9, and 19.0 h, respectively. Results of pulmonary function measurements obtained at 1.0 ATA before and after the 3.0-ATA exposures, which were completed in the first two years of Predictive Studies V, were reported previously (8). An initial series of 2.0-ATA exposures, all of the 1.5-ATA exposures, and a baseline series of 1.0-ATA air control exposures were completed during the third year. The 2.5-ATA exposure series was performed during the next year, and a second series of 2.0-ATA exposures was completed during the fifth year. Each subject participated in only one O_2 exposure at 2.5, 2.0, or 1.5 ATA.

Selected parts of the pulmonary component of Predictive Studies V were summarized in the proceedings of two related symposia (6, 7). This paper contains extensive data presentations and statistical analyses that are not available in the earlier summaries and also includes additional measurements that were not published previously. Both direct and indirect effects of

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pulmonary O_2 toxicity were observed. Superimposed on these effects were related consequences and subsequent reactions that together contributed to the apparently wide variation in individual susceptibility to pulmonary O_2 poisoning.

METHODS

O_2 exposures were carried out at absolute pressures of 1.5, 2.0, and 2.5 ATA in one compartment of an environmental chamber system that has been described (25). The chamber was large enough to accomodate one or two subjects, two investigators, and the sensors or transducers of equipment needed for all measurements. Total ambient pressure was maintained within ±10 mmHg, with tighter control when desired for specific measurements. Air temperature inside the chamber was maintained between 24 and 27°C.

Control exposures were performed at 1.0 ATA in the same chamber with the same measurement equipment and the same gas-administration system delivering air instead of O_2. Duration of these experiments was designed to simulate an average 1.5-ATA O_2 exposure, with an appropriate postexposure period for recovery measurements.

Subjects and Exposure Limits

Vital statistics for the normal male nonsmokers who participated in these experiments are summarized in Table 1. Average durations of O_2 breathing for each series are also shown. The subjects were thoroughly trained in the performance of all pulmonary function measurements. Maximum exposure durations were predicted on the basis of past experience with symptom severity (10) and analysis of probable acceleration at higher pressures. The selected limits were judged to be long enough to produce significant, but fully reversible, symptoms and/or objective manifestations of pulmonary or neurological O_2 toxicity. In addition, objective and subjective criteria were established for the discretionary termination of any exposure before the preselected limit. This preliminary design scope proved to be sensible. All experimental protocols were reviewed and approved by the Human Studies Committee of the University of Pennsylvania. Informed consent to all procedures was given on two separate occasions.

Experimental Procedures

General. Subjects were studied in pairs for all but one of the initial 2.0-ATA experiment series (*series I*) and all but one of the 1.5-ATA series. Subsequently, only one subject was studied in each experiment at 2.5 ATA and in the second 2.0-ATA series (*series II*). Control measurements were obtained on several days before exposure and were repeated on the experiment day before the start of O_2 breathing. On the experiment day or days, the total time required for subject preparation, the final set of preexposure measurements, exposure, and the first several hours of the postexposure period ranged from ~30 h for the 2.5-ATA experiments to ~44 h for the 1.5-ATA series.

O_2-administration system. Gas from an external liquid O_2 source was piped into the chamber, humidified, and conducted to a reservoir bag, from which it was inspired by the subject through 1.5-in., smooth-bore, kink-proof plastic tubing (Vacumed Clean-Bor) connected to a lightweight, plastic, nonrebreathing oronasal face mask with an inflatable seal (Vital Signs). Relative humidity of the inspired gas was ~80% at chamber temperature. Flow-volume curves, spirometry, and concurrent nonpulmonary measurements were performed without interruption of O_2 breathing by breath holding for brief periods while transferring from the mask to a noseclip and nonbreathing valve assembly. Expired gas was conducted by plastic tubing to an "overboard dump system," except when it was collected to measure ventilation and gas exchange.

Mask O_2 concentration, which was monitored continuously with a solid oxide electrochemical cell analyzer (model SA-3, Applied Electrochemistry), remained consistently above 98%. End-tidal CO_2 concentration was monitored with a Beckman LB-2 infrared CO_2 analyzer.

Pulmonary Function Measurements

Flow-volume curves and spirometry were performed during exposure at increased ambient pressures and before and after exposure at 1.0 ATA with a Vacumed model 1603 computerized spirometry system, which had software modified by the manufacturer to permit incorporation of pressures that were greater than atmospheric. Ohio Medical Products dry spirometers, models 840 and 827, were used for volume and flow measurements inside and outside the chamber, respectively. All lung volumes and flow rates were corrected to BTPS conditions. For both flow-volume curves and spirometry, the best of three acceptable trials was used.

Density dependence of flow was determined at 1.0 ATA by comparing three flow-volume curves performed while subjects were breathing air with three similar curves, each of which was performed after three vital capacity (VC) breaths of 80% He-20% O_2. The three curves on air breathing were always performed first. On the basis of preprogramed volume and flow criteria, the computer selected one curve of each set for comparison. The difference in air and He-O_2 flow rates at 50% VC was calculated as a percentage of the airflow rate, and the volume at which the two flow rates converged (isoflow) was expressed as liters above residual volume (RV).

N_2 closing volume was measured at 1.0 ATA by a modification of Fowler's method (8). After inhaling one VC breath of 100% O_2, the subject exhaled at a controlled rate of 0.3–0.4 l/s into a Stead-Wells spirometer equipped with a potentiometer for measurement of volume, while expired N_2 concentration was measured with a rapid-response N_2 meter (model 47302A N_2 analyzer, Hewlett-Packard). The average of four acceptable trials was used to determine closing volume and the *phase III* slope.

Airway resistance (Raw) and thoracic gas volume were measured at 1.0 ATA while the subject panted in a constant-volume Collins body plethysmograph system. The subject kept his cheeks rigid during the panting maneuver by pressing his palms against them. The average of three acceptable trials was calculated for each parameter. Airway conductance was calculated as the reciprocal of Raw, and specific conductance was calculated as airway conductance/thoracic gas volume.

Lung compliance was measured in the body plethysmograph immediately after maximal lung inflation as the slope of the volume-pressure curve both during slow inhalation

Table 1. *Vital statistics of subjects*

Pressure	*n*	Age, yr	Ht, cm	Wt, kg	Duration,* h
1.5 ATA	9	25.1 ± 6.0	179.5 ± 3.8	79.4 ± 9.5	17.7 ± 0.8
2.0 ATA *series I*	7	23.6 ± 4.8	179.2 ± 10.1	74.9 ± 9.9	9.7 ± 1.4
2.0 ATA *series II*	8	23.0 ± 3.8	181.4 ± 4.7	74.4 ± 6.7	8.4 ± 1.8
2.5 ATA	8	25.2 ± 2.8	185.7 ± 7.7	79.3 ± 9.3	5.7 ± 0.4

Values are means ± SD; *n*, no. of subjects. *Average exposure duration.

from functional residual capacity (FRC) to total lung capacity (TLC) and during slow exhalation from TLC to FRC. For the inspiratory measurement, the subject inspired fully to TLC, then expired to FRC, gave a hand signal, and inspired again to TLC over 10–12 s while inspired volume and esophageal pressure were measured concurrently. The expiratory maneuver was performed by initial inspiration to TLC followed by expiration over 10–12 s to FRC. Esophageal pressure was measured with a 10-cm-long Hyatt balloon (Vacumed no. 1180) sealed over one end of a 100-cm length of PE-200 tubing with holes in the end enclosed by the balloon. After the empty balloon was passed into the stomach, 8.0 ml of air were injected and 7.5 ml were removed. The balloon was slowly withdrawn until the positive pressure deflection on sniffing became negative, indicating it was in the lower end of the esophagus. An additional 10-cm length of tubing was withdrawn, and the tubing was securely taped to the subject's nose. Static compliance was measured as the slope of the expiratory volume-pressure curve over ~0.5 liter above FRC. The average of four acceptable trials was used. Overall compliance for the entire lung volume from FRC to TLC was also measured as the total volume change divided by the total pressure change. The inspiratory volume-pressure curves were used for this purpose because they were more reproducible than the corresponding expiratory curves in most subjects.

Maximum respiratory pressures were measured with a Statham P23Dd pressure transducer, while the subject exerted maximal effort against the closed valve of a valve-mouthpiece assembly that was tightly gripped by the lips. Transient pressure spikes on a strip-chart recorder were ignored for this measurement to ensure that the pressure change could be sustained for at least several seconds. Maximum inspiratory pressure was measured at both RV and FRC, whereas expiratory pressure was measured at TLC and FRC. For each measurement, the best of at least two acceptable trials was used. Respiratory pressures were measured at 1.0 ATA before compression and at 1.5, 2.0, or 2.5 ATA at the end of O_2 exposure.

Arterial blood was sampled anaerobically from a radial artery into precision-bored glass syringes lined with heparin solution. Analyses for P_{O_2}, P_{CO_2}, and pH were performed in duplicate with an electrode block assembly (model 168, Ciba Corning Diagnostics) adapted for use at increased ambient pressure. The electrode block was maintained at 37.0°C, and measured values were corrected to body temperature. Rectal temperature was measured with a thermistor thermometer (range 35–45°C; model 46, Yellow Springs Instrument).

Mean alveolar P_{O_2} during air breathing was calculated with the alveolar gas equation (17). Alveolar P_{O_2} during O_2 breathing was calculated by subtracting alveolar water vapor pressure and P_{CO_2} from the inspired P_{O_2}. Alveolar water vapor pressure was determined from the measured body temperature, and P_{CO_2} was assumed to be equal to the measured arterial P_{CO_2}.

CO diffusing capacity ($D_{L_{CO}}$) was measured with a Collins modular lung analyzer, by using 0.3% CO-10% He-balance air as the inspired gas. After calibration of He and CO analyzers, the subject wearing noseclips took two normal breaths on the mouthpiece, exhaled completely to RV, signaled, and then inhaled as quickly and fully as possible to TLC. At the end of a 10-s breath hold period designated by a buzzer, the subject exhaled quickly. The measured inspired volume and breath hold time were entered along with the expired He and CO concentrations into a computer for calculation of $D_{L_{CO}}$, TLC, and the ratio of $D_{L_{CO}}$ to alveolar volume (D_L/V_A). Average values of four separate determinations were obtained for each variable, with at least 5 min between successive measurements for elimination of the inhaled He and CO.

Measured values of TLC were used along with values for slow vital capacity (SVC) and inspiratory capacity (IC) obtained by spirometry to calculate RV (TLC − SVC) and FRC (TLC − IC).

Measurement Sequences

The rate of development of pulmonary O_2 poisoning was monitored by repeated performance of flow-volume curves and spirometry at regular intervals during the O_2 exposures at 1.5, 2.0, and 2.5 ATA. Initial values obtained within the first few minutes of O_2 breathing were used as controls for these measurements because timed lung volumes and flow rates are known to be significantly reduced by the greater density of inspired gas at increased ambient pressures (10, 36).

In addition to the objective measurements of pulmonary function, pulmonary symptoms previously associated with O_2 toxicity (10) were rated as absent (0), mild (+1), moderate (+2), or severe (+3) by each subject before, at regular intervals during, and after O_2 exposure. Average ratings were calculated for each exposure interval.

Arterial blood gases were measured while subjects were breathing O_2 at the start and end of each exposure. Before and after O_2 exposure, blood gases were measured at 1.0 ATA while subjects were breathing air at rest and during light exercise (100 W) on a bicycle ergometer. Alveolar P_{O_2} was determined concurrently with each arterial P_{O_2} measurement.

All other pulmonary function indexes were also measured at 1.0 ATA on the experiment day before the start of O_2 breathing. For all except the first 2.0-ATA series, additional control measurements of Raw and lung compliance were obtained on one previous day, and additional measurements of flow-volume curves on air and HeO_2, spirometry, closing volumes, and $D_{L_{CO}}$ were obtained on three separate preexposure days. Preexposure control measurements for the initial 2.0-ATA series included one set of Raw and lung compliance measurements and a total of two to four sets of the other pulmonary function measurements. Average values of all preexposure control measurements for each subject were used as controls for the postexposure and follow-up measurements.

Bronchoalveolar Lavage (BAL)

After topical anesthesia of the nasal mucosa with 2% viscous lidocaine, the bronchofiberscope (model BF-B2, Olympus) was passed transnasally to the level of the hypopharynx, where anesthesia of the pharyngeal mucosa, larynx, and bronchial mucosa was achieved by injecting 2% lidocaine through the aspiration channel. The tip of the bronchoscope was then advanced to a subsegmental right middle lobe bronchus. Up to 300 ml of sterile, isotonic saline were introduced into the isolated subsegment in 50-ml aliquots. After each injection, lavage fluid was aspirated into a sterile trap. The negative pressure required for aspiration was reduced by placing the subject in a recumbent position.

Mucus clumps were removed from lavage fluid by passing it through two layers of sterile gauze and a 250-μm stainless steel mesh. After the suspension was centrifuged at 400 *g* and 4°C for 15 min, the supernatant was decanted and saved for the protein determination. The cell pellet was washed twice in Hanks' balanced salt solution and resuspended in RPMI medium (GIBCO). Total cell counts were made on a Coulter counter (model ZF, Coulter Electronics). Cell viability was

determined by trypan blue exclusion. Smears for differential counting were made with a cytocentrifuge (Shandon Southern Instruments) and stained with Diff-Quik (Harleco). At least 500 cells were counted for each differential count. Protein in the lavage supernatant was measured by the Lowry method by using bovine serum albumin (500 μg/ml) as a standard. Results were expressed as protein concentration per milliliter of lavage fluid.

Statistical Analysis

By using preexposure or early exposure control values, potential effects of O_2 toxicity were evaluated by ANOVA with repeated measures, followed by *t*-tests comparing each data point during exposure or postexposure with the appropriate control value when the overall *F*-value was significant. The level of significance was considered as $P < 0.05$.

RESULTS

Average effects of continuous O_2 exposure on selected lung volumes and flow rates are summarized in Tables 2 and 3 for the 1.5-ATA O_2 exposures, Tables 4 and 5 for 2.0 ATA, and Tables 6 and 7 for 2.5 ATA. Table 4 contains data for both series of 2.0-ATA experiments, except for one subject whose end-exposure flow-volume data were lost because of a computer malfunction. The postexposure values in Table 5 include only 2.0-ATA *series II* subjects because they had earlier and more frequent measurements than did the 2.0-ATA *series I* group, and none of the *series II* subjects had BAL. In addition to the pulmonary measurements, neurological and cardiovascular functions were monitored at regular intervals during and after the O_2 exposures (24). Actual measurement times were recorded for each subject, and grouped average times are listed in Tables 2–7 and 11.

Many of the pulmonary function measurements that were performed during and/or after the prolonged O_2 exposures were not significantly changed. With a few exceptions, results of these measurements were omitted from data tables and figures to conserve space. They may be obtained on request from the Environmental Biomedical Research Data Center (23) of the Institute for Environmental Medicine.

Flow-Volume Curves

Of the multiple lung volumes and flow rates that are obtainable from a flow-volume curve, the forced vital capacity (FVC), 1-s forced expired volume ($FEV_{1.0}$), $FEV_{1.0}$-to-FVC ratio ($FEV_{1.0}$/FVC), and maximal midexpiratory flow rate (FEF_{25-75}) were selected as the most useful indexes for monitoring and comparing the effects of pulmonary O_2 toxicity during continuous O_2 breathing at 1.5, 2.0, and 2.5 ATA and during the postexposure recovery periods at 1.0 ATA. With respect to preexposure control values at 1.0 ATA, additional control measurements at the start of O_2 breathing at each pressure reflected the effects of increased gas density on timed lung volumes and flow rates ($FEV_{1.0}$, $FEV_{1.0}$/FVC, and FEF_{25-75}). Therefore, these initial exposure measurements, including FVC, were used as controls for all subsequent measurements at increased ambient pressure, and the preexposure 1.0-ATA values were used as controls for measurements obtained during the postexposure recovery period at 1.0 ATA.

Both FVC and $FEV_{1.0}$ decreased progressively during continuous O_2 breathing at each pressure (Tables 2, 4, and 6), and average reductions were statistically significant by 11.8, 5.4, and 4.9 h of exposure at 1.5, 2.0, and 2.5 ATA, respectively. Average FVC and $FEV_{1.0}$ decrements near the end of O_2 exposure were 20.4 and 14.0% for 17.5 h of O_2 breathing at 1.5 ATA, 21.0 and 22.2% for 8.8 h at 2.0 ATA, and 13.8 and 12.8% for 5.7 h at 2.5 ATA, respectively. Reversal of the FVC and $FEV_{1.0}$ changes appeared to occur more slowly after cessation of prolonged O_2 breathing at 1.5 ATA (Table 3) than after the shorter exposures at 2.0 or 2.5 ATA (Tables 5 and 7).

The average $FEV_{1.0}$/FVC ratio remained essentially unchanged during O_2 breathing at each pressure, but it was reduced during the early recovery period after exposure at 2.0 and 2.5 ATA (Tables 5 and 7). The postexposure reduction in $FEV_{1.0}$/FVC was statistically significant at 1.4 and 2.3 h after the 2.0-ATA O_2 exposure (Table 5).

Average changes in FEF_{25-75} were variable and not statistically significant during O_2 breathing at 1.5 and 2.5 ATA (Tables 2 and 6). At 2.0 ATA, however, significant reductions of 21.9 and 19.2%, respectively, occurred at average exposure durations of 6.7 and 8.8 h (Table 4). In the 2.0-ATA *series II* subject group (Table 5), average FEF_{25-75} was significantly reduced by 28.2% at the end of exposure and by 32.2 and 25.1%, respectively, at average postexposure intervals of 1.4 and 2.3

Table 2. *Effects of continuous O_2 exposure at 1.5 ATA on lung volumes and flow rates*

	Exposure Duration, h						
	0.2 (Control)	3.8	7.9	11.8	14.1	16.8	17.5
Parameter	%Change from control value						
FVC, liters	5.63 ± 0.90	−1.1 ± 2.9	−4.2 ± 5.2	−9.2 ± 8.4*	−11.8 ± 6.3*	−18.7 ± 14.1*	−20.4 ± 11.6*
$FEV_{1.0}$, liters	4.18 ± 0.61	0.6 ± 4.8	−5.2 ± 8.2	−10.4 ± 11.5*	−9.8 ± 8.9*	−13.8 ± 16.0*	−14.0 ± 16.2*
$FEV_{1.0}$/FVC†	0.75 ± 0.07	0.76 ± 0.08	0.74 ± 0.08	0.74 ± 0.09	0.76 ± 0.08	0.79 ± 0.09	0.80 ± 0.06
FEF_{25-75}, l/s	3.53 ± 0.90	3.8 ± 10.4	−3.3 ± 13.1	−10.8 ± 18.3	−4.4 ± 14.5	−2.0 ± 25.8	−1.0 ± 27.0
SVC, liters	5.75 ± 0.69	−0.7 ± 3.0	−4.7 ± 6.3	−7.9 ± 8.3	−14.2 ± 12.7*	−20.1 ± 16.3*	−22.5 ± 16.6*
IC, liters	3.38 ± 0.72	−2.0 ± 17.0	−7.4 ± 19.4	−13.8 ± 16.4	−17.5 ± 20.3*	−27.9 ± 20.3*	−28.9 ± 21.4*
ERV, liters	2.30 ± 0.29	6.9 ± 12.5	3.9 ± 12.5	4.4 ± 7.3	−4.6 ± 15.9	−6.1 ± 14.4	−11.0 ± 11.8*

Values are means ± SD; $n = 9$ subjects. FVC, forced vital capacity; $FEV_{1.0}$, 1-s forced expired volume; FEF_{25-75}, maximal midexpiratory flow rate; SVC, slow vital capacity; IC, inspiratory capacity; ERV, expiratory reserve volume. *Significantly different from control value, $P < 0.05$. †Data are average measured values rather than %changes.

Table 3. *Recovery of lung volumes and flow rates after O_2 exposure at 1.5 ATA*

Parameter	Preexposure Control	Postexposure Duration, h			
		3.6	13.0	34	58
		%Change from control value			
FVC, liters	5.55 ± 0.69	−13.3 ± 10.4*	−8.2 ± 4.9*	1.5 ± 2.3	1.4 ± 3.1
$FEV_{1.0}$, liters	4.58 ± 0.46	−9.5 ± 10.7*	−9.4 ± 7.7*	0.5 ± 4.6	0.3 ± 5.1
$FEV_{1.0}$/FVC†	0.83 ± 0.06	0.86 ± 0.08	0.82 ± 0.09	0.82 ± 0.06	0.82 ± 0.06
$FEF_{25–75}$, l/s	4.72 ± 0.89	2.9 ± 21.7	−11.3 ± 19.1	−0.4 ± 13.0	−0.9 ± 13.5
SVC, liters	5.66 ± 0.73	−12.7 ± 11.2*	−7.2 ± 4.4*	2.4 ± 3.3	2.2 ± 5.2
IC, liters	3.40 ± 0.78	−14.8 ± 12.6*	−6.4 ± 10.2	4.1 ± 11.4	9.0 ± 16.8
ERV, liters	2.26 ± 0.25	−7.3 ± 17.6	−6.7 ± 16.4	2.2 ± 12.3	−5.0 ± 15.1
TLC, liters	7.13 ± 0.88	−2.7 ± 9.5	−3.6 ± 7.9	1.2 ± 6.1	−2.9 ± 3.2
FRC, liters	3.72 ± 0.48	9.4 ± 13.7	0.9 ± 22.9	0.0 ± 12.6	−11.0 ± 12.9*
RV, liters	1.46 ± 0.36	37.8 ± 43.4	9.2 ± 46.5	−4.1 ± 30.4	−21.1 ± 23.2
$\%\Delta\dot{V}_{max,50}$‡	45.2 ± 10.3	−19.9 ± 22.9*	−0.6 ± 28.5	−3.1 ± 15.5	3.8 ± 14.6
III slope, $\%N_2$/l†	3.0 ± 0.9	4.0 ± 2.1	4.6 ± 1.8*	3.9 ± 1.4	3.3 ± 1.3

Values are means ± SD; n = 9 subjects. TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; $\%\Delta\dot{V}_{max,50}$, difference in maximal expiratory flow rates on He-O_2 and air at 50% FVC expressed as %airflow rate; III slope, slope of *phase III* of single-breath N_2 washout test. Six subjects had bronchoalveolar lavage at 8.5–10.0 h postexposure. * Significantly different from control value, $P < 0.05$. †Data are average measured values rather than %changes. ‡Changes are expressed as average differences from control values rather than %changes.

h. Average $FEF_{25–75}$ was also significantly reduced by 30.0 and 30.8%, respectively, at average intervals of 0.6 and 1.4 h after O_2 breathing at 2.5 ATA (Table 7). Overall, the data indicate that some individuals had unusually large reductions in $FEF_{25–75}$ and that the largest decrements occurred during the first few hours after O_2 exposure at 2.0 and 2.5 ATA.

Spirometry

Slow vital capacity (SVC) and its components [IC and expiratory reserve volume (ERV)] were measured in addition to the flow-volume curves to determine whether or not significant air trapping occurred as an effect of pulmonary O_2 poisoning and also to extend the previous finding (10) that the observed reduction in VC occurred entirely within the IC component of this lung volume. In contrast to the observed effects of increased gas density on timed lung volumes and flow rates, and in agreement with the lack of effect on FVC, average SVC values at the start of O_2 exposure were not reduced with respect to preexposure control values at 1.0 ATA. Changes in SVC during and after O_2 breathing at all three pressures were generally similar to, but slightly larger than, the corresponding FVC changes in most cases. Average decrements in SVC were 22.5, 23.2, and 17.3%, respectively, at the end of O_2 exposures at 1.5, 2.0, and 2.5 ATA (Tables 2, 4, and 6). Corresponding decrements in IC at the same pressures were 28.9, 18.4, and 23.0%, respectively. The only statistically significant changes in ERV were average reductions of 11.0 and 22.7% at the end of the 1.5- and 2.0-ATA O_2 exposures. The similarity of the FVC and SVC measurements, both with respect to absolute values and percent changes, indicates that significant air trapping did not occur during continuous O_2 breathing at 1.5, 2.0, or 2.5 ATA.

Average control values and changes in TLC, which was measured concurrently with $D_{L_{CO}}$, are included in Tables 3, 5, and 7 for comparison with the other lung volumes. The only statistically significant change in TLC was a 5.5% decrement measured at 5.8 h after the 2.0-ATA O_2 exposures (Table 5). Average RV was not significantly changed after any of the O_2 exposures (Tables 3, 5, and 7). At an average recovery time of 5.5 h after the 2.5-ATA exposures (Table 7), average FRC was significantly increased by 13.3%. Significant changes in

Table 4. *Effects of continuous O_2 exposure at 2.0 ATA on lung volumes and flow rates*

Parameter	Exposure Duration, h				
	0.5 (Control)	3.7	5.4	6.7	Final‡
	%Change from control value				
FVC, liters	6.00 ± 0.81	−3.6 ± 6.8	−8.1 ± 12.5*	−13.1 ± 16.3*	−21.0 ± 14.3*
$FEV_{1.0}$, liters	4.10 ± 0.51	−5.5 ± 6.7	−10.5 ± 14.3*	−18.0 ± 19.3*	−22.2 ± 22.0*
$FEV_{1.0}$/FVC†	0.69 ± 0.06	0.67 ± 0.07	0.66 ± 0.07	0.64 ± 0.07	0.66 ± 0.09
$FEF_{25–75}$, l/s	3.02 ± 0.69	−6.0 ± 9.4	−9.8 ± 19.6	−21.9 ± 24.4*	−19.2 ± 32.5*
SVC, liters	6.18 ± 0.84	−5.0 ± 10.7	−9.4 ± 13.8*	−14.4 ± 16.5*	−23.2 ± 15.8*
IC, liters	3.35 ± 0.83	−4.1 ± 20.8	−13.3 ± 22.7	−17.6 ± 17.6*	−18.4 ± 30.3*
ERV, liters	2.82 ± 0.61	−2.4 ± 18.3	−3.9 ± 18.2	−8.6 ± 31.2	−22.7 ± 29.6*

Values are means ± SD; n = 14 subjects. * Significantly different from control value, $P < 0.05$. †Data are average measured values rather than %changes. ‡Average values for 14 subjects at average exposure duration of 8.8 h (range 5.5–10.5 h).

Table 5. *Recovery of lung volumes and flow rates after O_2 exposure at 2.0 ATA*

Parameter	Preexposure Control	End Exposure§	Postexposure Duration, h: 1.4	2.3	5.8	12.7	30	54
			%Change from control value					
FVC, liters	5.71 ± 0.80	−21.9 ± 11.5*	−12.6 ± 14.4*	−5.6 ± 12.8	−3.9 ± 4.5	−3.4 ± 4.2	0.5 ± 2.3	1.7 ± 3.4
$FEV_{1.0}$, liters	4.47 ± 0.62	−28.0 ± 19.0*	−25.6 ± 25.2*	−13.2 ± 15.1*	−8.5 ± 11.1	−8.6 ± 8.6	−2.5 ± 5.4	−0.2 ± 6.4
$FEV_{1.0}$/FVC†	0.78 ± 0.07	0.62 ± 0.08	0.65 ± 0.14*	0.72 ± 0.07*	0.74 ± 0.08	0.74 ± 0.07	0.76 ± 0.08	0.77 ± 0.07
FEF_{25-75}, l/s	4.21 ± 1.14	−28.2 ± 31.3*	−32.2 ± 42.5*	−25.1 ± 28.9*	−11.9 ± 19.0	−14.3 ± 15.6	−6.5 ± 13.1	−2.6 ± 15.1
SVC, liters	5.77 ± 0.76	−24.3 ± 13.6*	−15.3 ± 17.7*	−8.2 ± 17.4	−4.1 ± 4.4	−3.8 ± 4.2	1.1 ± 3.2	1.2 ± 3.4
IC, liters	3.64 ± 0.48	−24.3 ± 18.9*	−22.7 ± 11.1*	−23.0 ± 9.5*	−10.1 ± 8.5*	−9.0 ± 10.2	1.2 ± 7.6	−8.0 ± 12.8
ERV, liters	2.13 ± 0.40	−21.4 ± 25.6	1.9 ± 33.3	18.0 ± 45.7	6.3 ± 18.1	4.8 ± 16.6	1.9 ± 13.5	15.6 ± 14.7
TLC, liters	6.87 ± 1.03	NM	NM	NM	−5.5 ± 6.6*	−2.9 ± 4.9	2.0 ± 5.7	4.5 ± 7.7
FRC, liters	3.24 ± 0.68	NM	NM	NM	0.1 ± 11.0	4.0 ± 11.8	3.8 ± 13.4	18.0 ± 13.0*
RV, liters	1.11 ± 0.36	NM	NM	NM	−13.4 ± 34.9	0.9 ± 23.4	10.4 ± 36.8	21.8 ± 40.0
$\%\Delta\dot{V}_{max,50}$‡	43.5 ± 18.6	NM	NM	NM	−17.6 ± 20.7*	−8.4 ± 21.8	4.3 ± 21.6	−9.0 ± 18.5
III slope, $\%N_2$/l†	3.9 ± 0.8	NM	NM	NM	5.1 ± 1.8	4.5 ± 1.1	4.6 ± 1.1	4.1 ± 0.7

Values are means ± SD; $n = 8$ subjects. NM, not measured. *Significantly different from control value, $P < 0.05$. †Data are average measured values rather than %changes. ‡Changes are expressed as average differences from control values rather than %changes. §Measured at 2.0 ATA.

FRC that were initially measured >50 h after the O_2 exposures at 1.5 and 2.0 ATA (Tables 3 and 5) were probably unrelated to pulmonary O_2 poisoning.

Quantitative progression of effects. Quantitative measurements of the rates of development of pulmonary O_2-poisoning effects over the range of O_2 pressures presently in use require the identification of pulmonary function indexes that are significantly and progressively reduced during continuous O_2 breathing at those pressures. Lung volumes that fulfilled these criteria included the FVC, $FEV_{1.0}$, SVC, and IC (Tables 2, 4, and 6). Average rates of decrease in SVC during O_2 breathing at 1.5, 2.0, and 2.5 ATA are shown in Fig. 1. Average SVC fell progressively at each O_2 pressure, and the rate of fall increased with elevation of the inspired P_{O_2}. Similar response patterns were observed with the FVC, $FEV_{1.0}$, and IC data. Selection of percent change in SVC as the pulmonary function index for describing rate of development of a pulmonary O_2-poisoning effect allows the incorporation of data from 10 additional subjects studied previously at 2.0 ATA (10). It also facilitates direct comparisons with similar data obtained in other laboratories (4, 11, 14, 28).

Pulmonary symptoms. Most of the subjects studied at 1.5 or 2.0 ATA experienced pulmonary symptoms that included chest pain, cough, chest tightness, and dyspnea. The sequence and individual characteristics of these symptoms were similar to those described previously (10). Individual symptoms were rated as absent (0), mild (+1), moderate (+2), or severe (+3) by each subject at regular intervals during O_2 breathing. Although the combination and severity of pulmonary symptoms varied among different individuals, their average intensities were moderately severe by the end of the O_2 exposures at 1.5 and 2.0 ATA (Fig. 1). In contrast, the subjects who breathed O_2 at 2.5 ATA for 5–6 h (Fig. 1), or at 3.0 ATA for 3.5 h (8), had relatively mild symptoms. No pulmonary symptoms occurred during air breathing control experiments that were even longer than the 1.5-ATA O_2 exposures.

Exceptional degrees of pulmonary effects at 2.5 ATA. Two of the eight subjects who breathed O_2 for 5–6 h at 2.5 ATA had an early onset of prominent pulmonary effects (Fig. 2). These two subjects had average changes in $FEV_{1.0}$, FEF_{25-75}, and SVC of about −38, −54, and −41%, respectively, at an average exposure duration of 5.2 h, compared with corresponding changes of −4, +7, and −9% in the remaining six subjects at 5.8 h of O_2 breathing. Average differences between the two subsets of subjects were even greater during the early recovery period. At postexposure intervals of 0.6 and 1.4 h, the two subjects had progression of the $FEV_{1.0}$ and FEF_{25-75}

Table 6. *Effects of continuous O_2 exposure at 2.5 ATA on lung volumes and flow rates*

Parameter	Exposure Duration, h: 0.1 (Control)	2.2	3.1	4.9	5.7
	%Change from control value				
FVC, liters	5.92 ± 0.94	−5.0 ± 5.8	−4.9 ± 5.2	−12.2 ± 11.6*	−13.8 ± 12.8*
$FEV_{1.0}$, liters	3.99 ± 0.54	−7.2 ± 5.6	−7.5 ± 3.2	−13.8 ± 14.1*	−12.8 ± 17.2*
$FEV_{1.0}$/FVC†	0.68 ± 0.06	0.66 ± 0.05	0.66 ± 0.07	0.66 ± 0.06	0.68 ± 0.06
FEF_{25-75}, l/s	2.85 ± 0.71	−7.8 ± 13.4	−7.8 ± 8.8	−11.7 ± 24.5	−8.2 ± 33.2
SVC, liters	6.20 ± 0.88	−3.5 ± 5.0	−5.4 ± 5.5	−13.4 ± 13.4*	−17.3 ± 15.5*
IC, liters	3.65 ± 0.45	−5.2 ± 6.6	−6.7 ± 8.5	−22.3 ± 12.6*	−23.0 ± 14.6*
ERV, liters	2.55 ± 0.53	−0.3 ± 13.2	−3.1 ± 13.8	−1.5 ± 17.7	−10.6 ± 20.5

Values are means ± SD; $n = 8$ subjects. *Significantly different from control value, $P < 0.05$. †Data are average measured values rather than %changes.

Table 7. *Recovery of lung volumes and flow rates after O_2 exposure at 2.5 ATA*

Parameter	Preexposure Control	Postexposure Duration, h						
		0.6	1.4	2.2	5.5	10.7	34	57
		%Change from control value						
FVC, liters	5.65 ± 0.89	−10.8 ± 16.0*	−11.9 ± 15.6*	−3.1 ± 7.6	−0.8 ± 6.4	−0.6 ± 6.5	1.8 ± 3.5	2.2 ± 4.1
$FEV_{1.0}$, liters	4.62 ± 0.69	−19.5 ± 26.9*	−21.7 ± 29.2*	−12.2 ± 24.2	−1.9 ± 5.6	−1.2 ± 5.5	0.7 ± 4.6	0.6 ± 3.8
$FEV_{1.0}$/FVC†	0.82 ± 0.05	0.71 ± 0.14	0.70 ± 0.18	0.73 ± 0.18	0.81 ± 0.07	0.82 ± 0.06	0.81 ± 0.07	0.81 ± 0.06
$FEF_{25–75}$, l/s	4.68 ± 1.18	−30.0 ± 33.6*	−30.8 ± 34.3*	−18.3 ± 27.2	−4.5 ± 5.7	−0.4 ± 10.3	−3.1 ± 8.5	−2.6 ± 7.6
SVC, liters	5.84 ± 0.91	−11.4 ± 20.4*	−9.9 ± 17.9*	−3.6 ± 10.2	−2.0 ± 6.1	−1.7 ± 7.1	2.0 ± 5.7	0.8 ± 4.0
IC, liters	3.64 ± 0.53	−21.1 ± 21.0*	−23.7 ± 19.4*	−9.7 ± 11.4	−15.0 ± 8.7*	−10.3 ± 9.2	−3.4 ± 4.4	−1.6 ± 6.9
ERV, liters	2.20 ± 0.62	9.1 ± 39.6	22.2 ± 58.5	12.7 ± 40.9	23.7 ± 28.9	15.6 ± 19.2	13.2 ± 16.9	6.7 ± 14.6
TLC, liters	7.18 ± 1.08	NM	NM	NM	−1.4 ± 2.5	−1.5 ± 2.3	0.5 ± 3.8	−1.0 ± 3.6
FRC, liters	3.54 ± 0.78	NM	NM	NM	13.3 ± 11.0*	8.2 ± 9.1	4.6 ± 9.0	0.1 ± 8.8
RV, liters	1.34 ± 0.34	NM	NM	NM	5.4 ± 27.6	5.0 ± 29.9	−1.1 ± 33.4	−6.4 ± 20.7
$\%\Delta\dot{V}_{max,50}$‡	53.4 ± 15.7	NM	NM	NM	−5.8 ± 15.5	−20.4 ± 46.9	−22.1 ± 34.0	−2.1 ± 14.2
III slope, $\%N_2$/l†	2.2 ± 1.0	NM	NM	NM	2.7 ± 1.6	2.7 ± 1.4	2.7 ± 1.4	3.4 ± 0.9*

Values are means ± SD; $n = 8$ subjects. *Significantly different from control value, $P < 0.05$. †Data are average measured values rather than percent changes. ‡Changes are expressed as average differences from control values rather than %changes.

decrements to 61–68% and 84–85%, respectively, whereas corresponding SVC reductions were 42–34%. The other six subjects had average decrements ranging from 12–13% for $FEF_{25–75}$ to essentially complete recovery of SVC during the early postexposure period. Both subjects who had large objective changes also had relatively severe pulmonary symptoms near the end of O_2 breathing and during the first 1–2 recovery hours.

Recovery from effects of O_2 poisoning on pulmonary function. Average rates of SVC recovery after prolonged O_2 breathing at 2.5, 2.0, and 1.5 ATA are shown in Fig. 3. Data for the *series I* and *II* 2.0-ATA subjects are shown separately. The most rapid recovery rates occurred after breathing O_2 at 2.5 ATA for an average duration of 5.7 h and at 2.0 ATA (*series II*) for 8.4 h. In these two subject groups, SVC increased rapidly during the first 5–10 h of recovery and returned to preexposure control values within 15–30 h. Rate of SVC recovery was slower after an average 17.7-h exposure at 1.5 ATA, but this may have been related, at least in part, to the performance of BAL in six of these subjects at 8.5–10 h of recovery. Although transient reductions in lung volumes and flow rates have been found after BAL (34), average rate of SVC recovery in the six subjects who had this procedure was similar to that in three other 1.5-ATA subjects who did not. In a group of five subjects (*series I*) who breathed O_2 at 2.0 ATA for an average time of 9.1 h, performance of BAL at 8–10 h of recovery was associated with average SVC decrements of 13.6 and 21.5%, respectively, before and after lavage (Fig. 3).

Density Dependence of Flow

The average difference between maximum expiratory flow on He-O_2 with respect to that on air breathing at 50% of VC decreased significantly after O_2 breathing at 1.5 or 2.0 ATA by average values of 19.9 and 17.6%, respectively (Tables 3 and 5). After O_2 breathing at 2.5 ATA, the average difference in maximum flow was reduced by 20.4 and 22.1% at average postexposure intervals of 10.7 and 34 h, respectively, but neither of these changes was statistically significant (Table 7). The SDs for the 10.7- and 34-h data in Table 7 are unusually large because, in one of the eight subjects, the maximum expiratory flows on He-O_2 were consistently equal to or lower than the matching air values for these recovery times. This unexpected phenomenon occurred at no other time in this subject and was never observed in any of the other subjects.

There were no statistically significant changes in isoflow volumes that were calculated as part of the density dependence of flow measurements (data not shown). Most of the average postexposure volumes remained within 2% of preexposure control values. The largest observed change was a 3.4% increment at 30 h after the 2.0-ATA (*series II*) exposures.

Ventilation Uniformity

N_2 closing volumes were not significantly changed after O_2 breathing at any of the three pressures (data not shown). However, the slope of *phase III* increased significantly from an average preexposure value of 3.0 to 4.6% N_2/l at 13 h after O_2 breathing at 1.5 ATA (Table 3). The *phase III* slope also increased from a control value of 3.9 to 5.1% at 5.8 h after the 2.0-ATA exposures (Table 5), but this change was not statistically significant. It does not appear likely that the delayed rise in *phase III* slope at 57 h after O_2 breathing at 2.5 ATA (Table 7) can be attributed to the prior O_2 exposure.

Raw

There were no statistically significant changes in Raw or specific conductance after exposure to any of the three O_2 pressures.

Pulmonary Compliance

Static compliance at lung volumes near FRC was not significantly changed at average measurement times of 3.6, 5.0, and 5.5 h, respectively, after the O_2 exposures at 1.5, 2.0, and 2.5 ATA. Although many of the observed changes in lung volumes and flow rates had reversed at least partially by the time compliance measurements were obtained, TLC was still significantly reduced in

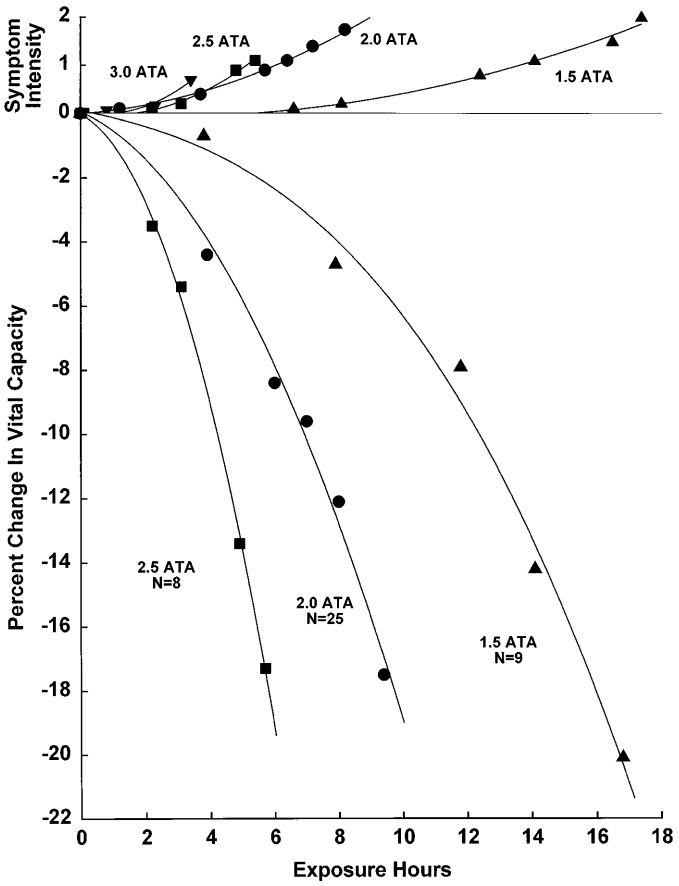

Fig. 1. Rates of development of pulmonary symptoms and slow vital capacity (SVC) decrements during continuous O_2 exposures at 3.0, 2.5, 2.0, and 1.5 ATA. Symptom intensities were determined as overall averages for 4 pulmonary symptoms in 10, 8, 13, and 9 subjects, respectively, at 3.0, 2.5, 2.0, and 1.5 ATA. Numbers of subjects (*n*) included in average SVC data at 2.5, 2.0, and 1.5 ATA are shown. SVC was not measured during 3.0-ATA exposures (8). Of 25 2.0-ATA subjects, 15 were studied as part of Predictive Studies V and 10 were studied in a previous series of experiments (10). Smooth curves were drawn by eye through average SVC data and symptom scores. The mathematical description of the overall data, for derivation of pulmonary oxygen tolerance predictions, is being derived by a log probit, "dose-effect" analysis. At each O_2 pressure, decrease in SVC started before onset of symptoms and became significant while symptom intensity was still mild. Although average rates of symptom development correlated in general with average rates of SVC reduction, this did not always occur in individual subjects.

the 2.0-ATA subjects. Therefore, compliance measurements at the highest possible lung volume were evaluated to investigate the possibility that decreased compliance may have contributed to the TLC reduction. Both groups of 2.0-ATA subjects (Table 1) were included in this evaluation. One *series I* subject was excluded because he had BAL several hours before his compliance measurements. Compliance measurements preceded BAL in the six other 2.0-ATA *series I* subjects who had this procedure. In the composite group of 14 men, average preexposure control values for total volume and pressure changes during slow inspiration from FRC were 2.78 liters and 15.1 cmH_2O, respectively. This volume added to FRC gave a total lung volume that was 92.6% of the TLC measured by He dilution, indicating that most subjects did not reach TLC during the very slow inspiration. The average control volume-to-pressure ratio was 0.189 l/cmH_2O. At an average postexposure duration of 5.0 h, average volume, pressure, and volume-to-pressure ratio values were significantly reduced to 2.16 liters (−22.2%), 13.5 cmH_2O (−10.5%), and 0.166 l/cmH_2O (−12.1%), respectively. In the same subjects, average TLC and SVC were significantly reduced by 8.0 and 8.9%, respectively.

Interpretation of the observed postexposure changes in lung compliance is aided by comparison of our data with the volume-pressure relationships measured by Turner et al. (35) in normal subjects within the same age range as our subjects. The curve in Fig. 4 shows the relationship of lung volume (expressed as %TLC) to static transpulmonary pressure found by Turner et al. In our subjects, average pre- and postexposure FRC volumes represent 52 and 51%, respectively, of the control TLC volume. Both lung volumes intersect the curve at ~5.5 cmH_2O. The preexposure total lung volume (92.6% TLC) in our subjects plotted at a transpulmonary pressure of 20.6 cmH_2O (5.5 + 15.1 cmH_2O) lies just below the curve (Fig. 4). Applying the same methods to our postexposure data, the total lung vol-

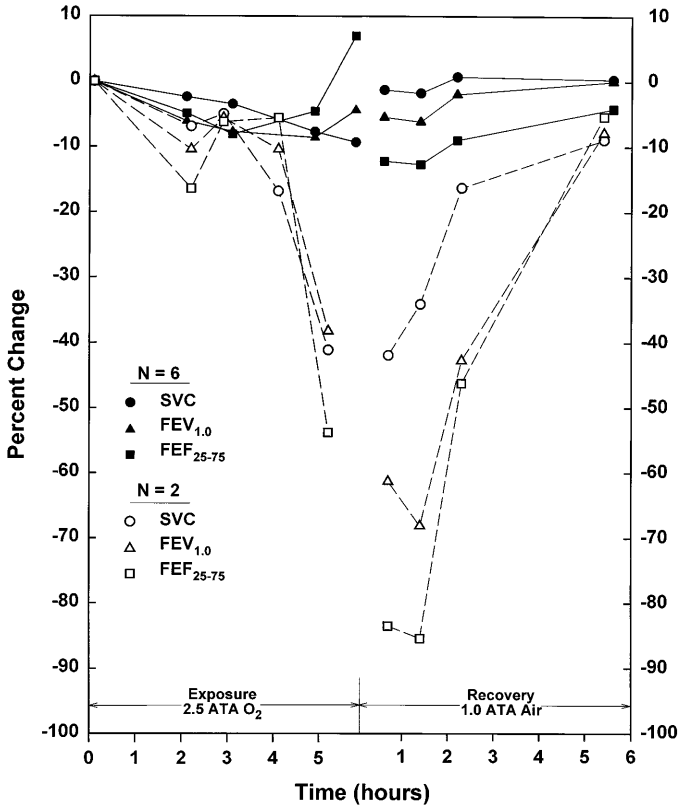

Fig. 2. Pulmonary function changes during and after O_2 breathing at 2.5 ATA for 5–6 h. Average changes in SVC, 1-s forced expired volume ($FEV_{1.0}$), and maximal midexpiratory flow rate ($FEF_{25–75}$) for 2 subjects who had unusually large deficits are compared with corresponding values in 6 other subjects who had much smaller changes. Percent changes during O_2 breathing at 2.5 ATA were calculated from control measurements at start of exposure. Preexposure control measurements at 1.0 ATA were used for postexposure recovery data. *n*, No. subjects.

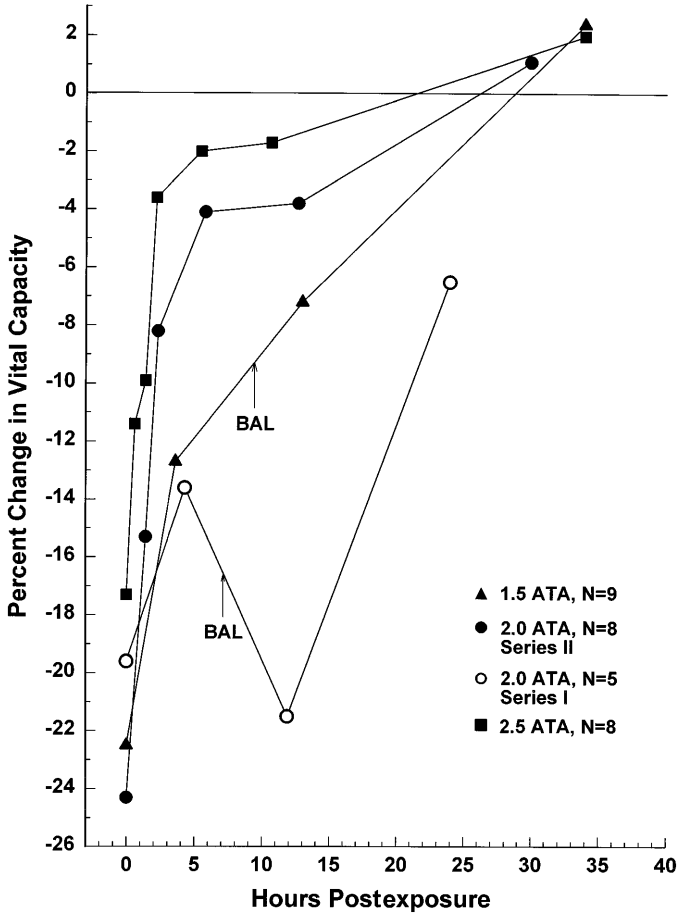

Fig. 3. Average rates of SVC recovery after O_2 exposures at 2.5, 2.0, and 1.5 ATA. BAL, bronchoalveolar lavage. *n*, No. of subjects. See text for discussion.

ume is 82% of the control TLC at a transpulmonary pressure of 19.0 cmH_2O (5.5 + 13.5 cmH_2O). The greater deviation of the postexposure point from the curve of Turner et al., which exceeds the change expected from the associated decrease in pressure (1.6 cmH_2O), is consistent with a postexposure reduction in compliance over the upper one-half of the lung. The fact that average SVC was decreased by ~23% at the end of O_2 exposure at 2.0 ATA (Table 4) and by only 9% at the time lung compliance was measured indicates that the postexposure point in Fig. 4 may reflect partial recovery from a larger reduction in lung compliance at the end of exposure.

There were no significant changes in lung compliance at near-maximal lung volumes after the O_2 exposures at 1.5 and 2.5 ATA in agreement with the concurrent observations that average TLC values after these exposures were not significantly different from preexposure control volumes (Tables 3 and 7).

D_{LCO}

Both D_{LCO} and D_L/V_A were significantly reduced after the O_2 exposures at 1.5, 2.0, and 2.5 ATA. Average percent reductions in D_{LCO} are shown in Fig. 5, and significant changes are indicated. After the 1.5-ATA exposures, the D_{LCO} changes were statistically significant only at 13 h (−10.8%), but average values were still reduced by 7.8% at 7 days postexposure. Average changes in D_L/V_A (not shown) were similar, with a significant 9.6% reduction at 34 h postexposure and a persistent change of −8.2% at 7 days. After the O_2 exposures at 2.0 and 2.5 ATA, average D_{LCO} reductions were statistically significant at all measurement times out to 8–9 days postexposure. Average changes in D_L/V_A were usually similar quantitatively but were not significant at all measurement points. At 2–4 h after the previously described 3.5-h exposures at 3.0 ATA (8), an average 1.8% decrease in D_{LCO} (n = 11) was not statistically significant (Fig. 5). In the subjects who had persistent D_{LCO} reductions after O_2 exposure, extended follow-up measurements obtained up to 5 mo later in all subjects who were available confirmed recovery to preexposure control levels.

Arterial Oxygenation and Acid-Base Balance

Average values for selected indexes of arterial oxygenation and acid-base state that were measured before, during, and after O_2 exposures at 1.5, 2.0, and 2.5 ATA are summarized in Tables 8–10. Pre- and postexposure measurements were made at rest and during exercise at 100 W on a bicycle ergometer while subjects were breathing air at 1.0 ATA. The selected indexes were also measured during O_2 breathing at the start and end of each exposure. Six subjects who breathed O_2 at 1.5 ATA for an average time of 17.6 h had a significant postexposure fall in arterial P_{O_2} during exercise (Table 8). Average alveolar-arterial P_{O_2} differences before and after O_2 exposure were 12.3 and 24.7 Torr, respectively. Arterial oxygenation was not significantly changed during or after the O_2 exposures at 2.0 or 2.5 ATA (Tables 9 and 10). Several statistically significant

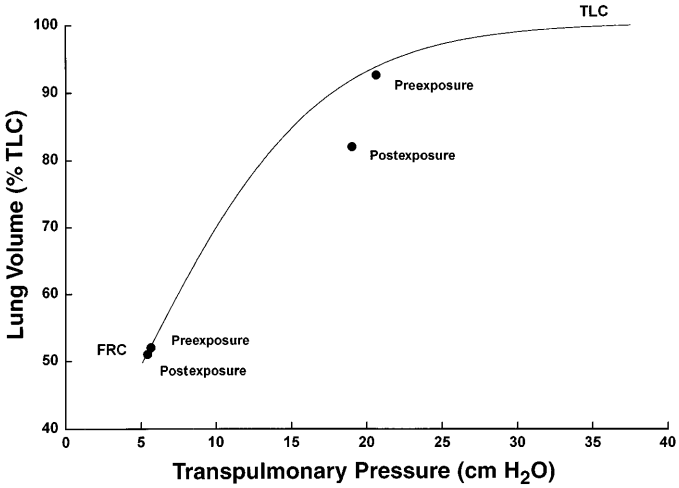

Fig. 4. Lung compliance before and after O_2 exposure at 2.0 ATA. See text for discussion. Curve from data of Turner et al. (35) represents average volume-pressure relationships for 20 subjects between ages of 18 and 33 yr. Transpulmonary pressures were measured at lung volumes of 50, 60, 70, 80, 90, and 100% total lung capacity (TLC). FRC, functional residual capacity.

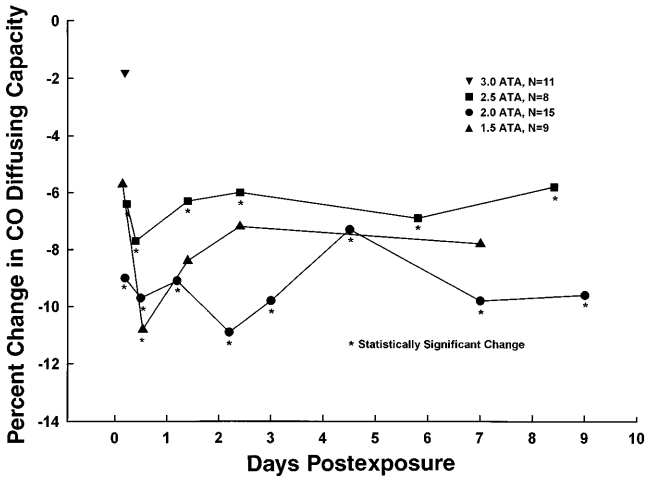

Fig. 5. Pulmonary diffusing capacity for CO after O_2 exposures at 1.5, 2.0, 2.5, and 3.0 ATA. Average percent changes relative to preexposure control values are shown. *n*, No. subjects. *$P < 0.05$.

changes in arterial P_{CO_2}, pH, or HCO_3^- were observed under various conditions of exposure (Tables 8–10). All of these changes were quantitatively small and may reflect the duration of exposure as much as any effects of hyperoxygenation.

BAL

Results of BAL procedures and related analyses are summarized in Fig. 6. Although an attempt was made to obtain pre- and postexposure data in the same subjects, this was not always possible. Results were analyzed by one-way ANOVA for different groups. Average BAL fluid return varied from 70 to 80% with no significant differences among the three groups. Average protein concentrations were also unchanged after O_2 exposure. Neutrophil percent did change significantly from a control value of 0.4 to 16.5 and 9.2% after O_2 exposure at 1.5 and 2.0 ATA, respectively. Alveolar macrophage proportions also changed from a control value of 93.1 to 77.3 and 75.4%, respectively, after the 1.5- and 2.0-ATA exposures. Both changes were statistically significant. Average total cell counts were 9.2, 11.1, and 20.3×10^4 in control, 1.5-, and 2.0-ATA groups, but neither of the postexposure changes was significant. Tracheal erythema was observed in many of the postexposure subjects.

Control Exposures to Air at 1.0 ATA

Control exposure measurements obtained in 5 of the 1.5-ATA subjects (~6 mo after their O_2 exposures) are summarized in Table 11. These measurements were made with the subjects inside the chamber while breathing humidified air via face mask at 1.0 ATA for an average duration of 19.8 h. Repeated measurements were continued thereafter to simulate a postexposure interval of ~12 h. The initial pulmonary measurements (0.1 h) were made during the early morning hours, and the final measurements (31.7 h) were obtained during the next afternoon. The only statistically significant changes were 3.5 and 4.3% reductions in FVC at the start and end of the control experiments. Corresponding SVC changes of +0.1 and −5.4% were not statistically significant. The same five subjects had significant FVC and SVC reductions of 19.7 and 20.5%, respectively, after breathing O_2 at 1.5 ATA for an average duration of 17.8 h.

Maximum Respiratory Pressures

Average changes in maximum respiratory pressures at the end of O_2 exposure at each pressure are summarized in Table 12. Maximum expiratory pressures at both TLC and FRC were significantly reduced by 18.3 and 15.5%, respectively, in subjects after breathing O_2 at 1.5 ATA for an average duration of 17.7 h. Corresponding changes in maximum inspiratory pressures were small and not statistically significant. After breathing O_2 at 2.0 ATA for an average duration of 9.0 h, subjects' maximum inspiratory pressures at RV and FRC were significantly reduced by 17.8 and 12.8%, respectively. An 11.7% reduction in maximum expiratory pressure at TLC was not statistically significant, and maximum expiratory pressure at FRC was essentially unchanged. There were no significant changes in maximum respiratory pressures after breathing O_2 at 2.5 ATA for an average duration of 5.7 h or after breathing air at 1.0 ATA for an average period of ~20 h.

Table 8. *Arterial oxygenation and acid-base balance before, during, and after continuous O_2 exposure at 1.5 ATA*

Condition	Alveolar P_{O_2}, Torr	Arterial P_{O_2}, Torr	(A-a)D_{O_2}, Torr	Arterial P_{CO_2}, Torr	Arterial pH	Arterial HCO_3^-, meq/l
			Rest air 1.0 ATA (n = 7)			
Preexposure	106.5 ± 4.4	94.0 ± 4.2	12.5 ± 3.2	36.5 ± 2.6	7.443 ± 0.020	26.8 ± 2.4
Postexposure	101.2 ± 8.3	85.4 ± 15.1	15.7 ± 9.3	37.0 ± 3.4	7.422 ± 0.033	25.7 ± 2.0
			Exercise air 1.0 ATA (n = 6)			
Preexposure	105.8 ± 6.6	93.5 ± 8.5	12.3 ± 5.3	39.7 ± 4.0	7.382 ± 0.023	24.5 ± 3.1
Postexposure	107.6 ± 3.8	82.9 ± 9.6*	24.7 ± 8.3*	37.1 ± 2.9	7.389 ± 0.032	23.2 ± 2.5*
			Rest O_2 1.5 ATA (n = 8)			
Start exposure	1,060 ± 8	970 ± 59	90 ± 66	33.2 ± 7.6	7.444 ± 0.082	23.1 ± 1.7
End exposure	1,063 ± 7*	962 ± 73	101 ± 78	30.4 ± 7.6*	7.460 ± 0.090	21.7 ± 1.9*

Values are means ± SD. *n*, No. of subjects; (A-a)D_{O_2}, alveolar-arterial O_2 difference. *Significantly different from control value, $P < 0.05$.

Table 9. *Arterial oxygenation and acid-base balance before, during, and after continuous O_2 exposure at 2.0 ATA*

Condition	Alveolar P_{O_2}, Torr	Arterial P_{O_2}, Torr	(A-a)D_{O_2}, Torr	Arterial P_{CO_2}, Torr	Arterial pH	Arterial HCO_3^-, meq/l
			Rest air 1.0 ATA (n = 15)			
Preexposure	105.2 ± 5.9	88.2 ± 7.1	17.0 ± 6.3	40.4 ± 2.7	7.405 ± 0.019	25.5 ± 1.5
Postexposure	101.2 ± 7.5*	86.9 ± 9.7	14.2 ± 8.6	42.2 ± 3.1	7.386 ± 0.023*	25.5 ± 1.0
			Exercise air 1.0 ATA (n = 15)			
Preexposure	110.5 ± 4.1	89.9 ± 4.7	20.6 ± 6.0	40.6 ± 1.8	7.375 ± 0.019	24.1 ± 1.8
Postexposure	109.9 ± 5.9	91.0 ± 6.4	18.6 ± 6.8	40.2 ± 2.9	7.375 ± 0.022	23.6 ± 1.8
			Rest O_2 2.0 ATA (n = 11)			
Start exposure	1,439 ± 4	1,342 ± 39	97 ± 37	34.5 ± 4.0	7.442 ± 0.027	23.5 ± 1.4
End exposure	1,437 ± 4*	1,345 ± 64	91 ± 64	36.6 ± 4.0*	7.415 ± 0.028*	23.5 ± 1.4
			Rest air 1.0 ATA 30-h follow-up (n = 8)			
Preexposure	103.8 ± 6.7	85.7 ± 8.7	18.2 ± 5.8	41.3 ± 2.4	7.403 ± 0.009	25.3 ± 1.6
Follow-up	102.5 ± 4.3	87.8 ± 5.0	14.7 ± 3.5	41.2 ± 3.5	7.401 ± 0.016	25.4 ± 1.8
			Exercise air 1.0 ATA 30-h follow-up (n = 8)			
Preexposure	113.0 ± 3.6	89.5 ± 5.4	23.5 ± 5.5	40.8 ± 2.3	7.373 ± 0.022	23.4 ± 2.1
Follow-up	113.2 ± 3.0	92.1 ± 5.7	21.0 ± 4.0	40.4 ± 1.3	7.372 ± 0.011	23.2 ± 1.0

Values are means ± SD. *n*, No. of subjects. * Significantly different from control value, $P < 0.05$.

DISCUSSION

This study summarizes the average effects on selected indexes of pulmonary function that were measured during and after continuous O_2 breathing at 1.5, 2.0, and 2.5 ATA for durations that produced prominent consequences of pulmonary O_2 poisoning. Another pulmonary component of the integrated series, which described the effects of breathing O_2 at 3.0 ATA for 3.5 h, has been reported previously (8). A major purpose for the performance of the composite study was to obtain data that can be used for the predictive derivation of pressure-duration, dose-response descriptions of toxic O_2 effects on sensitive indexes of pulmonary function throughout the selected range of conditions. The postexposure data were obtained to describe the relative rates at which functional deficits are reversed on resumption of air breathing at 1.0 ATA. Together with prior studies (4, 9–11, 14, 16, 28, 30), the results provide the basic data that facilitate improved quantitative predictions of O_2 effects in varied pressure-duration exposure combinations (5).

Variable Patterns and Degrees of O_2 Effects on Pulmonary Function

All of the O_2 exposures produced significant decrements in pulmonary mechanical function, and the patterns and magnitudes of these effects varied markedly among the different P_{O_2}-duration combinations. Relative changes in average expiratory and inspiratory lung volumes and flow rates are compared in Fig. 7 to illustrate some of these differences. At the end of the O_2 exposures at 1.5 ATA, the changes in expiratory parameters varied from essentially no change in FEF_{25-75} (−1%) to a 25% decrease in peak expiratory flow rate, whereas all four inspiratory parameters were decreased by 22–23%. At the end of the 2.0-ATA exposures, statistically significant decrements in all four expiratory parameters ranged from 19 to 22%, and forced inspiratory vital capacity was similarly decreased by 22%, but forced inspiratory volume in 1 s, peak inspiratory flow rate, and maximal inspiratory flow rate at 50% of inspired volume were reduced by 33,

Table 10. *Arterial oxygenation and acid-base balance before, during, and after continuous O_2 exposure at 2.5 ATA*

Condition	Alveolar P_{O_2}, Torr	Arterial P_{O_2}, Torr	(A-a)D_{O_2}, Torr	Arterial P_{CO_2}, Torr	Arterial pH	Arterial HCO_3^-, meq/l
			Rest air 1.0 ATA (n = 7)			
Preexposure	103.4 ± 5.5	91.6 ± 4.9	11.8 ± 5.4	38.2 ± 3.7	7.428 ± 0.022	24.9 ± 1.1
Postexposure	103.0 ± 7.4	89.1 ± 10.3	13.9 ± 6.6	39.5 ± 4.7	7.403 ± 0.037	24.4 ± 1.3
			Exercise air 1.0 ATA (n = 8)			
Preexposure	104.4 ± 3.7	88.4 ± 4.3	16.0 ± 2.0	41.2 ± 1.9	7.382 ± 0.016	24.2 ± 1.4
Postexposure	105.1 ± 4.5	86.2 ± 6.2	18.9 ± 4.1	40.2 ± 2.4	7.384 ± 0.017	23.7 ± 1.4*
			Rest O_2 2.5 ATA (n = 8)			
Start exposure	1,807 ± 7	1,697 ± 45	110 ± 48	33.1 ± 2.0	7.465 ± 0.026	23.5 ± 1.8
End exposure	1,807 ± 7	1,735 ± 56	72 ± 52	33.5 ± 2.1	7.445 ± 0.041	22.9 ± 2.5

Values are means ± SD. *n*, No. of subjects. * Significantly different from control value, $P < 0.05$.

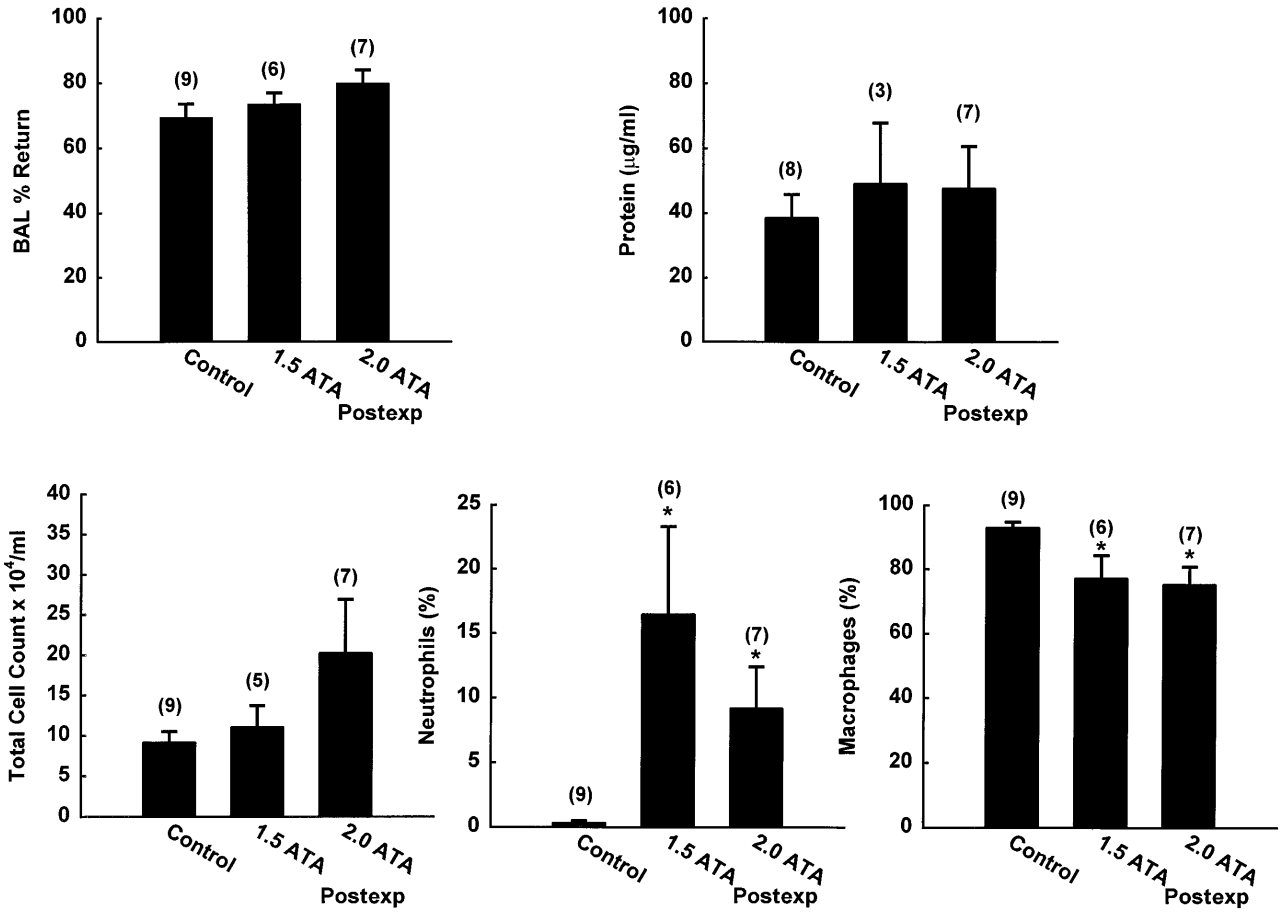

Fig. 6. Effects of O_2 exposure at 1.5 and 2.0 ATA on BAL fluid protein concentrations and inflammatory cell counts. Average values ± SE are shown. Numbers of subjects included in each average are shown in parentheses. Postexp, postexposure. *$P < 0.05$.

34, and 39%, respectively. Inspiratory flow rate reductions that exceeded the corresponding expiratory deficits were also found previously after O_2 breathing at 2.0 ATA (10). The relatively large decrements in inspiratory flow rates found in the present subjects are in accord with the concurrent 18% reduction in maximum inspiratory pressure at 2.0 ATA (Table 12).

In contrast to the predominant effects on lung inspiratory function observed at the end of the 2.0-ATA O_2 exposures, several indexes of lung expiratory function

Table 11. *Pulmonary function during air breathing at 1.0 ATA*

Parameter	Preexposure Control	Exposure Duration, h				
		0.1	8.0	17.5	22.8	31.7
		%Change from control value				
FVC, liters	5.29 ± 0.77	−3.5 ± 4.2*	−0.8 ± 0.9	−2.8 ± 1.2	−0.3 ± 1.2	−4.3 ± 1.7*
$FEV_{1.0}$, liters	4.31 ± 0.48	−4.3 ± 2.3	−1.1 ± 2.8	−2.8 ± 2.5	0.7 ± 3.0	−2.9 ± 5.7
$FEV_{1.0}/FVC$†	0.82 ± 0.04	0.81 ± 0.06	0.82 ± 0.06	0.82 ± 0.06	0.82 ± 0.05	0.83 ± 0.05
FEF_{25-75}, l/s	4.29 ± 0.51	−3.5 ± 9.8	0.7 ± 9.5	−2.4 ± 8.7	5.5 ± 9.8	2.1 ± 13.3
SVC, liters	5.33 ± 0.64	0.1 ± 4.3	−0.1 ± 2.8	0.0 ± 5.3	0.0 ± 4.8	−5.4 ± 4.5
IC, liters	3.36 ± 0.73	−1.5 ± 10.2	3.6 ± 19.3	0.6 ± 13.1	−1.5 ± 12.9	−4.6 ± 10.5
ERV, liters	1.97 ± 0.38	4.4 ± 16.8	−5.4 ± 21.5	−0.5 ± 11.4	1.5 ± 9.3	−8.0 ± 11.6
TLC, liters	6.55 ± 1.13	NM	NM	NM	0.9 ± 1.9	−4.2 ± 5.4
FRC, liters	3.19 ± 0.77	NM	NM	NM	2.9 ± 13.4	−5.3 ± 17.5
RV, liters	1.22 ± 0.62	NM	NM	NM	4.3 ± 20.0	−2.5 ± 30.2
$\%\Delta\dot{V}_{max,50}$‡	45.2 ± 13.9	NM	NM	NM	10.6 ± 19.0	8.4 ± 23.9
III slope, $\%N_2$/l†	2.7 ± 2.9	NM	NM	NM	1.8 ± 1.4	3.0 ± 1.5

Values are means ± SD; $n = 5$ subjects. *Significantly different from control value, $P < 0.05$. †Data are average measured values rather than %changes. ‡Changes expressed as average differences from control values rather than %changes.

Table 12. *Effects of O_2 exposure on maximum respiratory pressures*

Parameter	Preexposure Control	End Exposure	
		Change	%Change†
1.5 ATA O_2 (n = 9)			
MIP (RV)	118.5 ± 36.4	−4.2 ± 14.5	−3.5
MIP (FRC)	109.4 ± 32.1	0.5 ± 20.6	0.4
MEP (TLC)	112.3 ± 23.0	−20.5 ± 23.4*	−18.3
MEP (FRC)	93.8 ± 19.7	−14.5 ± 16.0*	−15.5
2.0 ATA O_2 (n = 11)			
MIP (RV)	132.3 ± 24.8	−23.5 ± 22.5*	−17.8
MIP (FRC)	118.5 ± 20.7	−15.2 ± 16.6*	−12.8
MEP (TLC)	133.7 ± 38.6	−15.6 ± 27.2	−11.7
MEP (FRC)	120.6 ± 22.7	−1.5 ± 21.4	−1.2
2.5 ATA O_2 (n = 8)			
MIP (RV)	135.6 ± 39.8	4.1 ± 24.8	3.0
MIP (FRC)	122.0 ± 32.5	−6.2 ± 18.6	−5.1
MEP (TLC)	149.2 ± 54.7	−14.3 ± 27.5	−9.6
MEP (FRC)	120.3 ± 31.9	2.0 ± 10.3	1.7
1.0 ATA air (n = 5)			
MIP (RV)	112.1 ± 32.5	−3.4 ± 17.4	−3.0
MIP (FRC)	85.9 ± 22.9	6.6 ± 8.3	7.7
MEP (TLC)	102.0 ± 14.6	−1.3 ± 20.4	−1.3
MEP (FRC)	89.7 ± 16.7	1.8 ± 19.1	2.0

Values are means ± SD expressed in cmH_2O. *n*, No. of subjects; MIP (RV), maximum inspiratory pressure at residual volume; MIP (FRC), maximum inspiratory pressure at functional residual capacity; MEP (TLC), maximum expiratory pressure at total lung capacity; MEP (FRC), maximum expiratory pressure at functional residual capacity. *Significantly different from control value, $P < 0.05$. †Calculated from average change with respect to average control value.

were most affected in the two subjects who had the largest pulmonary function changes at 1.4 h after cessation of O_2 breathing at 2.5 ATA (Figs. 2 and 7). Although average FVC and forced inspiratory vital capacity decrements for these two individuals were nearly identical, the average changes in $FEV_{1.0}$, peak expiratory flow rate, and FEF_{25-75} greatly exceeded the corresponding inspiratory reductions (Fig. 7). Average changes for the other six subjects at 1.4 h after the 2.5 ATA exposures ranged from −4 to −13% for the expiratory parameters (Fig. 2) and from −2 to +1% for the inspiratory values. Maximum respiratory pressures for the two subjects represented in Fig. 7 did not differ significantly from the average values for all eight subjects (Table 12).

Yet another pattern of changes in pulmonary function (not shown in Fig. 7) was found in a subject who convulsed after breathing O_2 for 3 h at 3.0 ATA (8). With respect to preexposure control values, results of flow-volume curves performed 4 h after the convulsion indicated that this subject had increased his maximal flow rates during early expiration (25% of expired volume) and early inspiration (25% of inspired volume) by 33 and 83%, respectively. Corresponding average flow rates in 12 other subjects who did not convulse during 3.5-h exposures at 3.0 ATA were reduced by 12 and 4%, respectively. Bronchodilation induced by sympathetic stimulation may have been the basis for the unusual postconvulsion results.

Direct and Indirect Effects of Pulmonary O_2 Toxicity

It is well established that the effects of O_2 toxicity are initiated by the propagation of O_2-derived free radicals that interact with nearby enzymes and cellular constituents (5, 21). However, these direct effects induce and are accompanied by cellular and tissue reactions that are poorly defined and cannot now be distinguished from the initial biochemical events. Evaluation of the subsequent pulmonary function deficits is further complicated by the fact that they represent responses to a composite of direct and indirect toxic effects along with the consequences of these effects. Although it will not be possible to fully define the pathological origins of the functional deficits found in our subjects, reasonable cause and effect associations for some of our observations can be made and probable targets for the earliest effects of pulmonary O_2 toxicity can be identified.

Acute inflammatory effects. The increased percentages of neutrophils found postexposure in BAL fluid (Fig. 6), tracheal erythema, and associated symptoms of tracheal irritation (Fig. 1) are all consistent with acute inflammatory responses to prolonged O_2 breathing at 1.5 and 2.0 ATA. Lavage fluid protein concentrations were not increased postexposure (Fig. 6). Our results differ from those of Davis et al. (12), who found an increased albumin concentration with no changes in lung inflammatory cells in subjects who breathed O_2 at 1.0 ATA for an average period of 17 h. There are important differences between the two studies with respect to both the relative degrees of pulmonary O_2 poisoning and the timing of BAL procedures. The 1.0-ATA subjects had BAL immediately after O_2 exposure and had no pulmonary function measurements for at least 2 wk (12). Breathing O_2 at 1.0 ATA for 17 h would be expected to decrease VC by <5% (14). Our subjects had more severe O_2 exposures, but BAL was delayed for average postexposure intervals of 9.4 and 7.3 h after O_2 breathing at 1.5 and 2.0 ATA, respectively, to allow time for extensive postexposure measurements of pulmonary function. It is also possible that the divergent results of the two studies may reflect responses to different combinations of O_2 pressure and exposure duration such as those illustrated in Fig. 7.

The seven subjects who had BAL after O_2 exposure at 2.0 ATA also had measurements of 24-h urine desmosine contents as a possible index of acute lung injury. Frozen samples of urine collections from our subjects were analyzed in a different laboratory by Starcher et al. (32). Unexpectedly, urine desmosine content was significantly reduced on the day of exposure and one day postexposure, with partial recovery on the second postexposure day. These results are consistent with decreased elastin degradation despite the increased percentage of neutrophils in BAL fluid. They are also consistent with the observation that human neutrophil β_2-integrin-dependent adherence is reversibly inhibited by hyperbaric O_2 exposure (33).

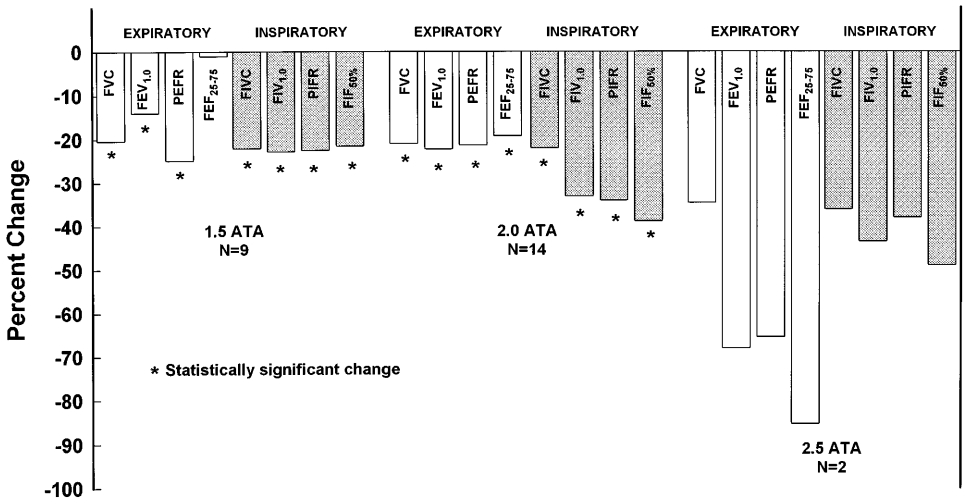

Fig. 7. Average changes in expiratory and inspiratory lung volumes and flow rates after O_2 exposures at 1.5, 2.0, and 2.5 ATA. *n*, No. subjects; FVC, forced vital capacity; PEFR, peak expiratory flow rate; FIVC, forced inspiratory vital capacity; $FIV_{1.0}$, forced inspiratory volume in 1 s; PIFR, peak inspiratory flow rate; $FIF_{50\%}$, maximal inspiratory flow rate at 50% of inspired volume. See text for discussion. $*P < 0.05$.

Pulmonary-central nervous system interaction. It is considered probable that the unusually early onset, prominent magnitude, and rapid reversal of the effects found in two of the 2.5-ATA subjects (Fig. 2) are consistent with an exacerbation of localized manifestations of pulmonary O_2 poisoning by interaction with concurrent effects of O_2 toxicity on the central nervous system. Interaction of pulmonary and neurological effects of O_2 toxicity has been well documented in animal studies (9), but not yet in humans. The form of pulmonary-neurological interaction that has been demonstrated most clearly in animals is an augmentation of direct toxic effects and superimposed lung tissue reactions by the severe sympathetic discharge induced by O_2 convulsions (2). As stated above, a relatively mild form of such an interaction may have occurred in a subject who convulsed while breathing O_2 at 3.0 ATA (8).

Although none of the subjects convulsed during O_2 breathing at 2.5 ATA, some other form of pulmonary-neurological interaction may have occurred. Vagally induced narrowing of peripheral airways could have contributed to the large decrements in $FEV_{1.0}$ and FEF_{25-75} that occurred in the two subjects at 2.5 ATA (Fig. 2), as well as the rapid onset and reversal of these effects. Although there is no direct evidence of vagally induced bronchoconstriction, some of the observed cardiac responses to O_2 exposure could reflect prominent vagal influences. One subject had a syncopal episode associated with extreme bradycardia during O_2 breathing at 3.0 ATA (29). In another subject, who breathed O_2 at 2.0 ATA for 8 h, complete blunting of the reflex tachycardia that occurs in response to active standing was found at 2 h postexposure (29). The demonstration that vagally induced bradycardia occurs during O_2 breathing at 1.0 ATA (15) indicates that both of the cardiac events observed at higher O_2 pressures may represent augmentation of vagal influences on cardiac function.

Effects on peripheral airways. Evidence that the larger airways did not contribute significantly to the observed reductions in midexpiratory flow rates is provided by the absence of significant changes in Raw or specific airway conductance after any of the O_2 exposures. The occurrence of relatively large decrements in FEF_{25-75} concurrently with smaller percent changes in FVC and $FEV_{1.0}$ after breathing O_2 at 2.0 and 2.5 ATA (Tables 5 and 7), as well as after the previously reported 3.0-ATA exposures (8), lends further support to an increased small airway Raw (26). The significant reductions in density dependence of flow that were found after O_2 breathing at 1.5 and 2.0 ATA (Tables 3 and 5) are also considered to be consistent with flow limitation in peripheral airways, where normally laminar flow is less density dependent than in larger more proximal airways where flow is normally turbulent (13).

The relative changes in FEF_{25-75} over the range of O_2 pressures shown in Fig. 7 are consistent with a progressive narrowing of peripheral airways at higher O_2 pressures, probably via an interaction of direct pulmonary effects with indirect central nervous system effects of O_2 toxicity. Average values of FEF_{25-75} varied from no change at the end of the 1.5-ATA exposures (Fig. 7), to a statistically significant reduction of 19% at the end of O_2 breathing at 2.0 ATA, to a maximal decrease of 85% at 1.4 h postexposure in the two subjects who had the largest changes at 2.5 ATA (Figs. 2 and 7).

Effects on lung compliance. Static compliance at near-maximal lung volumes was significantly reduced after the O_2 exposures at 2.0 ATA (Fig. 4). A previous group of five subjects who breathed O_2 at 2.0 ATA for an average duration of 9.3 h (16) had a significant 16% reduction in dynamic lung compliance measured during normal tidal breathing. In two subjects who breathed O_2 at 1.0 ATA for 30 and 48 h (4), dynamic compliance measured over full VC breaths was reduced by 50 and 22%, respectively. Most of the human subjects studied in this laboratory and elsewhere (4) have had relatively small and clinically insignificant reductions in lung compliance under conditions that were necessarily limited to the production of early, reversible degrees of pulmonary O_2 poisoning. However, extensive animal investigation has shown that decreased compliance is

consistently produced by severe to near-lethal degrees of pulmonary O_2 toxicity (9).

Burger and Mead (3) showed that 3 h of quiet O_2 breathing at pressures ranging from 0.39 to 2.0 ATA were accompanied by absorption atelectasis with significant reductions in static lung compliance that could be reversed rapidly by a series of deep breaths. In contrast, one subject, who took deep breaths every 15 min during an 11-h O_2 exposure at 2.0 ATA, experienced severe symptoms with no associated reductions in VC or lung compliance. Although we cannot say for certain that absorption atelectasis did not contribute significantly to the compliance changes found in our subjects (Fig. 4), there were no significant changes in alveolar-arterial P_{O_2} differences measured at the end of the O_2 exposures at 1.5, 2.0, and 2.5 ATA (Tables 8–10). Furthermore, lung compliance was not reduced after the O_2 exposures at 1.5 and 2.5 ATA. The possibility that the observed compliance changes can be attributed, at least in part, to a reversible impairment of surfactant synthesis or secretion is supported by the finding that rabbits had reversible reductions in pulmonary surfactant and lung compliance after 64 h of O_2 breathing at 1.0 ATA (18).

Respiratory muscle effects. Maximum respiratory pressures were measured in these subjects to confirm and extend a previous observation that inspiratory force appeared to be reduced after prolonged O_2 breathing at 2.0 ATA (16). Although maximum inspiratory pressure was significantly decreased after the present 2.0-ATA exposures (Table 12), the concurrent decrements in maximum expiratory pressure were unexpectedly smaller and not statistically significant. At the end of the 1.5-ATA O_2 exposures, the observation that maximum expiratory pressure was significantly reduced with essentially no measurable effect on inspiratory force was equally unexpected. Previous in vitro studies indicate that skeletal muscle is relatively resistant to O_2 toxicity (1, 31). Reduction in TLC or an increase in RV at the end of the O_2 exposures would introduce mechanical disadvantages during expiration and inspiration, respectively, but this would not account for the opposite results found at 1.5 and 2.0 ATA. We know of no other published measurements of respiratory muscle force in human subjects exposed to toxic O_2 pressures.

Effects on VC. Decrease in VC is one of the most consistent manifestations of pulmonary O_2 poisoning that has been observed in studies of pulmonary tolerance to O_2 pressures of 0.75 ATA or higher (4, 5, 9–11, 14, 28). Rates of fall increase progressively with elevation of the inspired P_{O_2} (Fig. 1). Reversal of O_2-induced VC decrements usually occurs within 24 h (Fig. 3), but complete recovery can be delayed for several days (10) or even weeks (4) in some severely exposed subjects. Despite its initial observation more than 50 years ago (11), the pathophysiological basis for this effect is not completely understood. The most likely mechanism is a composite of effects in which individual components vary at different O_2 pressures and exposure durations. Decreased lung compliance (Fig. 4) and reduced force of inspiration (Table 12, Fig. 7) appear to contribute to VC reduction in at least some conditions of O_2 exposure. Additional factors, such as pulmonary edema and atelectasis, will very likely be involved if exposures are continued beyond the early, reversible degrees of pulmonary O_2 poisoning that were experienced by our subjects.

Recovery from Effects of O_2 Poisoning on Pulmonary Function

Recovery from pulmonary O_2 poisoning has to be considered a complex process that involves several overlapping sequences that include rapid reversal of early intracellular biochemical events, a slower recovery from alterations in cellular structure and function, and in more severe exposures, may involve repair of irreversible structural damage (22). Even with the fully reversible degrees of pulmonary O_2 poisoning that were produced in our subjects, the rates and patterns of recovery varied among different components of measurable pulmonary functions. For example, after both the 2.0- and 2.5-ATA exposures, SVC increased rapidly during the early postexposure hours (Fig. 3), whereas FEF_{25-75} fell to its lowest values during the same period before beginning to recover within the next few hours (Fig. 2). The deterioration or delayed recovery of midexpiratory flow rates during the early postexposure period could not represent the continued direct action of O_2 radicals on lung enzymes and cells. A more likely possibility is that the observed postexposure changes reflect some type of functional or structural reaction to the direct pulmonary effects that occurred during the preceding period of toxic O_2 exposure.

In contrast to the rapid recovery of SVC after O_2 exposure (Fig. 3), small but statistically significant reductions in $D_{L_{CO}}$ persisted for at least 8–9 days postexposure (Fig. 5). However, the $D_{L_{CO}}$ changes were not associated with detectable impairment of arterial oxygenation, with the single exception of a significant decrease in arterial P_{O_2} and increase in the alveolar-arterial P_{O_2} difference during exercise while subjects were breathing air after the 1.5-ATA O_2 exposures (Table 8). Decrease in $D_{L_{CO}}$ was associated with a significant reduction in pulmonary capillary blood volume in a previous group of subjects studied after O_2 exposure at 2.0 ATA (30), but these measurements were not continued beyond 20 h postexposure. Regardless of the pathophysiological mechanisms for the occurrence and delayed reversal of $D_{L_{CO}}$ deficits (Fig. 5), this measurement appears to be a sensitive index of complete recovery from pulmonary O_2 poisoning.

Human Limits of Pulmonary O_2 Tolerance

As stated previously, one of the primary objectives of Predictive Studies V was the identification and quantitative assessment of pulmonary manifestations of O_2 toxicity in continuous exposures that approach the practical limits of human tolerance over a range of O_2 pressures that are useful in diving and general hyperbaric medicine. Although pulmonary symptoms and

statistically significant changes in pulmonary function occurred at all O_2 pressures that were studied, these effects consistently limited the safe or subjectively tolerable duration of exposure only at 1.5 and 2.0 ATA (Fig. 1). Actual exposure durations ranged from 16.8 to 19.0 h at 1.5 ATA and from 5.5 to 11.9 h at 2.0 ATA. Pulmonary effects were also limiting in two of the eight subjects studied at 2.5 ATA (Fig. 2). Of the 13 subjects who had pulmonary function measurements before and after breathing O_2 at 3.0 ATA for 3.5 h (8), 2 experienced extreme anxiety that was precipitated by a prominent sensation of chest tightness near the end of exposure. For most of the other subjects who were studied at 3.0 ATA, a reversible constriction of visual field area was an evident limiting manifestation of O_2 toxicity (24).

In the subjects whose exposure durations at any pressure were considered to be limited by subjective or objective effects of pulmonary O_2 toxicity, the patterns and magnitudes of measured effects varied widely at different pressures (Fig. 7) and among different individuals (Fig. 2). Although the reasons for these differences are not fully understood at the present time, it is important to recognize that all of the observed effects were fully reversible and, with few exceptions, were relatively small in magnitude and functional significance when compared with the changes that are considered to be clinically significant in various forms of pulmonary disease (17). It is equally important to be aware that continuous exposures beyond the P_{O_2}-duration limits selected for this study could produce more severe effects of O_2 toxicity that are not completely reversible. The same outcome could be produced by closely repeated exposures of the same individual to effects of pulmonary O_2 toxicity that are fully reversible after a single exposure.

After the extensive investigation of pulmonary manifestations of O_2 toxicity that is described in this study, change in VC remains one of the most useful quantitative indexes of pulmonary O_2-poisoning effect in well-trained subjects who can perform spirometry or flow-volume curves at regular intervals during continuous O_2 exposures (Fig. 1). Decrease in VC appears to be one of the most consistent and sensitive manifestations of hyperoxic impairment of pulmonary function, and the relative rates of VC decrease over the selected range of O_2 pressures (Fig. 1) reflect increasing degrees of direct toxic actions on lung cells and enzymes at increasing levels of inspired P_{O_2}. Such relationships can be used to establish guidelines for safe and effective applications of hyperoxia in therapy and diving. They also provide baseline control data for subsequent development of practical methods for investigating extension of inherent O_2 tolerance. However, even if the degrees of direct toxic actions are the same, individual variability exists in the measurable consequences of these actions (Fig. 2), along with dissimilar patterns of pulmonary function deficits for different combinations of O_2 pressure and exposure duration (Fig. 7). This indicates that no single index of pulmonary function is uniquely satisfactory for monitoring the rate of development of pulmonary O_2-poisoning effects in all individuals and under all pressure-duration conditions of exposure. The deviations from the average predictive relationships, which occur in different individuals or under varying conditions of toxic O_2 exposure and subsequent recovery, may actually represent differences, not in susceptibility to the chemical events that occur during prolonged O_2 breathing, but in the consequences of or reactions to those chemical events.

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