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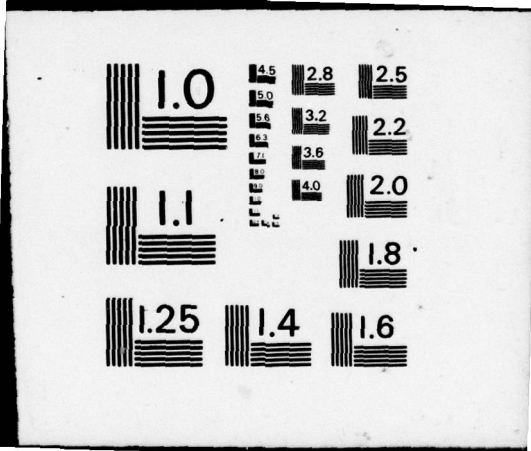
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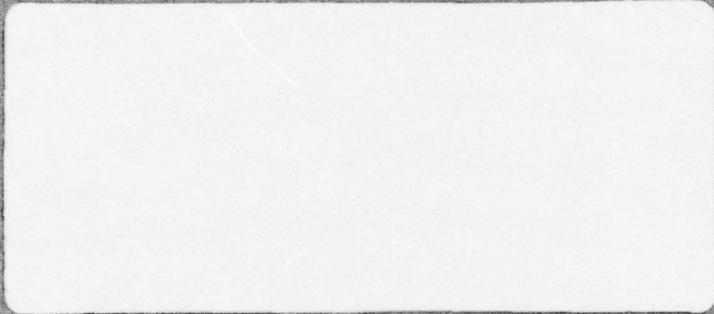


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ANNUAL REPORT

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February 8, 1977

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In pursuit of the primary objective of improving understanding and treatment of cardiopulmonary deterioration in shock, the emphasis for the calendar year 1976 was on the associated pulmonary dysfunction which is a frequent determinant of survival and the role of oxygen toxicity. As indicated in the six month report the isolated isogravimetric perfused canine lung showed susceptibility to ventilation with 100 percent oxygen manifested by evidence of early interstitial pulmonary edema. These studies were intended to investigate the possible protective role of transient anoxia utilizing the same preparation ventilated with 100 percent nitrogen for a period of one hour prior to exposure to 100 percent oxygen. The results of these studies were presented to the American Physiological Society Federation Meetings in Philadelphia, August, 1976.

Materials and Methods

Adult mongrel dogs were used ranging in weight from 18 - 24 kilograms anesthetized with pentobarbital (3 mg/kgm). The animals were screened for dirofilaria and any animals showing heart worms at the time of thoracotomy were excluded from study. Ventilation by endotracheal tube using a positive pressure respirator allowed a left lateral thoracotomy and isolation of the left lower lobar vessels and bronchus. The animal was heparinized and exsanguinated to prime the perfusion circuit. The left lower lobe was excised and appropriate connections made for perfusion with a relatively atraumatic compression pump at physiologic pressures and utilizing a disc deoxygenator exposed to 95 percent nitrogen and five percent CO₂. The lung was ventilated with a constant volume respirator at a rate of 12 cycles per minute and a volume of 3 cc. per gram lobe per cycle. Pulmonary artery and pulmonary vein were cannulated for pressure measurements on an oscillographic recorder. The preparation was placed on a plastic balance tray attached to a strain gauge device for continuous weight measurement. Pressures were adjusted to an acceptable physiologic range and the flow increased to the maximal level which could be tolerated without producing

a continuous weight gain. Ventilatory adjustments were made based on pulmonary venous blood gas determinations. Isogravimetric pulmonary capillary pressures were measured by the stop flow technique assuming that the equilibration point reflected effective hydrostatic pulmonary capillary pressure. Alveolar-arterial oxygen gradients, pulmonary vascular resistance, and pulmonary compliance were calculated from direct observations. In addition to direct measurements of weight gain, the wet to dry weight ratio was obtained at the conclusion of the study by oven drying.

Results

Control observations were made in a group of nine lungs ventilated with ambient air for a minimum of four hours. In these lungs there was no significant measured weight gain at the end of four hours although there was a slight decrease in pulmonary compliance. There were no statistically significant changes in any of the other measured or calculated variables. The group of 13 lungs was ventilated with an FI_{O_2} of one for four hours and compared with a group of four lungs ventilated with 100 percent nitrogen for one hour prior to four hours of ventilation with FI_{O_2} 1.0. All experimental lungs were perfused for a period of 30 minutes to insure stable physiological performance prior to the interventions. The oxygen ventilated lungs showed a significant increase in weight gain as shown in Figure 1 and the weight gain to dry weight ratio was significantly increased after four hours ($P < .025$). The nitrogen ventilated lungs also showed a significant increase in the weight gain to dry weight ratio at four hours ($P < .025$) and at five hours ($P < .001$) compared to controls. When the N_2 group was compared to the O_2 group after equal periods of ventilation with FI_{O_2} 1.0 the results showed a comparable increase in the weight gain/dry weight ratio at one hour ($P < .5$) but a significantly greater increase after four hours ($P < .005$, Figure 2). Absolute wet/dry weight ratios were calculated at the termination of each experiment and increased from controls of 3.7 to 5.03 in the O_2 groups ($P < .001$) and 5.5 in the N_2 group ($P < .001$). The O_2 and N_2 groups did not differ

significantly from each other ($P < .5$, Table 1) in terms of final wet/dry ratios.

The PCI of control lungs did not show a significant increase after four hours (7.89 vs. 8.57, $p < .5$) nor did the O_2 ventilated group increase significantly (7.89 vs. 9.21, $p < .5$, Figure 3). The N_2 ventilated group, however, showed a significant increase from 7.89 to 14.06 at four hours ($p < .01$, Fig. 3). When the N_2 ventilated group was compared to the O_2 ventilated group at equal periods of FI_{O_2} of 1.0 the differences at one hour (10.53 vs. 7.66) and at four hours (14.43 vs. 9.21) were significant ($p < .05$, Fig. 4).

A-a gradients were calculated only for the O_2 and N_2 ventilated lungs. The value of 256 mmHg after four hours of O_2 was not significantly different from the value of 234 mmHg seen after one hour of O_2 in the O_2 ventilated group. Similarly comparable values of 177 mmHg after four hours of O_2 and 160 mmHg after one hour of O_2 in the N_2 ventilated group were not significantly different. The change in A-a gradient therefore was essentially the same for both groups (9.5% vs. 10.5%).

Blood gas determinations showed no significant difference between the PVO_2 in the control lungs at time 0 and after four hours ($p < .5$). Similarly there were no significant differences between the O_2 lungs at one hour and four hours ($p < .5$) and the N_2 lungs at one hour and four hours ($p < .4$, Table 2). No statistical differences were noted between the O_2 and N_2 groups after equal periods of time on 100 percent O_2 ($p < .2$, Table 2). As an index of the severity of the anoxic ventilation, the mean PVO_2 after one hour of N_2 ventilation was 17.8 mmHg.

None of the three groups showed a significant change in pulmonary vascular resistance (PVR) or compliance (Fig. 6) after four hours, nor was there a significant difference between the O_2 and N_2 groups at equal periods of exposure to FI_{O_2} 1.0 in regard to these measurements.

Discussion

These studies are not strictly comparable to the clinical situation where the problem is not anoxic ventilation but instead hypoxemia perfusion. Therefore, further studies were undertaken utilizing the same preparation in order to assess the

role of profound hypoxemia in modified vulnerability to oxygen toxicity. Two groups of animals were studied, Group I having a perfusion PO_2 of 19-29 mmHg and Group II having a perfusion PO_2 of 11-15 mmHg, the distinction between the two based on previous observations suggesting that moderate hypoxemia as utilized in Group I provided relatively more protection and more profound hypoxemia as utilized in Group II. There was little difference between the groups on preliminary comparison but when one hour of nitrogen ventilation was added to the protocol prior to the ventilation with FI_{O_2} 1.0 several differences were noted. In nine animals studies in Group I with nitrogen ventilation, an increase of an average of 10 gms weight occurred after anoxia followed by total weight gain of 43 gms average after three hours of FI_{O_2} 1.0 ventilation. In contrast six lungs in Group II following anoxic ventilation showed a smaller weight gain with a total of 27 gm weight gain following three hours of FI_{O_2} 1.0 ventilation. There were comparable increases in PCI from control of 11 in both groups to 15.7 mmHg in Group I at the end of the study period and 15.6 mmHg in Group II. Similarly comparable increases in peak inflation pressure of the lobes reflected an equivalent decrease in pulmonary compliance. Pulmonary venous gases and A-a gradients were similar in both groups. Pulmonary vascular resistance, however, appeared to be somewhat less in Group II since the pulmonary artery pressure increased from 18 to 22 mmHg mean in Group II while the increase in Group I was from 18 to 26 mmHg although the small number of observations did not permit statistical comparisons.

Conclusions

These studies suggest that previously held assumptions regarding protective effects of hypoxemia against oxygen toxicity are probably invalid. This is particularly true in the case of anoxic ventilation as indicated in the first set of studies which showed an increase in interstitial edema and exaggeration of changes in pulmonary capillary pressures as a consequence of relatively short periods of ventila-

tion with FI_{O_2} 1.0 oxygen. The consequences of more profound anoxic perfusion are less dramatic but appear again to offer no protection from the extravasation of fluid through pulmonary capillaries as a consequence of ventilation with FI_{O_2} oxygen. Slight differences were observed when the perfusion PaO_2 was lowered below 15 mmHg and combined with a period of anoxic ventilation. These lungs showed less edema formation than those perfused with a PaO_2 of 15 - 29 mmHg subjected to the same period of anoxic ventilation. It seems doubtful, however, that one could attribute any particularly protective role to these findings and the levels of PaO_2 utilized were far below those seen clinically. Consequently the potential additive effect of oxygen toxicity in the generation of the wet lung syndrome appears to be much earlier in onset than previously suspected, selective in its effects of pulmonary capillary permeability with less alteration in pulmonary mechanics and gas exchange, and not likely to be ameliorated by either hypoxemic ventilation or perfusion.

Part II

Clinical Studies

A. Vascular Surgery

The problem of septic shock has particular ramifications in the patient in whom a prosthetic graft has been inserted. Although this problem is fortunately uncommon there is no uniform agreement on the method of management of these patients and accordingly a review of the experience at the Medical College of Virginia was undertaken and compared with a collective review of all of the publications in English related to the problem. On the basis of this review and comparison of results, specific protocols for management were established depending on the area of graft insertion, and this information was provided as Technical Report I entitled "Vascular prosthetic infections: collected experience and results of treatment". This report pointed out the need for aggressive management of suspected graft infections above the inguinal ligament requiring early exploration and probable excision of the graft

if the diagnosis were confirmed followed by assessment of the lower extremities for viability and the need for revascularization. Extra-anatomical sites for revascularization were recommended such as axillo-femoral grafting when revascularization was proved to be essential. Below the inguinal ligament a more conservative approach was felt to be possible provided that flow was still present in the grafts. Under these circumstances local debridement and irrigation appeared to be effective in reducing mortality and morbidity rates. In the absence of flow, however, the morbidity rate was high secondary to distal amputations and consequently the recommendation was for early excision of the graft and consideration for extra-anatomical sites of distal bypass for revascularization where possible.

In further pursuit of difficult post-traumatic vascular management problems a similar review was undertaken of clinical experience at the Medical College of Virginia in the treatment of penetrating carotid artery injuries. These results were compared with the published experience in English and a similar protocol for management of penetrating carotid injury prepared and published as Technical Report II. The conclusions reached were that all patients who did not manifest a neurological deficit preoperatively should have restoration of vascular continuity following penetrating carotid artery injury. This approach was associated with uniformly good results, did not subject the patient to permanent interruption of flow and possible adverse sequelae, and did not place the patient at greater risk due to progression of atherosclerotic disease. Those patients manifesting a significant neurological deficit short of coma also appeared to benefit from primary vascular repair. This method of treatment was shown to be significantly superior to carotid artery ligation. In comatose patients repair or reconstitution of flow was warranted if prograde flow was present. Neither repair nor ligation appeared to change the basically poor prognosis in comatose patients. Based on this review ligation of the carotid artery was felt to be indicated only for the comatose patient with no prograde flow or for technical reasons when repair was impossible.

B. Clinical studies of respiratory distress syndrome in the head injured patients

As of December, 1976, a total of twelve patients fulfilled criteria for hemodynamic monitoring in accordance with the head injury protocol. All catheters were inserted within the first 24 hours of admissions. Delays in right heart catheterizations were secondary to repeated diagnostic and/or operative procedures. Catheters remained in place for a period of 48 to 72 hours for routine monitoring and longer as dictated by the patient's clinical course. Ten of the twelve patients developed no cardiopulmonary dysfunction as determined by physical examination, arterial blood gases, chest x-ray and hemodynamic evaluation. For this group of patients, the initial catheterization data was averaged. The average blood pressure was 142/79 mmHg with a range of 170/100 mmHg to 104/40 mmHg. Right atrial pressures averaged 4 mmHg with a range of 12 to 0 mmHg. Right ventricular pressures averaged 30/1 mmHg with a range of 50/4 mmHg to 22/1 mmHg. Main pulmonary artery pressures were 24/10 mmHg with a range of 42/14 mmHg to 15/1 mmHg. Mean main pulmonary artery pressures averaged 15 with a range of 26 mmHg to 6 mmHg. Pulmonary capillary wedge pressures averaged 7 mmHg with a range of 13 mmHg to 0 mmHg. Cardiac outputs averaged 7.65 liters with a range of 10 to 5.03 liters/minute. Though none of these patients developed the adult respiratory distress syndrome, the routine monitoring of a few of these patients did yield some interesting data. Three of the patients were given bolus mannitol for management of cerebral edema. Prior to the infusion of mannitol, the three cases had pulmonary capillary wedge pressures of 14 mmHg, 3 mmHg, and 2 mmHg with cardiac outputs respectively of 5.6 L/min., 6.4 L/min., and 3.88 L/min. Following the bolus infusion of mannitol pulmonary capillary wedge pressures were re-measured along with cardiac outputs. At the maximum, the pulmonary capillary wedge pressures reached 20 mmHg, 16 mmHg, and 20 mmHg. Outputs respectively increased to 8.76 L/min., 13.8 L/min., and 10.25 L/min. The average percent increase was 459 percent for the pulmonary capillary wedge pressure and 112 percent for the cardiac out-

put. All three of these patients were under the age of 30 and had no known cardiovascular disease. It would be conceivable that patients with cardiovascular disease and a flat Starling's curve could develop pulmonary edema from a cardiogenic basis if bolus mannitol infusion was given. In addition, mannitol has been well shown to increase cerebral blood flow and it would appear from this data that a significant proportion of this increase in cerebral blood flow must be attributed to a direct increase in cardiac output due to volume loading.

Two of the twelve patients developed fatal adult respiratory distress syndrome (ARDS). The first case developed ARDS 72 hours following admission. The white blood cell count and temperature were elevated. A septic focus was subsequently identified and appropriate antibiotics instituted. Initial catheterization data revealed a blood pressure of 110/60 mmHg, a right atrial pressure of 0 mmHg, a right ventricular pressure of 20/0 mmHg and main pulmonary artery pressure of 23/8 mmHg with a mean of 13 mmHg, and a pulmonary capillary wedge pressure of 7 mmHg. Cardiac output was 5.18 L/min. Continued hemodynamic monitoring did not demonstrate an increase in the pulmonary capillary wedge pressure. Pulmonary capillary wedge pressure fell to 3 mmHg with a concomitant increase in cardiac output to 8.35 L/min. with increasing sepsis. The patient was volume expanded with crystalloid and colloid. However, the wedge pressure failed to increase. Despite continued efforts to resuscitate the patient, oxygenation became more difficult and despite the addition of a FI_{O_2} of 1.0 and positive end expiratory pressure of 15 cm water pressure; the patient expired. In an analysis of 36 previous cases of the adult respiratory distress syndrome we found that 14 of these cases had septicemia and septic shock as the etiology of their ARDS. In addition, patients with ARDS and a systolic blood pressure of less than 100 mmHg had an overall mortality rate of 89 percent.

The second patient was transferred to the Medical College of Virginia with an acute subdural hematoma, numerous long bone fractures, and was in shock at the time of arrival for an unknown period of time. Craniotomy was performed for evacuation of subdural hematoma and an exploratory laparotomy was negative. Within 24 hours

the patient had a second episode of shock, and at this time FI_{O_2} requirements began to progressively increase. At the time of initial catheterization she had an arterial pressure of 160/90 mmHg, right atrial pressure of 8 mmHg, a right ventricular pressure of 42/1 mmHg, pulmonary artery pressure 42/14 mmHg with a mean of 28 mmHg. Pulmonary capillary wedge pressure was 10 mmHg. Cardiac output was 5.54 L/min. As the ARDS developed, there was no increase in her pulmonary capillary wedge pressure. Plasma colloid osmotic pressures were measured and were found to be 21 torr. Despite the use of 20 cm of positive end expiratory pressure and an FI_{O_2} of 1.0, the patient became more hypoxic and died a pulmonary death. Review of her clinical course suggest numerous possible etiologies such as shock lung, coagulation disorders consistent with disseminated intravascular coagulation or the fat emboli syndrome. Definitive laboratory studies were negative.

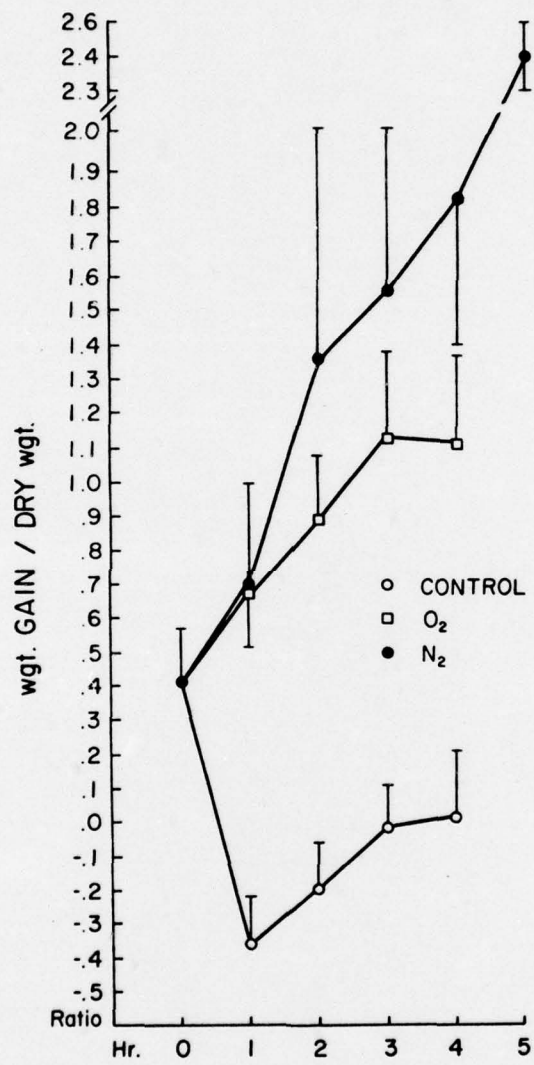


Fig. 1

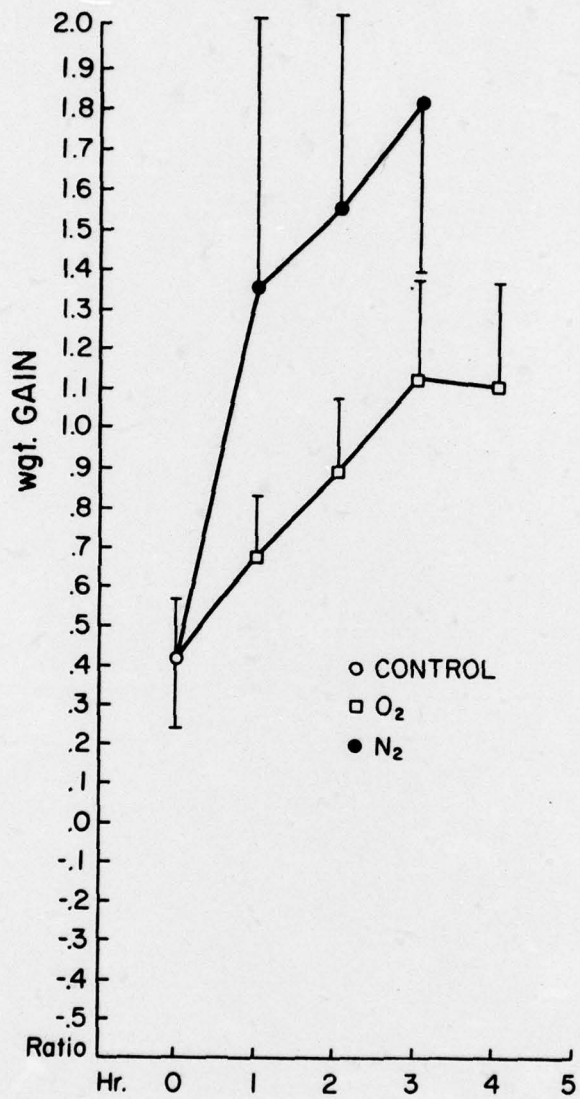


Fig 2

TABLE I - WET/DRY WEIGHT RATIO

CONTROLS - 3.7

CONTROL VS O₂ - p < .001

O₂ GROUP - 5.03

CONTROL VS N₂ - p < .001

N₂ GROUP - 5.5

N₂ VS O₂ - p < .5

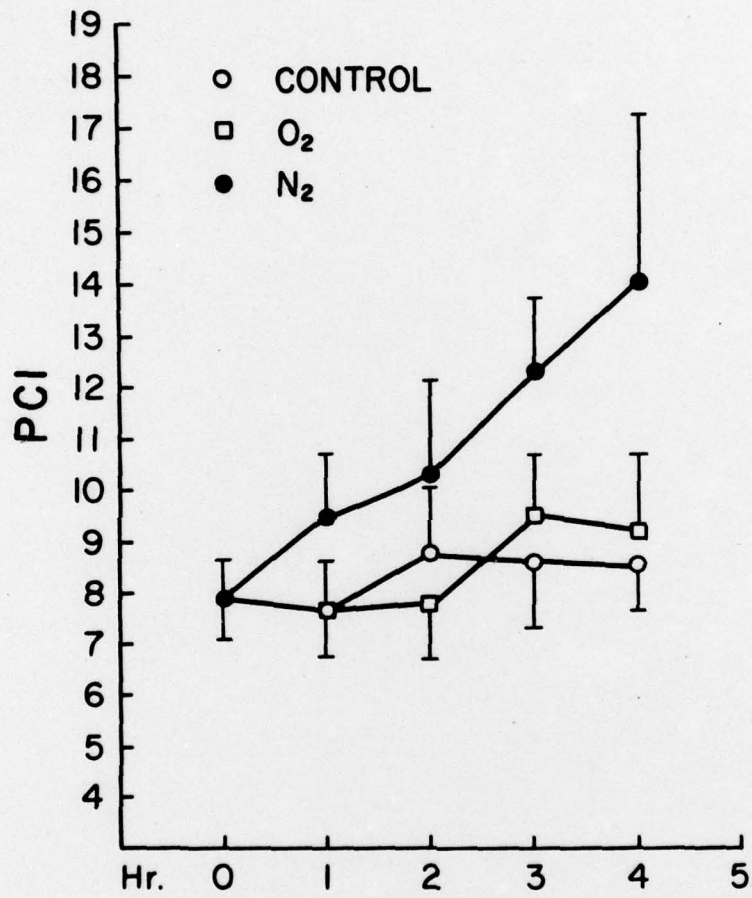


Fig. 3

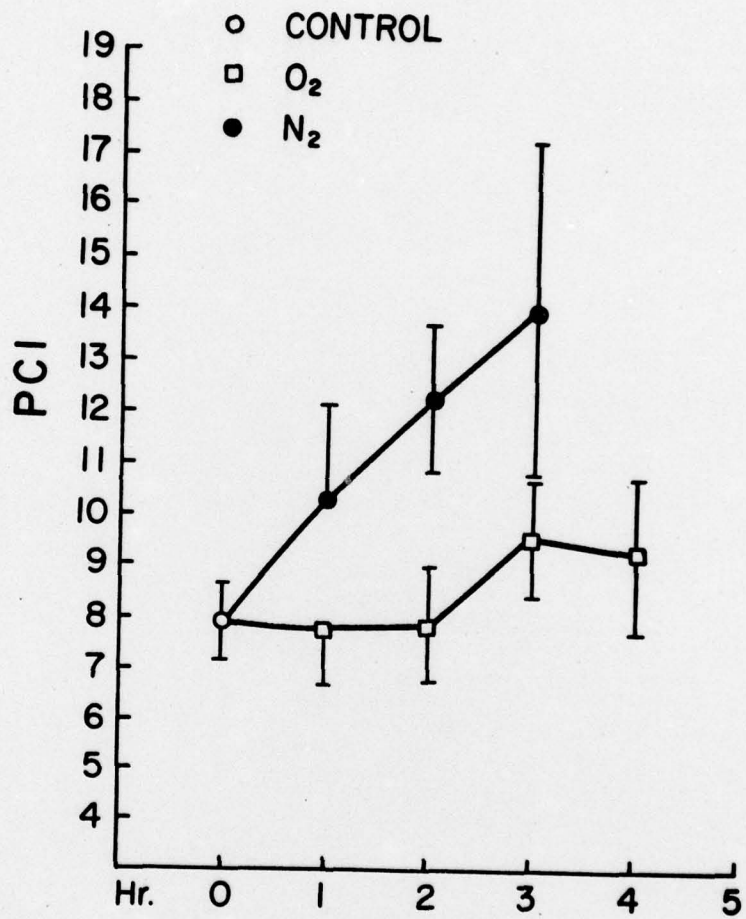


Fig. 4

TABLE 2 - PVO₂

	TIME 0	4 HOURS
CONTROL	99.1 ± 22.19	86.6 ± 53.93
	1 HOUR O₂	4 HOURS O₂
O₂ GROUP	462.5 ± 72.535	440.75 ± 65.901
N₂ GROUP	510.0 ± 37.638	487.00 ± 30.837

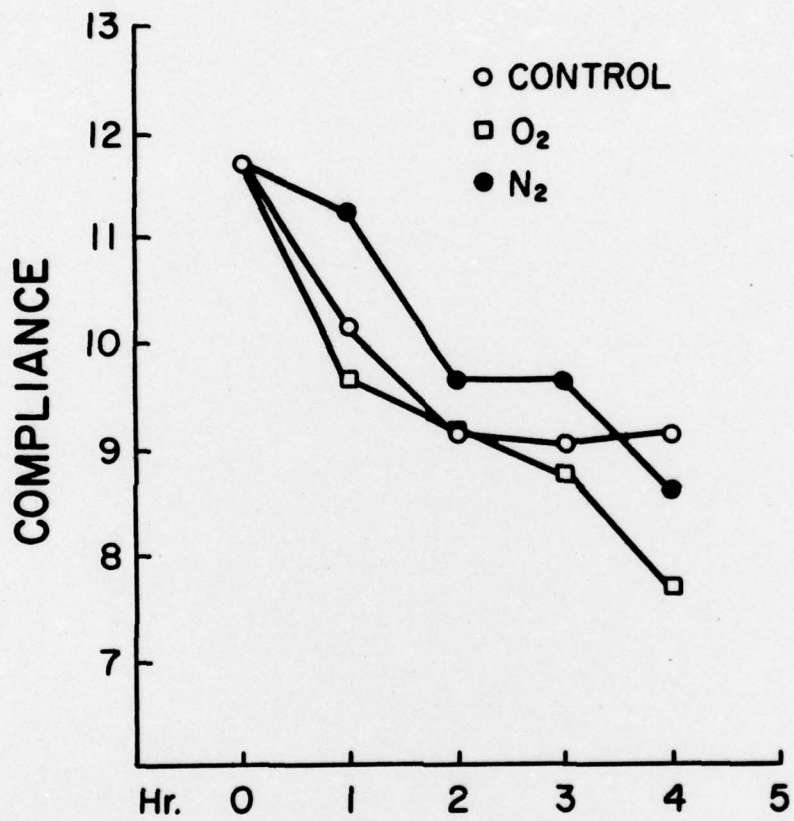


Fig. 6

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