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PREDICTING PULMONARY O_2 TOXICITY: A NEW LOOK AT THE UNIT PULMONARY TOXICITY DOSE.

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Pulmonary O_2 toxicity becomes a concern in U.S. Navy operations during long saturation dives or decompression procedures and during treatment of difficult cases of decompression sickness. Currently, the Unit Pulmonary Toxicity Dose (UPTD) concept based on changes in vital capacity is used as a guide for predicting the risk associated with cumulative O_2 exposures. In this report, we review the general model which gave rise to the UPTD, include a current summary of available vital capacity data, and perform a quantitative statistical analysis to explicitly test parameters in the model as well as to evaluate the contribution of individual variability to this index. A simplified model relating P_{O_2}, time of exposure, and predicted change in vital capacity is proposed: $\% \Delta VC = -0.011 (P_{O_2} - 0.5)(\text{time})$ where P_{O_2} is given in ATA and time in minutes. As with the UPTD, the effect of cumulative exposures can be calculated by summing the effect predicted at each level of P_{O_2} exposure. We discuss the limitations of changes in VC as the index of pulmonary O_2 toxicity. Individual susceptibility is the single largest source of variability, accounting for 35% of the uncertainty of any prediction.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

INTRODUCTION

Oxygen (O_2) enriched mixtures are used in many routine operational settings, and breathing 100% O_2 is an integral part of U.S. Navy recompression tables. The physiological and operational advantages of O_2 usage must be carefully balanced against its potential hazards, the nature of which depend on the partial pressure of O_2 (P_{O_2}). At dry ambient pressures greater than approximately 3 ATA, exposure to 100% O_2 produces a variety of central nervous system symptoms; exposure to lower pressures facilitates a slower toxic process that produces lung injury.

In 1970, Clark and Lambertsen suggested that decreases in vital capacity could be used to predict the onset, rate of development, and degree of severity of the toxic process in the lung caused by O_2 exposure. They developed a predictive graphical model relating P_{O_2}, time of exposure, and toxicity expressed as a decrement in vital capacity (VC). Subsequently, Bardin and Lambertsen (1970) developed a mathematical description of this graphical process. This mathematical model had some minor complexities that made on-site calculation inconvenient, so they developed an equivalent dose concept: the Unit Pulmonary Toxicity Dose (UPTD). This concept permitted calculation of predicted effects from cumulative O_2 exposures. We will examine closely the derivation and usefulness of the UPTD, which is currently used in the U.S. Navy. Because this is based on the measurement of vital capacity, we included an extensive review and summary of these data.

BACKGROUND

In Navy operations, pulmonary O_2 toxicity becomes a risk during long saturation dives or decompression procedures where it is desirable to maintain O_2 levels as high as possible, and during long or difficult treatments of decompression sickness. Currently, for saturation dives, chamber P_{O_2} of 0.4

ATA is recommended similar to the clinical setting where a P_{O_2} of 0.4 ATA is considered safe for indefinite exposures, while a P_{O_2} of 0.6 to 0.7 ATA is considered acceptable for 24 h. Recompression treatments are carried out at 60 fsw (2.8 ATA), followed by some time at 30 fsw (1.9 ATA), and consist of alternating exposures of O_2 and air. United States Navy Recompression Tables 5 and 6 (U.S. Navy Diving Manual, 1978) are similar, except that Table 6, designed for treatment of more serious decompression sickness, has one extra 20 min O_2/5 min air cycle at 60 fsw, and two 60 min O_2/15 min air cycles at 30 fsw instead of one 20 min O_2/5 min air cycle. Table 6A is used for treatment of air embolism and adds a 30 min air exposure at 165 fsw that exposes the patient to a P_{O_2} of 1.05 ATA. The Manual states that extra O_2 exposures may be added at each of the stops and, in fact, extension or repetition of the tables is determined from the patient's response by the Diving Medical Officer. Before extending the tables, the physician will often refer to the UPTD for guidance when there is a concern about the development of pulmonary O_2 toxicity.

Evidence of Pulmonary O_2 Toxicity: Animal Studies

The fact that O_2 exposure is potentially very harmful to the lungs of animals and man was observed about 100 years ago, yet O_2 toxicity remains a challenging clinical and physiological problem. Until recently, most information was derived from survival or histological studies. Small mammals such as dogs, cats, rats, guinea pigs, and mice survive approximately three days on O_2 at 1 ATA, while primates tolerate seven to 14 day exposures. The first thorough serial study of lung pathology was done with rats (Kistler, Caldwell, and Weibel, 1967), and revealed a progressive thickening of the air-blood barrier, due primarily to interstitial edema, followed by interstitial accumulation of cells and fibrin strands. The endothelium sustained the earliest and ultimately the most severe damage, while the epithelium was largely spared. The lungs of primates and ventilated human patients undergo similar changes (Kapanci et al., 1972; Barber, Lee, and Hamilton, 1970), except that there is destruction of Type I epithelial cells followed in time by a proliferation of Type II epithelial cells. These proliferative and fibrotic changes are reversible over two to three months if the primates are first gradually weaned off the high O_2 tensions (Kaplan et al., 1969; Kapanci et al., 1969; Wolfe et al., 1978).

Although these histological studies suggested gradual impairment of diffusing capacity and perhaps of gas exchange, recent animal experiments (Harabin and Farhi, 1978; Matalon, Nesarajah, and Farhi, 1982; Harabin, Homer, and Bradley, 1984), not confounded by anesthesia, mechanical ventilation, or restraint showed that progressive hypoxemia did not occur. While there were terminal alterations in gas exchange, it was difficult to ascribe hypoxemia as the cause of death.

Several animal studies have been conducted to determine whether lengthy exposures to moderately elevated P_{O_2}s produced pathological changes, and it appeared that these exposures were not without effect. Total lung capacity decreased 15% in rats exposed to 60% O_2 for seven days due to decreased lung compliance (Hayatdavoudi, 1981). These animals' lungs showed significant histological changes, including edema, decreased alveolar air volume, increased numbers of alveolar macrophages, and decreased endothelial volume and thickness. Lungs of rats exposed to 50% O_2 for 90 days showed increased numbers of vesicles, fluid accumulation, and platelet aggregates (Harrison, 1974). Finally, rats exposed to 33% O_2 for up to two weeks lost weight, had decreased pulmonary surface area for gas exchange, and had increased numbers of eosinophilic granulocytes (Kistler, Caldwell, and Weibel, 1966).

Evidence of Pulmonary O_2 Toxicity: Human Studies

A limited number of studies have documented the pathogenesis of pulmonary injury in normal men exposed to O_2 for 6 to 74 h at pressures ranging from 0.83 to 2.0 ATA (Caldwell et al., 1966; Clark and Lambertsen, 1970; Clark and Lambertsen, 1971a; Comroe et al., 1945; Dewar et al., 1972; Dolezal, 1962; Fisher et al., 1968; Ohlsson, 1947; Puy et al., 1968; Van de water et al., 1970; Widell et al., 1974). Strong subjective symptoms of pulmonary O_2 toxicity developed in most men after 6 to 14 h at 1 ATA with shorter periods of latency at higher P_{O_2}s, and increased severity as exposure was lengthened. The clinical manifestations included sore throat, substernal pain, coughing (particularly upon deep inspiration), headache, anorexia, and paresthesias. In studies that will be described in detail later (Comroe et al., 1945; Ohlsson, 1947; Caldwell et al., 1966; Clark and Lambertsen, 1971a; Dolezal, 1962) vital capacity decreased. In two other studies conducted for 5 to 6 h at 2 ATA, vital capacity decreased by 0 and 1.5%, respectively (Dewar et al., 1972; Widell et al., 1974). Carbon monoxide diffusing capacity (DLCO) fell in two studies (Caldwell et al., 1966; Puy et al., 1968); one study concluded that the membrane component was responsible (Caldwell et al., 1966), while the other found that pulmonary capillary blood volume had decreased (Puy et al., 1968). Alveolar-arterial O_2 gradients do not appear to change consistently throughout O_2 breathing (Clark and Lambertsen, 1971b; Puy et al., 1968; Dewar et al., 1972). Airway resistance was shown to increase by 30% (Dewar et al., 1972) or by less than 18% (Fisher et al., 1970). Reports of the effects on ventilatory frequency conflict (Ohlsson, 1947; Dolezal, 1962). Physiologic pulmonary shunt, cardiac output, extravasçular lung water, and pulmonary artery and systemic blood pressures were also not affected substantially by 2 ATA O_2 exposures that did not produce symptoms (Dewar et al., 1972; Van de water et al., 1970). Any documented changes that occurred were reversible, although recovery time varied from immediate to as long as two months.

While it is thus clear that exposure to 100% O_2 has the potential to produce pulmonary damage, questions whose answers are less clear include the following. How much O_2 exposure results in irreversible damage? What P_{O_2} is safe for long exposures? Is the Navy's choice of 0.4 ATA optimal? If the concentration of O_2 must be increased to 100% between 1 and 2.8 ATA, what length exposure is safe? Aside from intermittent exposure, are there ways that pulmonary O_2 toxicity can be prevented or ameliorated? What is the optimum intermittency schedule? Concerned with answering some of these questions and having reviewed most of the literature described above, Clark and Lambertsen (1970) proposed that change in vital capacity was the most reliable index of pulmonary O_2 toxicity for addressing some of these issues.

Vital Capacity as an Index of Pulmonary O_2 Toxicity

There are four major human studies in which vital capacity was measured serially throughout continuous O_2 exposures of significant length. In 1947, Ohlsson studied six subjects who breathed 80-88% O_2 at 1 ATA, and two control subjects who breathed a P_{O_2} between 0.21-0.35 ATA. We extracted the data from the figures in the paper; these are included in Table 1 and plotted as raw data and percentage changes in Fig. 1. Four of the six subjects developed symptoms (headache, substernal distress, paresthesias) after 6 to 24 h.

In 1966, Caldwell et al. studied four subjects, each of whom was subjected to 30, 48, 60, or 74 h of 0.98 ATA O_2 at atmospheric pressure. These data (also extracted from figures in the paper) are shown in Table 2 and Fig. 2. The authors claimed a fifth control subject had no changes in vital capacity, but there were no supporting data.

TABLE 1

Ohlsson (1947) Raw Vital Capacity Measured in Six Subjects Exposed to P_{O_2} of 0.83 ATA

Time (h)	Subject 1	2	3	4	5	6	7†	8†
0	5.3*	4.7	4.8	4.8	5.2	4.1	5.6	4.8
4.8	5.3	4.6	4.8	4.7	5.2	4.1	5.8	4.9
9.6	5.2	4.6	4.8	4.8	5.0	4.0	5.6	5.0
14.4	5.0	4.5	4.6	4.2	4.6	3.6	5.6	4.8
19.2	4.8	4.2	4.7	4.2	4.6	3.2	5.4	4.9
24	4.5	4.6	4.5	4.1	4.6	3.6	5.4	4.7
28.8	4.8	4.6	4.6	3.8	4.6	3.6	5.5	4.7
33.6	4.6	4.6	4.6	3.6	4.6	3.7	5.6	5.0
38.4	4.8	4.6	4.2	3.8	4.2	3.7	5.6	-
43.3	5.0	4.6	4.1	3.7	3.8	3.7	5.5	5.0
48	4.9	4.7	4.4	3.8	3.5	3.5	5.5	4.9
[illegible]	4.4	4.7	4.4	3.7	3.5	3.5	5.6	4.8

*Vital capacity is measured in liters.

†Subjects 7 and 8 were control subjects who breathed 0.21–0.35 ATA O_2.

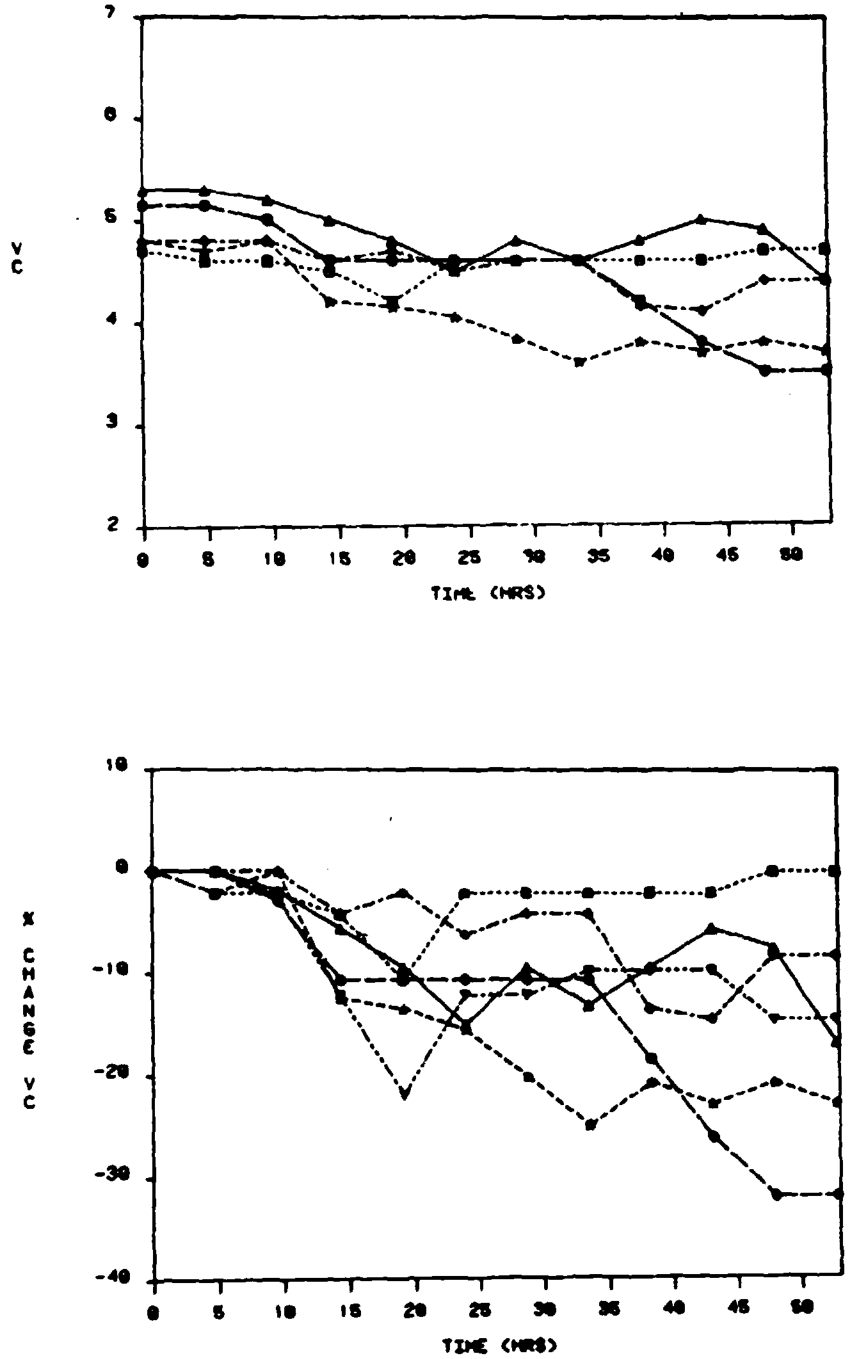


Fig. 1. Effect of exposure to 0.83 ATA O_2 on human vital capacity as reported by Ohlsson (1947). Top panel shows raw data (in liters) as a function of time; bottom panel shows data expressed as % change from the control value. Each line represents the time course for an individual subject (n = 6).

TABLE 2

Caldwell et al. (1966) Raw Vital Capacity Data Measured in Four Subjects Exposed to P_{O_2} of 0.98 ATA.

Time (h)	Subject 1	2	3	4
-84	-	6.1	-	-
-72	-	5.8	4.1	-
-60	-	6.0	4.2	-
-48	5.9*	5.5	4.2	-
-36	6.0	6.1	4.4	-
-24	6.1	6.1	4.4	5.6
-12	6.3	6.0	4.4	5.4
0	6.2	5.9	4.3	5.5
8	5.8	5.5	4.2	5.3
16	5.5	-	-	-
20	-	5.0	4.1	5.0
30	5.9	5.1	-	5.0
32	-	-	4.1	-
42	5.4	-	-	-
48	-	5.2	3.5	-
52	5.2	-	-	-
60	-	-	3.5	-
74	3.9	-	-	-

*Vital capacity is measured in liters.

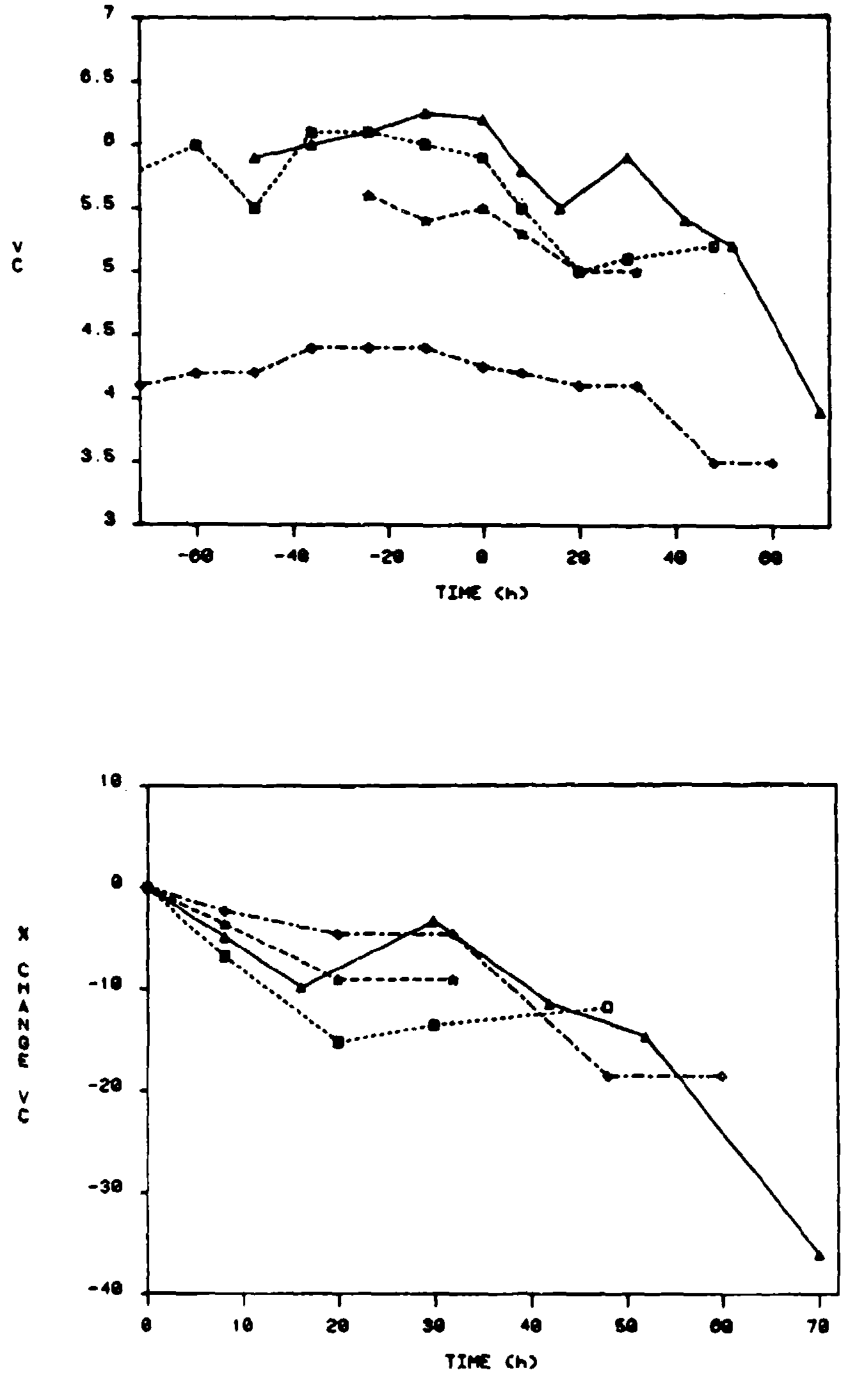


Fig. 2. Effect of exposure to 0.98 ATA O_2 on human vital capacity as reported by Caldwell et al. (1966). Panel A shows raw data (in liters) as a function of time; panel B shows data expressed as % change from the control value. Each line represents the time course for an individual subject (n = 4).

In 1971, Clark and Lambertsen (1971a) published data from 13 subjects exposed to 100% O_2 at 2 ATA for times ranging from 6 to 11.8 h. Exposures were terminated when a "significant reduction" in vital capacity developed or symptoms became severe. In 12 of 13 subjects, the first subjective symptoms developed in 3 to 6 h while the last subject was symptom free for 8 h. All subjects had chest pain, all but one coughed, most were very fatigued, nauseous, and dyspneic, one had paresthesias, and two fainted. The vital capacity results are shown in Table 3 (Clark and Lambertsen, 1970) and Fig. 3. Clark and Lambertsen eliminated subjects 12 and 13 from their analysis because the exposures were interrupted for 1-2 min every few hours for DLCO measurements. These subjects developed subjective and objective symptoms of O_2 poisoning, but the authors said these brief interruptions "appeared to have" delayed the onset of toxic effects. (We will analyze the effect of censoring the data of these two subjects)

Eckenhoff and coworkers (personal communication)[1] recently completed a series of 5 ATA air saturation (AIRSAT 4) dives at the Naval Submarine Research Laboratory in Groton, CT, in which serial vital capacity measurements were made in 12 experimental and six control subjects. The dive profile, Fig. 4, shows that the men breathed 0.3 ATA O_2 P_{O_2} for the first 12 h, 1.05 ATA O_2 for 48 h, and enriched O_2 mixtures for another 62 h during decompression. Controls were treated the same except that they were exposed to a P_{O_2} of 0.3 ATA during the 48 h. The results of all the vital capacity measurements made in twelve experimental subjects are shown in Fig. 5. Figure 6 includes only the first 60 h of the dive (includes up to the 1.05 ATA O_2 exposure segment) so that comparisons with data from Ohlsson (1947), Caldwell et al. (1966), and

[1]All references to Eckenhoff are personal communications, thus only his name will be cited in successive text.

TABLE 3

Clark et al.(1970) Raw Vital Capacity Data Measured in 13 Subjects Exposed to P_{O_2} of 2.0 ATA

Time (h)	Subject 1	2	3	4	5	6	7	8	9	10	11	12	13
0	5.0*	6.5	4.3	5.3	5.7	4.4	5.3	6.3	6.6	5.4	5.2	6.4	5.2
2	5.1	6.4	4.4	-	-	-	-	-	-	-	-	6.4	-
3	5.0	6.4	4.2	5.3	5.7	-	-	-	-	-	-	6.3	5.0
4	5.0	6.4	4.2	5.3	5.6	4.2	5.3	5.8	6.3	5.1	4.8	-	-
5	4.9	6.1	4.3	-	-	-	-	-	-	-	-	6.2	-
6	4.8	6.1	4.3	5.2	5.7	3.7	6.2	5.6	-	4.9	4.5	-	5.1
7	4.9	6.0	-	-	-	2.7	5.0	-	-	-	-	-	5.1
7.5	-	-	4.4	-	-	-	-	-	-	-	-	6.0	-
8	-	6.0	4.3	4.9	-	3.0	5.1	5.5	-	4.8	-	-	-
8.4	4.8	-	-	-	5.4	-	-	-	-	-	-	-	-
9	4.7	5.8	4.2	4.9	-	-	4.8	-	-	-	4.3	5.8	5.1
9.5	-	-	-	-	5.3	-	-	-	-	-	-	-	-
10.3	-	5.7	-	5.0	5.6	-	-	-	-	4.6	-	6.2	-
11	-	-	4.2	4.9	-	-	-	-	-	-	-	-	5.1
11.8	-	-	-	-	5.6	-	-	-	-	-	-	-	-

*Vital capacity is measured in liters.

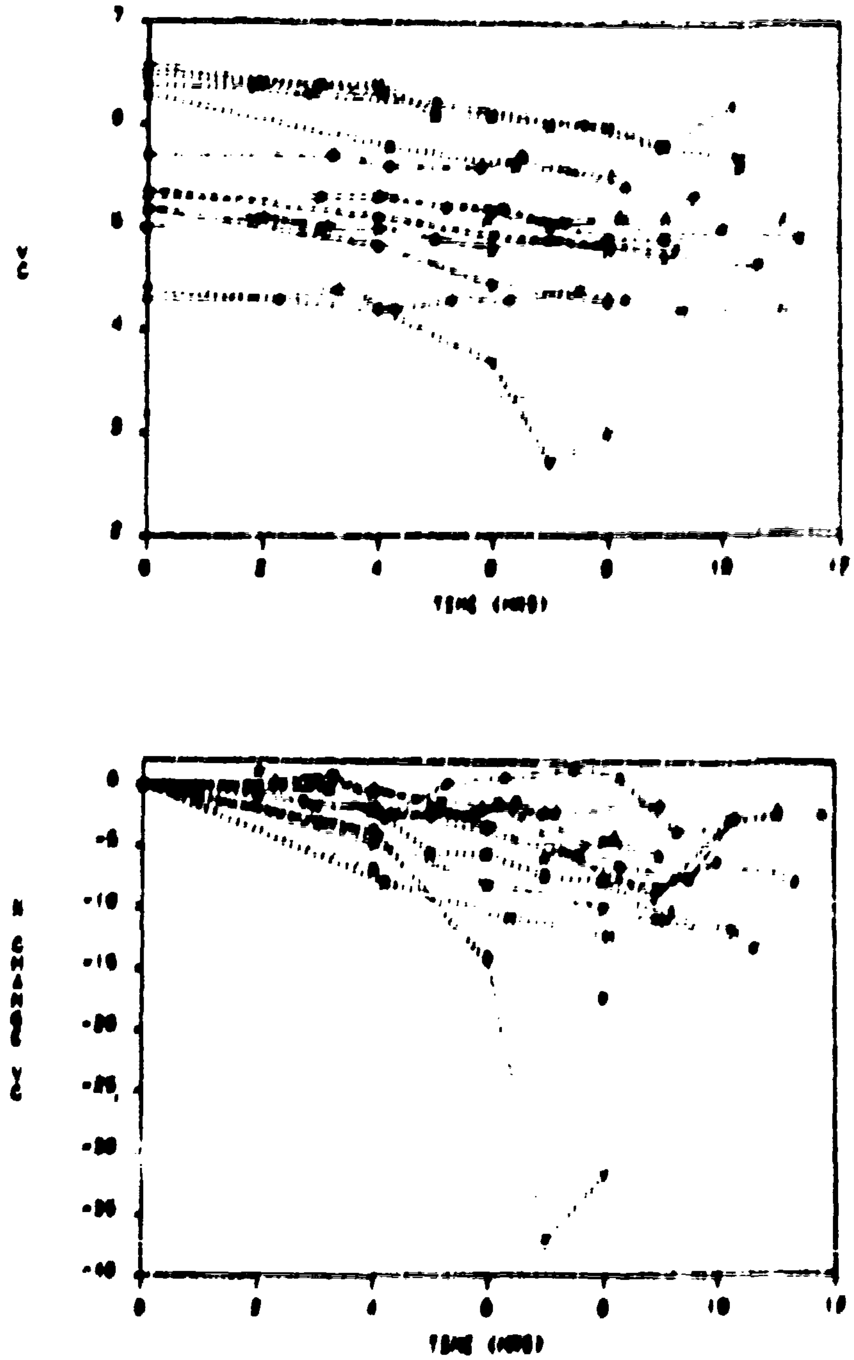


Fig. 3. Effect of exposure to 2.0 ATA O_2 on human vital capacity as reported by Clark and Lambertsen (1970). Top panel shows raw data (in liters) as a function of time; bottom panel shows data expressed as % change from the control value. Each line represents the time course for an individual subject (n = 13).

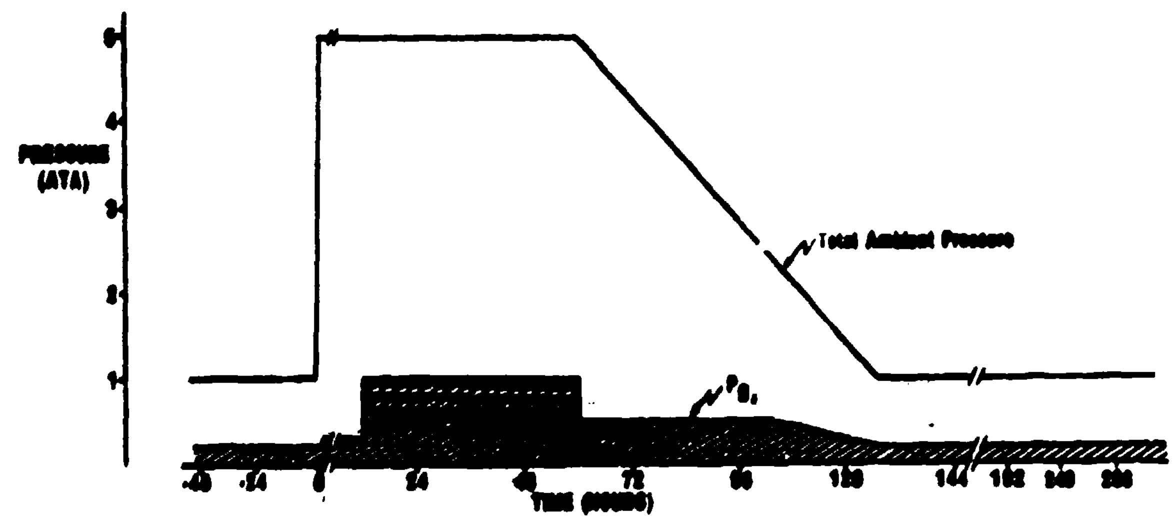


Fig. 4. Five ATA air saturation exposure profile utilized by Eckenhoff in 1983. The subjects were compressed to 5 ATA for 60 h and then slowly decompressed. Air was supplied for 48 h (resulting in a P_{O_2} of 1.05 ATA) followed by N_2-O_2 mixtures that kept P_{O_2} = 0.5 for 48 h. P_{O_2} was approximately 0.3 ATA at all other times during the profile.

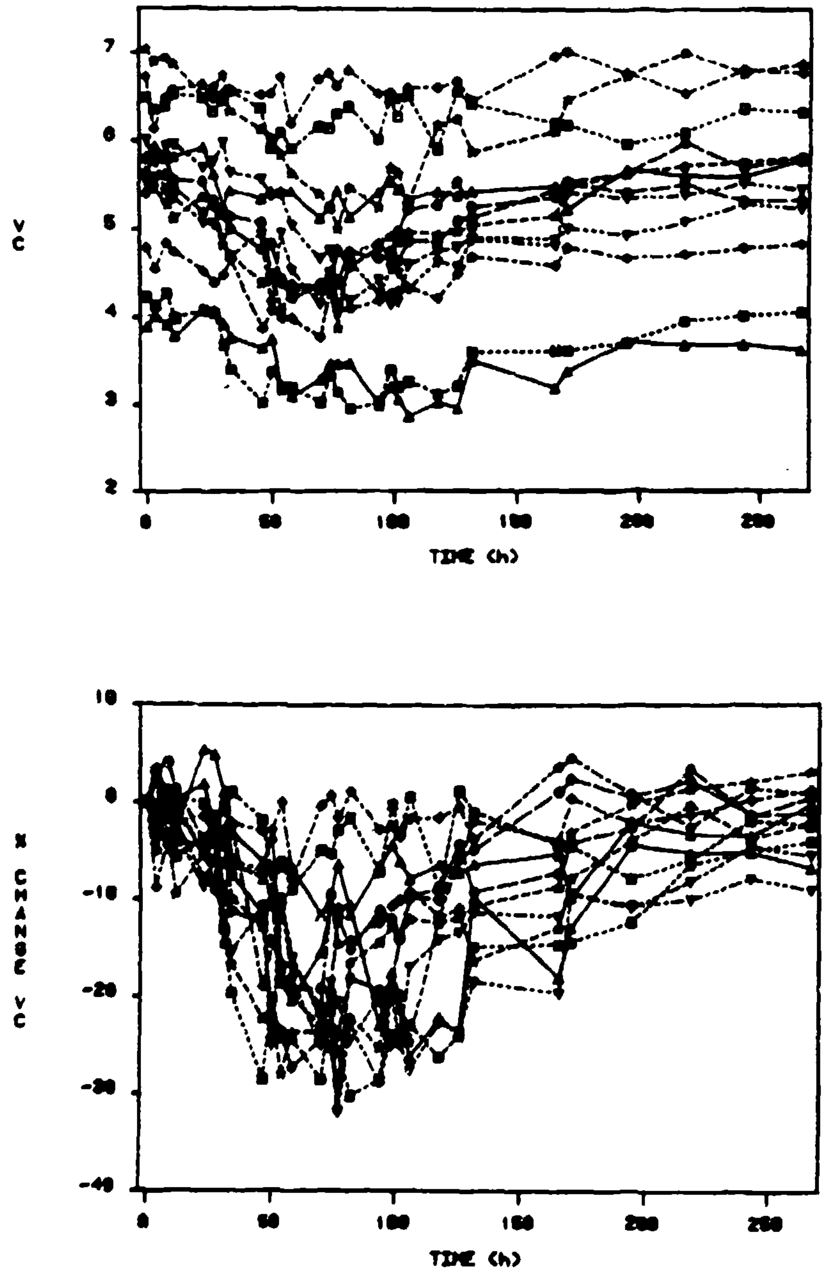
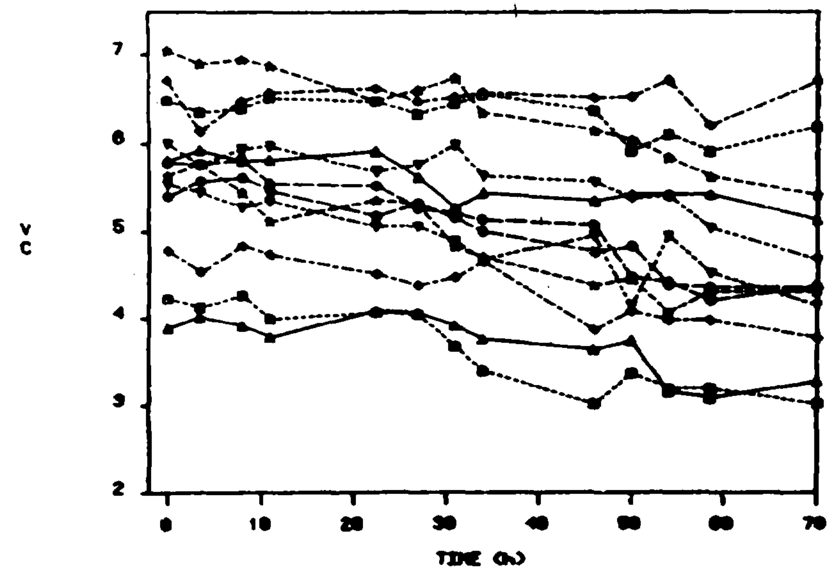


Fig. 5. All human vital capacity measurements reported by Eckenhoff in 1983 in 12 subjects participating in 5 ATA air saturation exposure diagrammed in Fig 4. Between 11 and 48 h, the subjects breathed 1.05 ATA O_2. Panel A shows raw data (in liters) as a function of time; panel B shows data expressed as % change from initial measurement. Each line represents the time course for an individual subject.



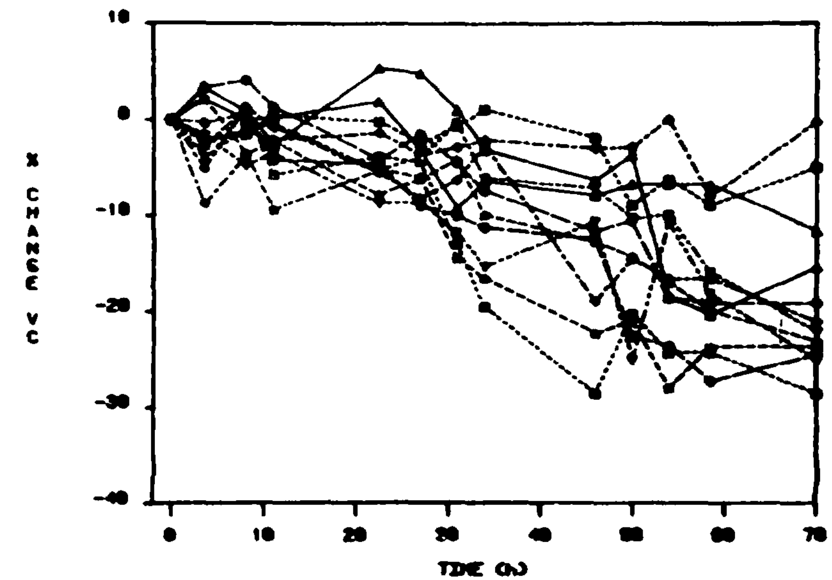


Fig. 6. Eckenhoff human vital capacity data collected during portion of profile when the subjects were supplied with a P_{O_2} of 0.30 for first 11 h and 1.05 ATA for next 48 h. Panel A shows raw data (in liters) as a function of time; panel B shows data expressed as % change from the control value. Each line represents the time course for an individual subject (n = 12).

Clark and Lambertsen (1970) are simplified. The results from the six control subjects are shown in Fig. 7, and Tables 4A and 4B include the raw data.

In 1945, Comroe et al. reported changes in vital capacity in groups of men exposed to 100%, 75%, and 50% O_2 as well as various schedules of intermittent exposure for 24 h. They did not provide actual vital capacity measurements. From the figures in their paper, however, we calculated the mean decrements in VC for each of these groups, and these data are included in Table 5. In those groups that developed symptoms (Groups A, B, D, E, F), the latency period ranged from 4 to 22 h with an average of 5.2 h. Subjects that received intermittent exposures developed symptoms that were "reduced in severity." No specifics were provided about the types of statistics used to analyze these data, but the claims were made that the VC decrement in men exposed to continuous 100% O_2 (Group A) was significant, that intermittency did not stay the development of toxicity, and that a P_{O_2} of 0.5, with or or without N_2 diluent, (Groups C, H) was completely safe. This study was used as a source to justify a P_{O_2} of 0.5 ATA as a safe exposure level (Clark and Lambertsen, 1970). This inference apparently arose from the development or nondevelopment of subjective symptoms only because the VC results are inconclusive.

A number of other studies were conducted to determine whether long exposures to only a moderately elevated P_{O_2} can be deleterious; these are listed in Table 6. (Control groups of Eckenhoff, and Ohlsson (1947) addressed this same issue). Several studies (Morgan et al., 1963a; Morgan et al., 1963b; Dubois et al., 1963) included only measurements made before and after experiments, while others included serial measurements (Michel et al., 1960; Morgan et al., 1961; Fisher et al., 1970; Fife et al., 1973). We re-expressed

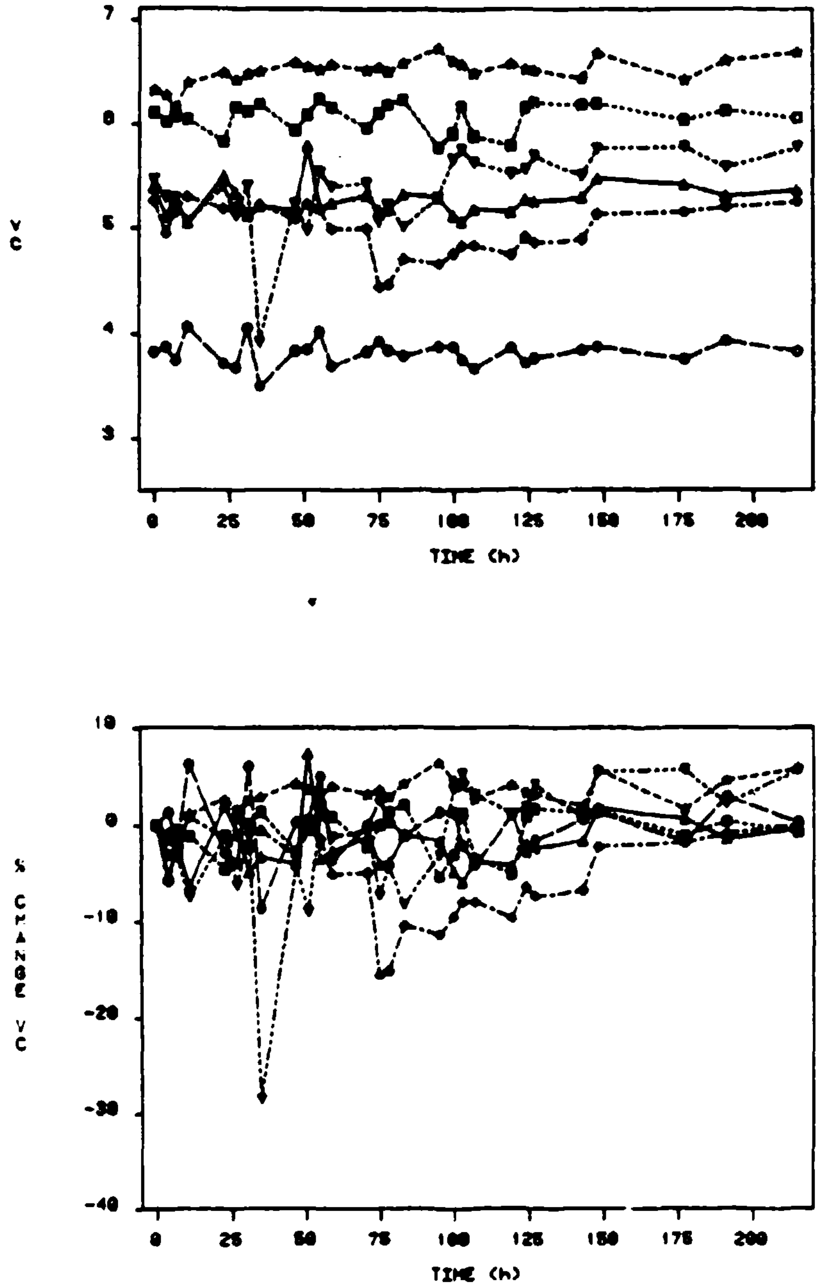


Fig. 7. Vital capacity measurements made in six control subjects studied by Eckenhoff in 1983. These subjects were exposed to the depth profile shown in Fig. 4 but were supplied with a P_{O_2} of 0.3 ATA for 48 h when experiments breathed 1.05 ATA O_2. The top panel shows raw data (in liters) as a function of time; the bottom panel shows data expressed as % change from initial measurement. Each line represents the time course for an individual subject (n = 6).

TABLE 4A

Eckenhoff Raw Vital Capacity Data Measured in 12 Experimental Subjects Exposed to 5 ATA Air Saturation Dive

Time (h)	PO_2 (ATA)	Subject 1	2	3	4	5	6	7	8	9	10	11	12
0	0.21	3.9*	6.5	6.7	5.7	5.8	5.5	5.8	4.2	4.8	7.0	5.4	6.0
3.5	0.3	4.0	6.4	6.1	5.8	5.8	5.5	5.9	4.1	4.5	6.9	5.6	5.8
8	0.3	3.9	6.4	6.5	5.5	5.8	5.3	5.8	4.3	4.8	7.0	5.6	5.9
11.5	0.3	3.8	6.5	6.6	5.1	5.6	5.4	5.8	4.0	4.7	6.9	5.5	6.0
11	1.05	4.1	6.5	6.6	5.4	5.5	5.1	5.9	4.1	4.5	6.5	5.2	5.7
15	1.05	4.1	6.3	6.5	5.3	5.3	5.1	5.6	4.1	4.4	6.6	5.3	5.8
[illegible]	1.05	3.9	6.5	6.5	4.8	5.2	4.9	5.3	3.7	4.5	6.8	5.2	6.0
[illegible]	1.05	3.8	6.6	6.6	4.7	5.1	4.7	5.4	3.4	4.6	6.3	5.0	5.6
[illegible]	1.05	3.6	6.4	6.5	4.4	5.1	5.0	5.4	3.0	3.9	6.1	4.8	5.6
39	1.05	3.7	5.9	6.5	4.5	4.5	4.2	5.4	3.4	4.1	6.0	4.8	5.4
43	1.05	3.2	6.1	6.7	4.1	4.4	5.0	5.4	3.2	4.0	5.8	4.4	5.4
47.5	1.05	3.1	5.9	6.2	4.3	4.2	4.5	5.4	3.2	4.0	5.6	4.4	5.0
59	0.5	3.3	6.2	6.7	4.3	4.4	4.2	5.1	3.0	3.8	5.4	4.4	4.7
63	0.5	3.5	6.2	6.8	4.3	4.5	4.5	5.3	3.3	4.3	5.2	4.3	4.8
66	0.5	3.5	6.3	6.6	3.9	4.4	4.4	5.4	3.1	4.1	5.0	4.8	4.1
71	0.5	3.5	6.4	6.8	4.7	4.7	4.2	5.1	3.0	4.1	5.5	4.6	4.6
83	0.5**	3.0	6.0	6.5	4.8	4.7	4.4	5.4	3.0	4.2	5.3	4.8	4.3
88		3.2	6.5	6.6	4.9	4.7	4.2	5.6	3.4	4.3	5.7	4.8	4.6
91		3.1	6.3	6.5	4.9	5.0	4.2	5.5	3.2	4.3	5.7	4.7	4.5
[illegible]		2.9	6.5	6.6	5.0	5.2	4.6	5.4	3.3	4.3	5.3	4.9	4.3
[illegible]		3.0	5.9	6.6	5.0	5.3	4.8	5.4	3.1	4.2	6.2	4.9	4.6
[illegible]		3.0	6.6	6.7	5.0	5.5	4.8	5.4	3.2	4.5	6.3	5.1	4.6
[illegible]	0.21	3.5	6.4	6.5	5.1	5.3	4.9	5.4	3.6	4.7	5.9	5.1	4.9
[illegible]	0.21	3.2	6.2	7.0	5.2	5.4	4.9	5.5	3.6	4.6	6.1	5.5	4.8
[illegible]	0.21	3.4	6.2	7.0	5.5	5.6	5.0	5.2	3.6	4.8	6.5	5.5	5.4
[illegible]	0.21	3.7	6.0	6.8	5.6	5.6	4.9	5.7	3.7	4.7	6.8	5.4	5.4
[illegible]	0.21	3.7	6.1	6.6	5.7	6.0	5.1	5.6	4.0	4.7	7.0	5.5	5.4
[illegible]	0.21	3.7	6.4	6.8	5.8	5.7	5.3	5.6	4.0	4.8	6.8	5.3	5.5
[illegible]	0.21	3.6	6.3	6.8	5.8	5.8	5.2	5.8	4.1	4.8	6.9	5.3	5.5

*Vital capacity is measured in liters.

**Decompression occurred between 83 and 120 h and P_{O_2} was gradually brought back to 0.21 ATA.

TABLE 4B

Eckenhoff Raw Vital Capacity Data Measured in 6 Control Subjects Exposed to 5 ATA with P_{O_2} of 0.3 ATA

Time (h)	PO_2 (ATA)	Subjects 1	2	3	4	5	6
0	0	5.4*	6.1	5.3	6.3	3.8	5.5
4	0.3	5.1	6.0	5.0	6.3	3.9	5.3
7	0.3	5.3	6.1	5.2	6.2	3.7	5.3
11	0.3	5.1	6.0	5.3	6.4	4.1	5.1
23	0.3	5.5	5.8	5.2	6.5	3.7	5.4
27	0.3	5.3	6.2	5.2	6.4	3.7	5.1
31	0.3	5.1	6.1	5.1	6.5	4.1	5.4
35	0.3	5.2	6.2	5.2	6.5	3.5	3.9
47	0.3	5.2	5.9	5.1	6.6	3.8	5.2
51	0.3	5.7	6.1	5.2	6.6	3.8	5.0
55	0.3	5.2	6.2	5.2	6.5	4.0	5.5
59	0.3	5.2	6.2	5.0	6.6	3.7	5.4
71	0.5	5.3	6.0	5.0	6.5	3.8	5.4
85	0.5	5.2	6.1	4.4	6.6	3.9	5.1
88	0.5	5.2	6.2	4.5	6.5	3.8	5.2
93	0.5	5.3	6.2	4.7	6.6	3.8	5.0
105	0.5**	5.3	5.8	4.7	6.7	3.9	5.3
110		5.1	5.9	4.8	6.6	3.9	5.7
113		5.1	6.2	4.8	6.6	3.7	5.8
117		5.2	5.9	4.8	6.5	3.7	5.6
129		5.2	5.8	4.8	6.6	3.9	5.5
134		5.3	6.2	4.9	6.5	3.7	5.6
137	0.21	5.3	6.2	4.9	6.5	3.8	5.7
153	0.21	5.3	6.2	4.9	6.4	3.8	5.5
158	0.21	5.5	6.2	5.1	6.7	3.9	5.8
177	0.21	5.4	6.0	5.2	6.4	3.8	5.8
191	0.21	5.3	6.1	5.2	6.6	3.9	5.6
225	0.21	5.4	6.1	5.3	6.7	3.8	5.8

*Vital capacity is measured in liters.

**Decompression occurred between 83 and 120 h and P_{O_2} was gradually brought back to 0.21 ATA.

TABLE 5

Summary of Comroe et al. (1945) Study

Exposure	Number of Subjects	Mean Change in VC (±SD) (ml)	% Developing Symptoms
A 100% O_2*	34	-254 (±405)	82
B 75% O_2	9	-274 (±186)	55
C 50% O_2	10	-244 (±182)	0
D 1 min air/3 h O_2	7	-185 (±169)	86
E 5 min air/3 h O_2	7	-287 (±167)	100
F 15 min air/3 h O_2	7	-104 (±184)	86
G Air	10	+210 (±380)	0
H 100% O_2, PB=380	6	-97 (±188)	0

*All exposures lasted 24 h.

TABLE 6

Human Vital Capacity Response to Low and Moderate P_{O_2} Exposures

P_{O_2} (ATA)	PB (ATA)	Time (h)	% VC (by Subj. No.) 1	2	3	4	5	6	Reference
0.32	0.34	336	-2.9	-2.5	0.3	-6.5	-	-	Morgan et al., 1963a
0.23	0.25	408	-13.7	-2.0	-5.8	-7.4	-3.7	-12.3	Morgan et al., 1963b
		408	-12.7	-3.5					
0.23	0.24	24	-3.4	-	-	-	-	-	Morgan et al., 1961
-	-	48	-	-7.0	-	-	-	-	-
-	-	120	-	-13.0	-	-	-	-	-
-	-	192	-	-10.0	-	-	-	-	-
-	-	276	-	-11.0	-	-	-	-	-
-	-	336	-	-10.0	-	-	-	-	-
-	-	384	-1.0	-10.0	-	-	-	-	-
0.3	0.3	336	0.6	6.1	1.5	-	-	-	Dubois et al., 1963
0.55	0.67	24	-3.3	-22.0	-3.0	3.7	-2.4	3.5	Michel et al., 1960
-	-	48	0	-15.9	0	6.7	5.8	3.9	-
-	-	72	-3.1	-26.2	2.1	1.4	21.0	13.8	-
-	-	96	-10.1	-23.9	4.0	0.6	13.5	16.6	-
-	-	120	-1.6	-18.6	2.4	0.5	10.2	15.1	-
-	-	144	1.7	-21.0	4.5	3.8	10.7	14.1	-
0.47	2.4	72	0	0	-10.3	-	-	-	Fife et al., 1973
-	-	96	0	2.5	-10.3	-	-	-	-
-	-	120	2.2	-2.5	-3.0	-	-	-	-
-	-	144	2.2	-2.5	-3.0	-	-	-	-
0.21	2.2	120	-3.3	5.5	1.9	-3.4	-	-	Fisher et al., 1970
-	-	288	-4.1	-0.2	4.8	-1.5	-	-	-
-	-	456	-1.2	0.5	2.9	-0.9	-	-	-
-	-	624	-5.3	2.1	4.3	-1.1	-	-	-
-	-	792	-5.9	4.7	3.2	-3.0	-	-	-
-	-	960	-1.7	4.2	3.5	-1.7	-	-	-
-	-	1128	-3.1	7.0	7.4	0.4	-	-	-
-	-	1296	-0.2	5.2	7.7	0.3	-	-	-
0.5	2.5	720	+3.1	+0.3	-	-	-	-	Dougherty et al., 1978
0.58	2.8	624	+5.9	+9.3	-	-	-	-	Dougherty et al., 1978
0.5	2.5	168	-3.4	+5.9	+5.7	-	-	-	Dougherty et al., 1978
0.33	0.33	720	(n=4)	-	-	-	-	-	Robertson et al., 1964
0.33	0.92	720	(n=4)	-	-	-	-	-	Robertson et al., 1964
0.42	2.0	24	(n=12)	-	-	-	-	-	Dougherty et al., 1968
0.48	2.5	168	(n=3)	-	-	-	-	-	Widell et al., 1973
0.21	4.0	336	(n=6)	-	-	-	-	-	Wright et al., 1973
0.3- 0.6	31- 61.6	552- 744	(5/17 decreased)			-	-	-	Lemaire et al., 1975
0.50	45.7	264	(n=8, 5% decrease)			-	-	-	Hyacinthe et al., 1981
0.40	45.7	188	(n=4)	-	-	-	-	-	Broussolle, 1987

the Fife et al. (1975) data as percentage of change from the first vital capacity measured at depth as dense gas breathing caused an immediate decrease. From this collection of experiments, P_{O_2} exposures ranging from 0.21 to 0.48 ATA produced little subjective evidence of toxicity. Some pain upon inspiration was reported after nine days in the Morgan, et al (1961) study, but this may have been due to the dry gas environment. Fisher et al. (1970) claimed that the dense gas environment may have led to strengthening of ventilatory muscles and a subsequent increase in VC, but we believe the data did not strongly support this idea. Subjects exposed to a P_{O_2} of 0.55 ATA (Michel, Langevin, and Gell, 1960) experienced substernal tightness beginning on the second day. This study showed an enormous amount of variability, and the 16.6 and 21% increases in two subjects' vital capacity suggest that these subjects may not have been well trained in this maneuver. We excluded these data from the final analysis.

Several of the entries in Table 6 (Robertson et al., 1964; Dougherty and Schaefer, 1968; Widell et al., 1973; Wright et al., 1973), include no individual values or any indication of individual or group variability. The mean values reported all appeared stable, although these were not useful for our analyses. Lemaire's (1975) paper summarized the results of six saturation dives conducted at barometric pressures ranging from 30-61 ATA, where P_{O_2} was kept between 0.3 and 0.45 ATA at depth and at 0.6 during decompression. He reported that five of 17 subjects had "decreased" vital capacity, but no statistics were provided. Hyacinthe, et al (1981) reported that VC decreased 5% in eight subjects exposed to a P_{O_2} = 0.5 ATA after an 11 day saturation at 45.7 ATA. Breunsele's (1982) final report on the Kntex dives (17 days saturation at 45.7 ATA, P_{O_2} = 0.4 ATA) showed no decrement in VC immediately after the dive and a 3% decrement after 48 h. The third SHAD dive study cited by Dougherty et al. (1978) included daily 8 h excursions to 100 fsw on air. Air at 100 fsw results in a P_{O_2} of .64 ATA and yet these authors reported that P_{O_2} reached a maximum of 1.79 ATA. They did not explain this discrepancy. One subject was treated for decompression sickness (1.85 ATA O_2 for 40 min) after which his vital capacity dropped abruptly by 28%.

Qualitatively, vital capacity changes appear to be an extremely variable response among individuals. During O_2 exposure, vital capacity can remain unchanged, change gradually and steadily, or drop suddenly (Figs. 1-6). The results in Table 6 do not lend themselves to an immediate conclusion about what the typically safe P_{O_2} exposure is. Chest pain is a characteristic complaint resulting from O_2 exposure, and this raises the question whether changes in VC represent a change in effort more than an underlying pulmonary disease process. In studies where VC decreased with O_2 exposure, anecdotal evidence was provided that the change in vital capacity did not correlate with subjective symptoms and, furthermore, that during recovery functional changes outlasted symptoms.

The reproducibility of the vital capacity measurements is usually considered to be in the range of approximately 200 ml or to have a standard deviation that is approximately 2.5% of the VC (Rahn, Fenn, and Otis, 1949; Dougherty et al., 1978). Clark and Lambertsen (1971a) claimed a pooled 95% confidence interval of 60 ml which was unusually small, although how this calculation was made was not specified. Eckenhoff's control studies (Fig. 7) showed the variation obtained in normal men exposed to a P_{O_2} of 0.3 ATA, while they performed multiple VC maneuvers over long exposures. Although there was no doubt that these data showed a different trend than those obtained in the experimental group (Figs. 5 and 6), there probably was a small (1-2%) decrement, even with exposure to only a slightly elevated P_{O_2}.

If one accepts that the decrement in VC represents more than fatigue, there remains disagreement about whether atelectasis or some direct lung tissue damage is the mechanism responsible. Burger and Mead (1969) presented fairly convincing evidence for atelectasis. They showed that 3 h of 0.39, 0.5, 1.0, or 2.0 ATA of 100% O_2 altered the pressure-volume characteristics of the mens' lungs such that at high lung volumes a smaller pleural pressure developed on the first pressure-volume maneuver, but this appearance of reduced compliance was quickly reversible on subsequent efforts. This change in lung mechanical property was documented as uncorrelated with chest pain. The subjects were encouraged not to sigh or breath deeply, and the investigators found that the apparent decrease in compliance was quickly reversible with subsequent full lung inflation. Eckenhoff's new data offer conflicting evidence. His subjects had nearly 4 ATA of N_2 diluent to breathe, so absorptional atelectasis should have been minimized. These subjects had significant decrements in VC (Figs. 5, 6).

Evidence for Tolerance to O_2 Exposure

A final application of the vital capacity index is the detection of the development of tolerance to O_2 exposure. Several studies have shown that a degree of tolerance is acquired when exposure to O_2 is intermittent. That is, an animal will tolerate more total time in O_2 when exposure is not continuous but interrupted by periods of exposure to air or N_2-O_2 mixtures. Wright et al. (1966) used powerful statistical techniques to show that 4 h of air per day was the shortest interruption able to prolong survival in mice exposed to 100% O_2 at 1 ATA. In a master's thesis, Hall (1967) tested a series of intermittency schedules with shorter time periods (< 1 h) on groups of guinea pigs breathing O_2 at 3 ATA. On the basis of the time it took 50% of the animals (ED50) to develop several symptoms, he proposed that 20 min of O_2

followed by 5 min of 7% O_2 in N_2 (this resulted in a normoxic P_{O_2} at 3 ATA) was the most efficient schedule.

Widdell et al. (1974) tested three intermittency schedules on professional divers who breathed O_2 at 2 ATA. The experiments were terminated at the subject's discretion; the results are summarized in Table 7. In this study VC did not decrease in the three subjects who were exposed to continuous O_2. The men who received intermittent exposures of air tolerated longer mean O_2 exposures with fewer symptoms. These subjects had larger mean decrements in VC but Table 7 shows that they chose to tolerate more time in O_2. As is often the case with human studies, the number of subjects was small and the variability of results so large that conclusions must be considered tentative at best. These authors concluded that the 25 min O_2/5 min air schedule was most effective.

Hendricks et al. (1977) conducted an intermittency study designed to complement Clark and Lambertsen's (1971a) 2 ATA continuous O_2 experiment. Five experimental subjects and one control subject breathed 20 min of O_2 followed by 5 min of normoxic N_2-O_2 (P_{O_2} = 160 torr) at 2 ATA until VC decreased by 10% or symptoms became severe. This experiment was also influenced by the design of Hall's (1967) thesis, which utilized this normoxic mixture during the O_2 breaks. (The design was different from that currently utilized by the U.S. Navy for recompression treatments because compressed air is the breathing gas, not 7% O_2 in N_2.) The results of the Hendricks et al. (1977) study are provided in Table 8 and Fig. 8. These 5 subjects seemed to tolerate longer O_2 exposures (Fig. 8A) than did subjects exposed to continuous O_2 (Fig. 3) before developing significant changes in VC. These subjects developed symptoms of O_2 toxicity 1 to 2 h before changes in VC were detected, and the decrease in VC was said to continue for 4 h after termination of the

TABLE 7

Summary of Widell et al. (1974) Intermittency Study*

	Continuous O_2	25 min O_2/ 5 min air	20 min O_2/ 20 min air	10 min O_2/ 20 min air
# Subjects	3	5	8	3
O_2 Time tolerated	5.[illegible]	8.2	6.9	5.1
O_2 Time to first symptoms	2.6	4.3	3.9	3.3
Total time tolerated	6.0	9.8	13.8	15.4
% VC change (± SD)	-1.53 (1.79)	-2.64 (1.3)	-7.5 (2.97)	-1.17 (0.58)

* Times are all mean responses in hours.

TABLE 8

Hendricks et al. (1977) Data on Percent Change in Vital Capacity in Five Subjects Exposed to Intermittent O_2 Exposure* at 2 ATA.

O_2 Time (h)	Subject 1	2	3	4	5	6†
1	1.5*	.6	.6	-2.0	0.6	+1.0
3	2.0	-1.0	-1.5	-1.0	0.0	+1.2
5	5.5	1.0	-2.0	1.0	0.0	+1.8
7	3.0	0.0	-2.0	0.0	-2.0	+ .5
9	2.0	-1.0	1.0	-1.0	-3.0	+ .8
11	0.0	-3.0	-7	-2.0	-2.0	+1.2
13	-3.0	-9.0		-5.0	-6.0	+1.2
14	-5.0	-10.0				
15	-7.0	-11.0				

* Intermittent exposure equals 20 min O_2/5 min 7% O_2.
† Subject was a control who continually breathed 7% O_2.

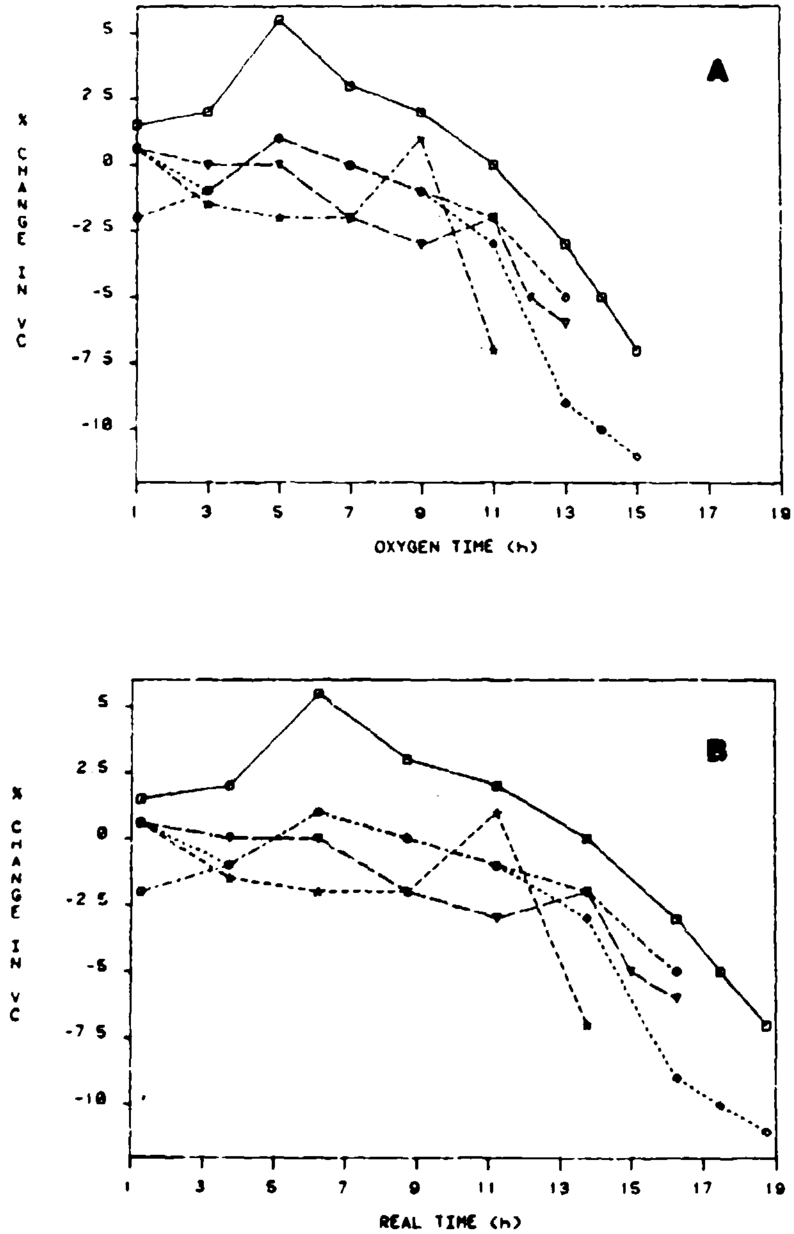


Fig. 8. Effect of exposure to intermittent O_2 exposure at 2 ATA on human vital capacity as reported by Hendricks et al. (1977). Four subjects were exposed to 20 min of 100% O_2 followed by 5 min of 7% O_2 in N_2. Data are expressed as % change from the control value. Each line represents the time course for an individual subject. Panel A shows vital capacity as a function of time spent in O_2 while panel B shows vital capacity as a function of the actual time of exposure.

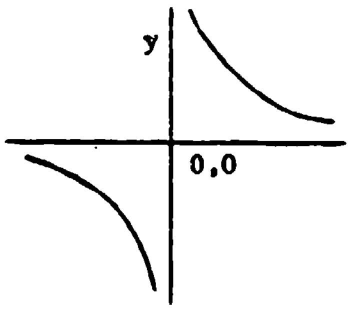
O_2. Symptoms persisted (or even worsened) for only 2-4 h post exposure and recovery was usually complete in 24 h.

Moselhi, Abdallah, and Azab (1980) compared pulmonary function in 67 control subjects with that of 65 divers who had dived with 100% O_2 to 1 to 2 atm for 90 min twice a week over a range of two to 10 years. No difference in mean values of lung volumes, flows, or diffusing capacity in ventilation with exercise could be detected.

Evaluation of the UPTD Concept: Background

Clark and Lambertsen (1970) proposed that the relationship between inspired P_{O_2} and duration of exposure required to produce toxic effects is in the general form of a rectangular hyperbola: at high P_{O_2}s a short exposure will produce an effect, while at low P_{O_2}s a longer time is required to produce an effect. A rectangular hyperbola has the mathematical form:

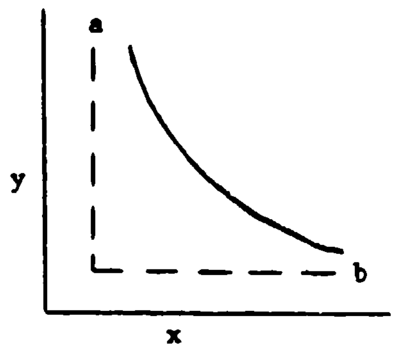
$$xy = \text{constant}$$



[1]

In the physiological case, only the positive values are relevant, focusing attention on the upper right hand quandrant. The most general form of the rectangular hyperbola allows the curve to have asymptotes other than 0,0.

$$(x-a)(y-b) = \text{constant}$$



[2]

For pulmonary O_2 toxicity, the axes would be:

$$(\text{Time} - a)(P_{O_2} - b) = \text{constant} \qquad [3]$$

This equation describes the collection of all combinations of exposure times and P_{O_2}s resulting in the same toxicity. Clark and Lambertsen (1970) chose the time asymptote, a, to be 0, reasoning that at an infinitely high P_{O_2}, a vanishingly small amount of time would be required to produce damage. They chose the P_{O_2} asymptote (b) to be 0.5 ATA by deduction from the literature we reviewed above. Because Clark was carrying out a graphical analysis, a linear transformation was convenient. Using his asymptotes and taking logarithms resulted in the equation:

$$\log\left(\frac{(P_{O_2} - 0.5)}{(t)^{-1}}\right) = \log(\text{constant}) \qquad [4]$$

Clarks's graphical analytical technique resulted in figures showing parallel isopleths, each one representing the combinations of time and P_{O_2} exposures required to produce a given decrement in vital capacity. Both the linear and the log transforms are shown in Fig. 9. These are well known figures and first appeared in Clark and Lambertsen's (1970) thesis. These curves were derived by plotting the median response time for a given VC change in the three studies carried out at P_{O_2}s of 0.83, 0.98, and 2.0 ATA, with a total of 23 subjects (Ohlsson, 1947; Caldwell et al., 1966; Clark and Lambertsen, 1970). Because of this logarithmic transformation, it was necessary for Clark and Lambertsen (1970) to censor some data collected early in the exposures (Logarithms cannot be taken of zero and negative numbers). Fluctuations within the 95% confidence interval of the control measurement were assigned the value of 0 and not used in the analysis. Clark and Lambersten (1970) also imposed a threshold on the Caldwell et al. (1966) data set by assuming there

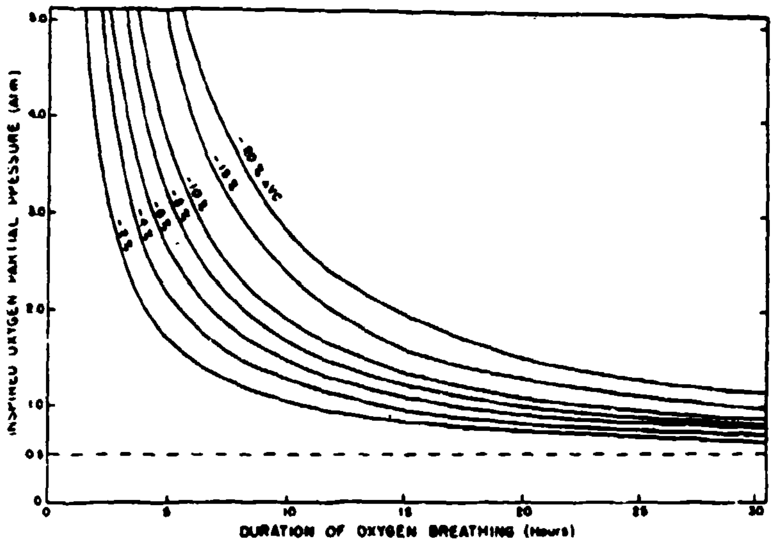


Fig. 9a. Clark's pulmonary oxygen tolerance curves in normal men based on vital capacity changes in the median subject. Each isopleth shows the combinations of P_{O_2} and time of exposure required to produce a given decrement in vital capacity.[2]

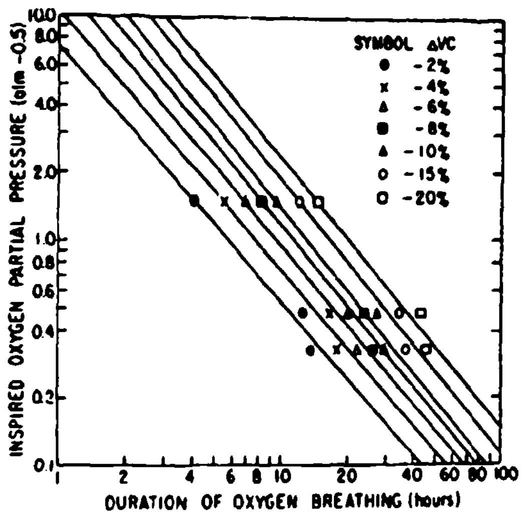


Fig. 9b. Clark's pulmonary oxygen tolerance curves in normal men based on vital capacity changes in the median subject. This is a log-log transform of Fig. 9a.

was no change for the first 5 h of exposure. Clark proposed that the cumulative pulmonary toxicity of any combination of O_2 exposures could be calculated from these graphs by determining the decrement from any P_{O_2} and time exposure combination by moving horizontally for the duration of the exposure at a constant P_{O_2} and up and down along the isopleths as P_{O_2} is changed.

Bardin and Lambertsen (1970) and Wright (1972) showed how this same process could be achieved numerically (rather than graphically), and they introduced the UPTD idea. Because they wished to weight more heavily the 2 ATA data, they felt that the slope of the log-log plot shown in Fig. 10b was closer to -1.2 than -1.0. They therefore modified Eqn. 3 to include the exponent m in the denominator

$$\log \frac{(P_{O_2} - .5)}{(t)^m} = \log(b) \qquad [5]$$

where b was a constant and m was estimated as -1.2. Taking the antilog of both sides, the equation became:

$$P_{O_2} - .5 = b(t)^m \qquad [6]$$

where P_{O_2} is given in atmospheres, t is time in minutes, and m is -1.2. The constant, b, represents some constant level of toxicity - a given percentage decrement in VC. Isopleths that show increments in toxicity are parallel (Fig. 9b) because m is constant, The expected decrement in vital capacity after any time at any P_{O_2} can be calculated in terms of an equivalent dose. This dose represents the time that would have been required if the exposure had been to O_2 at 1 ATA.

$$\text{pulmonary toxicity dose} = t \cdot \left(\frac{.5}{P_{O_2} - .5}\right)^{-\frac{1}{1.2}} \qquad [7]$$

where t is time in minutes. If P_{O_2} is 1 ATA, the UPTD is just the time of exposure. If P_{O_2} is some other value, the UPTD indicates the time at 1 ATA which would have yielded an equivalent toxicity. Equivalent times at different P_{O_2} exposures may then be summed to calculate the total equivalent exposure. The defined UPTD relates to a decrease in VC as shown iu Table 9. The UPTD definitions were derived from Fig. 9b, which shows for example that after 10.25 h (615 min) of O_2 at 1 ATA there is a 2% decrease in VC.

METHOD

Instead of the serial graphical process used by Clark and Lambertsen (1970) we did a coordinated (computer) analysis that allowed us to explicitly test certain features of the hyperbolic relationship (Eqn. 6) (the exponent, m, and the asymptotes for time and P_{O_2}), and to evaluate the contribution of individual variability. The latter effect was not addressed in the original model as only the median individual response was graphed. We did a nonlinear least squares analysis, titting the data (subject, % change in VC, P_{O_2}, and time of exposure) to the equation.

$$\% \Delta VC = B(s)\ (P_{O_2} - B(1))[(t - B(2))]^{B(3)} \qquad [8]$$

This equation is a more general form of Eqn. 6. B(1) is the P_{O_2} asymptote (in ATA) which Clark set at 0.5 ATA; t is time in minutes; B(2) is the time asymptote which Clark set to 0; B(3) is the exponent m, which Bardin and Lambertsen (1970) proposed was 1.2; and B(s) is a siope parameter, which can be different for every subject.

This model did not assume a linear effect: if the exponent B(3) > 1.0, the relationship between ΔVC and time at any given P_{O_2} will curve downward, as

TABLE 9

Unit Pulmonary Toxicity Dose Definition

UPTD	Median % VC Decrement
615	-2
825	-4
1035	-6
1230	-8
1425	-10
1815	-15
2190	-20

shown in Fig. 10. Varying B(e) from below 0 to larger negative numbers will increase the slope or the change in VC with time. Lowering the P_{O_2} asymptote (B(1)) will also lead to a prediction of a larger decrement in VC after any time at a given elevation in P_{O_2}.

This nonlinear fitting technique is exactly analogous to linear regression, but because it may appear more complicated, a short description may be worthwhile. An educated guess is made for starting parameters B(1), B(2), and B(3) (for example, 0.5, 0, -1.2) as well as for B(e). With this set of B's, for every combination of subject, time of exposure, and P_{O_2}, an estimated % ΔVC is calculated and compared with the actual (measured) % ΔVC. This difference (estimated - measured) is squared and summed over all data points. Thus, a sum of squared errors (SSE) is computed. The parameters (B's) are then altered slightly by the computer, estimated % ΔVC is recalculated, and the SSE is recalculated. This process is repeated until the SSE is minimized. In this model, when the P_{O_2} to which the subject was exposed was less than the B(1) (P_{O_2} asymptote) being tested, any change in VC was considered error. The assumption was that exposure to a P_{O_2} below the "safe" P_{O_2} should have produced no decrement in VC. To make statistical comparisons about asymptotes and exponent, parameters are fixed (at values representing a null hypothesis to be tested) and a new SSE is calculated. An F test is performed to determine which parameters provided the better fit (or to evaluate the null hypothesis).

The described analysis was carried out on the data summarized in Table 10. Original data were first re-expressed as percent of change from the control value. When control values were measured several times, all pre-experimental values were averaged. Data from the first 60 h (which

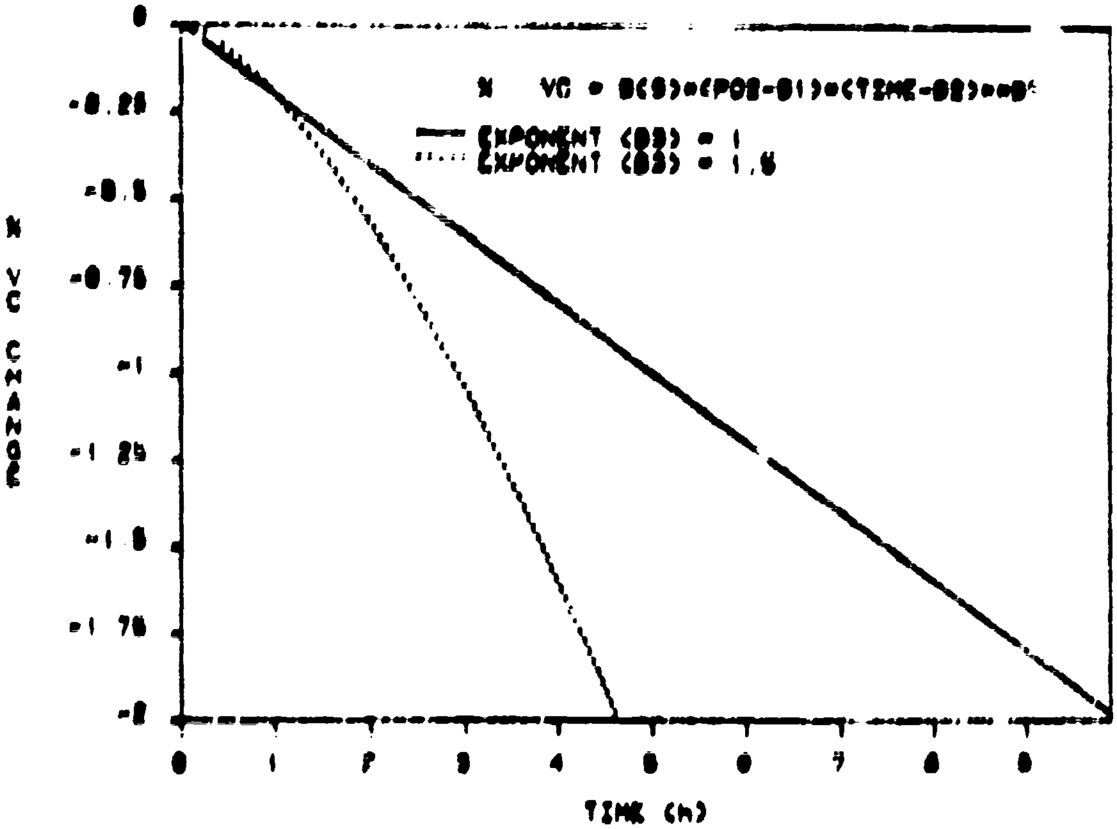


Fig. 10. Effect of exponent on the shape of the predicted change in vital capacity as a function of time. When the exponent is > 1.0 (dashed line) the response curve bends downward indicating slow changes initially followed by increasingly rapid changes.

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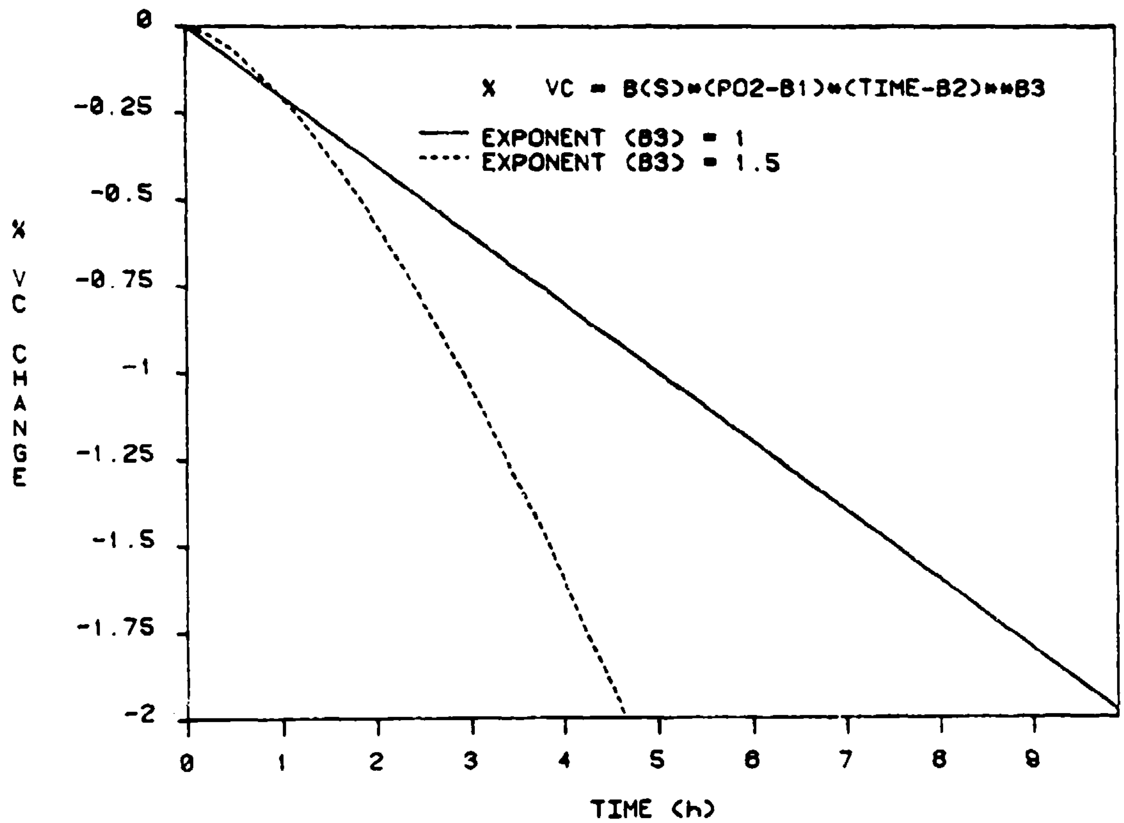

Fig. 10. Effect of exponent on the shape of the predicted change in vital capacity as a function of time. When the exponent is > 1.0 (dashed line) the response curve bends downward indicating slow changes initially followed by increasingly rapid changes.

TABLE 10

Summary of data used for analysis

PO_2 (ATA)	Number Subjects	Number Data	Reference
2.0	13	73	Clark and Lambertsen, 1971
1.05	12*	96	Eckenhoff, 1984
0.98	4	18	Caldwell, et al., 1966
0.83	6	66	Ohlsson, 1947
0.47	3	12	Fife, et al., 1973
0.3	6†	55	Eckenhoff, 1984
0.28	2	18	Ohlsson, 1947
0.23	2	8	Morgan, et al., 1961
0.21	4	32	Fisher, et al., 1970
0.32	4‡	4	Morgan, et al., 1963a
0.3	3‡	3	Dubois, et al., 1963
0.23	8‡	8	Morgan, et al., 1963b

* Each of these subjects was exposed to 0.3 ATA of O_2 for 12 h prior to the 1.05 ATA exposure. Three VC measurements were obtained during this time and these data were also utilized (No. data = 47).

† One subject was used as an experimental and a control.

‡ These data were measurements taken before and after exposures and were therefore not used in the model where a separate B(s) was estimated for each subject.

included 12 h at 0.3 ATA and 48 h at 1.05 ATA in the experimental group) of the Eckenhoff experiments were included in the analysis. As mentioned in the Background Section, we omitted the Michel, et al., (1960) study because of its large variability and those studies which did not provide individual data. Our final data set had 440 measurements of %ΔVC on 66 subjects with P_{O_2}s from 0.21 to 2.0 ATA and exposure times from 1.8 to 1296.0 h. There were serial vital capacity measurements on 51 subjects (425 data points). All results will be expressed as (±SE) and a $p < 0.05$ was considered significant.

RESULTS

Individual Variation

We began by pooling all of the data and fixed the asymptotes for P_{O_2} (B(1)) at 0.5, time (B(2)) at 0, and assigned the exponent the value 1.2 as Bardin and Lambertsen (1971) did. A much better fit was obtained if a separate B(s) was permitted for each subject than if one slope (the average or pooled slope) was used for all subjects ($F_{49,390} = 9.6$, $p < 0.001$). When one slope was selected to represent all subjects, B(s) = -0.006; when individual slopes were calculated, B(s) ranged from -0.029 to -0.0008 ($\%h^{-1}$ ATA^{-1}). We will comment more about the range of B(s) later.

With the pooled slope, the fit of the model had a residual standard deviation of 6%; when individual slopes were permitted, the model fit the data with a standard deviation of 3.7%, a decrease of 35%. Inclusion of individual slopes decreased the SSE from 15,000 to 6,800, a decrease of more than 50%. These results showed quantitatively what was obvious qualitatively by examination of Figs. 1-3, 5, and 6, i.e., the tremendous amount of individual variability in this response. Some subjects maintained VC nearly unchanged throughout O_2 exposures, while others experienced rapid and dramatic decrements in VC.

Choice of Exponent (m)

Having determined that individual slope parameters were appropriate, we then examined the exponent B(3) (the m of the UPTD). With P_{O_2} fixed at 0.5 ATA and the exponent estimated freely from the data, this exponent was selected to be 1.0008 (±0.07), which was not statistically distinguishable from 1.0. We fixed the exponent at 1.2 (as Bardin and Lambertsen (1970) suggested) and this significantly worsened the fit ($F_{1,388} = 5.79$, $p < 0.025$).

Because the UPTD is based on a suggested exponent of 1.2, we carried out the same analysis using only the data from which the UPTD concept was derived (Ohlsson, 1947; Caldwell et al., 1966; Clark and Lambertsen, 1970), shown in Tables 1-3. This data set had 23 subjects and 157 data points. As we did not need to work with log transformed data we did not have to censor VC data which showed no change or small increases. We were also able to explicitly test whether subjects 12 and 13 were distinguishable from the rest of the subjects and thus whether they needed to be excluded. As when all data were used for analysis, allowing for individual slopes significantly improved the fit ($F_{22,134} = 14.46$, $p < 0.01$). An exponent (B(3) or m) of 0.98 (±0.093) best fit the data. This value was not different from 1.0 but provided a significant improvement over 1.2 ($F_{1,134} = 4.34$, $p < 0.05$). The above results were unaffected by inclusion or exclusion of Clark and Lambertsen's subjects 12 and 13.

P_{O_2} and Time Asymptotes

Next, we explicitly tested whether the VC data were helpful in estimating the P_{O_2} (B(1)) and time (B(2)) asymptotes suggested by the model or whether inferences from the literature would continue to be necessary. A significant improvement in the fit was obtained when B(1) was fixed at values

< 0.5 ATA compared to 0.5 ATA (or even 0.6 or 0.7) (we tried 0.4, 0.3, 0.376, and 0.2 ATA). When B(1) was freely estimated, a value of B(1) = 0.376 ATA was chosen. This parameter had a large SE and the precision of all the slope parameters was lost, which suggested that the data simply would not support selection of all of the parameters shown in Eqn. 8. These results do not encourage raising the choice for the P_{O_2} asymptote above the current choice of 0.5 and even suggest lowering this value somewhat. The data do not allow a more precise recommendation about the "safe" P_{O_2} because the number of useful points obtained at low P_{O_2}s is limited and many of these include only before and after (as opposed to serial) measurements. It is important to note that lowering the P_{O_2} asymptote below 0.5 ATA produced less than a 1% improvement in the SD of the fit (and the SSE decreased by 2.0%, from 6,766 to 6,628). This contribution pales in comparison to the 35% improvement obtained by inclusion of individual slopes (and a 50% decrease in the SSE). A time asymptote of 0 as proposed by Clark and Lambertsen (1970) remains reasonable. With B(1) fixed at 0.376 ATA and B(3), the exponent, fixed at 1.000, the time asymptote was chosen to be a number less than 1 h with a standard error that made it indistinguishable from 0 (0.002 h ± 1.07).

UPTD SSE Comparison

Finally, we compared our model's SSE with the SSE obtained with the UPTD. We calculated the number of UPTDs for each data point using Eqn. 7. To relate the UPTD to %ΔVC, we fitted the 7 data points in Table 9 to two different equations: one linear and one sigmoidal (more details of this analysis appear in Appendix 1). The predicted %ΔVC was calculated, compared to the measured and this difference was summed and squared to calculate an SSE for each equation. The SSE for the linear and sigmoid equations were 17,820 and 19,850, respectively, each of which is larger than the SSE of our model (approximately 15,000 for the pooled B(s) model, 6,000 for the individual B(s) model).

DISCUSSION

We reviewed the general model from which the UPTD concept was derived (Bardin and Lambertsen, 1970) and performed a coordinated quantitative analysis that permitted explicit testing of parameters in the model. We utilized more data than did the original authors and included vital capacity data accumulated since 1970. This analysis showed that the single greatest contributor to uncertainty in this model was the extreme variability in individual response. The standard deviation of the model's fit dropped by nearly one-half when individual slope parameters (B(s))were chosen. At this time, there is no way to predict a given individual's slope, or even whether an individual's response (slope) will be the same on different occasions. With parameters which minimized the error of the fit of the model (B(1) = 0.376 ATA, B(2) = 0, B(3) = 1.0) slopes (B(s)) ranged from +0.0021 to -0.082, $\%h^{-1}$ ATA $^{-1}$ in 38 individuals; the distribution of these slopes is shown in Fig. 11. Figure 12 emphasizes the importance of this individual variation. With the P_{O_2} asymptote = 0.5 ATA and exponent = 1.0, after 20 h exposure to a P_{O_2} of 1.0 ATA the predicted decrement in VC varied from an average value of -5% to 1% and up to 12%, depending on whether a median slope was chosen, or a slope belonging to the highest 10% or lowest 10% group of resistant individuals. Figure 13 shows how VC would decrease as a function of time at 4 different P_{O_2}s in an individual of median susceptiblity. Individual variability introduces large uncertainty at every P_{O_2}. For example, exposure to 10 h at a P_{O_2} of 2.0 ATA produced a median decrement of about 8%, but with an 80% confidence interval of changes ranging from 2-18%. The impact of variations in the other parameters was much less important given the powerful

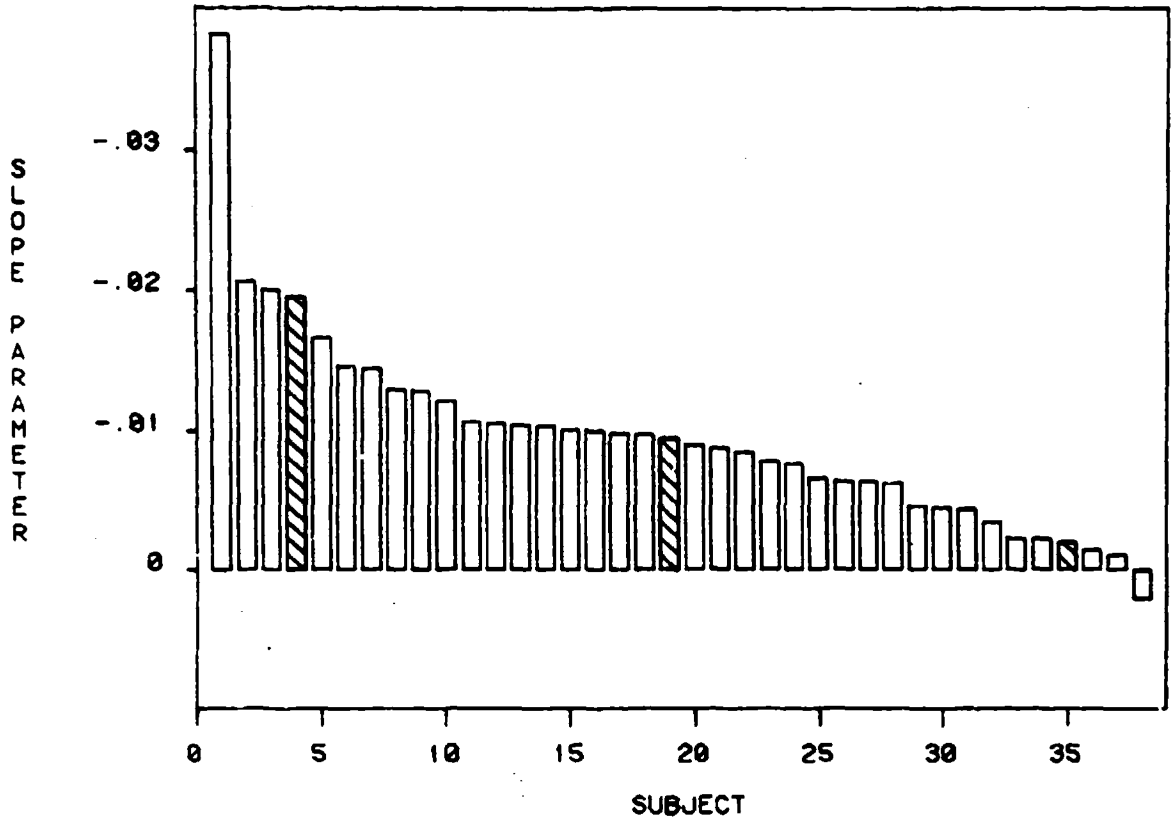

Fig. 11. Range and distribution of individual slope parameters for 38 individuals in which serial VC measurements were made. Cross-hatched bars indicate slope for individuals of highest 10%, median, and lowest 10% susceptibility, respectively. The median value was -0.009 h^{-1} ATA^{-1}.

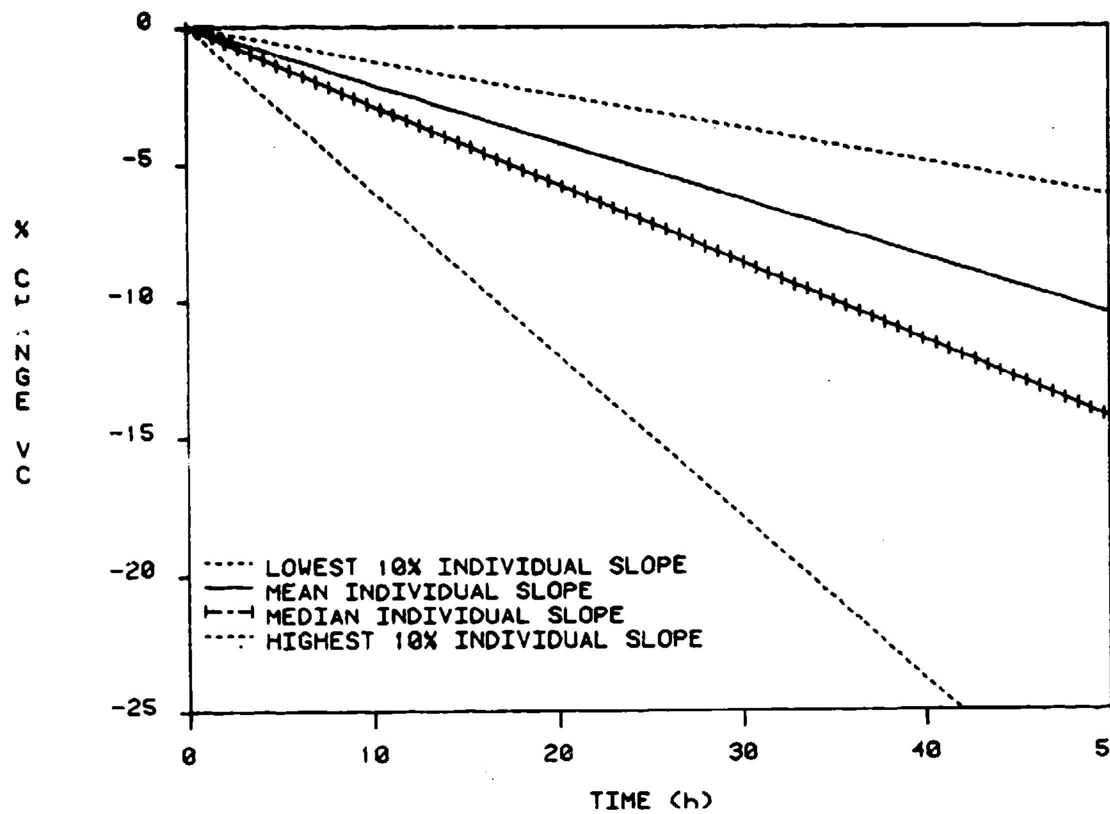

Fig. 12. Effect of individual variation on the predicted % decrease in vital capacity resulting from exposure to a P_{O_2} of 1.0 ATA. When Eqn. 7 was fitted to all available human vital capacity data, a significant improvement was achieved when a separate slope was permitted for each subject, but a wide range of slopes resulted. This figure shows how the range of slopes affects the predicted change in vital capacity. The 38 slopes calculated for each subject were ordered; the fourth lowest and fourth highest slopes (approximately the bottom and top 10%, respectively) as well as the median slopes were used to calculate predicted VC changes. The mean individual slope line was generated using the slope obtained when only one slope was calculated for all subjects.

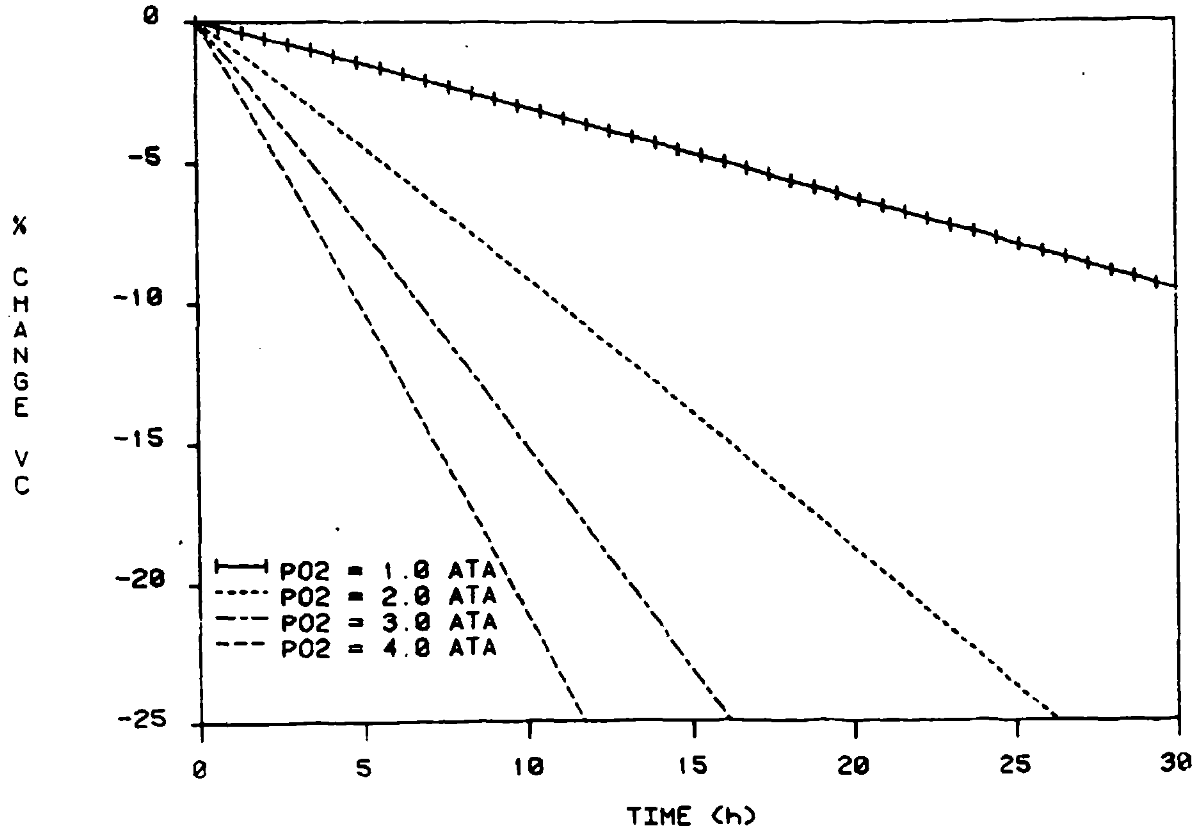

Fig. 13. Predicted decrement in vital capacity for an individual of median susceptibility exposed to 4 P_{O_2}s. For simplicity, confidence limits are not included, but at each P_{O_2} a wide envelope of VC changes (such as shown on Fig. 12) would be included in the 80% confidence limits.

influence individual variability had on the response. Our analysis showed that a P_{O_2} asymptote below 0.5 ATA was preferable to the previous estimate of 0.5. Here, precision on this estimate must await experiments where serial VC measurements are made in groups of human subjects given lengthy exposures with moderate P_{O_2} elevations. An exponent (B(3) or m) of 1.0 minimized the error of the fit; the previous estimate of 1.2 increased the error. Our analysis shows the model that best fits the data of an individual of median susceptibility would be:

$$\% \Delta VC = -0.009(P_{O_2} - 0.38)(\text{time})$$

This is the model with parameters that "minimize" the error. For reasons of simplicity, however, with essentially no loss of precision in the predictive capabilities of the model, we recommend the following modification. The cumulative effect of any combination of exposures to time and P_{O_2} for an individual of median suspectibility can be predicted by summing the values obtained with the expression:

$$\% \Delta VC = -0.011(P_{O_2} - 0.5)(\text{time})$$

where P_{O_2} is in ATA and time is in minutes, as has routinely been done with the UPTD calculation. In fact, our literature search shows that there is really no evidence to support or refute the legitimacy of this summation. It is conceivable that some recovery occurs to a certain extent when P_{O_2} is lowered from some experimental level but is kept above normoxic. Conversely, damage may occur at a different rate if P_{O_2} is raised in steps. None of these questions have been answered.

Table 11 shows the effect of the modification in parameters in the simplified versus the minimized model and compares the predictions with those obtained from the UPTD Model. The minimized model is based on quantitative data fitting, which included no censoring or transformation of data, a larger,

TABLE 11

Predicted % Decrease in VC by Different Models

P_{O} (ATA)	Time of Exposure (h)	Minimized Model	Simplified Model	UPTD Model
1.0	10.25	5.7	5.6	2.0 (615)*
	24	13.3	13.2	9.0 (1,440)
	48	26.8	26.4	>20.0 (2,880)
2.0	5	7.3	8.3	>3.0 (750)
	10	14.5	16.5	10.0 (1,500)
	15	21.9	24.8	19.0 (2,250)
USN Table 5†		2.0	2.3	<1.0 (326)
USN Table 6†		3.0	4.0	>2.0 (633)
USN Table 6 + extensions†		4.3	5.4	>4.0 (846)
USN Table 6A†		4.0	4.5	>2.0 (664)
USN Table 6A + extensions†		5.3	5.8	>4.0 (877)

* Number in parentheses is number of UPTD units.

† Calculated assuming no recovery during air breaks; during decompression times, average depth is assumed.

Minimized model: $\% \Delta VC = -0.009(P_{O_2} - .38)(\text{time})$

Simplified model: $\% \Delta VC = -0.011(P_{O_2} - 0.5)\text{time}$

$$\text{UPTD} = \text{time} \cdot \left(\frac{.5}{P_{O_2} - .5}\right)^{-\frac{1}{1.2}}$$

more current data set, and no assumptions about asymptotes. Thus comparisons with the UPTD model are mainly of historical interest. Although our model appears to make more conservative predictions (i.e., larger VC decrement for any given exposure) given that each predictor has a standard deviation of 6%, the models are very similar. We recommend retaining the 0.5 P_{O_2} asymptote for convenience so the only new number that needs to be remembered is the median slope -0.011.

Clearly, this analysis shows that a decrease in vital capacity is not an ideal index of the development of pulmonary O_2 toxicity and we are not the first to make this criticism (Widell et al., 1974; Gardette and Lemaire, 1975). It is a measurement for which a subject needs training, it is effort dependent, and, as this report quantifies, VC is variable among individuals. The index is based on the response of an individual of median susceptibility, therefore placing sensitive individuals at a much higher risk.

The question is still open as to what underlying toxic process changes in VC represent. It is clearly a reversible effect (Clark and Lambertsen, 1970, Eckenhoff; Caldwell et al., 1966; Hendricks et al., 1977), but we do not know yet how to account for recovery (as during intermittent exposure) with this model. The Navy currently recommends O_2 exposures that would result in a 2% median decrement in VC under normal circumstances (exposure to one U.S. Navy Table 6) and suggests a maximum exposure that would be expected to produce a 10% decrement under extreme conditions. We do not know, however, whether either of the changes in lung volume produced by these decrements is of functional significance.

SUMMARY

In the U.S. Navy, pulmonary O_2 toxicity becomes a concern during saturation diving, periods of long decompression, and during treatment of decompression sickness. The current practice for determining O_2 limits depends on changes in vital capacity as predicted by the UPTD. We reviewed the general model from which the UPTD concept was derived and performed a coordinated quantitative analysis that permitted explicit testing of parameters in the model. We suggested a simplified linear predictive equation that relates P_{O_2} and time of exposure to change in vital capacity:

$$\% \Delta VC = -0.011(P_{O_2} - 0.5)(\text{time})$$

where P_{O_2} is given in ATA and time in minutes. As with the UPTD, the effect of cumulative exposures can be calculated by summing the effect predicted at each level of P_{O_2} exposure, although we point out that experiments have not been done to support the validity of this summation. We showed that individual susceptibility is the single largest source of variability accounting for 35% of the uncertainty of any prediction.

REFERENCES

1. Barber, RE, J Lee, and WK Hamilton. Oxygen toxicity in man: A prospective study in patients with irreversible brain damage. New Engl J Med 1970; 283:1,473-1,484.

2. Bardin, H, and CJ Lambertsen. A quantitative method for calculating cumulative pulmonary oxygen toxicity. Use of the unit pulmonary toxicity dose (UPTD). Philadelphia: Institute for Environmental Medicine, University of Pennsylvania; 1970.

3. Broussolle, B. Entex V: Experience de plongee profonde a 450 m avec 12 jours de sejour au fond. Rapport Final du Contrat, Direction des Recherches et Etudes Techniques, Marine Nationale 80/1,247. Toulon/Naval, France: Ministere de la Defense; 1982.

4. Burger, EJ, and J Mead. Static properties of lungs after oxygen exposure. J Appl Physiol 1969; 27:191-197.

5. Caldwell, PRB, WL Lee, Jr, HS Schildkraut, and ER Archibald. Changes in lung volume, diffusing capacity, and blood gases in men breathing oxygen. J Appl Physiol 1966; 21(5):1,477-1,483.

6. Clark, JM, and CJ Lambertsen. Pulmonary oxygen tolerance in man and derivation of pulmonary oxygen tolerance curves. Institute for Environmental Medicine Report No. 1-70. Philadelphia: Institute for Environmental Medicine, University of Pennsylvania; 1970.

7. Clark, JM, and CJ Lambertsen. Rate of development of pulmonary O_2 toxicity in man during O_2 breathing at 2.0 ATA. J Appl Physiol 1971a; 30(5):739-752.

8. Clark, JM, and CJ Lambertsen. Alveolar-arterial O_2 differences in man at .2, 1, 2, and 3.5 ATA inspired P_{O_2}. J Appl Physiol 1971b; 30(5):753-763.

9. Comroe, Jr, JH, RD Dripps, PR Dumke, and M Deming. Oxygen toxicity. J Am Med Assoc 1945; 128:710-717.

10. Dewar, KMS, G Smith, AA Spence, and I McA Ledingham. Effect of hyperoxia on airways resistance in man. J Appl Physiol 1972; 32:486-490.

11. Dolezal, V. The effect of longlasting oxygen inhalation upon respiratory parameters in man. Physiol Bohemoslov 1962; 11:149-158.

12. Dougherty, JH, RL Fraye, DA Miller, and KE Schaefer. Pulmonary function during shallow habitat air dives (SHAD I, II, III). Underwater Physiology VI. Bethesda, MD: Federation of American Societies for Experimental Biology; 1978:193-204.

13. Dougherty, JH, and KE Schaefer. Pulmonary functions during saturation excursion dives breathing air. Aerosp Med 1968; 39:289-292.

14. Dubois, AB, RW Hyde, and E Hendler. Pulmonary mechanics and diffusing capacity following simulated space flight of 2 weeks duration. J Appl Physiol 1963; 18(4):696-698.

15. Eckenhoff, RG. Data obtained by personal communication and presented in tables 4A and 4B.

16. Fife, WP, HL Edwards, WW Schroeder, FD Ferrari, and LR Freeberg. Effect of the hydro-lab environment on pulmonary function. Hydro-Lab Journal 1973; 2:73-80.

17. Fisher, AB, RW Hyde, RJM Puy, JM Clark, and CJ Lambertsen. Effect of oxygen at 2 atmospheres on the pulmonary mechanics of normal man. J Appl Physiol 1968; 24(4):529-536.

18. Fisher, AB, AB DuBois, RW Hyde, DJ Knight, and CJ Lambertsen. Effect of 2 months undersea exposure to N_2-O_2 at 2.2 ATA on lung function. J Appl Physiol 1970; 28(1):70-74.

19. Gardette, B, and C Lemaire. Variations de la capacite vitale en fonction de la Quantite d'oxygene inhalee au cours des decompressions. Revue de Medecine Subaquatique et Hyperbare 1977; 61:66-69.

20. Hall, DA. The influence of the systematic fluctuation of P_{O_2} upon the nature and rate of the development of oxygen toxicity in guinea pigs. Philadelphia, PA: Univ. of Pennsylvania; 1967. Thesis.

21. Harabin, AL, and LE Farhi. Arterial hyperoxemia with tissue hypoxia during exposure to 100% O_2 at 1 ATA. Physiologist 1978; 21(4):50.

22. Harabin, AL, LD Homer, and ME Bradley. Pulmonary oxygen toxicity in awake dogs: Metabolic and physiologic effects. J Appl Physiol Respir Environ Exercise Physiol, 1984; 57(5):1480-1488.

23. Harrison, GA. Ultrastructural response of rat lung to 90 days exposure to oxygen at 450 mm Hg. Aerosp Med 1974; 45(9):1,041-1,045.

24. Hayatdavoudi, G, JJ O'Neil, BE Barry, BA Freeman, and JD Crapo. Pulmonary injury following continuous exposure to 60% O_2 for 7 days. J Appl Physiol Respir Environ Exercise Physiol 1981; 51:1,220-1,231.

25. Hendricks, PL, DA Hall, WL Hunter, Jr, and PJ Haley. Extension of pulmonary O_2 tolerance in man at 2 ATA by intermittent O_2 exposure. J Appl Physiol Respir Environ Exercise Physiol 1977; 42(4):593-599.

26. Hyacinthe, R, P Giry, and B Broussolle. Evolution of vital capacity and lung diffusing capacity for CO in eight subjects after a 450 meters simulated dive. Medecine Aeronautique et Spatiale Medecine Subaquatique et Hyperbare 1981; 20:77-80.

27. Kapanci, Y, R Tosco, J Eggermann, and VE Gould. Oxygen pneumonitis in man: Light and electron microscopic morphometric studies. Chest 1972; 62:162-169.

28. Kapanci, Y, ER Weibel, HP Kaplan, and FR Robinson. Pathogenesis and reversibility of the pulmonary lesions of oxygen toxicity in monkeys. II. Ultrastructural and morphometric studies. Lab Invest 1969; 20(1):101-118.

29. Kaplan, HP, FR Robinson, Y Kapanci, and ER Weibel. Pathogenesis and reversibility of the pulmonary lesions of oxygen toxicity in monkeys. I. Clinical and light microscopic studies. Lab Invest 1969; 20:94-99.

30. Kistler, GS, PRB Caldwell, and ER Weibel. Electron microscopic and mophometric study of rat lungs exposed to 97% oxygen at 258 torr (27,000 feet). Aerospace Medical Research Laboratories Report AMRL-TR-66-103. Wright-Patterson Air Force Base, Ohio: Aerospace Medical Division, Air Force Systems Command; 1966.

31. Kistler, GS, PRB Caldwell, and ER Weibel. Development of fine structural damage to alveolar and capillary lining cells in oxygen-poisoned rat lungs. J Cell Biol 1967; 33:605-628.

32. Lemaire, C. Determination du taux d'hyperoxie acceptable pour les plongees au long cours par la mesure de la capacite vitale. 1975; Medecine Aeronautique et Spatiale Medecine Subaquatique et Hyperbare 1975; 12:82-86.

33. Matalon, S, MS Nesarajah, and LE Farhi. Pulmonary and circulatory changes in conscious sheep exposed to 100% O_2 at 1 ATA. J Appl Physiol 1982; 53:110-116.

34. Michel, EL, RW Langevin, and CF Gell. Effect of continuous human exposure to oxygen tensions of 418 mm Hg for 168 h. Aerosp Med 1960; 31:138-144.

35. Morgan, TE, F Ulvedal, and BE Welch. Observations in the SAM two-man space cabin simulator. II. Biomedical effects. Aerosp Med 1961; 32:591-601.

36. Morgan, TE, RJ Cutler, ES Shaw, F Ulvedal, JJ Hargreaves, JE Moyer, RE McKenzie, and BE Welch. Physiologic effects of exposure to increased oxygen tension at 5 psig. Aerosp Med 1963a; 34:720-726.

37. Morgan, TE, F Ulvedal, RJ Cutler, and BE Welch. Effects on man of prolonged exposure to oxygen at a total pressure of 190 mm Hg. Aerosp Med 1963b; 39:589-592.

38. Moselhi, M, SM Abdallah, and YM Asab. Pulmonary function in men with intermittent long-term exposure to hyperbaric oxygen. Undersea Biomed Res 1980; 7:149-157.

39. Navy, Department of. U.S. Navy Diving Manuals. Washington, D.C.: Dept. of the Navy; 1978: Vol. 1, Chapt. 8. Available from: Naval Sea Systems Command, Washington, D.C.; 0094-LP.001-9010.

40. Ohlsson, WTL. A study on oxygen toxicity at atmospheric pressures. Acta Med Scand 1947; 128(Suppl 190):1-93.

41. Puy, RJM, RW Hyde, AB Fisher, JM Clark, J Dickson, and CJ Lambertsen. Alterations in the pulmonary capillary bed during early O_2 toxicity in man. J Appl Physiol 1968; 24(4):537-543.

42. Rahn, H, WO Fenn, and AB Otis. Daily variations of vital capacity, residual air, and expiratory reserve including a study of the residual air method. J Appl Physiol 1949; 1(10):725-736.

43. Robertson, WG, JJ Hargreaves, JE Herlocher, and BE Welch. Physiologic response to increased oxygen partial pressure II. Respiratory studies. Aerosp Med 1964; 35:618-622.

44. Van de Water, JM, KS Kagey, IT Miller, DA Parker, NE O'Connor, JM Sheh, JD MacArthur, RM Zollinger, and FD Moore. Response of the lung to 6 to 12 hours of 100 percent oxygen inhalation in normal man. N Engl J Med 1970; 283:621-626.

45. Widell, PJ, PB Bennett, P Kivlin, and W Gray. Pulmonary oxygen toxicity in man at 2 ATA with intermittent air breathing. Aerosp Med 1974; 45:407-410.

46. Widell, PJ, AA Pilmanis, LW Chapman, VM Pilmanis, and RR Given. Physiological effects of saturation diving: Oxygen toxicity, stress and fluid volume regulation. Hydro-Lab J 1973; 2(1):57-72.

47. Wolfe, WG, LA Robinson, JP Moran, and JE Lowe. Reversible pulmonary oxygen toxicity in the primate. Ann Surg 1978; 188:530-543.

48. Wright, WB. Use of the University of Pennsylvania, Institute for Environmental Medicine procedure for calculation of cumulative pulmonary oxygen toxicity. Naval Experimental Diving Unit Report No. 2-72. Washington, D.C.: Navy Experimental Diving Unit; 1972.

49. Wright, WB, AB Fisher, PL Hendricks, JS Brody, and CJ Lambertsen. Pulmonary function studies during a 14-day continuous exposure to 5.2% O_2 in N_2 at pressure equivalent to 100 fsw (4 ATA). Aerosp Med 1973; 44:837-843.

50. Wright, RA, HS Weiss, EP Hiatt, and JS Rustagi. Risk of mortality in interrupted exposure to 100% O_2: Role of air vs. lowered P_{O_2}. Am J Physiol 1966; 210:1,015-1,020.

APPENDIX 1. UPTD SSE Comparison

Linear regression on the 7 data points resulted in the following equation:

$$\% \Delta VC = -0.0114 \cdot UPTD + 5.60733$$

This linear model assumes a threshold effect: below a certain number of UPTDs (approximately 492) there would be no change in VC predicted. We forced this to be true by resetting any positive % ΔVC prediction to zero.

The data were also fit to a sigmoid curve of the general form:

$$y = \frac{1}{1 + \left(\frac{x50}{x}\right)^n}$$

where x = number of UPTDs, and y = % ΔVC. The following parameters were estimated: x50 = 4619, n = 1.86.

In calculating the UPTDs for each data point, when the exposures $PO_2 < 0.5$ ATA, the predicted % ΔVC was set to zero.