HYPERBARIC RESEARCH IN CHRONIC PULMONARY DISEASE[1]

A Hypothesis and a Brief Review

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Introduction

Interest in what is called "hyperbaric oxygenation" has been accelerating rapidly in the past decade. Literally, the term means "oxygen at pressures above atmospheric levels." This usage is not strictly accurate because it implies the presence of only one significant effect, that of increased oxygen pressure. Use of the modality actually involves a multitude of effects whose significance will vary with the circumstances of the exposure.

The mechanisms of the action of hyperbaric oxygenation are:

The *gas density* effect (specific). This is mass per unit volume, i.e., the presence of 2, 3, 4..... N molecules of gas in the volume formerly occupied by a single molecule.

The *pressure* effect (nonspecific). This is the force exerted per unit of area. It is distinct from the gas density, because it can be reproduced by any gas or combination of gases.

The *adiabatic* effect (nonspecific). This is a change in the heat energy level of the environment without a correspondingly direct specific heat energy transfer to that environment.

The effect of *total environmental control* (specific). All matter entering or leaving the hyperbaric environment must, of necessity, be under the actual control of an operator. In addition to the major gases, this matter includes dusts, aerosols, volatile contaminants, and toxic gases in trace amounts.

The *psychologic* effect (nonspecific). Confinement inside a sealed chamber with all of the above effects must exert some influence upon the psyche of all of the occupants. This is particularly true with regard to patients, as, in their case, the exposure is a choice determined by "desperation" rather than by knowledge or training.

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Thus, in speaking of results of exposure to hyperbaric oxygenation or, more correctly, to "hyperbaric environments," considerable care is needed to evaluate the results accurately and, especially, to identify the factor(s) responsible for these results. The potential etiologic confusion may account in part for the long, irregular, and halting progress of this technique in medical therapy.

History

The use of hyperbaric oxygenation in modified medical form began in the nineteenth century (1). By the middle of that period, major hospitals in many western European cities possessed chambers for the administration of "compressed air baths." One of the first diseases to be treated in this manner was phthisis. In the great majority of cases, this chronic, progressive condition was probably pulmonary tuberculosis. Evidently the results of exposing the phthisic patient to pressure was so clinically unrewarding, and occasionally disastrous, that this type of therapy was soon abandoned. On the basis of this experience, further exposure of persons with pulmonary disease to pressure was forbidden. The stricture has persisted to the present day, having had repeated reinforcement from the experience of naval forces. A wide variety of other diseases were also treated in the chambers, with varying results, due to the lack of basic physiologic knowledge. Thus, few useful data were derived from this "premature" association of medicine and the engineering sciences. By the early twentieth century, serious use of exposure to compressed air as a form of medical therapy had disappeared except in the treatment of a specific industrial complication, caisson disease.

During the next fifty years, the various national naval forces had almost exclusive dominion in the field of hyperbaric exposure and investigation. Research and development centered about the delineation, and the prevention, of hazards associated with extreme and/or prolonged exposure to pressure. There was a de-

tailed search for methods and techniques to increase the safety of such exposure. This was a tremendous task in itself (2), and without such data and experience the present developing medical uses would be severely restricted. During this period, little information was obtained with regard to the medical therapeutic potentialities of this modality. The reasons are fairly obvious. In the first place, the program of diving activities in the various navies is almost completely unconcerned with medical considerations. Second, there is a lack of available abnormal "material" for study, should the occasion present itself: the standards of health and physical fitness required for this branch of military service are so high that significant physiologic abnormalities, in great enough concentration for empirical observation and experimentation, are essentially nonexistent.

After the Second World War, and coincidental with the tremendous technologic developments in medicine, there was a resurgence of interest in hyperbaric oxygenation. Surgeons (3) and radiologists (4) were the first to adopt this technique. One of the first physiologic applications was to "drench" the tissues of the body with oxygen (4–6). Another was to increase the partial pressure of oxygen in order to promote elimination of carbon monoxide, as these two gases compete for hemoglobin (7). Pioneer developments, then, were concerned primarily with the gas density effect, specifically that of oxygen. The restriction that patients with obvious pulmonary disease were not to be exposed to pressure was still generally observed.

A hyperbaric research unit[2] was established at the Medical Center of the Hospital of the Good Samaritan, Los Angeles, California, in 1963, under the sponsorship and direction of Drs. Hurley Motley and Reginald Smart. The primary interest was in the potential of this therapy in cardiorespiratory diseases. Discussion with the donor of the pressure chamber, Dr. Walter Wakelin, centered about his observation that scuba divers with emphysema and/or asthma seemed to benefit considerably from a "dive." A search was then made for evidence of emphysema in currently active scuba divers, but none could be found. This is not too surprising in view of the effort level required for this accomplishment. However, a former scuba diver with emphysema and asthma was found who was certain that, were he to resume the sport, he would be much improved. For a variety of reasons, he never did. Theoretically, however, it seemed likely that a specific type of pressure exposure might very well be beneficial. *This type would certainly not be a pressure exposure comparable to that encountered in diving practice, either civilian or naval.* This deduction was based upon the writer's limited knowledge of some of the pathophysiology of emphysema and of the aerodynamics of gas flow in biologic systems.

In full awareness of the actual and potential hazards involved, the following hypothesis was developed; and an experimental situation, involving patients with pulmonary emphysema, was set up to test the hypothesis.

Hypothesis

Assumption I: It was assumed, first, that emphysema is a nonuniform disease process with areas of minimal to maximal disruption in close continuity, and that the functional loss (disability) does not clearly reflect the degree of the disease.

Assumption II: It was also assumed that one of the possible reasons for a disparity in the structural versus functional defects is the presence of progressive air-trapping. This mechanism, active in the most abnormal areas, would lead to a gradually increasing space-volume encroachment upon the surrounding areas. If the surrounding areas were more "normal" (and, hence, functional), then this crowding would result in a far greater loss in function than would be expected from the loss of the maximally involved portion alone.

Assumption III: A third assumption was that the "crowding" phenomenon would be a potentially reversible aspect of the disease. In the past, treatment of this aspect has been directed toward attempts to resect the most involved areas of the lung in an attempt to give the remainder more room to work.

Assumption IV: The fourth assumption was that the value of the ratio of the volume of an airspace (lobular or cystic) to the volume of the conducting airway to that airspace, al-

[2] A hyper-hypobaric, single-lock chamber (rated from 0.5 to 4 atmospheres absolute) was donated through the kind generosity of Dr. Walter Wakelin, of Glendale, California. Dr. Wakelin and his associates were also instrumental in setting up this unit for the hospital.

though relatively constant in normal lungs, is not only much more variable in emphysema, but also is significantly greater in the most involved areas. This would mean that there is considerable variation in the amount of air per unit of time that can enter differing portions (of equal volumes) of the emphysematous lung. This not only has been demonstrated by detailed studies (8), but also is substantiated by clinical observation. Certainly there is little or no anatomic distortion, disruption, or destruction of the bronchiolar airways in acute (reversible) bronchial asthma. However, spirometry at the time of maximal illness discloses the same type of pattern and degree of expiratory obstruction as is present in the chronic severely emphysematous patient. What, then, accounts for the difference in the time taken to arrive at this obstructed end-point? In asthma, progression can be measured in hours and days, whereas in emphysema the time interval is months or years. Inasmuch as the expiratory phase seems essentially similar, then the difference must be on the inspiratory side. The asthmatic person must still possess normal, or almost normal, inspiratory flow, particularly as his augmented breathing effort (with its increased intrathoracic negative pressure) would tend to keep his airways maximally open on inspiration. As emphysema follows a much more prolonged course, then there must be less air trapped per unit of time. Because the functional expiratory defect is as great, then there must be a corresponding inspiratory defect to compensate. Hence, little air is delivered to the areas with maximal air-trapping, which accounts for the prolonged course of emphysema. This argument also assumes that "reversible asthma" is a diffuse uniform disease, in contrast to the nonuniform character of emphysema.

Poiseuille's Law states that the volume of flow through the channel varies directly as the fourth power of its radius and inversely as its length. If this equation is applicable to the tracheobronchial tree, then minimal changes in the airway caliber would be greatly magnified in terms of possible volume flow per unit of time.

Deduction

It seems logical to expect that, if the mass of gas entering the lungs were suddenly to be significantly increased, as by pressure, then the above-mentioned factors would significantly influence the intrapulmonary distribution of this added mass. In other words, as the density abruptly increased, the major portion of this new mass would flow preferentially into those areas of the lung with the most normal communication to the outside. In the absence of disease, or in the presence of diffuse uniform disease (such as "reversible asthma"), no such redistributive change should occur. In emphysema (to the degree that it is a nonuniform process) these distribution changes should be significant. The most abnormal areas (cystic) should receive the least part of this additional mass, as it is assumed that they would possess the most inadequate communication with the ambient atmosphere. Conversely, the remaining most normal (?) areas should receive the major portion of the added load.

The thorax is a closed cavity with a fixed maximal capacity. This limits the volume of its contained individual air spaces. Thus, to remain in equilibrium as pressure is rapidly increased, the air-containing spaces have the following possible responses:

(*1*) admission of sufficient additional gas to maintain density, volume, and pressure in equilibrium with the surrounding atmosphere as it changes;

(*2*) admission of excess gas to allow an increase in volume at the expense of adjoining areas (pressure and density remaining constant with atmospheric pressure and density);

(*3*) lag in admission of additional gas so that volume must diminish to keep density and pressure in equilibrium with the outside atmosphere.

In the presence of advanced disease (nonuniform), the most likely response of the abnormal areas would be the third, as pressure is rapidly increased. Thus, any adjoining, more normal (but previously compressed) area might then follow pathways (*1*) or (*2*). Normal areas should maintain their spatial integrity, making it possible, theoretically, to obtain a redistribution that might be beneficial, providing the above assumptions are correct.

Finally, the end result would be that the abnormal, overexpanded areas would have diminished in volume to a degree proportional to their lack of adequate communication with the atmosphere. The more normal areas might

then have expanded by a proportionate amount in order to maintain constant intrathoracic volume. Inasmuch as there is a tendency for these more normal areas to be relatively underexpanded (by virtue of the crowding effect), these changes, then, should have some beneficial value.

Reversing the pressurization procedure in returning to sea level should reverse the change. This was the hazard (air-trapping) that was mentioned previously. However, by decreasing the pressure at a fraction of the rate of increase it might be possible to avoid both the hazard and the reversal of the postulated beneficial effect. If the *negative* rate of change of pressure were both smooth enough and gradual enough, then most of the "trapped air" should have an opportunity to leave by the remaining normal channels. The escape of the air might be augmented by the use of agents to promote maximal bronchodilatation. Thus, some of the benefit of pressure exposure could be retained.

An experimental protocol was drawn up to test the above hypothesis, using human volunteers. After considerable study, periods of review, and discussion among numerous interested official and responsible parties at the hospital, a program was approved. Funds were obtained[3] to establish the Hyperbaric Research and Therapy Unit and to perform the trial experiments, and the study was instituted.

Material and Methods

Patients with significant pulmonary emphysema were recruited on a volunteer basis from those who had been on maximal, stable medical therapy for their disease for at least three months prior to their enrollment in the study. This therapy was maintained without change throughout the study. Twenty-four persons passed the initial screening tests, and 17 persisted through the base-line study period.

The results of the initial pulmonary function studies in these volunteers are shown in table 1. The severity of the emphysematous process ranged from moderately severe to far advanced, as can be seen from the patient data. A major portion of the screening procedure was the repeated performance of detailed pulmonary function tests on multiple occasions. (In their initial enthusiasm, the investigators almost exhausted the first 7 volunteers with the rigorous study schedule; in fact, 3 of the 7 subsequently withdrew because of this work load, and many others have since been lost to the study because of premature withdrawal.)

The studies included the performance of a complete spirogram and lung volume determination (helium method) on at least ten to twenty occasions prior to hyperbaric exposure, and then daily determinations afterward for as long as the volunteers would tolerate. The following were also run before and after exposure, on some or all of the volunteers: roentgenograms of the chest (routine posteroanterior films on inspiration and expiration); an audiogram; an electrocardiogram; a routine physical examination; arterial blood studies during rest, and after rest and exercise; a nitrogen washout test; and quantitative measure of sputum production.

The patient was instructed to take his usual morning intermittent positive pressure treatment and medication (aminophylline) on the day of exposure. If he omitted the medication, he was given a dose upon arrival at the hospital. His usual medical program (antimicrobial drugs, intermittent positive pressure, bronchodilator, steroid, expectorant, et cetera) was discontinued until he returned home in the afternoon or evening.

Once pre-exposure tests were completed, the patient received 30 or 60 mg. of pseudoephedrine hydrochloride. An aqueous solution of aminophylline (500 mg., in 30 ml.) was administered rectally ten minutes before pressurization to ensure maximal effect when decompression began. The nasal cavities were sprayed with 0.5 per cent neosynephrine solution or its equivalent just before pressurization.

Pressurization was begun slowly to allow equilibration, then accelerated to a rate of 3 to 4 p.s.i. per minute to a maximum of 2 atmospheres absolute. A qualified medical attendant was always present in the chamber. The total time at "top pressure" was determined by the program and tests planned, but efforts were made to keep it as short as possible, usually ten minutes, with a maximum of 30 minutes.

Decompression was preceded by the administration of isoproterenol by aerosol, and then a *smooth pressure decrease at the rate of 0.3 to 0.5 p.s.i. per minute was begun.* An index of the patient's expiratory ventilatory status was monitored frequently during decompression. If any marked decrease occurred, isoproterenol was administered by aerosol, and descent was stopped until the previous level was regained. If any sudden drop of pressure occurred, the chamber was rapidly returned to the preceding pressure (or higher, if necessary); and the decompression procedure was reinstituted.

Once the patient reached sea level, he was allowed to rest for two hours to allow both the tension and the medication effect of the chamber exposure to dissipate. When this period of time had elapsed, the planned tests were performed. Following the tests and a period of observation, the patient was sent home, with instructions to resume

[3] Original support and continuing assistance came from the Donate-Once-Club, an employee group of the North American Aviation Company, Inc., Los Angeles, California.

TABLE 1

PULMONARY FUNCTION DATA ON PATIENTS WITH PULMONARY EMPHYSEMA PRIOR TO HYPERBARIC EXPOSURE

Patient Data	Residual Volume		Vital Capacity			Forced Expiratory Volume			Expiratory Reserve (4) Mean S.D.	Total Lung Capacity		Oxygen Uptake (5) Mean S.D. (ml./min. m²-BSA)	Residual % TLC Observed (Predicted)	Maximal Breathing Capacity	
				Supine	Standing	(1) 3 sec.	(2) 1 sec.	(3) ½ sec.							
Initials Age Sex	Predicted	Observed Mean S.D. % of Predicted	Predicted	Observed Mean S.D. % of Predicted		Mean Standard Deviation % of Observed Mean Vital Capacity				Predicted	Observed Mean S.D. % of Predicted			Predicted	Observed Mean S.D. % of Predicted
H.D.*	1,568	2,397	3,661	2,461	2,391	1,133	673	480	1,228	5,230	4,799	135	49.8%	108	19.4
65		482		154	125	78	40	31	66		118	17	(30)		2
M		153%		67%	65%	47%	28%	20%			92%				17.9%
H.R.	1,508	2,849	4,523	4,274	3,842	2,211	1,180	706	1,821	6,030	6,785	104	56.6%	132	38.4
53		168		221	251	94	60	57	140		187	9	(25)		4
M		189%		94%	90%	57%	31%	18%			112%				29.1%
R.A.	1,620	2,597	3,780	4,709	4,934	2,108	1,145	730	2,466	5,400	7,238	144	35.9%	107	36.0
66		199		217	175	115	45	21	183		202	13	(30)		2
M		160%		124%	130%	43%	23%	15%			134%				33.5%
H.T.*	1,330	2,420	3,990	4,673	4,857	2,849	1,701	1,128	1,806	5,320	6,977	141	33.4%	126	72.0
55		135		208	205	189	120	70	208		206	20	(25)		6
M		192%		117%	122%	59%	35%	23%			131%				56.9%
H.K.	1,461	3,651	3,409	3,268	3,283	1,620	770	445	1,609	4,870	6,791	152	53.8%	109	14.0
63		231		155	178	148	106	85	130		154	14	(30)		3
M		250%		96%	96%	50%	23%	14%			139%				12.9%
L.B.	1,508	2,733	4,522	5,543	5,645	3,285	2,077	1,237	2,120	6,030	8,276	120	33.0%	138	62.0
55		210		173	172	122	90	90	121		265	15	(25)		3
M		181%		125%	125%	58%	37%	22%			137%				44.8%
P.J.	1,596	3,727	3,724	3,487	2,627	914	537	398	2,145	5,320	7,293	144	51.1%	119	7
60		172		147	276	147	169	100	195		197	9	(30)		2
M		233%		94%	70%	35%	20%	15%			137%				5.9%
G.S.*	1,498	3,626	4,492	4,620					2,344	5,990	7,976	126	45.5%		
56		217		240					165		270	12	(25)		
M		242%		92%							133%				

C.S.	1,944	4,857	4,536	2,921	(2,442)	(1,332)	(799)	(577)	1,297	6,480	7,776	124	62.4%	131	(24.5)
60		124		168					151		139	16	(30)		
M		250%		64%	(54%)	(54%)	(33%)	(24%)			120%				(18.7%)
R.M.	1,620	5,636	3,780	2,563	(1,931)	(707)	(309)	(221)	1,414	5,400	8,167	127	69.0%	110	(7.3)
64		222		164					134		155	10	(30)		
M		348%		68%	(51%)	(37%)	(16%)	(11%)			151%				(6.6%)
W.B.	1,542	3,611	3,598	3,339	3,120	(2,091)	(1,262)	(872)	1,492	5,140	6,980	124	51.7%	102	(38.7)
72		231		172					164		309	24	(30)		
M		234%		93%	(87%)	(67%)	(40%)	(28%)			136%				(37.9%)
M.P.	1,465	3,076	4,395	4,972	(3,642)	(1,821)	(888)	(577)	2,030	5,860	7,915	125	38.9%	129	(41.7)
63		158		115					314		202	12	(30)		
M		209%		113%	(83%)	(50%)	(24%)	(16%)			135%				(32.4%)
K.A.*	1,148	2,152	3,442	2,496	(1,869)	(1,326)	(652)	(435)	1,239	4,590	4,770	149	45.1%	93	(24.0)
55		194		175					170			15	(25)		
F		187%		72%	(54%)	(71%)	(35%)	(23%)			104%				(25.8%)
F.R.	1,419	2,710	3,311	2,052	(1,989)	(1,149)	(619)	(398)	946	4,730	4,758	100	56.9%	144	(17.0)
64		224		90					116			14	(30)		
M		191%		62%	(60%)	(58%)	(31%)	(20%)			101%				(14.9%)
D.R.	1,535	2,018	4,605	4,402	(3,933)	(2,229)	(1136)	(656)	1,807	6,140	6,258	141	32.2%	152	(43.5)
32		247		184					240		197	16	(25)		
M		131%		96%	(85%)	(57%)	(29%)	(17%)			102%				(28.6%)
C.B.*	1,596	3,244	3,724	3,125	(3,094)	(1,547)	(597)	(442)	1,981	5,320	6,387	120 ± 14	50.8%	110	(28.1)
65		198		133					214			11	(30)		
M		203%		84%	(83%)	(50%)	(19%)	(14%)			120%				(25.5%)
S.Mc.	1,486	2,989	4,459	5,239	(4,420)	(2,564)	(1,326)	(972)	2,574	5,945	8,423	136	35.6%	126	(53.3)
49		173		141					147			13	(25)		
M		201%		117%	(99%)	(58%)	(40%)	(22%)			142%				(42.7%)

* Smokers.

Patients were on a stable medical regimen during this control period. The "observed mean" refers to the mean of the best values obtainable by the patient in his/her particular category. Values in the mean column that are bracketed ( ) are not the "best" mean.

his usual medical program and to return daily for the follow-up studies.

The results of the procedures and tests were analyzed in a manner permitting summation and comparison of the various volunteers' tests (9). Repeat exposures were performed, and variations of the above program were carried out to evaluate certain aspects of the program.

Results

The results of the exposures to pressure in the first 7 patients (those with correspondingly complete spirometric studies) are presented in figures 1 to 4. The graphic data in these figures are arranged in the following manner to permit easy comparison: The group of data on the left of each figure represents the frequency distribution of all of the tests in (a) the baseline study period, (*b*) the period two hours to two weeks after hyperbaric exposure (2 atmospheres absolute), and (*c*) the period four hours to one week after hypobaric exposure (0.5 atmospheres absolute). The group of data on the right of each figure represents the frequency distribution of all of the tests in (*a*) the baseline study period, and (*b*) the temporal sequence of test results following hyperbaric (and hypobaric) exposures at specific time intervals. The Y axis (perpendicular) represents the number of cases, and the X axis (horizontal) represents the deviation (of each test) from the "best mean" (O) in multiples of standard deviation.

Residual volume determinations (figure 1):

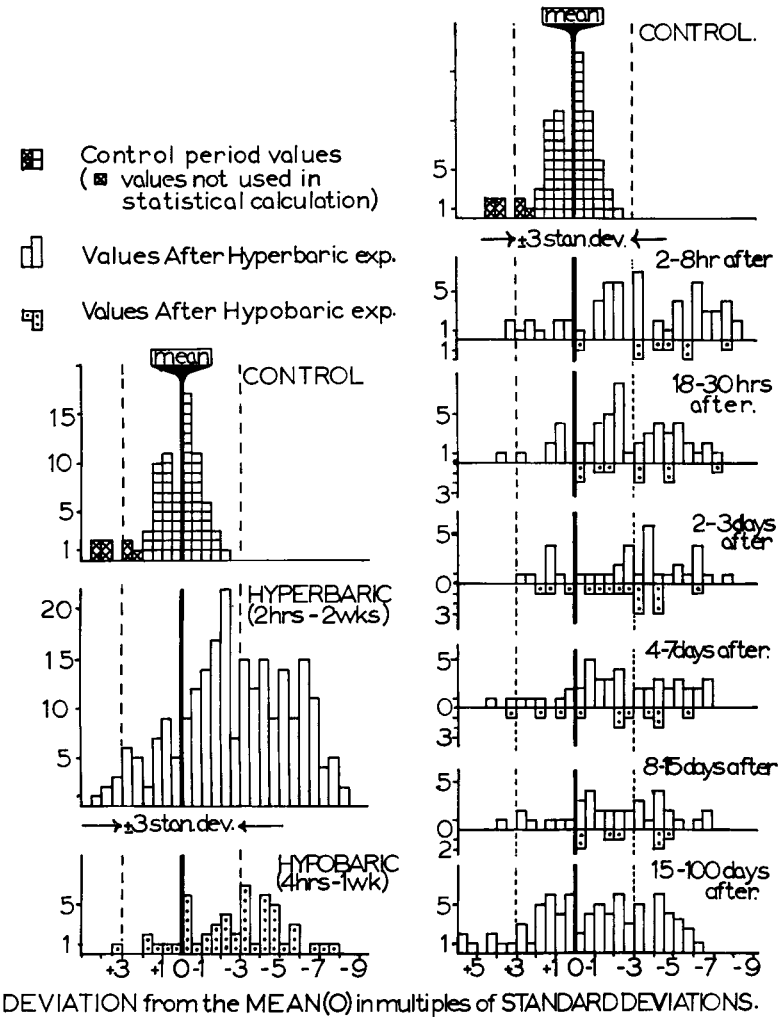

Fig. 1. Residual volume in seven patients with pulmonary emphysema before and after hyperbaric (2 atmospheres absolute) and hypobaric (0.5 atmosphere absolute) exposures.

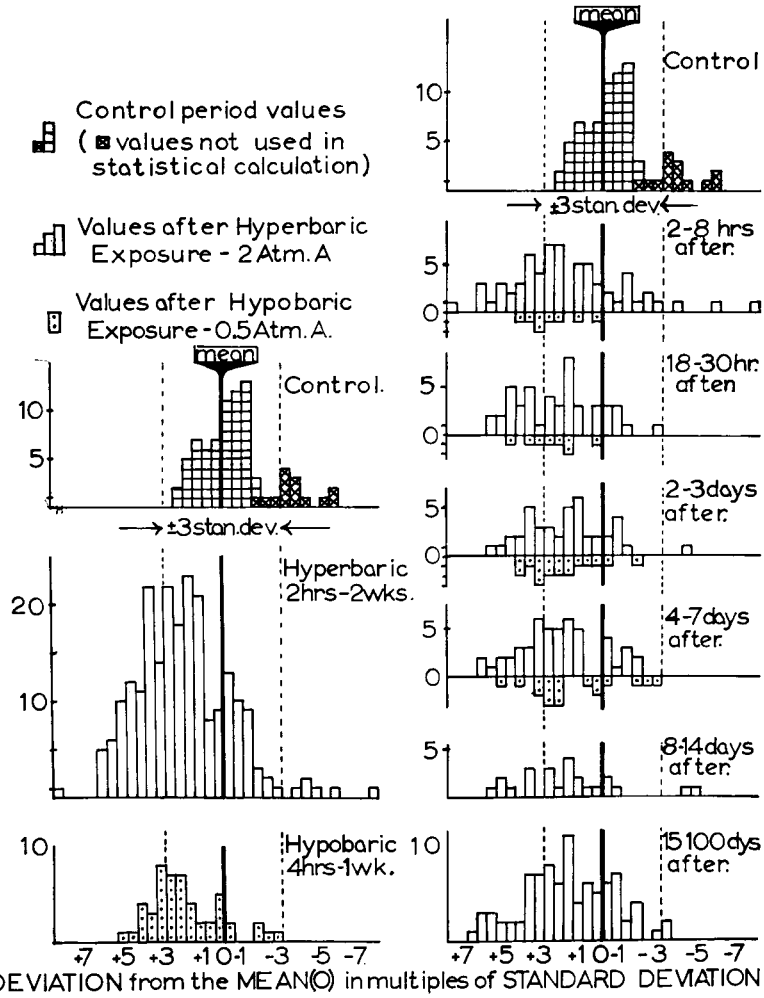

FIG. 2. Expiratory reserve in seven patients with pulmonary emphysema before and after hyperbaric and hypobaric exposures.

In this test the results after both hyperbaric and hypobaric exposure show a marked shift to the right (toward smaller absolute values). The "mean" of these results would probably fall in the region of the −3 standard deviation line. The chronologic sequence shows a sudden shift immediately after exposure, then a trend back to the previously established base line in the succeeding days. There is still a moderate skew in the second week; but, in the period exceeding two weeks, with few exceptions, the distribution has almost returned to the original pattern.

Expiratory reserve determinations (figure 2): Again there is a massive shift in distribution after both hyperbaric and hypobaric exposure. The skew is to the left (toward greater absolute values). The temporal sequence is different from that of the residual volume. There is an immediate shift after exposure, but almost no tendency to return to the previous base line in the immediate postexposure period.

Oxygen uptake determinations (figure 3): This test reveals no change after exposure, except for a wider scatter, due probably to the increased number of determinations. After both hypobaric and hyperbaric exposure, the temporal sequence shows no obvious tendencies such as are demonstrated in the other tests (figures 1, 2, and 4).

Vital capacity distribution (figure 4): This test demonstrates a marked change from the

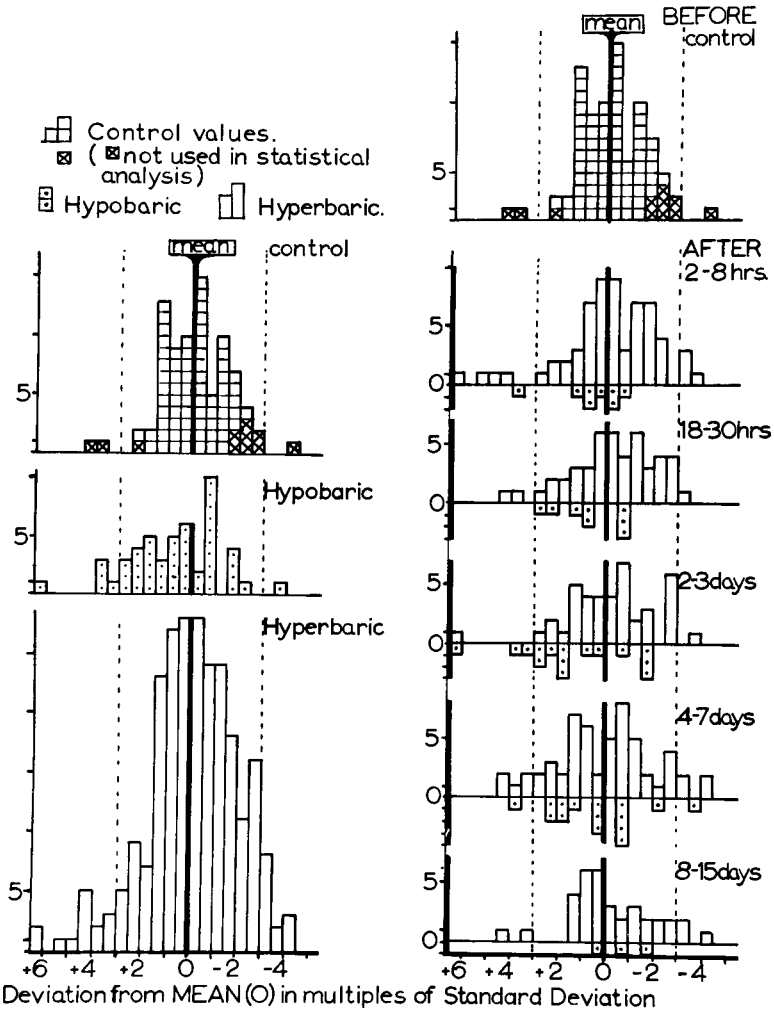

FIG. 3. Oxygen uptake (in milliliters per minute per square meter of body surface area) in seven patients with pulmonary emphysema before and after hyperbaric and hypobaric exposures.

base-line period after both hyperbaric and hypobaric exposure. The shift is to the left (toward greater absolute values), and the temporal pattern mirrors that of the residual volume.

Long-term changes in the pulmonary function tests (figure 5): The graphic distribution of these tests in their base-line period and for the period exceeding two weeks after hyperbaric exposure is illustrated in figure 5. Residual volume has almost returned to the base-line distribution, with some exceptions. Expiratory reserve still shows a persisting marked change. Oxygen consumption shows no change. Vital capacity shows a bimodality, but is more akin to the distribution of residual volume than to expiratory reserve. (No long-term follow-up was available following hypobaric exposure.)

Spirometric measurements (figure 6): In figure 6 it is shown that there was no change in the distribution of the spirometric measurements before and after hyperbaric exposure. The data also indicate that there was no change in the dynamic, or performance, tests as contrasted with the static lung volume tests.

Variations in the study procedure: In addition to the basic protocol outlined above, several variations were carried out to evaluate certain aspects of the program. These were not

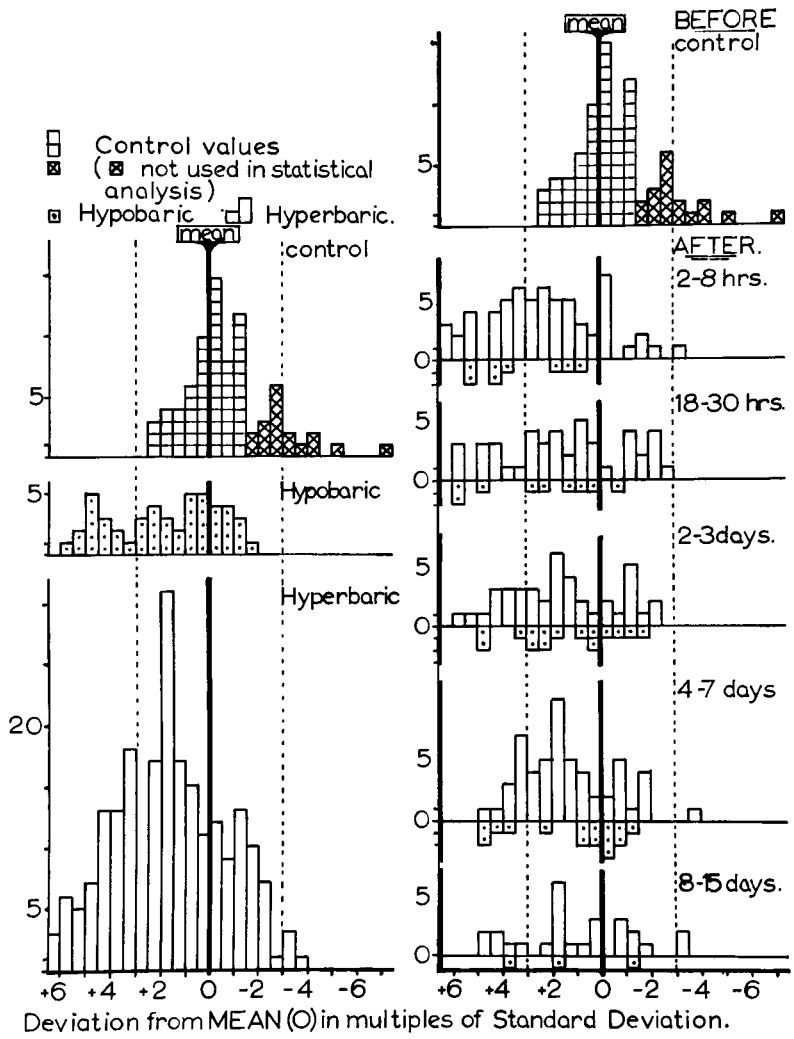

FIG. 4. Vital capacity (supine) in seven patients with pulmonary emphysema before and after hyperbaric and hypobaric exposures.

applied to all patients, nor studied in as great detail. The variations and their results are as follows:

In 8 of the 16 patients, the first pressure exposure was a sham. Everything outlined in the protocol was done except that the exhaust valves in the chamber were left open, and there was a noise, but no pressure. In 7 of the 8 (all emphysematous) *no significant changes occurred* in any of the measurements discussed above, although all of them stated they "felt better" for a few days. In the eighth patient, a young asthmatic who was thought to have fixed obstructive disease, there was a dramatic improvement in vital capacity, residual volume, and expiratory reserve that persisted for a period exceeding six weeks. His oxygen consumption remained unchanged. This benefit was not paralleled by any improvement in his spirometric measurements. Subsequently, however, when he was given a pressure exposure, no such change occurred.

One of the patients was subjected to the outlined protocol, except that the drugs were not given. The measurements after exposure were identical to those before exposure.

Five of the patients had an equivalent period of breathing ambient 100 per cent oxygen in

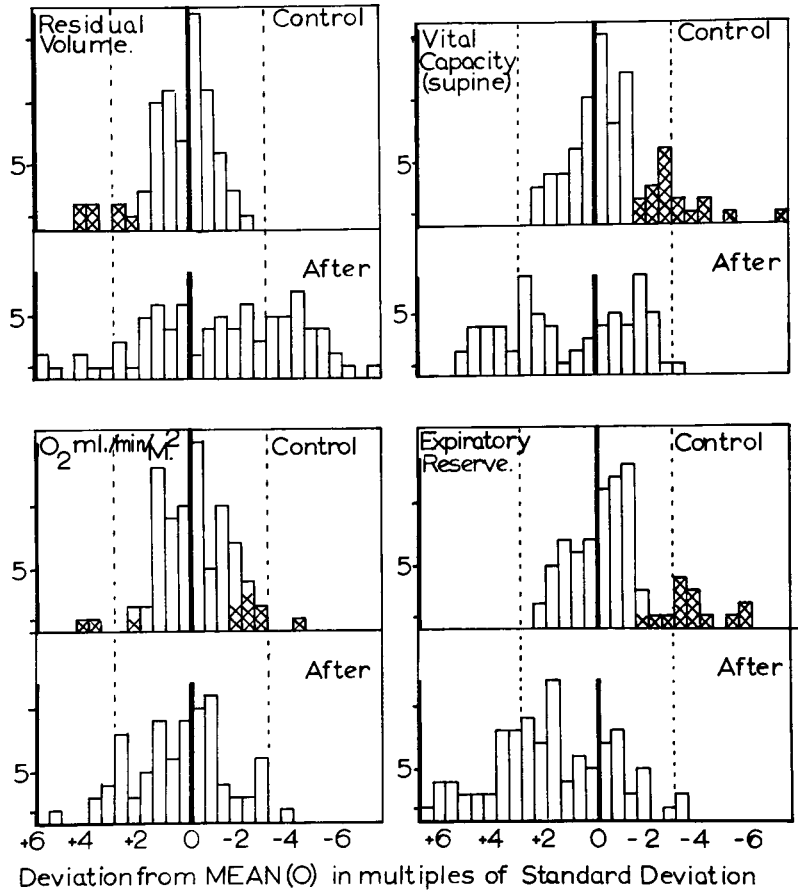

FIG. 5. Lung volume tests in seven patients with pulmonary emphysema 15 to 100 days after hyperbaric exposure (1.5 to 2 atmospheres absolute).

the chamber, both with and without the usual chamber medication, but with no pressure. Again, no difference was noted in measurements before and after the exposure.

The hyperbaric exposure was performed exactly as outlined in the 5 patients above on seven occasions, the only difference being that the patients breathed either 100 per cent oxygen or a mixture of 60 per cent helium and 40 per cent oxygen during the major portion of the procedure. The results were essentially identical to the patients' response to breathing air.

Four of the volunteers were exposed to a "mirror image" pressure sequence in an altitude chamber (hypobaric) (1 to 0.5 atmospheres absolute) (10). While breathing 100 per cent oxygen to prevent hypoxia, they were slowly decompressed to 18,000 feet and then rapidly pressurized to sea level. The medication routine was the same in this "mirror image" sequence; and, although the absolute pressure change was less (7.5 p.s.i.a. instead of 15 p.s.i.a. differential), the relative magnitude (factor of 2) was identical. The results were similar to the hyperbaric sequence as illustrated in figures 1–4. The reason for this last variation was to test whether or not the rate of change of pressure was the critical factor in the program.

Normal control subjects: Test data for the normal attendants who accompanied these patients on their pressure cycles are not yet available in a similar, graphic form. This is due, primarily, to the difficulty in obtaining the large numbers of tests necessary for such an analysis in normal persons who are otherwise busily engaged. However, the figures so far available in the normal group fail to show any significant change (even in several hardy

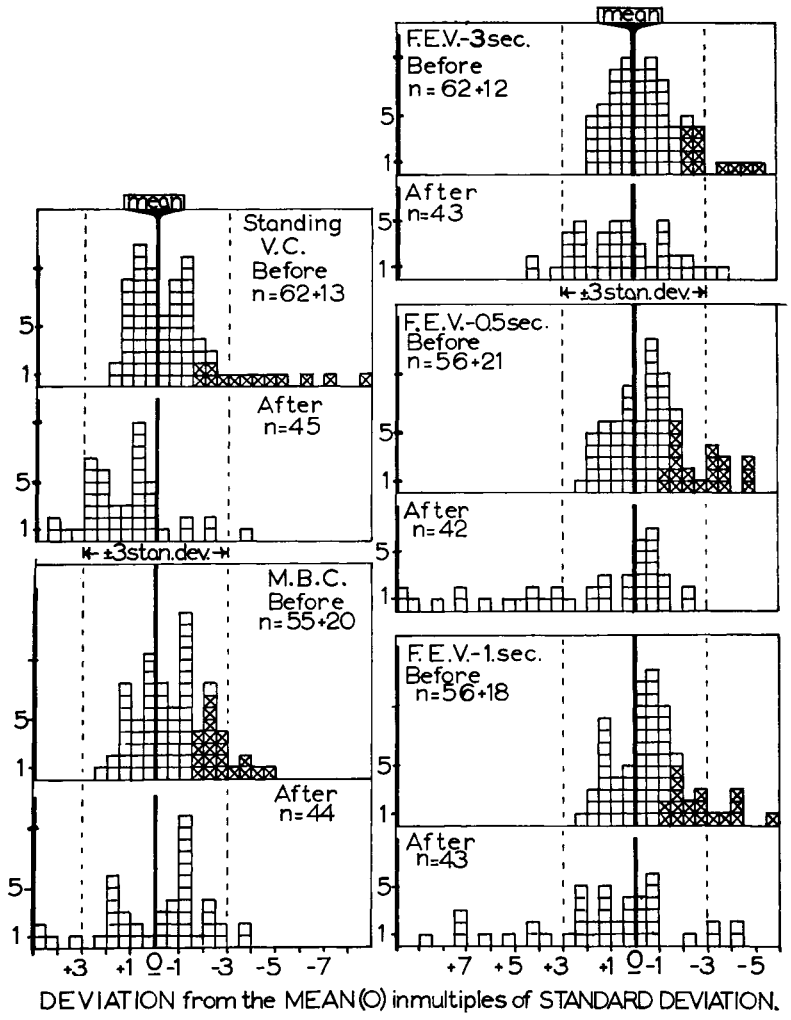

FIG. 6. Spirometric measurements (performed on the 13.5-liter Collins spirometer) in seven patients with pulmonary emphysema before and after hyperbaric exposure.

souls who took the same medication as the patients).

Deleterious influences: In the first group of 10 patients, 3 were heavy smokers. These 3 were the ones who showed no consistently significant change after exposure. Two showed significant changes immediately afterward, but not subsequently. One of them was "induced" to give up smoking temporarily (for one week). On the third exposure he showed a marked change, which persisted for three days. He then resumed smoking, and the fourth exposure again failed to produce significant change.

The second group of patients included 4 smokers of the 7. None had significant, persisting changes while they smoked. It was concluded, therefore, that, whatever the reason, heavy smoking either reverses or prevents measurable changes in lung volume as compared with the changes in the nonsmoker.

A prolonged period of heavy air pollution, associated with elevated temperatures, occurred during the study. Exposures (3) during this period resulted in no change in persons who either previously, or subsequently, showed the usual marked changes in the measurements illustrated above.

The third factor that was identified as preventing the "beneficial" pressure changes in this group of emphysema patients was an

episode of acute or subacute bronchitis and/or pneumonitis (viral or bacterial). Two other factors that may also be of significance are strong emotion (fear) and allergy. To date, however, no data have been assembled on these two factors.

Discussion

The results of hyperbaric exposure outlined above certainly seem to fall together rather neatly: There is a sudden improvement in expiratory reserve, which persists; there is no change in oxygen consumption; and there is a sudden decrease in residual volume, which does not parallel the expiratory changes, with a corresponding increase in vital capacity. Both of the latter measurements slowly return to their previous base line. These changes can also be induced by exposure to hypobaric pressure gradients, and seemingly are not influenced by the gas(es) breathed during pressure exposure. The changes can be prevented or reversed by heavy cigarette smoking, air pollution, or pulmonary infection. There is no corresponding improvement in the dynamic spirometric measurements, which are dependent upon summated effects of bronchial caliber and expiratory air flow.

A possible explanation for the above series of observations is that a redistribution of air within the thorax *does* occur as a consequence of this specific type of pressure exposure. The decrease in residual volume is reflected in a corresponding increase in the exchangeable air —vital capacity. The air-trapping mechanism(s) present in each patient seem unaffected by these changes, and will cause a gradual reaccumulation of air in the cystic areas. Any factor that potentiates air-trapping will hasten the return to the previous base-line level of the residual volume.

The benefit to the patient seems far greater than the measurable changes. During the period of decreased residual volume, the patient seems to be on a more efficient plane in his work of breathing. The benefit from the ability to breathe at a lower level of the thoracic volume, although not measurable with gross tests, may be much more apparent to the patient because of its cumulative nature. Thus, it was noted that the majority of the patients experienced subjective and clinical improvement in the week following exposure, and this was far greater than any change that was being measured. Evidently this physical process of redistribution of air can be repeated many times without losing its effect or causing any measurable deterioration in the tests monitored.

An additional benefit of this study is the fact that 15 patients with significant emphysema and one patient with severe asthma were exposed to pressures of 2 atmospheres absolute on 110 occasions, and none was worse after the exposures, and no mortality or morbidity resulted from these *careful* exposures. The importance of this is in the demonstration that patients with significant pulmonary disease *can* be safely exposed to pressure *if* extreme care and intelligent monitoring are available. Such exposures are still highly hazardous and present potentially life-threatening situations, and they should not be entered into lightly.

This is an age of increasing urbanization and industrialization. Under such circumstances, one of the prices paid for greater life-expectancy is the increasing variety and prevalence of chronic pulmonary disease. The current emphasis on the potentialities of hyperbaric oxygenation is primaily directed to disease states associated with advancing age, the degenerative diseases of the cardiovascular system associated with regional and/or systemic hypoxia. Unfortunately, this is the same patient group in whom the incidence of obstructive pulmonary disease is at its maximum.

The results of an unwitting standard rapid decompression in such elderly patients are not likely to be much better now than they were in the nineteenth century, particularly if the patient ill with a disease that has just responded gratifyingly to hyperbaric oxygenation suffers from pulmonary barotrauma. More efficient means of recognizing minimal but significant obstructive pulmonary disease are certainly needed before widespread use of this modality is advisable. In the meantime, careful and detailed studies of lung volumes should be pursued in patients with diseases that might respond to exposure to hyperbaric environments.

Summary

Attempts to treat chronic pulmonary disease with exposure to increased pressures began in the nineteenth century. The results were such that this approach to treatment was totally abandoned, the basic reason probably being in-

adequate knowledge. One hundred years later another trial of pressure exposure in chronic pulmonary disease was initiated. This attempt was based upon a hypothesis combining data on the nonuniformity of the disease process in emphysema with relevant data from the fields of physics and aerodynamics. The postulated critical factor was the rate of change of pressure, both positive and negative.

Multiple pressure exposures in 16 disabled emphysema volunteers resulted in a significant improvement in residual volume, vital capacity, and expiratory reserve in 10 of the 16 patients. Factors preventing such changes were identified as smoking, air pollution, pulmonary infection, and the presence of diffuse uniform disease.

As the peak incidence of hypoxic disease occurs in the advanced age group, in which obstructive pulmonary disease incidence is at its maximum, the demonstration that patients with pulmonary obstruction can safely be exposed to pressure (intelligently administered) has significance in the future widespread expansion of hyperbaric medicine.

Sumario

Investigaciones en el Campo de la Presión Hiperbárica en las Enfermedades Pulmonares Crónicas

Los intentos de tratar las enfermedades pulmonares crónicas con exposición a presiones elevadas se iniciaron en el siglo XIX. Los resultados fueron tales que este medio de tratamiento fue descartado, probablemente debido a la falta de conocimientos. Cien años después hubo otro ensayo de exposición a altas presiones a pacientes con enfermedades pulmonares crónicas. Este intento se basó en una hipótesis que combinó los datos de la falta de uniformidad del proceso anatomopatológico en el enfisema con datos pertinentes en los campos de la física y aerodinámica. El factor postulado de mayor significación fué la velocidad en el cambio de presión, tanto en su fase positiva como en la negativa.

Múltiples exposiciones a altas presiones en 16 voluntarios incapacitados con enfisema, produjo una mejoría significativa en el volumen residual, la capacidad vital y en la reserva expiratoria en 10 de los 16 enfermos. Se identificaron ciertos factores que impedían la mejoría, a saber, el fumar, la contaminación del aire, la infección pulmonar y la presencia de enfermedad difusa y uniforme.

En vista de que la mayor incidencia de las enfermedades hipóxicas ocurre en la edad avanzada, cuando la incidencia de la enfermedad pulmonar obstructiva llega a su máximo, esta demostración de pericia al someter impunemente a pacientes con obstrucción pulmonar a ambientes de alta presión, adquiere gran significación en la futura, amplia diseminación de la terapia hiperbárica.

Resume

Recherche hyperbarique dans la maladie pulmonaire chronique

Déjà au cours du dix-neuvième siècle des essais furent tentés afin de traiter la maladie pulmonaire chronique par des pressions d'air élevées. Les résultats furent tels que cette approche thérapeutique fut totalement délaissée. La raison profonde en est sans doute une connaissance scientifique insuffisante à cette époque. Cent ans plus tard, on a de nouveau procédé à un tel essai, utilisant les pressions d'air élevées dans la maladie pulmonaire chronique. Cette tentative était basée sur une hypothèse étayée à la fois par l'observation que le processus morbide dans l'emphysème n'était pas uniforme et par des données pertinentes obtenues dans le domaine de la physique et de l'aérodynamique. On a postulé que le facteur critique était le taux de changement de la pression, tant dans le sens positif que négatif.

Seize volontaires atteints d'emphysème qui les rendait invalides ont été soumis à plusieurs reprises à une pression positive. Chez 10 de ces 16 malades, il en est résulté une amélioration notable du volume résiduel, de la capacité vitale et de la réserve expiratoire. Les facteurs qui s'opposent à cette amélioration ont été identifiés comme étant respectivement l'habitude de fumer, la pollution de l'air, l'infection au niveau des poumons, et la présence d'une atteinte uniforme et diffuse.

Vu que l'incidence maximale de la maladie hypoxique survient dans le groupe d'âge avancé, lorsque la fréquence de la maladie obstructive du poumon est à son apogée, la démonstration du fait que les malades avec obstruction pulmonaire peuvent être soumis en toute sécurité à la pression élevée (à condition qu'elle soit administrée d'une manière adroite) ouvre l'horizon pour le développement de la médecine hyperbarique.

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