U. S. NAVAL AIR DEVELOPMENT CENTER

Johnsville, Warminster, Pennsylvania

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Pulmonary Hypertension Resulting from Oxygen Exposure

Naval Air Systems Command
Air Task R01 101 01 (RF-3-04)

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SUMMARY

Rats exposed to an atmosphere of 95 to 100% oxygen at a partial pressure of 516 mm Hg for periods of 30 days showed no obvious abnormalities. At the end of this exposure they were removed from the system and anaesthetized. Aortic and intratracheal pressures were measured by standard direct procedures in response to breathing air and oxygen and to transient increases in intratracheal pressure. Compared with the results in unexposed rats, the experimental animals showed an increase in pulmonary arterial pressure (PAP) and a decrease in mean aortic pressure. The increase in aortic pressure caused by breathing oxygen which was present in the unexposed animals could be elicited in the exposed rats. The increase in PAP is attributed to structural changes in the pulmonary vasculature associated with oxygen exposure and it is postulated that an increase in vascular resistance is responsible for a decreased cardiac output, giving rise to the systemic hypotension. Whereas mean aortic pressure fell during increased intratracheal pressure, mean pressure from the right heart did not change, suggesting that the right ventricle empties itself less well against the increased pressure.

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INTRODUCTION

Although oxygen breathing has come to be an important procedure in medicine and aviation over the past twenty years, it was with the advent of manned space flight and the possibility of long-term breathing of oxygen at abnormally high tensions that interest has been renewed in the limitations of this practice. The effects of breathing oxygen at high pressure are different depending on the tension. Thus, at very high pressures the predominant effects are neuromuscular and the time to produce these effects is a matter of hours (1, 2, 3). At one atmosphere and down to 650 mm Hg the dominant effects are pulmonary and the time to death in small animals is several days (4, 5, 6, 7). One other important difference exists for as Armstrong (8) and Comroe et al. (9) found, reducing the pressure to about 1/2 atmosphere would (a) allow animals to survive and (b) greatly reduce effects in men.

The use of oxygen in medicine and aviation has benefitted from the fact that the P_{O_2} used always was less than one atmosphere and the duration of the exposure was less than the time necessary to produce symptoms. The ease and efficiency with which oxygen can be administered in the hospital today, however, would tend to eliminate past benefits derived from such factors as the inefficiency of old methods. Similarly the manned space flight program would greatly extend the time crews would be required to breath 100% oxygen. The problem of prolonged exposure to partial pressures of oxygen greater than normal but less than atmospheric has therefore been the subject of investigation in several laboratories (10, 11, 12, 13).

Our approach has been to study the effects produced at the highest pressure compatible with the survival of rats and other small animals, the rationale being that whatever effects might occur at lower pressures would show up sooner and be more easily identified.

In a previous study, rats were subjected to 100% oxygen at 2/3 atmosphere for 30 days and the animals were recovered intact with no outward sign of difficulty (14). Microscopic examination of the lungs however, indicated that the small blood vessels were undergoing changes which in some instances appeared to be hypertrophic. These results raised the question as to whether there were accompanying functional changes. In order to investigate this question, rats were exposed to 100% oxygen at 2/3 atmosphere for 30 days, at the end of which time, the pulmonary arterial pressure was measured and compared with that of unexposed rats.

METHOD

Forty Sprague-Dawley rats, (Charles River CD's) were exposed to 100% oxygen at 2/3 atmosphere (516 mm Hg) for 30 days. The exposures were

carried out in an environmental system that has been described previously (15). The gas in the system was continuously circulated through a vessel containing lithium hydroxide for the removal of carbon dioxide. Gas entering the container (leaving the animal chamber) contained 0.5% CO_2 and it was completely removed so that gas re-entering the animal chamber was free of CO_2. A demand regulator sensed the pressure drop resulting from the absorption of CO_2 and added oxygen to restore the previously set pressure. Chamber temperature was 28 ± 1°C. The rats were supported on a wire mesh floor, below which there was a waste pan which contained anhydrous $CaCl_2$ and activated charcoal for stabilizing the waste. Every second day the chamber was opened in order to replace the pan. This operation required 1 to 2 minutes and the purge to 100% oxygen required 15 to 20 minutes. The percentage of oxygen was otherwise kept above 95%.

At the end of the run, the rats were taken from the chamber and anaesthetized with urethane (1 gm/kg intraperitoneally from a 1g/cc solution). An incision in the abdomen allowed dissection and cannulation of the abdominal aorta near the bifurcation using a small T tube attached to a polyethylene PE 205 catheter filled with heparinized, gas-free saline.

A skin flap was raised on the right side of the neck and the external jugular vein dissected free and isolated as a pillar from the flap to the chest. A two-part catheter was used in this part of the operation (see Figure 1). One part consisted of a piece of PE 205 about 7.5 cm long and formed at 45° in the last 0.5 cm; the second piece consisted of PE 90 formed somewhat in the shape of a hook so that it could be used to reach the pulmonary artery. Both catheters were equipped with markers of masking tape, placed near the transducer end to indicate the direction of the curved portion. The PE 90 had two additional markers consisting of loops of 3-0's black silk suture material tied to the catheter to indicate (1) where the end of the PE 90 emerged from the PE 205 and (2) where the 180° hooked portion emerged. Both of these markers were tied tightly but not to exclude sliding along the catheter. A Statham P23Dd transducer was used for aortic pressure and a P23BB for pulmonary arterial pressure.

Using the pressure pulse, as it was displayed as a spot of light on an oscillograph, as a guide, the PE 205 with the PE 90 slipped inside was introduced through an incision in the jugular and advanced to the ventricle by gently pushing and turning. The location was ascertained by the height of the pulse. A dummy galvanometer was used to indicate zero for this pulse. On reaching the ventricle the PE 205 was turned toward the rat's left and the PE 90 pushed through until the entire 180° portion had emerged from the tip of the PE 205. Then, using the presence of a positive diastolic pressure as a guide, it was maneuvered into the pulmonary artery. Whether the catheter reached the pulmonary artery depended to a large extent on whether it was properly shaped. The position of the catheter was ascertained at the end of the experiment by opening the chest. The trachea was then cannulated with a special device designed to allow the animal to breathe from a closed system and yet to prevent re-breathing. This turned

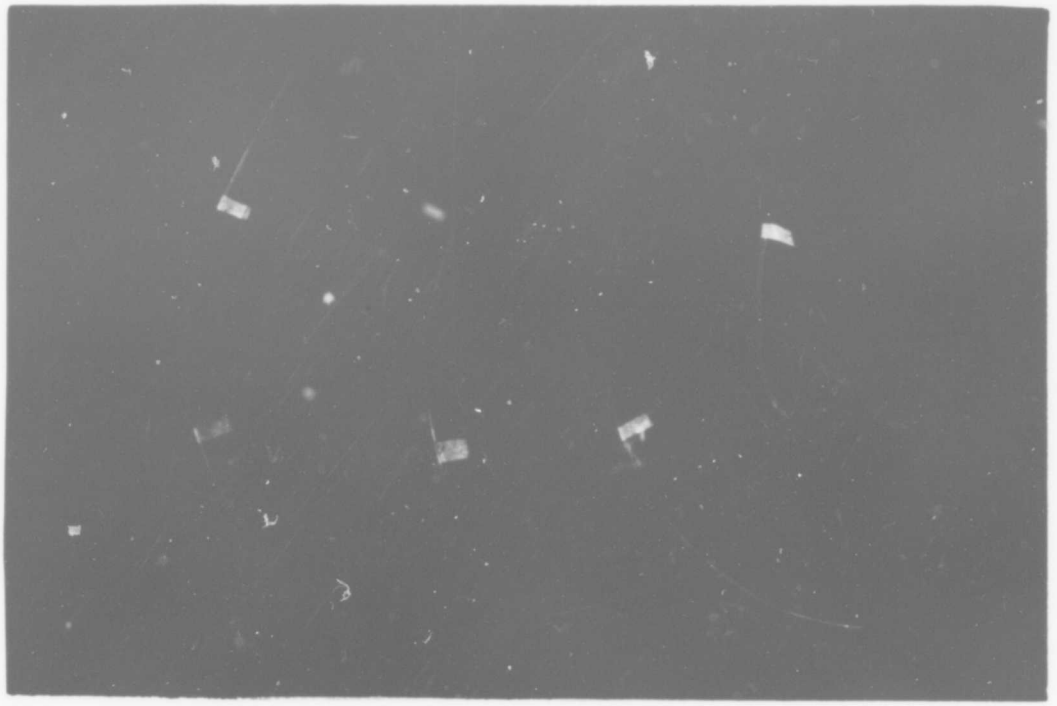

Figure 1. The catheter used for catheterization of the pulmonary artery. (See Text)

out to be a T-shaped cannula with one of the limbs closed and with a small container of LiOH mounted on the center limb. The device was constructed of nylon 4.5 cm long and 1.7 cm in diameter. A wire mesh cylinder 5 mm in diameter was mounted concentrically inside with LiOH granules placed between it and the nylon cylinder. Thus, a low resistance path was created for the movement of gas, while at the same time presenting a large surface area for the absorption of CO_2. The nylon cap which enclosed the container had two openings; one located centrally was connected to a passive gas reservoir—a condom, and a second opening was connected to a pressure transducer, (Statham P23B). The anaesthetized rats were supplied with air and oxygen using this system.

The oscillograph records from the experiments contained the ECG recorded from skin clips as electrodes, aortic pressure, right auricular, right ventricular or pulmonary arterial pressure, and respiration when the tracheal cannula was mounted. The output from the right heart transducer was made audible over a loudspeaker and displayed on a cathode ray oscilloscope. During the course of the measurements the intratracheal pressure was raised to about 8 mm Hg and the effect was recorded as were the effects of breathing air and oxygen.

RESULTS

Some characteristics of the pressure pulse of the rat seem worth mentioning. These are illustrated in Figures 2 and 3. Most of the time it was possible to distinguish the atrial pulse preceding ventricular contraction when the catheter was in the ventricle. The atrial pulse was interrupted by ventricular contraction near the peak of atrial systole during the rising or the falling phase. The time relations were such as to give a rising pulse of two or three phases depending on the length of time between atrial and ventricular systole. Figure 2 is a record of an animal in which atrial diastole begins before ventricular systole. The total pressure rise therefore involves rising, falling and rising phases to the peak of ventricular systole. Figure 3 shows a record of an animal in which the interval is shorter so that atrial systole is interrupted during its rising phase. In this instance there are only two rising phases to the right heart systole. When the atrial pulse was not present, the pulse resembled a sine wave.

Pressure in the pulmonary artery or the right ventricle as measured here against atmospheric pressure varied with respiration to such an extent that systolic pressure during inhalation was only slightly higher than diastolic pressure at the peak of exhalation (see Figure 4). Thus the variations in the peaks and troughs of systolic and diastolic pressures respectively were in phase with the variation that occurred in the intratracheal pressure. The systolic pressure reported below is the average of the maximum and minimum values. Aortic systolic pressure was similarly averaged, however, there was little or no respiratory variation in aortic diastolic

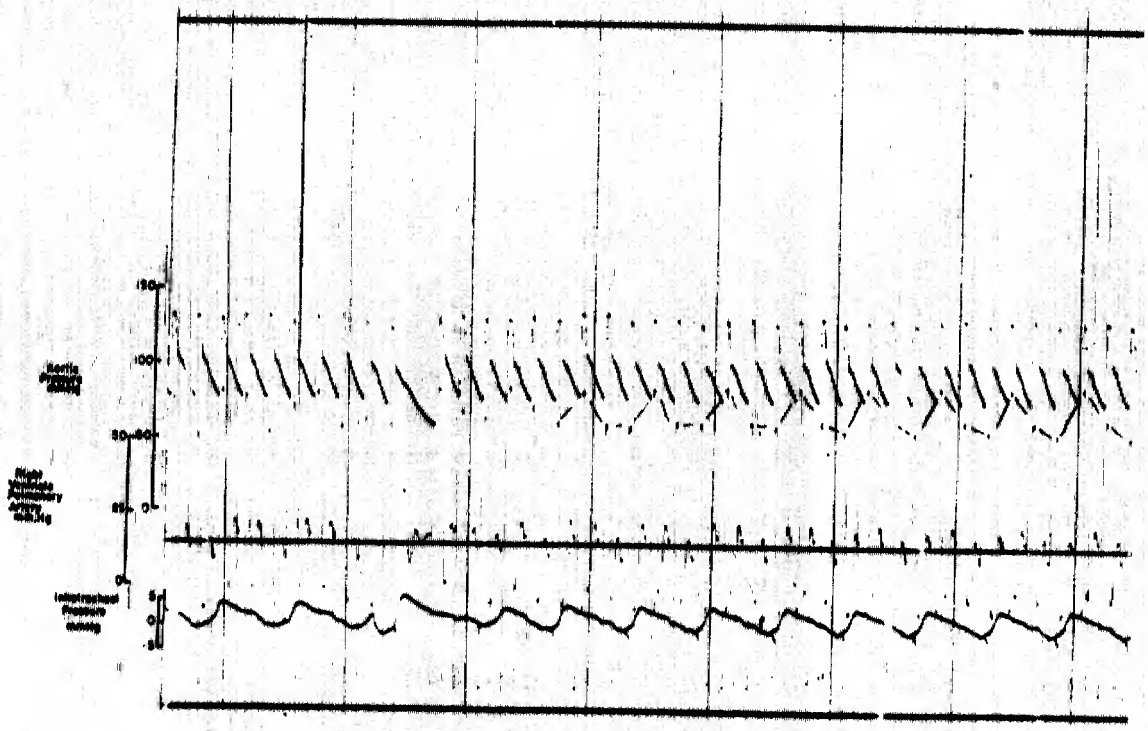

Figure 2. An oscillograph recording showing from the top, aortic, right ventricular and intratracheal pressure. The interruption in blood pressure pulses was probably caused by blocked A-V conduction. Note that atrial diastole has begun before the onset of ventricular systole. Lines drawn between peaks of sight ventricular pressure show the respiratory variation. ECG is the lowest trace. The smallest time interval shown is 1/10 sec., the heavy vertical lines are 1 second apart. (From an exposed animal)

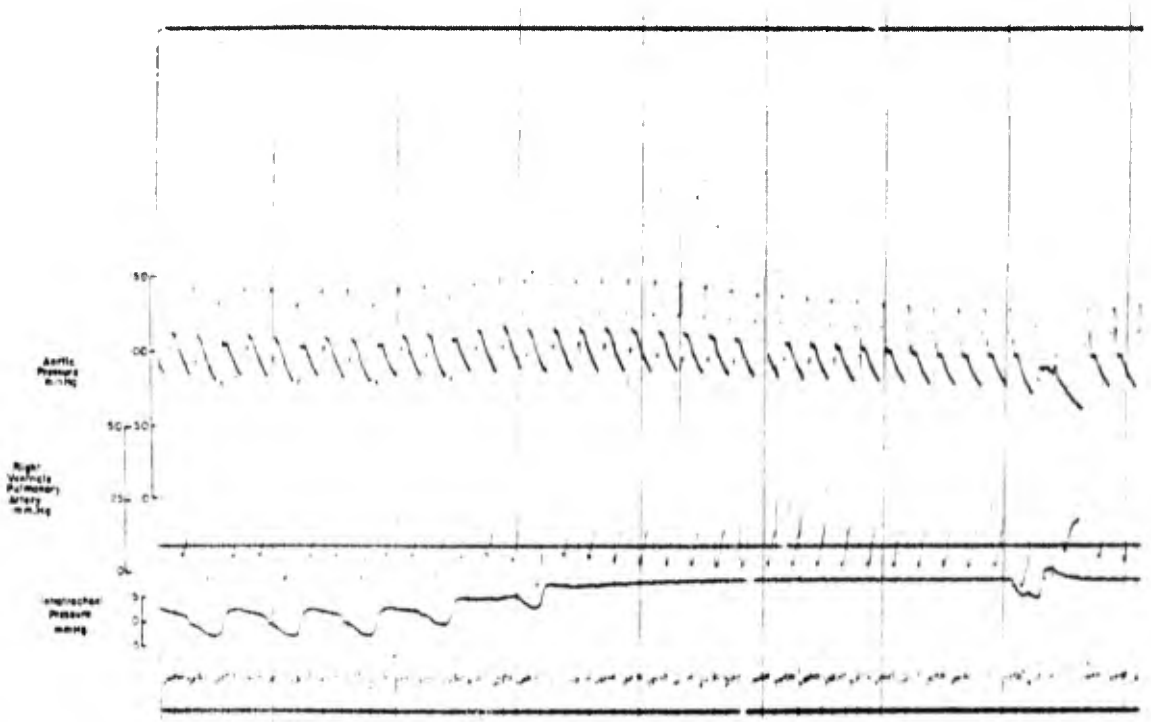

Figure 3. Oscillogram showing the same variables as Figure 1. Note that right atrial systole is interrupted before its maximum by ventricular systole. Intratracheal pressure was increased producing the apnea. ECG is the lowest trace. The smallest time increment shown is 1/10 sec., the heavy lines are 1 second apart. (From an exposed animal)

pressure. Mean pressures (M.P.) were computed using the equation

$$M.P. = (D + S)/2$$ where D = average diastolic pressure

S = average systolic pressure

The use of this equation for the right side is discussed below.

A summary of pressures obtained from the lesser circulation is given in Table I. In obtaining these, the exposed rats were removed from the environmental system to air at the end of the exposure; they were anaesthetized and prepared for the blood pressure measurements. Both groups of rats were administered oxygen as well as air during the measurements. This change appears to have had negligible effects as shown in the table. Maximum systolic and average systolic pressures however, are increased after exposure to oxygen for 30 days.

Table II shows the results of oxygen breathing on the systemic circulation. The column marked "Air" shows that the mean aortic pressure of rats exposed for 30 days to 100% oxygen at 516 mm Hg is lower than the unexposed control rats. The column marked "Oxygen" shows that both exposed and nonexposed rats respond to brief periods of oxygen breathing with increased mean pressure.

The effects of increasing the intratracheal pressure on systemic and pulmonary pressure can be seen in Table III. The well-known decrease in systemic pressure was recorded, in this case an increase of 7 mm Hg intratracheal pressure decreased the aortic pressure 15.0 mm Hg from a mean of 99.8 mm Hg. The exposed rats gave a similar response. In contrast the pulmonary arterial pressure showed little if any response to increasing the intratracheal pressure. The values in this table were obtained by taking the mean pressure in the same animal at roughly the same time at normal atmosphere pressure and at the increased value. When the average right systolic pressure of this group at increased intratracheal pressure was compared with that of the control group there was a similar lack of response.

Table IV compares pressures obtained from the right ventricle and the pulmonary artery in exposed and nonexposed rats. It should be mentioned that the same equation was used to compute these values. The minimum diastolic pressure in the right ventricle was frequently negative and the average diastolic pressure was therefore sometimes negative.

DISCUSSION

As can be seen in Figure 4, the attempt to evaluate the records in terms of systolic and diastolic pressure in the right and left hearts produced the array of measurements mentioned above. With the exception of the aortic diastolic pressure, a maximum and minimum occurred for each respiratory cycle and a representative value was obtained by averaging these measurements.

The equation given above was used for the calculation of mean pressure for all measurements regardless of position of the catheter. This method leaves something to be desired in the case of diastolic measurements from

TABLE I

Effect of Oxygen Exposure on Pressures
from the Right Heart when Breathing Air and Oxygen (mm Hg)

	Max. Systolic		Avg. Systolic		Mean Pressure		
Breathing Gas	Air	Oxygen	Air	Oxygen	Air	Oxygen	No.Rats
Exposed	45.3	42.4	37.6	35.4	15.5	16.1	17
Non-exposed	36.7	35.5	31.8	29.7	14.6	15.5	30

TABLE II

Effect of Oxygen Exposure on the Mean Aortic Pressure when Breathing Air and Oxygen (mm Hg)

Breathing Gas	Air	Oxygen	No. Rats
Exposed	79.6	88.7	17
Non-exposed	90.7	99.6	30

TABLE III

Effect of Increasing the Intratracheal Pressure on Systemic and Pulmonary Pressures in Rats Breathing Oxygen

	Normal I.P.	Increased I.P.	Diff.	ΔI.P.	No. Measurements
Mean Aortic Pressure					
Non-exposed	99.8	84.8	-15.0	7.0	17
Exposed	85.8	75.4	-11.2	9.4	24
Mean Right Heart Pressure					
Non-exposed	15.0	15.8	0.8	5.3	28
Exposed	17.4	13.9	-2.2	9.4	12

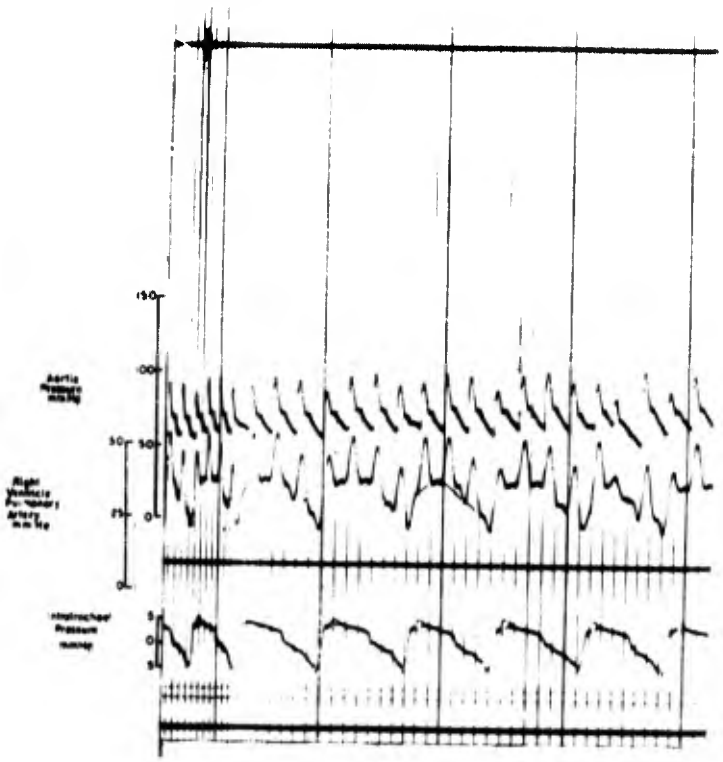

Figure 4. Oscillogram from an animal showing aortic, pulmonary arterial and intratracheal pressure. Lines connecting the minimum diastolic pressure show its relation to respiration. The smallest time interval shown is 1/10 sec., the heavy lines are 1 second apart. In the first section, paper speed was being changed.

the right ventricle because they are frequently negative, however, no attempt was made to scale out or normalize on this account. The values for mean pressure from the pulmonary circuit in Tables I and III are averages of mixed values from the right ventricle and the pulmonary artery and those in Table IV are separated. Diastolic pressure in the pulmonary artery was always positive.

The data indicate that the 30-day exposure to oxygen causes hypertension in the pulmonary circulation and there is an implication that it is caused by the effects of oxygen on the pulmonary vasculature. Previous work in this laboratory has demonstrated structural changes of a hypertrophic nature in the media of vessels in the lungs of rats similarly exposed. The mechanism of these changes is not understood but they were suggestive of an increased turnover of vascular tissue (14). Although the reported changes were related to larger vessels, it is felt that the initial response is probably in the endothelium. Some support for this idea is found in a report by Kistler, et al. who found from electron microscopic evidence that the endothelial component of the air blood barrier was most affected by high oxygen tension; the epithelium was largely intact when the endothelium was effectively destroyed (16).

The hypertension shown in the oxygen-exposed rats of these experiments in increasing the load on the heart, is in line with similar evidence by Karsner (17). He exposed rabbits to 80% oxygen for 6 days and found that they presented a typical picture of right heart failure with dilatation of the ventricle and visceral congestion presumably from increased venous pressure. Bennett, et al. (18) also studied the lesser circulation after oxygen exposure in rats. They exposed rats to compressed air giving an equivalent of 83.6% oxygen for 47 days and found an increase in the pulmonary arterial pressure, right ventricular dilatation and some connective tissue scarring in the hearts using an open-chest technique.

Thus, this aspect of oxygen toxicity falls in a category of experimental and clinical conditions that are related by dysfunction of the pulmonary circulatory system, including heart failure on the clinical side and the experimental administration of a great variety of agents and conditions on the other. Their study is instructive in the investigation of oxygen toxicity and the experimental work is of particular worth because there is better control of conditions. It should be mentioned, however, that from the clinical side Wagenvoort et al., state that many if not all of the new structural changes in the lungs are accompanied by pulmonary hypertension (19). Some unusual vascular formations have been reported previously with oxygen (14).

Since the factors producing increases in pulmonary arterial pressure could bring about increased transudation and edema formation, investigations on this subject are related to this aspect of oxygen toxicity (20, 21). It may be important to mention here that increased transudation can take place

TABLE IV

Comparison of Mean Pressures Obtained from the Pulmonary Artery in Exposed and Non-exposed Rats Breathing Air and Oxygen, (See Text)

	Air		Oxygen	
	R.V.	P.A.	R.V.	P.A.
Exposed	16.4	29.3[4]	16.6	23.9[4]
Non-exposed	13.9	19.1	15.5	18.9

without the appearance of edema, a situation that is certainly suggested by work on lung lymphatics (22). The detection of lung edema as outlined by Visscher (20) indicates that fluid storage in the lungs must be advanced before it can be detected by the usual clinical methods and it therefore is important to recognize the existence of a process that produces fluid at a rate less than the mobilized draining capacity of the lungs. Such a situation may not be recognized clinically but could qualitatively be the same as the edema forming process. The loss of fluid from the circulating blood could take place as a result of a change in the permeability characteristics (permittivity) (23) of the capillary membrane in the presence of a constant hydrostatic pressure or with an increase in that pressure with or without a change in permittivity. Other less direct causes have been mentioned (21).

In the production of pulmonary edema by steam, Aviado and Schmidt showed that there is a constriction of pulmonary veins to produce an increase in hydrostatic pressure (24). They pointed out that increased hydrostatic pressure is responsible for pulmonary edema caused by most agents (25). Regarding the edema of oxygen toxicity there is less certainty although several possibilities have been mentioned (21). In acute experiments oxygen has been found to cause a lowering of pulmonary arterial pressure (26) and a pulmonary vasoconstriction (27). Aside from this difference in results, the significance of these acute experiments to long-term breathing of oxygen remains to be demonstrated. However, in postulating an initial event in the development of toxicity, one or the other of these could be important. For example, it is possible that transudation be initiated by a direct increase in pulmonary arterial pressure, or a change in capillary permeability that could produce congestion from the formation of interstitial fluid could lead to an increased pulmonary arterial pressure. In this connection, Kistler, et al. have recently reported evidence from rats exposed to one atmosphere of oxygen. They found that the thickening of the air-blood barrier was due to the formation of interstitial fluid representing a change in capillary permeability (16).

Regarding pulmonary edema in the present experiments at P_{O_2} of 2/3 atmosphere, the evidence is not as clear as that seen at a P_{O_2} of one atmosphere. For such a demonstration it would be necessary to follow an exposure with an examination for increased transudation short of edema. This has not been demonstrated, however, if the presence of a small hydrothorax can be accepted as evidence of increased fluid, then the rats under conditions of the present experiments would be undergoing some increased transudation in their lungs.

The results of Table II indicate that an additional effect of the 30-day oxygen exposure is a systemic hypotension. From a hydrodynamic standpoint this could occur as a result of decreased peripheral resistance or decreased cardiac output or both. In acute experiments it has been shown that oxygen breathing does cause an increase in peripheral resistance (28) and Table II shows that this response has evidently survived the exposure.

The exposed rats did exhibit an increased arterial pressure in response to oxygen breathing. It is felt therefore that the implied increase in pulmonary vascular resistance indicated by the pulmonary hypertension might have given rise to a decreased output of the right heart and that the systemic hypotension is a reflection of this condition.

The results of Table III are of interest because of the contribution they make to our knowledge of mechanisms of increased intratracheal or intrapulmonic pressure on circulatory hemodynamics. It will be observed that increasing the intratracheal pressure caused a lowering of mean aortic pressure—in this case 7.0 and 9.4 mm Hg intratracheal pressure produced a lowering of 15.0 and 11.2 mm Hg in aortic pressure respectively for non-exposed and exposed rats. This kind of response is well documented in the literature (29). On the other hand, mean pressure in the pulmonary artery is hardly affected at all. Since pressure is maintained in the right ventricle and the pulmonary artery, it follows that right ventricular volume tends to remain near normal. This suggests therefore that ventricular volume (and systolic pressure) is maintained at the expense of the flow through the lungs. Right cardiac output falls as pressure is maintained and pulmonary vascular resistance increases as a result of the increased intratracheal pressure. This situation would be described by West's zone 2 when pulmonary arterial pressure > alveolar pressure > pulmonary venous pressure (30).

Therefore, this fall in systemic pressure during increased intrapulmonary pressure is not due wholly to decreased venous return; it would appear to be due to increased vascular resistance and decreased flow in the lungs caused by the increased intrapulmonary pressure. This would be confirmed by all experiments on increased intrapulmonary pressure in which venous pressure is measured, for in these, venous pressure rises along with the intrapulmonic pressure making the return to the right atrium adequate if not improved.

In the experiments reported here as well as in similar experiments made on animals exposed to oxygen, the measurements were made not in oxygen but in air. It was necessary to remove the animals from the environmental system and the oxygen to the laboratory. Therefore, we were unable to assess the effect of this change on the present results.

In summary, exposure of rats to 2/3 atmosphere P_{O_2} for 30 days leads to the development of a pulmonary hypertension and a systemic hypotension. The pulmonary effects are apparently caused by structural alterations in the pulmonary vasculature brought on by the oxygen, the resulting increased resistance reduces blood flow through the lungs giving rise to the systemic hypotension.

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13 ABSTRACT

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14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
1. 100% Oxygen Breathing 2. Prolonged Oxygen Breathing 3. High Oxygen Pressure 4. Animal Studies 5. Pulmonary Arterial Pressure Measurements 6. Pulmonary Hypertension 7. Systemic Hypotension						

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