Hypoxic ventilatory sensitivity in men is not reduced by prolonged hyperoxia (Predictive Studies V and VI)

R. GELFAND, C. J. LAMBERTSEN, J. M. CLARK, AND E. HOPKIN
Institute for Environmental Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania 19104-6068

Gelfand, R., C. J. Lambertsen, J. M. Clark, and E. Hopkin. Hypoxic ventilatory sensitivity in men is not reduced by prolonged hyperoxia (Predictive Studies V and VI). *J. Appl. Physiol.* 84(1): 292–302, 1998.—Potential adverse effects on the O_2-sensing function of the carotid body when its cells are exposed to toxic O_2 pressures were assessed during investigations of human organ tolerance to prolonged continuous and intermittent hyperoxia (Predictive Studies V and VI). Isocapnic hypoxic ventilatory responses (HVR) were determined at 1.0 ATA before and after severe hyperoxic exposures: *1*) continuous O_2 breathing at 1.5, 2.0, and 2.5 ATA for 17.7, 9.0, and 5.7 h and *2*) intermittent O_2 breathing at 2.0 ATA (30 min O_2-30 min normoxia) for 14.3 O_2 h within 30-h total time. Postexposure curvature of HVR hyperbolas was not reduced compared with preexposure controls. The hyperbolas were temporarily elevated to higher ventilations than controls due to increments in respiratory frequency that were proportional to O_2 exposure time, not O_2 pressure. In humans, prolonged hyperoxia does not attenuate the hypoxia-sensing function of the peripheral chemoreceptors, even after exposures that approach limits of human pulmonary and central nervous system O_2 tolerance. Current applications of hyperoxia in hyperbaric O_2 therapy and in subsea- and aerospace-related operations are guided by and are well within these exposure limits.

hypoxia; oxygen toxicity; oxygen poisoning; oxygen limits; oxygen tolerance extension; hyperbaric oxygen therapy; intermittent hyperoxia; carotid body; chemoreceptors; respiratory control

PATIENTS breathe O_2 at increased ambient pressures in therapeutic exposures for a variety of medical conditions in which beneficial effects have been demonstrated (2). Hyperoxia is also employed to improve the speed and safety of decompression procedures in scientific, commercial, and military diving as well as in aerospace operations (23). The carotid body structure, by virtue of the capillary density and high rate of perfusion, is exposed to high P_{O_2} levels when elevated partial pressures of O_2 are inspired. In the design of comprehensive programs (Predictive Studies, PS) to investigate limits of human organ tolerance to continuous hyperoxia (PS-V) (26) and extension of tolerance to hyperoxia in humans (PS-VI) (25), it was necessary to consider that toxic effects of prolonged O_2 exposures on these O_2-sensing organelles might be expressed as impairment of their hypoxia-sensing function. In recognition of this possibility, determinations of the ventilatory response to hypoxia were incorporated into the overall Predictive Studies experiment plans (10, 11, 13–15). Other investigators working concurrently have reported that the chemosensory hypoxic response function of the carotid body in cats was essentially obliterated by prolonged exposure to normobaric hyperoxia (22) and that the ventilatory response to hypoxia in rats was blunted progressively and reversibly by exposure to O_2 pressures ranging from 1.0 to 3.0 ATA (1, 27, 32). In contrast to the results reported in animals, those reported here show that hypoxic ventilatory sensitivity in humans is not attenuated after exposures to O_2 pressures of 1.5, 2.0, and 2.5 ATA for durations that produce measurable effects on central nervous system (CNS) and lung functions, approach the limits of human CNS and pulmonary tolerance, and substantially exceed those currently employed in hyperbaric O_2 therapy or in diving and aerospace operational uses of hyperoxia. Preliminary reports have been presented elsewhere (10, 11, 13, 15).

METHODS

The investigations described here represent one of several respiratory-related parts of the overall PS-V and PS-VI O_2 tolerance programs. Elements of the interdisciplinary investigative plans have been described elsewhere (25, 26). Briefly, the multiyear program included investigation of rates of development of visual, auditory-vestibular, neurological, pulmonary, cardiac, mental performance, and respiratory effects of hyperoxia over the O_2 pressure range of 1.5–3.0 ATA. Determinations of the hypoxic ventilatory response (HVR) were not part of the O_2 exposures at 3.0 ATA. "Modules" consisting of sequences of experimental measurements of specific duration were carried out at predefined intervals before, repeatedly during, and after experimental exposures to hyperoxia. HVR was determined in a laboratory room at 1.0 ATA before exposures in the pressure chamber were started (preexposure), after they were completed (postexposure), and on a subsequent day (follow-up). The same experiment procedures were followed in all exposures, which covered a span of , 4.5 yr (continuous O_2, PS-V) and 8 mo , 1 yr later (intermittent O_2, PS-VI).

Experiment protocols. In the following, the continuous exposures of PS-V are referred to by their O_2 exposure pressures, e.g., 0.2 ATA (or 1.0 ATA air), 1.5 ATA, 2.0 ATA, and 2.5 ATA O_2. The intermittent exposure of PS-VI is referred to as 2.0 ATA 30:30 (30 min O_2-30 min normoxia). Table 1 summarizes exposure pressures, durations, and numbers of subjects in the different subject groups. Table 2 summarizes elapsed times from preexposure determinations of HVR to start of O_2 breathing at elevated pressures, from end of O_2 breathing to postexposure determinations of HVR, and from end of O_2 breathing to follow-up determinations of HVR. Determination of HVR was a part of pre- and postexposure experiment preparations and sequences of measurements. It was grouped with determinations of the hypercapnic ventilatory response and alveolar-arterial O_2 gradients at rest and during light exercise. In the preexposure period, other events close in time frequently included arterial catheterization and pulmonary function tests. This was followed by an experiment control module at 1.0 ATA (26) and then compression to

Table 1. *Exposure pressures, number of subjects, oxygen exposure times, and observed values of rates of change of end-tidal P_{O_2} during HVR determinations*

O_2 Exposure Pressure, ATA	*n*	O_2 Exposure Time, h	Preexposure dP_{O_2}/dt	Postexposure dP_{O_2}/dt	Follow-up dP_{O_2}/dt
0.2	5*	20.0	10.46 0.8	9.36 0.8	
1.5	9	17.7	9.76 0.4	10.86 0.6	
1.5	5†	17.8	10.16 0.5	10.06 0.9	10.46 0.8
2.0	6‡	9.0	9.76 0.7	9.96 0.6	9.36 0.7
2.5	8	5.7	9.66 0.3	9.76 0.4	9.46 0.3
2.0 30:30	5§	14.3	8.56 0.7	8.96 0.5	9.56 0.6

Values are means 6 SE of rate of change of end-tidal P_{O_2} (dP_{O_2}/dt) in Torr/min for *n* subjects. Postexposure and follow-up values are not different from their corresponding preexposure controls. HVR, hypoxic ventilatory response 30:30, 30 min O_2-30 min normoxia. * Five subjects of the 0.2-ATA O_2 exposures are a subgroup of nine who participated at 1.5ATA O_2. Exposures at 0.2ATA O_2 followed those at 1.5ATA O_2 by , 6 mo. Preexposure values for 0.2ATA O_2 are therefore also follow-up values for subgroup of 5 subjects exposed at 1.5 ATA O_2 (see below). †These values are for subgroup of 5 subjects who participated in 0.2-ATA O_2 exposures. ‡Eight subjects participated. Results for 2 not included here due to relatively short durations of O_2 exposure. O_2 was discontinued early due to abrupt and rapid rate of decline in vital capacity. §Six subjects participated. Results for 1 not included because of limited range of end-tidal P_{O_2} and ventilation in preexposure HVR determinations.

the experiment pressure. Postexposure HVR determinations had to await completion of posthyperoxia experiment modules and repetitive tracking of recovery of pulmonary and visual functions. The scheduling of follow-up determinations on subsequent days also had to be coordinated with continued tracking of those functions. Follow-up determinations were not in the original plan for the 1.5-ATA exposures, which were the first ones with HVR determinations completed, since results of preliminary analysis indicated that postexposure ventilatory response to hypoxia was not attenuated. When further analysis indicated consistent elevation of postexposure ventilatory and respiratory frequency responses to hypoxia, delayed follow-up determinations could be scheduled for five of the nine subjects in that group (see Tables 1 and 2).

Subjects. Subjects were healthy male nonsmokers, selected from volunteers after medical examinations that included special attention to the physiological systems known to be targets of O_2 poisoning. Important to this component of the overall investigations were pulmonary function tests both before and after the O_2 exposures. Experiment protocols and informed consent procedures were approved by the Human Subjects Committee of The University of Pennsylvania.

Table 2. *Average elapsed times from preexposure HVR determinations to start of O_2 breathing and from end of O_2 exposure to postexposure and follow-up HVR determinations*

O_2 Exposure Pressure, ATA	Preexposure HVR to Start of O_2	End of O_2 to Postexposure HVR	End of O_2 to Follow-up HVR
0.2	7.7 h	0.6 h	
1.5	7.0 h*	1.9 h	
1.5†	6.1 h‡	2.3 h	6.4 mo§
2.0	7.4 h	3.7 h	1 day
2.5	10.4 h	3.6 h	10 days
2.0 30:30	12 days	3.2 h	1 day

* For 8 of 9 subjects; for 9th subject, 9 days. †*n* 5 5. ‡For 4 of 5 subjects of 1.5-ATA O_2 group who also had 0.2 ATA control exposures; for 5th subject, 9 days. §See Table 1 for explanation.

Apparatus and experimental procedures. The isocapnic ventilatory response to progressive hypoxia was obtained using the same experimental apparatus throughout the multiyear program. The rebreathing system, identical in function to that described by others (29), employed a Stead-Wells spirometer (Collins, Braintree, MA) in place of a bag-in-box to contain the rebreathed gas mixture. The spirometer was modified with a counterbalance to further reduce its low level of backpressure, and its pulley was coupled to a high-resolution servo-potentiometer to provide an electrical output to a rapid-response strip-chart recorder. End-tidal P_{O_2} ($P_{ET_{O_2}}$) and P_{CO_2} ($P_{ET_{CO_2}}$) were measured by sampling expired gas from the expiratory side of a low dead-space (, 15 ml) nonrebreathing valve (31) constructed in this laboratory. The rapid-response O_2 and CO_2 analyzers (model S-3A, Ametec, Pittsburgh, PA, and model LB-2, Sensormedics, Anaheim, CA) were calibrated with gas mixtures of precisely known O_2 and CO_2 concentrations (Air Products, Allentown, PA, and Scott Specialty Gases, Plumsteadville, PA). Their electrical outputs were also inscribed onto rapid-response strip-chart recorders.

The experimental apparatus was behind the supine subject's head, out of his range of vision. After rebreathing was started, $P_{ET_{CO_2}}$ rapidly reached the target isocapnic level of 42 Torr. The speed of a sealed blower in series with a CO_2 scrubber canister in a bypass loop was modulated to maintain this level of $P_{ET_{CO_2}}$ while $P_{ET_{O_2}}$ progressively declined. Rebreathing was ended when $P_{ET_{O_2}}$ reached the planned lower limit of 40 Torr, or sooner (rarely) at the subject's request. In both the 1.0-ATA air and 1.5-ATA O_2 exposure series, arterial blood was sampled just before rebreathing was finished for analysis of blood-gas tensions to determine the degree of correspondence of arterial P_{O_2} (Pa_{O_2}) with the target $P_{ET_{O_2}}$ level and $P_{ET_{CO_2}}$ with arterial P_{CO_2} (Pa_{CO_2}).

It was anticipated that residual pulmonary O_2 poisoning, exacerbated by deep breathing, would make it uncomfortable for subjects to complete rebreathing procedures during post-O_2 exposure determinations of HVR. This was later verified by , 30% of the subjects who reported pulmonary distress during stimulated ventilation while rebreathing. To minimize the duration of HVR determinations and subject discomfort and the possibility of premature experiment termination, the spirometer was initially filled with 8–9 liters of room air rather than with O_2-enriched air (29), which would have prolonged the rebreathing experiment. This did not affect HVR at low $P_{ET_{O_2}}$, but it did reduce its range at the high end.

Determination of ventilation, respiratory frequency, and tidal volume responses to hypoxia. In the procedures of data reduction described below, strip-chart records were analyzed to obtain ventilation, respiratory frequency, and tidal volume as functions of $P_{ET_{O_2}}$ over the time interval when $P_{ET_{CO_2}}$ was held constant. The ventilatory response to progressive hypoxia was characterized as an hyperbola (29), which made it convenient to compute ventilation values at 5-Torr $P_{ET_{O_2}}$ intervals for averaging across subjects to obtain group means. Respiratory frequency and tidal volume responses to hypoxia, which are infrequently employed in analysis of respiratory responses to hypoxia, have not been described mathematically. Group mean values at the same 5-Torr $P_{ET_{O_2}}$ intervals were obtained by linear interpolation between adjacent measured values.

For each hypoxia run, the portion of the strip-chart record after $P_{ET_{CO_2}}$ stabilization was subdivided into 30-s sections. For each section, average (per min) values of expired ventila-

tion, respiratory frequency, and $P_{ET_{O_2}}$ were obtained. Paired values (range 6–13 pairs) of ventilation and $P_{ET_{O_2}}$ formed a data set from which the mean squared best-fit hyperbola was obtained. All ventilation vs. $P_{ET_{O_2}}$ data sets but one converged to hyperbolic functions. For the lone exception (postexposure HVR in 1 of 9 subjects of 1.5-ATA O_2 group), a linear function was used to describe the data. Then, for each O_2 exposure pressure (0.2, 1.5, 2.0, and 2.5 ATA) and for each condition (preexposure, postexposure, follow-up), a group mean HVR hyperbola was obtained by averaging across subjects at $P_{ET_{O_2}}$ intervals of 5 Torr. The range of $P_{ET_{O_2}}$ values employed for each individual hyperbola was (with few exceptions of limited extrapolation) within the $P_{ET_{O_2}}$ range of its HVR determination. Therefore the range of averaged HVR values was limited to that of the subject with the smallest range.

Analogous procedures were carried out for respiratory frequency and tidal volume using interpolated values as described above. When possible, duplicate rebreathing experiments were completed and analyzed. In such cases, their average was employed in obtaining group means.

Hyperbolic representation of HVR. The hyperbolic function has been widely used to describe HVR, and its parameters have physiological interpretation (29)

$$\dot{V} = \dot{V}_o + A\dot{V}_o/(P_{O_2} - C)$$

Parameter $\dot{V}_o$, the horizontal asymptote, is the (hypothetical) ventilation at infinitely high O_2 tension at the isocapnic P_{CO_2} level. Its value establishes the vertical position of the hyperbola. Parameter C is the low P_{O_2} at which ventilation ($\dot{V}$) asymptotically approaches infinity, and its value establishes the hyperbola's horizontal position. The value of $A\dot{V}_o$ or A itself has been related to the "hypoxic ventilatory sensitivity" (shape or curvature) of HVR hyperbola. The curvilinear nature of HVR as a function of P_{O_2} and the difficulties in defining a simple measure of hypoxic ventilatory sensitivity have also been described (29).

Statistical analysis. Hyperbolas were fitted to the ventilation vs. $P_{ET_{O_2}}$ data sets by least mean square criteria by using BMDP statistical software. Comparisons of these (post- vs. preexposure, follow-up vs. preexposure) were complicated by the facts that the ranges of $P_{ET_{O_2}}$ were too restricted to provide reliable estimates of the asymptotes, and the value of the curvature parameter is highly sensitive to these estimates (29). Postexposure and follow-up curves (data) for ventilation, tidal volume, and respiratory frequency were compared with the preexposure controls at each $P_{ET_{O_2}}$ (5-Torr intervals) using a two-way analysis of variance (ANOVA) with repeated measures. Change in curvature or slope (hypoxic sensitivity) of ventilatory parameters was identified by a significant interaction between treatment (measurement condition, i.e., post- vs. preexposure, follow-up vs. preexposure) and $P_{ET_{O_2}}$. Post hoc individual comparisons were used to test changes at any specific $P_{ET_{O_2}}$. Tests of ANOVA effects were considered significant at $P \leq 0.05$. Significance levels for multiple individual comparisons were adjusted so that overall level was 0.05. Comparisons cited for other data were by paired *t*-test ($P \leq 0.05$).

RESULTS

A total of 122 HVR determinations were made on the 33 subjects represented in this report. The total consisted of 47 each pre- and postexposure and 28 follow-up determinations. Included in the total are 27 duplicate determinations.

Experimental conditions of HVR determinations. Experimental conditions other than hyperoxic exposure pressure and duration, which might influence comparison of postexposure and follow-up ventilatory responses to hypoxia with preexposure controls, include time rate of decrease in $P_{ET_{O_2}}$ (dP_{O_2}/dt) and the level of $P_{ET_{CO_2}}$ during imposed (controlled) isocapnia. The former has been observed to influence the slope of ventilation vs. arterial O_2 saturation (21), and the latter establishes its horizontal (ventilation) asymptote. Average values of dP_{O_2}/dt (Torr/min) are given in Table 1. None of the small differences in average value (post- vs. preexposure, follow-up vs. preexposure) are statistically significant. Table 3 presents time-averaged values of $P_{ET_{CO_2}}$ during controlled isocapnia. None of the small differences in average value (post- vs. preexposure, follow-up vs. preexposure) of the $P_{ET_{CO_2}}$ values in Table 3 are statistically significant.

Correspondence of $P_{ET_{CO_2}}$ with Pa_{CO_2} at end of rebreathing. To determine how well Pa_{CO_2} corresponded to the isocapnic levels of $P_{ET_{CO_2}}$, arterial blood samples were obtained at the end of rebreathing in the five subjects of the 1.0-ATA air group and in eight of the nine subjects of the 1.5-ATA O_2 exposure series. For the 1.5-ATA O_2 series, Pa_{CO_2} at the end of rebreathing and time-averaged $P_{ET_{CO_2}}$ over the rebreathing period were (avg ± SE) 42.7 ± 0.2 and 42.4 ± 0.2 Torr before exposures to hyperoxia and 43.1 ± 0.4 and 42.3 ± 0.2 Torr after the exposures. The 0.8-Torr postexposure arterial-end tidal difference is statistically significant but is small enough to be unimportant for the related comparisons below. Corresponding (essentially identical) values for the 1.0-ATA air series are 43.5 ± 0.4 and 43.0 ± 0.3 Torr (preexposure) and 43.2 ± 0.3 and 42.8 ± 0.2 Torr (postexposure).

Correspondence of Pa_{O_2} with target $P_{ET_{O_2}}$. The principal criteria for termination of rebreathing was reduction of $P_{ET_{O_2}}$ to the preestablished target value of 40 Torr. The other was any sign that the subject might lose consciousness (none did). Six of the subjects reported dimming of vision during preexposure or follow-up HVR determinations, and none during postexposure determinations.

Rebreathing was stopped before the target $P_{ET_{O_2}}$ was reached in some postexposure determinations at subject request, due largely to residual pulmonary discom-

Table 3. *Isocapnic levels of end-tidal P_{CO_2} during the HVR determinations*

O_2 Exposure Pressure, ATA	*n*	Preexposure	Postexposure	Follow-Up
0.2	5	43.06 ± 0.3	42.86 ± 0.2	
1.5	9	42.46 ± 0.2	42.36 ± 0.2	
1.5	5	42.36 ± 0.2	42.26 ± 0.1	43.06 ± 0.3
2.0	6	42.96 ± 0.04	43.36 ± 0.5	42.56 ± 0.1
2.5	8	42.96 ± 0.1	42.66 ± 0.2	42.96 ± 0.2
2.0 30:30	5	44.56 ± 0.8	44.56 ± 0.3	44.16 ± 0.1

Values are means ± SE in Torr for *n* subjects. Target end-tidal P_{CO_2} was 42 Torr. None of differences in isocapnic levels of end-tidal P_{CO_2} (post- vs. preexposure, follow-up vs. preexposure) are significant.

fort resulting from pulmonary O_2 poisoning exacerbated by the large tidal volumes during rebreathing. To see how well Pa_{O_2} values corresponded to the targeted end point, the arterial blood samples were analyzed for P_{O_2}. The target value was approximated closely in most subjects. For the 1.0-ATA air series, average 6 SE values of Pa_{O_2} at the end of rebreathing were 43.4 6 2.1 Torr (preexposure) and 43.8 6 1.2 Torr (postexposure). Corresponding values for the 1.5-ATA O_2 series are 38.1 6 1.6 and 41.4 6 2.0 Torr.

Effects of continuous O_2 exposures on curvature and position of HVR hyperbolas. Initial evaluation of the effects of the hyperoxic exposures on HVR of individual subjects was by visual inspection and comparison of each postexposure HVR with its corresponding preexposure control. Of 46 matched post- vs. preexposure determinations that could be compared, 45 postexposure curvatures visually appeared at least equal to their preexposure controls. One postexposure HVR of the 2.0-ATA 30:30 series had a markedly flatter curvature than its control. The duplicate postexposure HVR was not flatter than control. It was also evident by inspection that the dominant effect of the toxic O_2 exposures was on the position of HVR hyperbolas, which were elevated to higher levels of ventilation than were their corresponding preexposure controls.

The group-averaged HVRs are shown in Fig. 1, *A*–*E*. After 20 h of air breathing at 1.0 ATA (Fig. 1*A*), the postexposure HVR hyperbola, though virtually identical in position to its preexposure control, has a different degree of curvature (interaction is significant). By inspection, postexposure curvature is slightly greater than is that of its preexposure control. It is also clear that, after the continuous hyperoxic exposures (Fig. 1, *B*, *D*, and *E*), the ventilatory responses to hypoxia are not attenuated compared with their preexposure controls. Interaction is significant only for the 1.5-ATA exposure group of subjects, and the slope of the postexposure hyperbola is greater than its control (Fig. 1*B*).

All postexposure ventilatory hyperbolas are at higher levels of ventilation than are their preexposure counterparts (Fig. 1, *B*, *D*, and *E*), but the only differences between paired post- and preexposure values of ventilation that are at all significant are values of $P_{ET_{O_2}}$ for the 1.5-ATA O_2 exposures (Fig. 1*B*) and that at a $P_{ET_{O_2}}$ of 40 Torr for the 2.0-ATA O_2 exposures (Fig. 1*D*). It is of interest that the degree of increased ventilation of the postexposure hyperbolas is inversely related to exposure pressure (Fig. 1, *B*, *D*, and *E*). That this is principally an effect of respiratory frequency is shown below.

All follow-up HVR hyperbolas had returned to preexposure control levels by the time these determinations were made (Fig. 1, *C*–*E*). After the 1.5-ATA exposures, five of the nine subjects were available , 6 mo after that series was completed for follow-up HVR determinations (Fig. 1*C*). These determinations also served as preexposure controls for the 20-h 1.0-ATA air exposures (Fig. 1*A*, Table 1).

Effects of continuous O_2 exposure on breathing patterns during HVR determinations. Mean values of tidal volume (Fig. 2*A*) and respiratory frequency (Fig. 3*A*) responses to hypoxia were not significantly different from control values after 20-h air breathing at 1.0 ATA. Also after O_2 exposures, the pre- vs. postexposure tidal volume differences at corresponding values of $P_{ET_{O_2}}$ (Fig. 2, *B*, *D*, and *E*) are not statistically significant. Differences in mean values between follow-up and preexposure tidal volumes (Fig. 2, *C*–*E*) are not significant. Interaction is significant only for the follow-up vs. preexposure tidal volume differences of the 2.0-ATA O_2 exposure group, with follow-up curvature less than control (Fig. 2*D*).

Differences in mean values between follow-up and preexposure respiratory frequencies (Fig. 3, *C*–*E*) are not significant. Interaction is significant only for the follow-up vs. preexposure respiratory frequency differences of the 2.0-ATA O_2 exposure group, with follow-up curvature greater than control (Fig. 3*D*). With follow-up respiratory frequency curvature greater than control and follow-up tidal volume curvature less than control, follow-up ventilation curvature is the same as control (Fig. 1*D*).

In marked contrast to tidal volume differences, the differences between post- and preexposure respiratory frequency responses to progressive hypoxia are almost all significant (Fig. 3, *B*, *D*, and *E*). The only exceptions are the differences at $P_{ET_{O_2}}$ values of 70, 75, and 80 Torr of the 2.5-ATA O_2 exposures (Fig. 3*E*). Interaction is significant for the post- vs. preexposure respiratory frequency differences of both the 2.0- and 2.5-ATA O_2 exposure groups, with postexposure curvatures greater than their controls (Fig. 3, *D* and *E*).

Results for intermittent exposures at 2.0 ATA. There were no statistically significant effects of the intermittent 30:30 O_2-normoxic pattern exposures (post- vs. preexposure control) on ventilation, tidal volume, or respiratory frequency differences at any $P_{ET_{O_2}}$ (Figs. 1*F*,2*F*, and 3*F*). All average follow-up values of tidal volume are smaller than their preexposure controls, and the overall difference is significant, but individual differences are not (Fig. 2*F*). Follow-up values of respiratory frequency (Fig. 3*F*) are slightly larger than controls by , 2 breaths/min. The differences between follow-up and control values of ventilation are significant at $P_{ET_{O_2}}$ values of 40 and 45 Torr, and interaction is significant for these ventilation differences, with follow-up curvature less than control (Fig. 1*F*).

Differences in respiratory frequency as a function of O_2 exposure time. As stated previously, most postexposure respiratory frequencies after continuous hyperoxia are significantly larger than their preexposure counterparts. By inspection of Fig. 3, *B*, *D*, and *E*, it is evident that the post- vs. preexposure differences decrease as the toxic O_2 exposure pressure increases and O_2 exposure time decreases. To examine this relationship further, the frequency differences at a fixed $P_{ET_{O_2}}$ of 50 Torr have been plotted against total O_2 exposure time in Fig. 4, where each data point is identified with

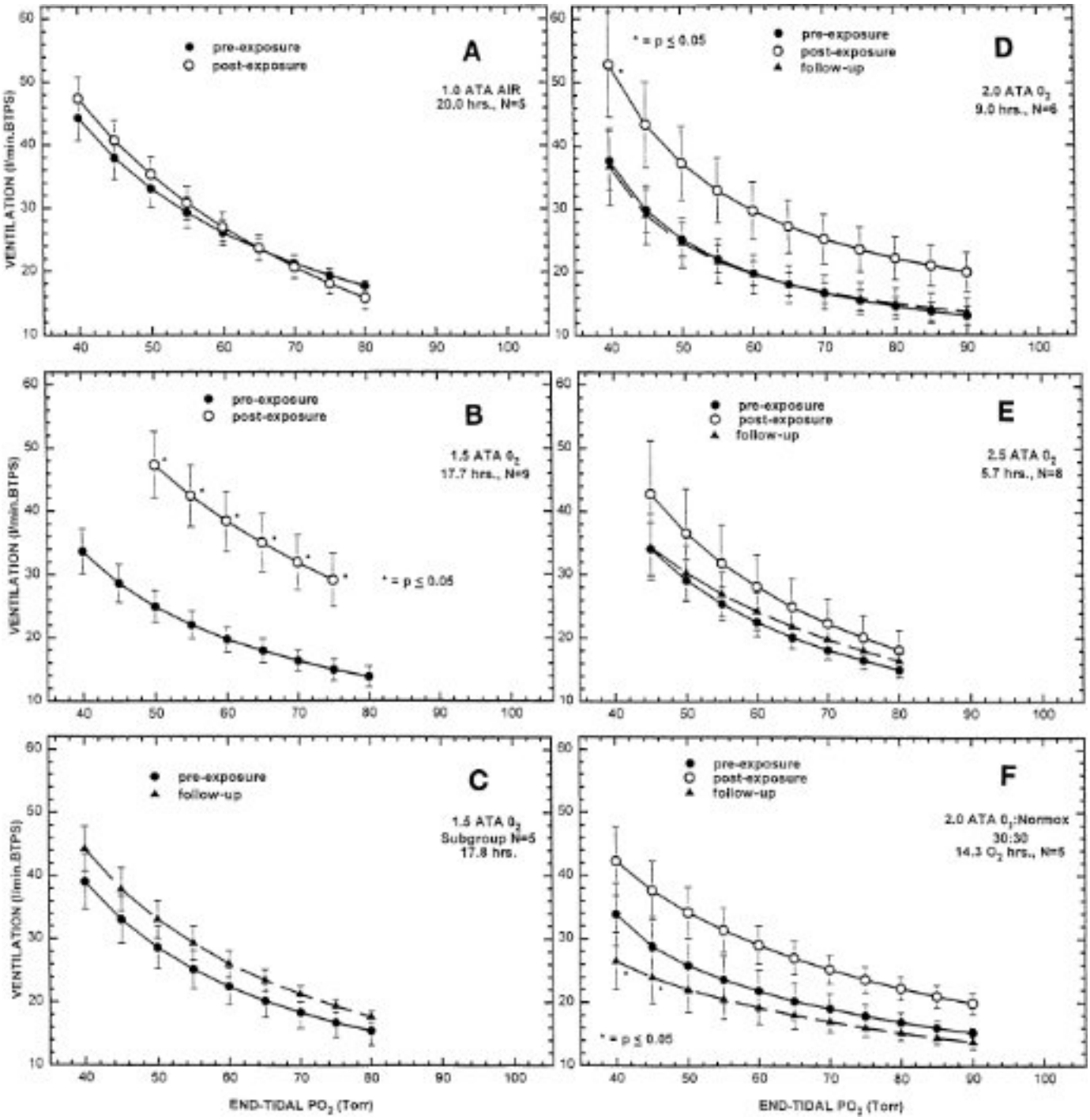

Fig. 1. Ventilatory responses to progressive isocapnic hypoxia for O_2 exposure pressures of Predictive Studies (PS)-V and -VI. 30:30, 30 Min O_2-30 min normoxia (Normox). Mean values 6 SE. * Significant differences between post- and preexposure ventilations and between follow-up and preexposure ventilations. Interaction is significant for 1.0-ATA air and 1.5-ATA O_2 post- vs. preexposure comparisons and for 2.0-ATA 30:30 follow-up vs. preexposure comparisons.

its exposure pressure. The solid line is the linear regression through the three continuous O_2 exposure points, which lie extremely close to it. The data point for the intermittent O_2 exposure at 2.0 ATA is shown for comparison with the continuous 2.0-ATA exposure. The former represents a smaller difference in respiratory frequency with a greater O_2 exposure time (14.3 O_2 h) compared with continuous O_2 exposure time (9.0 O_2 h) at the same pressure.

DISCUSSION

It is obvious by inspection of Fig. 1 that the abolition or attenuation of chemoreflex HVR reported to occur in animals after exposures to 100% O_2 at 1.0 ATA (22) and

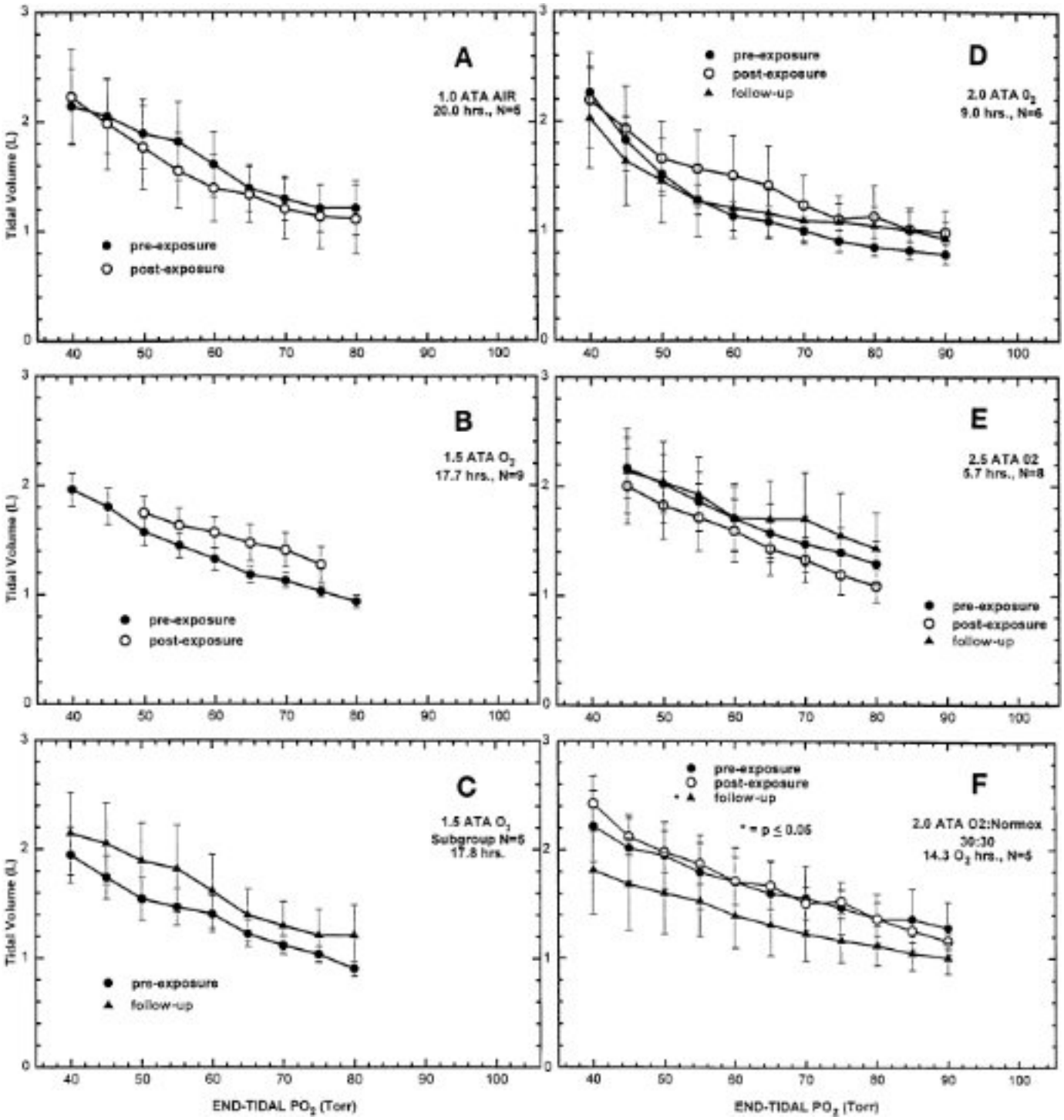

Fig. 2. Tidal volume responses to progressive isocapnic hypoxia for O_2 exposure pressures of PS-V and -VI. Mean values 6 SE. Only overall difference between follow-up and preexposure tidal volumes for 2.0-ATA 30:30 exposures is significant; individual differences are not (indicated by * at follow-up symbol label). Interaction is significant for 2.0-ATA O_2 follow-up vs. preexposure comparisons.

at elevated pressures (1, 27, 32) did not occur in the human subjects of these studies even after severe exposures at toxic O_2 pressures of 1.5, 2.0, and 2.5 ATA. Rather than abolition or attenuation of hypoxic ventilatory sensitivity, postexposure ventilatory hyperbolas had the same (Fig. 1, *D–F*) or greater (Fig. 1*B*) curvature than their preexposure controls. The increased curvature after the 17.7-h 1.5-ATA O_2 exposures (Fig. 1*B*) could have the same cause as the similar increase in curvature that followed the 20.0-h 1.0-ATA air ''exposures'' (Fig. 1*A*). The basis for this reversible increase in hypoxic ventilatory sensitivity (Fig. 1*C*), which may be unrelated to O_2 exposure, is not known. The follow-up HVR after the 2.0-ATA 30:30

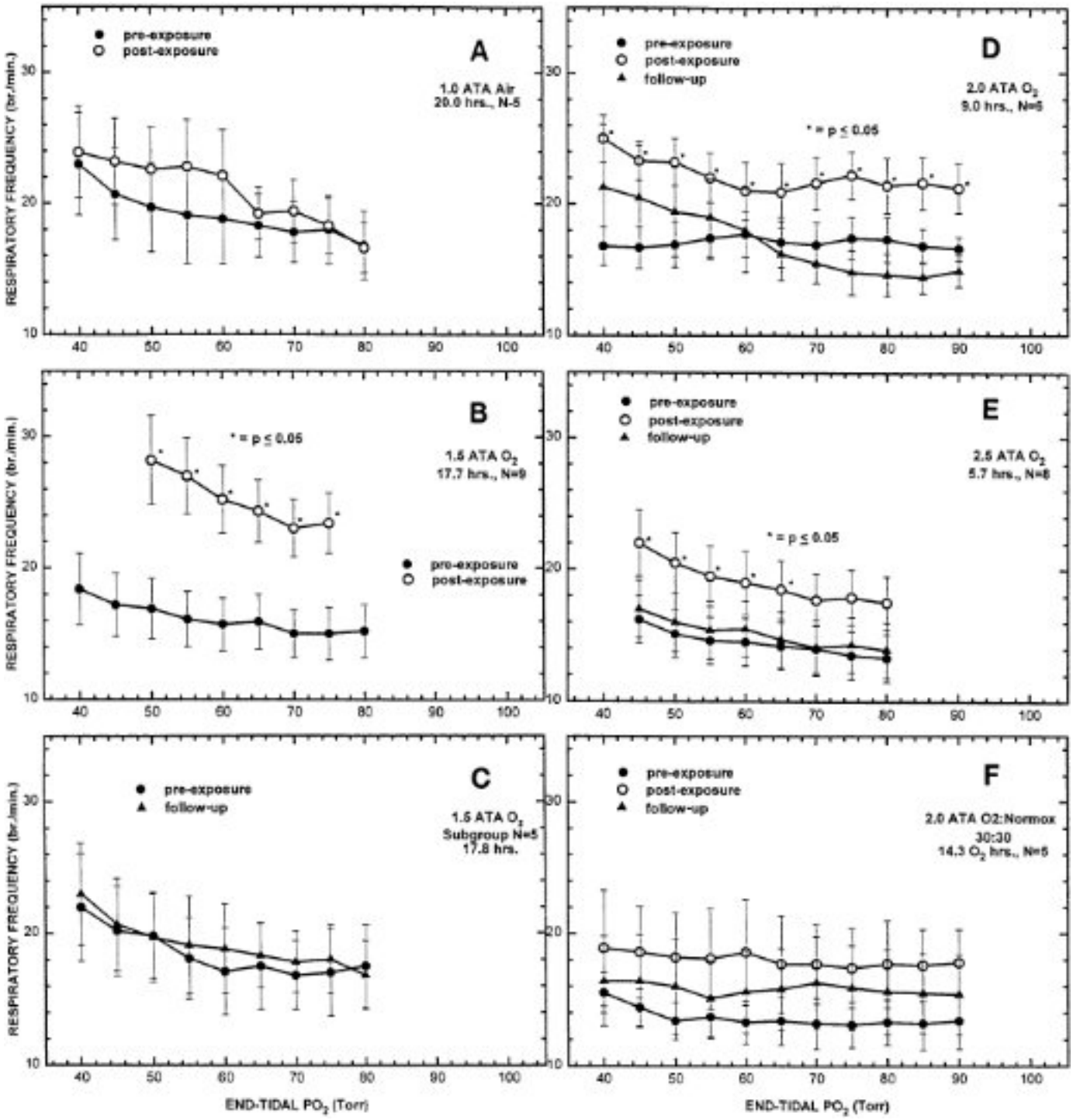

Fig. 3. Respiratory frequency responses to progressive isocapnic hypoxia for O_2 exposure pressures of PS-V and -VI. Mean values 6 SE. br, Breaths. Only differences between post- and preexposure respiratory frequencies are significant (indicated by *). Interaction is significant for 2.0- and 2.5-ATA O_2 post- vs. preexposure comparisons and for 2.0-ATA O_2 follow-up vs. preexposure comparisons.

exposures represents the single instance of reduced hyperbolic curvature observed here. Its basis is also unknown but may be related to sleep deprivation, which (for a period of 24 h) reduced HVR by 29% ($l \cdot min^{21} \cdot$ %saturation^{21}) (33). The subjects of this phase of the investigation could sleep only intermittently during the , 35-h period from the start of preexposure measurements to the end of postexposure measurements. The amount and nature of their sleep in the , 16-h period between the end of postexposure measurements and the follow-up measurements was not recorded. It is conceivable that residual consequences of an extended period of interrupted sleep may reduce HVR in the same way as does sleep (6) and sleep deprivation (33).

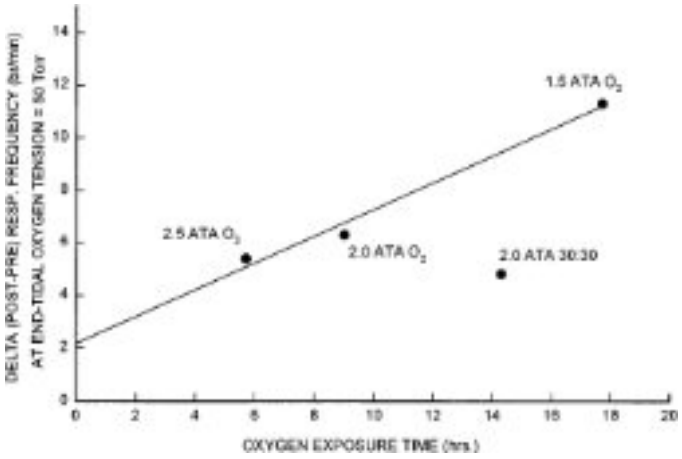

Fig. 4. Upward displacement (elevation) of postexposure respiratory frequency (f) responses to hypoxia above their preexposure controls, measured at end-tidal P_{O_2} of 50 Torr vs. O_2 exposure time. Solid line is linear regression through 3 points representing continuous O_2 exposures. Regression equation (r^2 5 0.9839) is Df 5 2.12 1 (0.51) 3 (O_2 h).

The upward displacements of the postexposure ventilatory hyperbolas were due to upward displacements of postexposure respiratory frequency responses to hypoxia, not to effects on tidal volume (Figs. 1–3). These respiratory control effects of exposure to elevated pressures of O_2 had almost entirely disappeared by the time follow-up HVR determinations were made. Analogous effects on the position of the hyperbolic relationship between the firing rate of the carotid sinus nerve and progressive isocapnic hypoxia in cats, as affected by potassium and norepinephrine, have been described (17).

Experiment conditions of HVR determinations. Factors other than the exposures to hyperoxia, which could affect the comparisons of postexposure and follow-up ventilatory responses to hypoxia with their preexposure controls, include differences in the rate of decrease of $P_{ET_{O_2}}$ during imposed isocapnia and differences in the isocapnic levels of imposed $P_{ET_{CO_2}}$ achieved. Rate of decrease in $P_{ET_{O_2}}$ has been shown to affect the slope of the relationship between ventilation and O_2 saturation of arterial blood (21). This can be ruled out as a factor in the current investigations, since there are no significant differences between corresponding pre- and postexposure and follow-up values of dP_{O_2}/dt (Table 1). Differences in isocapnic levels of $P_{ET_{CO_2}}$ would affect the horizontal asymptotes of the ventilatory responses to hypoxia. This is also not a factor in the current comparisons, since levels of controlled isocapnia within each exposure series are the same (Table 3).

Potential causes of increased postexposure respiratory frequency. It is significant that the postexposure HVR increments in ventilation are due principally to increments in respiratory frequency (Fig. 3), rather than in tidal volume (Fig. 2), since the normal ventilatory response to hypoxia in humans is largely an effect on tidal volume (7). The basis for these upward shifts of postexposure respiratory frequency responses to hypoxia (Fig. 3, *B* and *D–F*) is not known. Several possibilities are considered below.

Nonspecific effects related to pulmonary O_2 poisoning. The underlying cause of the observed ventilatory changes may be nonspecific, possibly related to the development of pulmonary O_2 poisoning during the exposures to hyperoxia from which recovery was gradual after exposure termination (3). The 1.5-ATA O_2 exposures, which had the largest increments in postexposure respiratory frequency responses to hypoxia (Figs. 3 and 4), also had the shortest (1.9 h) time lapse from the end of O_2 breathing to postexposure HVR determinations (Table 2) and were associated with only partial recovery from decrements in vital capacity at that time (3). The 2.0- and 2.5-ATA O_2 exposures, which had markedly smaller increments in postexposure respiratory frequency (Figs. 3 and 4), also had longer time lags to HVR determinations (Table 2) and more complete recovery from decrements in vital capacity when HVR determinations were made (3).

Other pulmonary effects of the exposures to hyperoxia were also seen (3). Alveolar-arterial O_2 differences measured during light exercise were elevated only after the 1.5-ATA exposures. Pulmonary diffusing capacity for carbon monoxide was significantly reduced by , 8–11% after continuous O_2 exposure at each of the three pressures. Specific lung compliance was reduced by , 22% after the 1.5- and 2.0-ATA exposures. These and possibly unobserved effects of pulmonary O_2 poisoning may have been associated with concurrent sensitization of tracheobronchial irritant receptors and/or lung J receptors (see Ref. 34 for a review).

Tracheobronchial irritant receptors can be sensitized or stimulated by pulmonary congestion and edema, which can cause tachypnea. J receptors respond to increased interstitial fluid and released mediators with rapid, shallow breathing (34). Physical examinations and chest X-rays did not detect evidence of pulmonary edema in subjects who had similar degrees of pulmonary O_2 poisoning in prior investigations (4, 28). However, potentially more sensitive methods provide indications of increased alveolar-capillary permeability, even with O_2 exposures (5, 16) that are less severe than those employed in PS-V. The hypoxia-induced hyperventilation during HVR determinations could have stimulated sensitized pulmonary receptors, causing or contributing to the observed elevation of postexposure respiratory frequency responses to hypoxia.

Figure 4 is consistent with duration of O_2 exposure, not exposure pressure, as the dominant factor in the increments of postexposure respiratory frequency responses to hypoxia. If indirect effects of pulmonary O_2 poisoning are in whole or in part responsible for the observed effects on respiratory frequency, time for development of O_2 toxic effects and reactions to them, rather than exposure pressure, appear to be the important factor.

Relationship to respiratory control factors. Post-O_2 exposure effects analogous to those documented here for HVR were seen as well for the hypercapnic ventilatory response. These were determined by rebreathing

in an O_2 background at 1.0 ATA closely after HVR determinations. Mean values of slope measured postexposure were larger than their preexposure controls after the 1.5, 2.0, and 2.5-ATA O_2 exposures by 56, 20, and 54%, respectively (12), and they were displaced to higher levels of ventilation than their controls (unpublished observations of PS-V). Both the increased slopes and the displacements were influenced more by enhanced respiratory frequency responses to CO_2 than by corresponding tidal volume responses. Increased sensitivity of CNS or peripheral chemoreceptors to CO_2 would have the potential to interact with the postexposure HVR, since HVR determinations were made with $P_{ET_{CO_2}}$ slightly above eucapnic levels. However, the observed effects on the hypercapnic ventilatory response may have the same basis as the changes seen in HVR.

Residual spontaneous hyperventilation after prolonged voluntary hyperventilation-hypocapnia has been reported (8). This is of interest here, since the subjects of these investigations had extended periods of mild hyperventilation and associated mild arterial hypocapnia, which accompanies the onset of hyperoxia (24) and persisted throughout the current prolonged exposures to high O_2 pressures (14). However, voluntary hyperventilation during air breathing as well as hyperventilation during acclimatization to altitude is accompanied by central alkalosis, whereas hyperventilation induced by hyperoxia is related to altered CO_2 transport with associated increases in brain P_{CO_2} and H^1 concentration (24). Thus a compensatory CNS acid-base shift in response to sustained alkalosis, which has been considered a possible cause of both residual spontaneous hyperventilation after voluntary hyperventilation and sustained hyperventilation at altitude (see Ref. 8), does not apply to this study. However, peripheral chemoreceptors and other systemic organs were exposed to sustained arterial hypocapnia during each O_2 exposure. This was associated with a significant reduction in arterial HCO_3^2 concentration from 23.1 to 21.7 meq/l, respectively, at the start and end of the 1.5-ATA exposures (unpublished observations of PS-V). The respiratory control consequences of peripheral chemoreceptor exposure to sustained hypocapnia in a hyperoxic background have apparently not been studied.

Although there was prolonged mild hyperventilation and arterial hypocapnia during the O_2 exposures, Pa_{CO_2} had returned to preexposure normocapnic levels by the time the postexposure HVR determinations were made. For all exposures, Pa_{CO_2} was measured with the subjects at rest breathing air in a laboratory room during determinations of alveolar-arterial O_2 differences with which HVR determinations were grouped. There were no significant differences between the pre- and postexposure values of Pa_{CO_2} (unpublished observations of PS-V).

Effects of O_2 poisoning might have modified respiratory frequency determining networks located in the central nervous system. The inspiratory duty cycle (%T_I 5 T_I/Ttot, where T_I is inspiratory duration and Ttot is total breath duration) decreased progressively with O_2 exposure time, at a rate roughly proportional to O_2 exposure pressure (9). However, the smallest effects on %T_I were seen during the 1.5-ATA O_2 exposures, the exposure pressure associated with the largest effects on respiratory frequency.

After human subjects breathed 100% O_2 at 1.0 ATA for 10 min, an augmented ventilation in response to sustained isocapnic hypoxia (20) and significant enhancement of HVR in 7 of 14 subjects studied (19) have been reported. The augmented ventilation (20) was due to increases in tidal volume, not frequency, and the enhanced HVR (19) was ascribed to unmasking (by prior O_2 breathing) of ''ambient air hypoxic ventilatory depression.'' Neither of these observations applies to the present results, since the periods of O_2 exposure were so brief.

Comparison of effects of continuous and intermittent hyperoxia at 2.0 ATA. Although the O_2 breathing duration of the 2.0-ATA intermittent 30:30 exposures (14.3 h) was considerably longer than the O_2 breathing duration of the 2.0-ATA continuous O_2 exposures (9.0 h), the post- vs. preexposure difference in respiratory frequency at $P_{ET_{O_2}}$ 5 50 Torr (Fig. 4) is smaller for the intermittent O_2 exposures than it is for the continuous ones. This amelioration of an effect of O_2 poisoning is consistent with previous observations that intermittent hyperoxia slows the rate of development of O_2 toxicity (18, 25).

Comparison with results of animal experiments. The current results represent the only human data of this kind that is known to the authors. Other investigators, using cats and rats in a variety of exposure conditions, had mostly different results. After exposures of cats to 100% O_2 at 1.0 ATA for 60–67 h, there was virtual flattening of the carotid body's chemosensory responses to graded, isocapnic hypoxia (22). These experiments differed from those of the present investigations in that the exposure duration was nearly lethal for the cats. Shorter exposures (1.5–2.25 h) at a higher O_2 pressure (5.0 ATA) by the same group had no effect on cat HVR (30). In experiments on rats, graded, reversible reduction of the transient ventilatory response to several breaths of hypoxic gas was found after exposures to hyperoxia over a range of pressures and durations comparable to those of this report (1, 27, 32). The degree of reduction in ventilation was proportional to both the O_2 exposure pressure and the exposure duration and was due chiefly to a reduction in respiratory frequency.

It is conceivable that the disparity between results in animals and humans is a consequence of a hypothetical rapid reversal in humans of HVR attenuation that might have occurred during the time interval between cessation of O_2 breathing and HVR determinations (Table 2). However, this is highly unlikely, since the effects observed in the animals were not rapidly reversed after cessation of O_2 breathing. As stated by the authors of the rat studies, the ventilatory response to hypoxia was measured in some animals immediately after cessation of hyperoxia, while in others it was

determined up to "a few hours" afterward (1). They found no correlation of results to time of measurement. Furthermore, reversal of effects in the rats occurred over several days (32). Although there was no interruption in O_2 breathing by the cats while they were prepared for experimental procedures (22), the blunting of hypoxic chemosensitivity in these animals did not recover during the 5- to 7-h post-O_2 exposure measurement period (S. Lahiri, personal communication).

The basis for the observed discrepancies in results of the animal and human studies is not evident. However, it is clear that the results in animals do not apply to humans. For the cats, the dissimilarity may be related to the differences in exposure conditions, whereas, for the rats, there are major contrasts in experimental procedures. Reduced respiratory frequency was seen during transient hypoxic ventilatory response determinations in the rats (1, 27, 32), whereas elevated respiratory frequency was observed in HVR determinations in humans.

Summary and conclusions. O_2 poisoning did not attenuate the hypoxia-sensing function of the carotid body in men after exposures that induced prominent toxic effects on pulmonary function. The hyperoxic exposures approached the limits of human CNS and pulmonary O_2 tolerance at 1.5, 2.0, and 2.5 ATA. By inference, these exposures to O_2 poisoning did not significantly impair the functions of other elements in the respiratory control loop, such as transmission of impulses from the carotid body to the CNS, their integration into the composite respiratory act, or transmission to and activation of the respiratory musculature. The observations also show that the postexposure elevation of mean values of ventilation was due to temporary elevation of respiratory frequency responses to hypoxia above their preexposure controls, possibly related indirectly to effects of pulmonary O_2 poisoning.

Implications. The current practical uses of hyperoxia in hyperbaric O_2 therapy and diving- and aerospace-related operations are guided by and are well within the exposure durations and pressures employed in these investigations.

The authors acknowledge the dedication of the volunteer subjects who participated in these studies, which was a component of a multiyear investigation of human organ system tolerance to continuous and intermittent hyperoxia (Predictive Studies V and VI). C. Hires and V. Tecco provided expert technical assistance in pressure chamber operations and logistical support. E. Cook, J. Bookspan, and E. Kuk assisted with data reduction and processing.

These investigations were supported in part by Naval Medical Research and Development Command Contracts N00014–81C-0826 and N0001488-K-0169, National Aeronautics and Space Administration Grant NAS9–17238, and Grant 52, the Benjamin Franklin Partnership of the State of Pennsylvania. All detailed results and analyses are maintained within the Environmental Biomedical Research Data Center, Institute for Environmental Medicine.

Address for reprint requests: R. Gelfand, Institute For Environmental Medicine, Rm. 1, John Morgan Bldg., University of Pennsylvania Medical Center, Philadelphia, PA 19104–6068.

Received 3 April 1997; accepted in final form 5 September 1997.

REFERENCES

1. **Arieli, R., D. Kerem, and Y. Melamed.** Hyperoxic exposure affects the ventilatory response to hypoxia in awake rats. *J. Appl. Physiol.* 64: 181–186, 1988.
2. **Camporesi, E. M.** *Hyperbaric Oxygen Therapy: A Committee Report*. Bethesda, MD: Undersea Hyperbaric Med. Soc., 1996.
3. **Clark, J. M.** Pulmonary limits of oxygen tolerance in man. *Exp. Lung Res.* 14: 897–910, 1988.
4. **Clark, J. M., and C. J. Lambertsen.** Rate of development of pulmonary O_2 toxicity in man during O_2 breathing at 2.0 ATA. *J. Appl. Physiol.* 30: 739–752, 1971.
5. **Davis, W. B., S. I. Rennard, P. B. Betterman, and R. G. Crystal.** Early reversible changes in human alveolar structures induced by hyperoxia. *N. Engl. J. Med.* 309: 878–883, 1983.
6. **Douglas, N. J., D. P. White, J. V. Weil, C. K. Pickett, R. J. Martin, D. W. Hudgel, and C. W. Zwillich.** Hypoxic ventilatory response decreases during sleep in normal men. *Am. Rev. Respir. Dis.* 125: 286–289, 1982.
7. **Easton, P. A., L. J. Slykerman, and N. R. Anthonison.** Ventilatory response to sustained hypoxia in normal adults. *J. Appl. Physiol.* 61: 906–911, 1986.
8. **Forster, H. V., and J. A. Dempsey.** Ventilatory adaptations. In: *Regulation of Breathing*, edited by T. F. Hornbein. New York: Dekker, 1981, vol. 17, pt. II, p. 881–883. (Lung Biol. Health Dis. Ser.)
9. **Gelfand, R., J. M. Clark, and C. J. Lambertsen.** Respiratory control timing characteristics during prolonged hyperoxia at 1.5, 2.0, 2.5 and 3.0 ATA (Predictive Studies V) (Abstract). *Undersea Biomed. Res.* 16, *Suppl.*: S93–S94, 1989.
10. **Gelfand, R., J. M. Clark, and C. J. Lambertsen.** Ventilatory response to hypoxia is preserved following prolonged hyperbaric hyperoxia at 1.5, 2.0, and 2.5 ATA in man (Predictive Studies V) (Abstract). *Undersea Biomed Res.* 17, *Suppl.*: S163, 1990.
11. **Gelfand, R., J. M. Clark, and C. J. Lambertsen.** Hypoxic and hypercapnic ventilatory responses following intermittent hyperoxia in man (Predictive Studies VI) (Abstract). *Undersea Hyperbaric Med.* 20, *Suppl.*: S46, 1993.
12. **Gelfand, R., J. M. Clark, and C. J. Lambertsen.** Ventilatory response to carbon dioxide is not diminished after human exposure to prolonged hyperbaric hyperoxia at 1.5, 2.0, and 2.5 ATA (Predictive Studies V) (Abstract). *Undersea Biomed. Res.* 18, *Suppl.*: S87, 1991.
13. **Gelfand, R., J. M. Clark, C. J. Lambertsen, and J. Pisarello.** Ventilatory response to hypoxia following prolonged hyperoxia at 1.5 ATA in man (Abstract). *Federation Proc.* 46: 827, 1987.
14. **Gelfand, R., J. M. Clark, C. J. Lambertsen, and J. Pisarello.** Effects on respiratory homeostasis of prolonged continuous hyperoxia at 1.5 to 3.0 ATA in man in Predictive Studies V. In: *Underwater and Hyperbaric Physiology IX*, edited by A. A. Bove, A. J. Bachrach, and L. J. Greenbaum, Jr. Bethesda, MD: Undersea Hyperbaric Med. Soc., 1987, p. 751–761.
15. **Gelfand, R., J. M. Clark, C. J. Lambertsen, and J. Pisarello.** Ventilatory response to hypoxia following prolonged hyperoxia at 2.5 ATA in man (in Predictive Studies V) (Abstract). *Undersea Biomed Res.* 15, *Suppl.*: S34–S35, 1988.
16. **Griffeth, D. E., W. E. Holden, J. F. Morris, L. K. Min, and G. T. Krishnamurthy.** Effects of common therapeutic concentrations of oxygen on lung clearance of ^{99m}Tc DTPA and bronchoalveolar lavage albumin concentrations. *Am. Rev. Respir. Dis.* 134: 233–237, 1986.
17. **Heinert, G., D. J. Paterson, G. E. Bisgard, N. Xia, R. Painter, and P. C. G. Nye.** The excitation of carotid body chemoreceptors of the cat by potassium and noradrenaline. In: *Modeling and Control of Ventilation*, edited by S. J. G. Semple, L. Adams, and B. J. Whipp. New York: Plenum, 1995, p. 323–330.
18. **Hendricks, P. L., D. A. Hall, W. H. Hunter, Jr., and P. J. Haley.** Extension of pulmonary O_2 tolerance in man by intermittent O_2 exposure. *J. Appl. Physiol.* 42: 593–599, 1977.
19. **Honda, Y., A. Masuda, T. Kobayashi, M. Tanaka, S. Masuyama, H. Kimura, and T. Kuriyama.** Individual differences in ventilatory and HR responses to progressive hypoxia following 100% O_2 exposure in humans. In: *Modeling and Control of*

Ventilation, edited by S. J. G. Semple, L. Adams, and B. J. Whipp. New York: Plenum, 1995, p. 283–286.

20. **Honda, Y., H. Tani, A. Masuda, T. Kobayashi, T. Nishino, H. Kimura, S. Masuyama, and T. Kuriyama.** Effect of prior O_2 breathing on ventilatory response to sustained isocapnic hypoxia in adult humans. *J. Appl. Physiol*. 81: 1627–1632, 1996.
21. **Igarashi, T., M. Nishimura, S. Kobayashi, K. Miyamoto, and Y. Kawakami.** Dependency on the rate of change in Pa_{O_2} of the ventilatory response to progressive hypoxia. *Am. J. Respir. Crit. CareMed*. 151: 1815–1820, 1995.
22. **Lahiri, S., E. Mulligan, S. Andronikou, M. Shirahata, and A. Mokashi.** Carotid body chemosensory function in prolonged normobaric hyperoxia in the cat. *J. Appl. Physiol*. 62: 1924–1931, 1987.
23. **Lambertsen, C. J.** Basic requirements for improving diving depth and decompression tolerance. In: *Underwater Physiology. Proceedings of Third Symposium on Underwater Physiology*, edited by C. J. Lambertsen. Baltimore, MD: Williams & Wilkins, 1967, p. 223–240.
24. **Lambertsen, C. J.** Chemical control of respiration at rest. In: *Medical Physiology* (14th ed.), edited by V. B. Mountcastle. St. Louis, MO: Mosby, 1980, vol. 2, chapt. 71.
25. **Lambertsen, C. J.** Extension of oxygen tolerance in man: philosophy and significance. *Exp. Lung Res*. 14: 1035–1058, 1988.
26. **Lambertsen, C. J., J. M. Clark, R. Gelfand, J. B. Pisarello, W. H. Cobbs, J. E. Bevilaqua, D. M. Schwartz, D. J. Montabana, C. S. Leach, P. C. Johnson, and D. E. Fletcher.** Definition of tolerance to continuous hyperoxia in man. An abstract report of Predictive Studies V. In: *Underwater and Hyperbaric Physiology IX*, edited by A. A. Bove, A. J. Bachrach, and L. J. Greenbaum, Jr. Bethesda, MD: Undersea Hyperbaric Med. Soc., 1987, p. 717–735.
27. **Liberzon, I., R. Arieli, and D. Kerem.** Attenuation of hypoxic ventilation by hyperbaric O_2: effects of pressure and exposure time. *J. Appl. Physiol*. 66: 851–856, 1989.
28. **Puy, R. J. M., R. W. Hyde, A. B. Fisher, J. M. Clark, J. Dickson, and C. J. Lambertsen.** Alterations in the pulmonary capillary bed during early O_2 toxicity in man. *J. Appl. Physiol*. 24: 537–543, 1968.
29. **Rebuck, A. S., and A. S. Slutsky.** Measurement of ventilatory responses to hypercapnia and hypoxia. In: *Regulation of Breathing*, edited by T. F. Hornbein. New York: Dekker, 1981, vol. 17, pt. II, p. 745–772. (Lung Biol. Health Dis. Ser.)
30. **Torbati, D., A. Mokashi, and S. Lahiri.** Effects of acute hyperbaric oxygenation on respiratory control in cats. *J. Appl. Physiol*. 67: 2351–2356, 1989.
31. **Von Dobelin, W.** A respiration valve with insignificant dead space. *Acta Physiol. Scand*. 18: 34–35, 1949.
32. **Waisman, D., R. Arieli, D. Kerem, and Y. Melamed.** Recovery of the hypoxic ventilatory drive of rats from the toxic effect of hyperbaric oxygen. *Aviat. Space Environ. Med*. 63: 280–286, 1992.
33. **White, D. P., N. J. Douglas, C. K. Pickett, C. W. Zwillich, and J. V. Weil.** Sleep deprivation and the control of ventilation. *Am. Rev. Respir. Dis*. 128: 984–986, 1983.
34. **Widdicombe, J. G.** Nervous receptors in the respiratory tract and lungs. In: *Regulation of Breathing*, edited by T. F. Hornbein. New York: Dekker, 1981, vol. 17, pt. I, p. 429–472. (Lung Biol. Health Dis. Ser.)