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The Cerebral Circulation And Metabolism In Chronic Pulmonary Emphysema With Observations On The Effect Of Inhalation Of Oxygen

Emory University School of Medicine
and
U. S. Naval School of Aviation Medicine

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THE CEREBRAL CIRCULATION AND METABOLISM IN CHRONIC PULMONARY EMPHYSEMA WITH OBSERVATIONS ON THE EFFECTS OF INHALATION OF OXYGEN

Report by

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Reduction in arterial oxygen tension or elevation of carbon dioxide tension, produced by altering the composition of the inspired air, have been shown to exert dilator effects upon the cerebral blood vessels in man and to cause an increase in cerebral blood flow (1). Similar changes in blood gas tensions commonly develop in chronic pulmonary emphysema as the disease process advances (2). Efforts to overcome the anoxemia in these patients by the administration of oxygen have been reported to result in untoward reactions (3,4,5) in approximately 10 per cent of cases (6). These reactions have included convulsive seizures, drowsiness, stupor, coma, and in rare instances, death.

There would appear, therefore, to be sound reasons for anticipating abnormalities in the cerebral circulation in patients with chronic pulmonary emphysema. This report presents our findings in nine such patients and in eight control subjects, in whom the cerebral circulation and metabolism were studied both before and during administration of 85-100 per cent oxygen. Observations on the changes in spinal fluid pressure and pulmonary ventilation with oxygen inhalation are also presented.

PATIENT MATERIAL AND METHODS

The nine patients in this study had a mean age of fifty years. They all gave a history of previous respiratory infections, chronic cough and exertional dyspnea of varying severity. Four of them had asthma of many years duration. On physical examination the patients showed kyphosis, an increase in anterio-posterior diameter of the thoracic cage, and a limited range of respiratory excursions. Two of them had clubbing of the fingers and six showed cyanosis of the nail beds, ears or mucosal surfaces. Roentgenograms of the chest showed signs of pulmonary emphysema with decreased density of lung fields, wide intercostal spaces and flattened diaphragms. Moderate or extensive degrees of pulmonary fibrosis were noted in four individuals. Seven patients had evidence of cor pulmonale with cardiac enlargement and dilatation of pulmonary arteries on X-ray examination. Five of these seven patients had evidence of congestive failure and the majority showed electrocardiographic evidence of right ventricular enlargement. In two individuals (C.G. and C.M.), the pulmonary arterial pressure, determined by cardiac catheterization, within a few days of the cerebral studies, were 13 and 60 mm. Hg, respectively. Although the pulmonary arterial pressure in C.G. was normal, his pulmonary arterial-pulmonary capillary pressure gradient was 16 mm. Hg, as compared with the normal mean in this laboratory of 6.7 mm. Hg. The cardiac indices (T-1824 dye) in C.G. and C.M. were 2.6 and 3.3 liters/min., respectively.

Eight patients, convalescing from such operations as herniorrhaphy and from various illnesses such as gonorrheal arthritis, dermatitis, and peptic ulcer, were used as control subjects. These patients had no evidence of intracranial or pulmonary complications. The mean values in these control subjects for cerebral blood flow, oxygen consumption and vascular resistance when they were breathing room air agreed very closely with those of a larger group of fourteen control subjects, who were not studied during oxygen administration.

The cerebral blood flow (CBF) was measured by the nitrous oxide technique of Kety and Schmidt (7), with the minor modifications previously described (8). The cerebral oxygen consumption ($CMRO_2$) was calculated from the CBF and the cerebral arteriovenous oxygen difference. The cerebral vascular resistance (CVR) was calculated from the CBF and the mean arterial pressure, measured directly from the femoral artery with a damped mercury manometer. Control observations of the cerebral circulation were performed with the patient breathing 21% oxygen, 15% nitrous oxide, and 64% nitrogen. Ten minutes later the subject was given 100% oxygen by face mask, for a period of 20 minutes. At the end of this time the gas was changed to 85% O_2, 15% N_2O and a second blood flow determination carried out.

Arterial and venous blood samples were drawn just before and at the end of each blood flow procedure. These samples were pooled and their oxygen and carbon dioxide content was measured by the combined procedure for these gases described by Peters and Van Slyke (9), with modifications required by the presence of nitrous oxide, as suggested by Kety and Schmidt. The nitrous oxide content of blood samples was determined by the manometric method of Orcutt and Waters (10), as modified by Kety and Schmidt. Oxygen capacity of blood was obtained by equilibrating the sample with air in a small flask, analyzing for oxygen manometrically, and making the usual correction for dissolved oxygen. Hemoglobin concentration was calculated from the oxygen capacity. Arterial pH was measured with the glass electrode of a Cambridge Model R.pH meter, with corrections for room temperature and instrument error. Arterial pCO_2 was calculated from the pH, CO_2 content and hematocrit, by means of the nomogram of Singer and Hastings (11). Arterial pO_2 was calculated from the pH and the per cent oxyhemoglobin saturation, using the dissociation curves of Dill (12).

The pulmonary ventilation was measured during inhalation of both 100% O_2 and 21% O_2, 79% N_2 by means of a demand regulator and Tissot spirometer, and corrected to BTPS, (body temperature, ambient pressure saturated with water vapor). Spinal fluid pressures were measured by means of a water manometer with the patient in the right lateral decubitus position. The pressures were followed with the patient breathing room air through a mask, and during inhalation of 100% oxygen.

RESULTS

There was an evident tendency for the cerebral blood flow to be higher in the patients with emphysema than in the control subjects (Table I and Fig. 1). The mean CBF value was 68 cc. in the emphysematous patients (.02 p .01) compared with 50 cc./100 Gm. brain/min. in the control subjects. Only two of the patients with emphysema had CBF values below the normal mean (Fig. 1). Since the mean arterial pressure in the patients with emphysema was normal, the mean cerebral vascular resistance was somewhat below that of the control subjects, though not significantly so (.6 p .5).

During the inhalation of 85-100% oxygen, the mean cerebral blood flow in the patients with emphysema rose from 68 to 79 cc./100 Gm./min. (.4 p .3). In contrast, the control subjects showed a decrease in CBF from a mean value of 50 cc. to 44 cc./100 Gm./min. A reduction in CBF during oxygen inhalation occurred in only two patients with emphysema, both of whom had initially low CBF values. The mean value for CBF in the emphysematous patients during inhalation of oxygen was significantly (p .01) different from that found in the control subjects during the same period.

The arterial pressure in both groups of patients was altered very little by oxygen. In general, the CVR in the patients with emphysema was reduced slightly by oxygen administration.

The mean cerebral oxygen consumption in the patients with emphysema was slightly less than the control average. Oxygen inhalation did not produce a change in the mean $CMRO_2$ in either the patients with emphysema or in the control subjects. Mental changes developed in only one patient (C.M.) during the oxygen period. This individual was moderately confused while breathing air, and became irrational and combative while breathing oxygen. Three hours later he became rational but had an amnesia for the events of the earlier period. The $CMRO_2$ in this patient, while he was breathing oxygen, was considerably higher than the baseline value.

Changes in the blood gases in the patients with chronic pulmonary emphysema were similar to those which have been reported by others (2). The mean arterial oxyhemoglobin saturation was 68 per cent, the mean pO_2, 39 mm. Hg, and the mean pCO_2, 58 mm. Hg, and the arterial pH, 7.36. Inhalation of oxygen raised the arterial oxygen saturation into the range 94-100 per cent in all patients except one (E.D.) and produced an increase in the mean pCO_2 to 70 mm. Hg and a reduction in arterial pH to a mean of 7.24. The acidosis and the increase in CO_2 tension and content observed in the emphysematous patients given oxygen are probably related to the depressive effect of oxygen on the pulmonary ventilation (Fig. 2). The average ventilations measured in four patients while breathing air for six minutes and oxygen for twelve minutes were 8.8 L./min., respectively.

The cerebral blood flow in the patients with emphysema, while they were breathing room air, could be correlated to some extent with the arterial tensions of oxygen and carbon dioxide. The two patients with the lowest CBF determinations had the highest pO_2 and lowest pCO_2 values, while the highest CBF values were found in patients with the lowest pO_2 and the highest pCO_2 levels (Fig. 3). The same type of multiple correlation cannot be attempted for the data of the oxygen period, since the arterial oxygen saturation was too high to permit accurate pO_2 readings from the dissociation curves. Six of the eight patients on whom arterial pCO_2 and pH data are available, showed a rise in CBF during oxygen administration. In each of these six patients there was an increase in pCO_2 and a decrease in pH, but the magnitude of the changes did not correlate well with the amount of increase in the cerebral blood flow. However, the patient (R.A) who had the greatest increase in CBF with oxygen also manifested the largest increase in pCO_2 and decrease in pH. The patient (J.B.) in whom the CBF fell slightly with oxygen had pCO_2 and pH changes similar to those found in the six patients in whom the CBF increased. The one patient (I.H.) who had an appreciable fall in blood flow had almost no change in either pCO_2 or pH.

Cerebrospinal fluid pressure in six patients with emphysema was slightly or moderately increased by oxygen inhalation (Fig. 4). The mean pressure with the patients breathing room air was 198 mm. C.S.F. During approximately ten minutes of oxygen inhalation, the pressure rose to an average peak value of 279 mm., with an extreme value of 470 mm. C.S.F. In five control subjects with asymptomatic neurosyphilis, the cerebrospinal fluid pressure either remained the same or fell slightly during oxygen breathing.

DISCUSSION

The elevation of the mean cerebral blood flow in the patients with emphysema when they were breathing air is entirely compatible with the known effects of alteration of the arterial tensions of oxygen and of carbon dioxide. The figures for mean arterial pO_2 and pCO_2 in these patients are seen to be decidedly abnormal, when compared with the values of 97.1 mm. Hg and 41.6 mm. Hg respectively in healthy young adults (13). A synergistic effect would be expected from reduction with pO_2 and elevation of the pCO_2. The observed reduction in CVR and increase in CBF were actually considerably smaller than would be predicted on the basis of the effects produced by rapid alterations in the arterial gas tensions (1). It is possible that the very gradual development of the abnormal tensions in emphysema allowed adaptive changes to take place in the cerebral vessels. A contributory factor may have been the maintenance of a relatively normal arterial pH in these patients through a compensatory increase in plasma bicarbonate. Reduction in arterial pH appears to favor an increase in cerebral blood flow (1,14).

Apart from changes in the arterial blood, the state of the heart itself might have been a factor influencing the cerebral blood flow. The importance of this factor is admittedly difficult to evaluate. It is of interest, however, that there was no tendency for the CBF to be lower in the patients with congestive failure. In other types of heart disease, congestive failure tends to be associated with a reduced cerebral blood flow (15).

The changes in arterial gas tensions and pH with the administration of oxygen evidently are relatively rapid. For some time, at least, the pulmonary ventilation is reduced, with a consequent rise in arterial CO_2 tension. The conventional explanation for the depression of respiration is the withdrawal of the hypoxic stimulus to chemoreceptor mechanisms. The associated fall in pH is most likely due to the combined effects of carbon dioxide retention and the increase in the amount of oxyhemoglobin in the arterial blood. The cerebral blood vessels under these circumstances are subjected to stimuli in competition: the dilator stimulus of an increase in pCO_2 and a decrease in pH, and the constrictor stimulus of a rise in O_2 tension. Despite the fact that the rise in pO_2 must have been several times as great as the increase in pCO_2, the resultant effect was dilator in most of the patients. Excluding the two patients (J.B. and I.H.) in whom the CVR rose with oxygen, the mean CVR values with air and oxygen breathing were 1.2 and 0.9 mm. Hg/cc./100 Gm./min. respectively.

Although the $CMRO_2$ during air breathing was below the control mean in seven of the nine patients, definite conclusions based on the small difference between the means are probably not warranted. Some reduction in $CMRO_2$ would not be surprising in chronically ill patients with long-standing abnormalities in the blood gas tensions. There was no evidence that overall cerebral metabolism, as indicated by the $CMRO_2$, was adversely affected by the relatively brief (30 min.) period of oxygen inhalation. It is of interest that, in the one patient (C.M.) whose mental status became worse with oxygen, there was an associated rise in cerebral oxygen consumption.

The increases in cerebrospinal fluid pressure with change in the inspired gas from air to oxygen also favor the conclusion that cerebral vasodilator effects were dominant during the period of oxygen breathing. The pressure changes, however, were in general moderate and in no case were extreme levels reached, such as have been reported by other workers (3).

SUMMARY

1. The cerebral blood flow (CBF), oxygen consumption ($CMRO_2$) and vascular resistance (CVR) were determined by the nitrous oxide technique before and during the administration of 85-100% oxygen in nine patients with chronic pulmonary emphysema and in eight control subjects.

2. In the patients with emphysema the mean CBF was significantly elevated, while the mean $CMRO_2$ was slightly below control values. There was a tendency for the emphysematous patients with the lowest arterial pO_2 and the highest pCO_2 values to show the highest blood flow values. The converse was also true.

3. Inhalation of 85-100% oxygen was generally followed by an increase in CBF in the patients with emphysema in contrast to the control patients in whom the CBF decreased. Two emphysematous patients who had the lowest CBF values while breathing air showed a decrease in CBF during inhalation of oxygen.

4. The mean $CMRO_2$ did not change in either group of patients with oxygen administration. One patient with emphysema exhibited mental aberrations which may have been aggravated by oxygen therapy. Oxygen caused an increase in spinal fluid pressures in the patients with emphysema and either no change or a fall in spinal fluid pressures in the control subjects.

5. Oxygen inhalation caused a depression of pulmonary ventilation in the patients with emphysema and resulted in a rise in arterial pCO_2 and a fall in pH. The moderate increase in pCO_2 and decrease in pH apparently more than offset the large increase in pO_2 and thus brought about a rise in cerebral blood flow.

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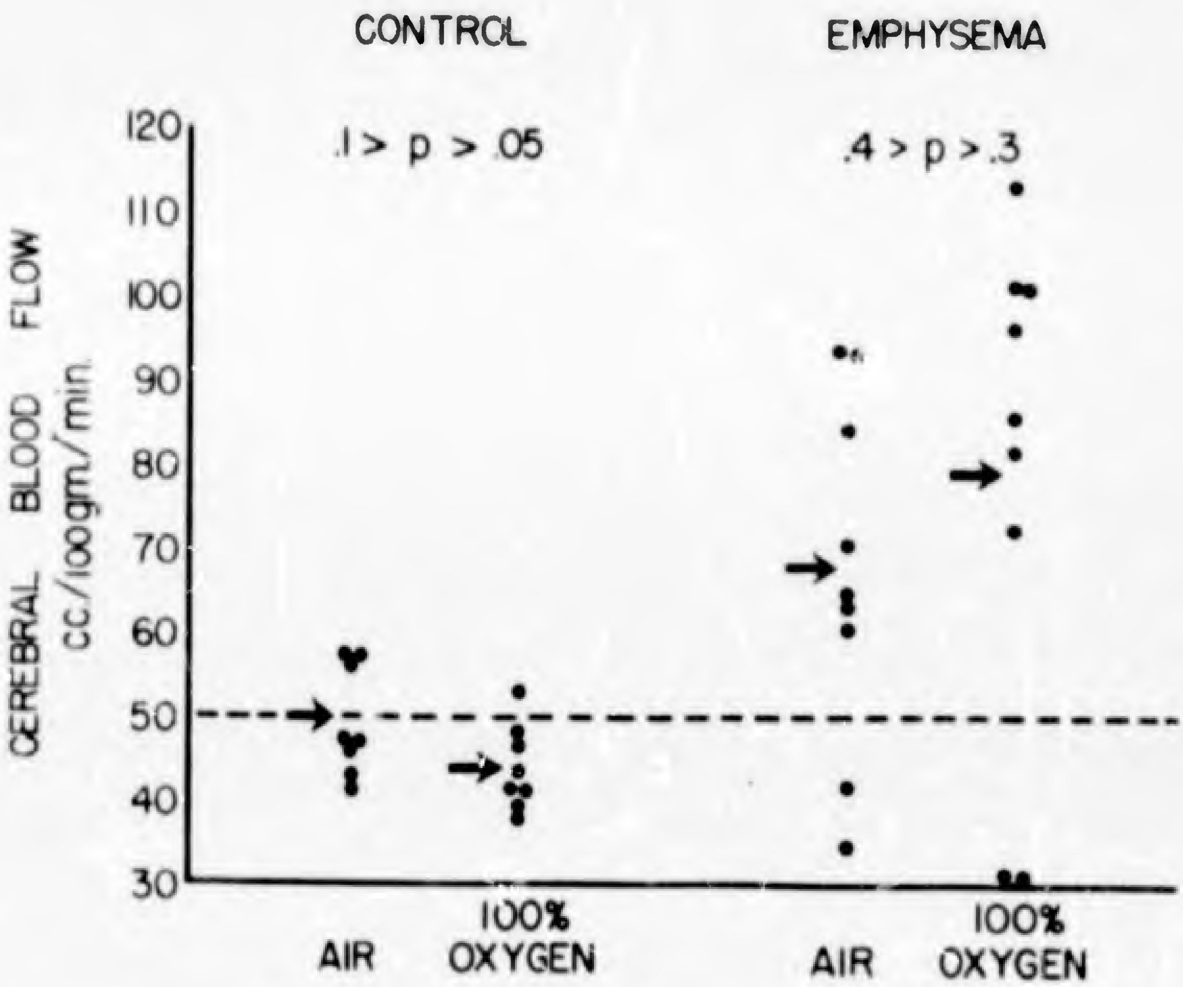

Figure 1 - Distribution of cerebral blood flow values in control subjects and in patients with emphysema during inhalation of air and of oxygen.

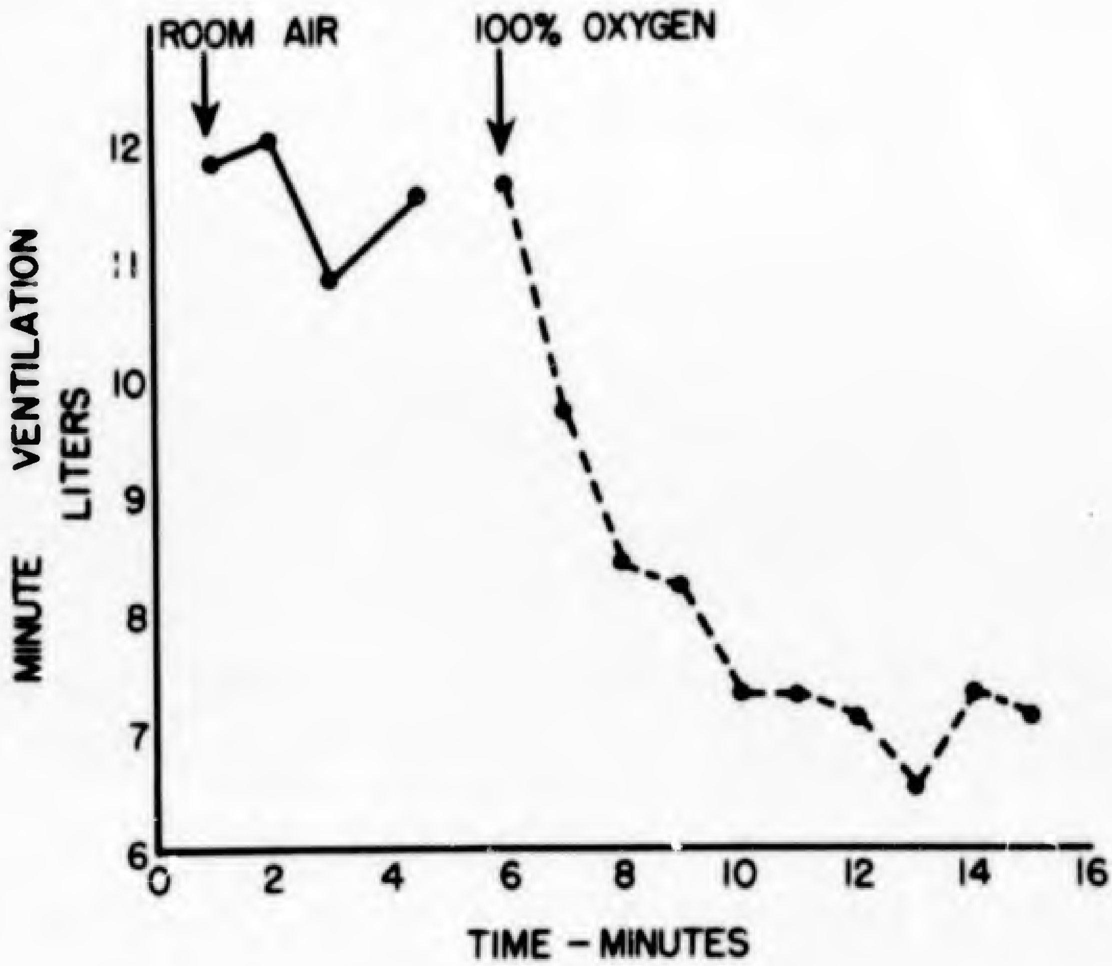

Figure 2 - Response of the pulmonary ventilation to oxygen administration in an elderly patient with severe chronic emphysema. Data on this patient's CBF are not included in this report.

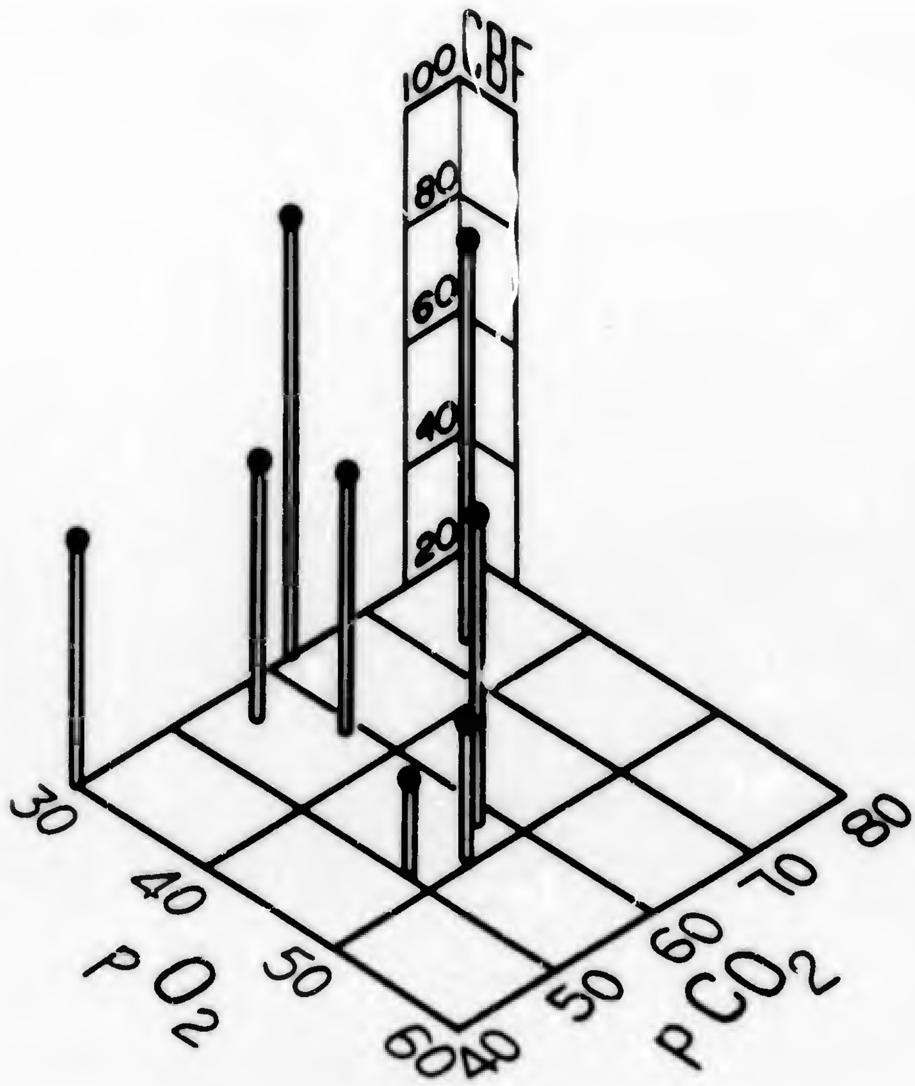

Figure 3 - Three-dimensional chart showing interrelationships between CBF (cc./100 Gm./min.), arterial pO_2 (mm. Hg) and arterial pCO_2 (mm. Hg) in eight patients with emphysema breathing air.

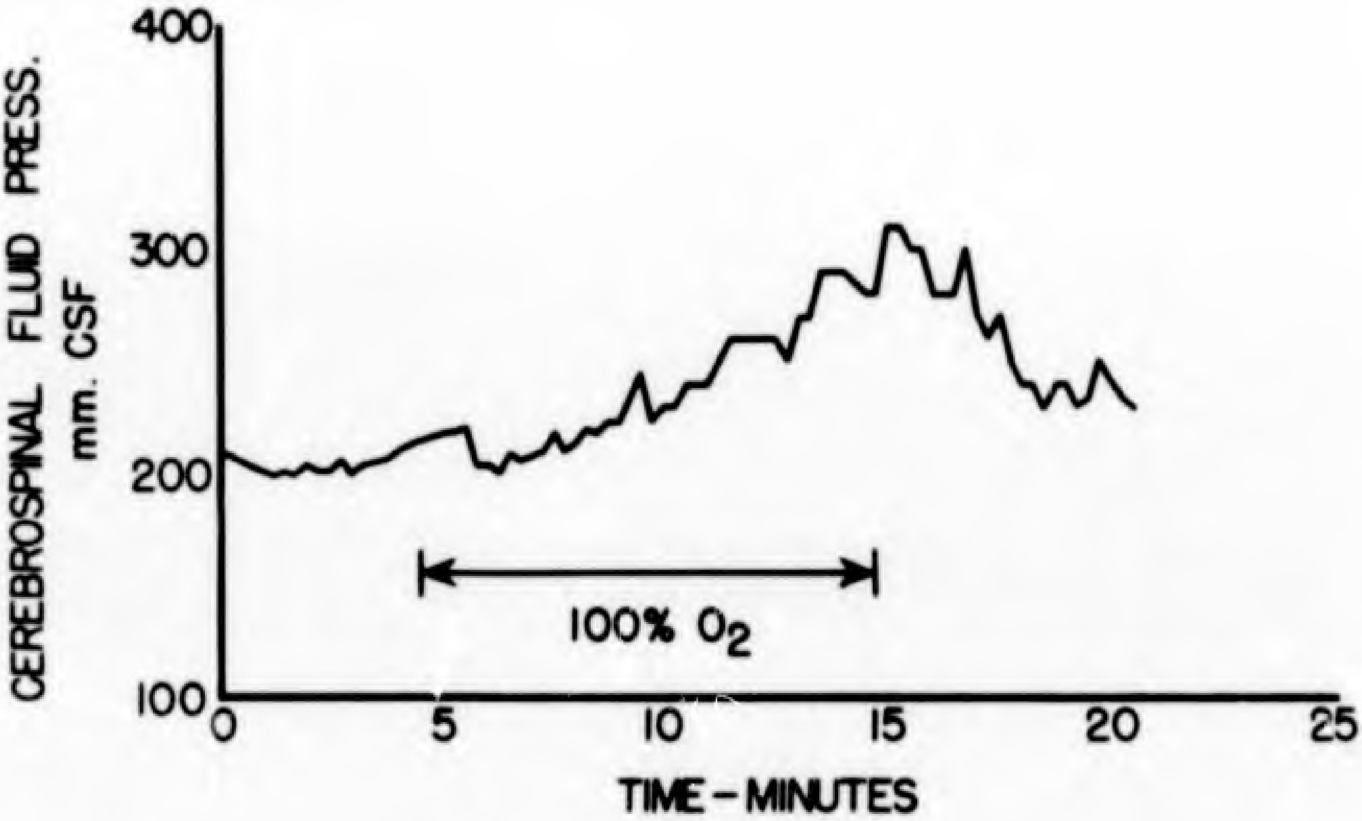

Figure 4 - Cerebrospinal fluid pressure before, during, and after administration of oxygen in patient (R.A.) with emphysema.

Pt.	Age	CBF cc./100 Gm./min. Air	CBF cc./100 Gm./min. O_2	CMRO2 cc./100 Gm./min. Air	CMRO2 cc./100 Gm./min. O_2	CVR mm.Hg/cc./100 Gm./min. Air	CVR mm.Hg/cc./100 Gm./min. O_2	Mean Art. Pressure mm.Hg. Air	Mean Art. Pressure mm.Hg. O_2	A-V Oxygen Vol.% Air	A-V Oxygen Vol.% O_2	Hemoglobin Gm./100 cc.	Art. HbO_2 Saturation % Air	Art. HbO_2 Saturation % O_2	Art. O_2 Cont. Vol.% Air	Art. O_2 Cont. Vol.% O_2
J.B.	54	35	30	2.8	2.8	3.0	3.5	103	106	8.0	9.2	16.7	81	95	18.4	21.5
I.H.	28	42	30	4.1	3.0	2.3	3.0	95	90	9.8	9.9	17.4	82	100	19.3	23.4
E.D.	53	61	73	2.1	2.8	1.8	1.4	108	103	3.4	3.9	11.3	60	75	9.3	11.5
M.K.	48	64	82	2.7	2.9	1.3	1.1	85	88	4.1	3.5	14.7	66	98	13.2	19.6
R.A.	59	64	97	3.3	2.9	1.3	0.8	84	80	5.1	3.0	16.0	73	98	15.7	21.0
C.C.	59	71	86	2.8	2.8	1.0	0.8	73	72	4.0	3.2	14.1	78	95	14.9	18.0
T.M.	32	85	102	2.4	1.4	1.2	1.0	104	98	2.9	1.4	13.9	60	94	11.3	17.7
J.J.	59	94	101	2.0	1.9	0.9	0.8	87	82	2.2	1.9	13.2	51	96	9.2	17.1
C.M.	56	94	113	2.2	3.7	0.8	0.7	79	84	2.3	3.3	13.1	60	99	10.8	17.6
Mean Values	50	68*	79*	2.7	2.7	1.52	1.46	91	89	4.6	4.4	14.6	68	93	13.6	18.6
Mean 8 control pts.	32	50	44	3.0	3.2	1.9	2.1	93	91	6.0	7.2	13.4			16.1	17.8

All mean values have been calculated from the data on individual patients.
*Denotes statistically significant difference from mean values obtained in control subjects breathing similar compositions of inspired gas.
‡The arterial pO_2 during inhalation of oxygen in patient E.D. was 43mm. Hg. The values in the other patients were too high to be read accurately from dissociation curves.

A

[illegible]globin [illegible]	Art. HbO2 saturation %		Art. O2 [illegible] Vol.%		Art. [illegible] Vol.%		Art. pH		Art. [illegible] mm.Hg		Art. [illegible] mm.Hg	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	
6.7	81	95	18.4	21.5	53.4	56.0	7.38	7.24	50	70	48	Asthma 46 years; chest markedly emphysematous; cor pulmonale.
7.4	82	100	19.3	23.4	53.9	53.5	7.34	7.32	54	56	50	Asthma 17 years; cor pulmonale; cyanosis and clubbing of fingers; moderate fibrosis of lungs.
1.3	60	75	9.3	11.5	49.2	50.3	7.42	7.34	39	47	30	Resolving pneumonitis; chronic pulmonary infection and fibrosis; cor pulmonale; ? early failure.
4.7	66	98	13.2	19.6	63.1	65.8	7.41	7.36	56	62	34	Respiratory disease since childhood; extensive fibrosis; cyanosis; cor pulmonale; congestive failure.
6.0	73	98	15.7	21.0	62.6	67.7	7.41	7.16	57	86	37	Asthma 8 years; cor pulmonale; died 2 weeks later with congestive failure.
.1	78	95	14.9	18.0	54.5	55.4	7.30	7.16	57	77	47	Bronchiectasis; pulmonary fibrosis; cyanosis; marked progressive cough 10 years duration.
1.9	60	94	11.3	17.7	61.2	66.4	7.25	7.15	73	96	35	Cor pulmonale; congestive failure 2 years; clubbed fingers; cyanosis.
3.2	51	96	9.2	17.1	63.8	65.5	7.34	7.20	62	84	29	Progressive exertional dyspnea 3 years; chest markedly emphysematous.
3.1	60	99	10.8	17.6	75.1	76.4	—	—	—	—	—	Asthma 19 years; cor pulmonale; cyanosis; congestive failure.
4.6	68	93	13.6	18.6	59.6	63.0	7.36	7.24	58	70	39	
3.4			16.1	17.8	47.6	47.3						

B