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The effect of anaesthesia and CO_2 on survival time and lung damage in rats exposed to high pressure oxygen

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LUNG damage, consisting of massive exudation of plasma and whole blood into alveolar spaces,[1, 2] and reflected by a gross increase in wet and dry lung weight, is a major manifestation of oxygen poisoning in mammals. This toxic effect of hyperbaric oxygen is delayed by anaesthesia.[3, 4] The protective effect of anaesthetics was shown for pentobarbital sodium[3] and recently for urethane[4] although Campbell[5] had previously reported that urethane did not protect animals against oxygen poisoning. The action of urethane anaesthesia in protecting animals against oxygen toxicity has been confirmed in the present experiments and a quantitative estimate of the degree of protection made, by comparing survival times of unanaesthetized and urethane anaesthetized rats at different pressures. The effect of adding carbon dioxide to the hyperbaric oxygen has also been examined.

Female Canberra Black rats 160–200 g were used. The six-compartment pressure chamber described previously[6] was flushed with the gas used for pressurization, then the pressure was increased at a rate of 1 atm/min. A continual gas flow of 1 l./min was maintained through the chambers during pressurization to prevent alterations in gas composition. The temperatures of each compartment were individually monitored and did not vary by more than 1° from existing room temperatures (17–22°) throughout an experiment. Rats were injected with 1·2 g of urethane per kg body weight for the anaesthetized groups.

Survival times were measured as the length of pressurization causing cessation of visible respiration. When breathing ceased the rat was decompressed, the lungs removed, lightly blotted and weighed.

The results are summarized in Table 1. Highly significant differences in survival times were obtained between control rats and anaesthetized rats, with anaesthesia approximately doubling the survival time at each pressure. All rats had severe macroscopic lung damage when examined at necropsy, with most lung weights exceeding double the normal value of 0·847 ± 0·025 g/180 g rat.[1] The average lung weights were similar for unanaesthetized and anaesthetized rats exposed to high pressure oxygen. The survival time vs. pressure curve was similar in shape to that previously reported for mice[7] and a linear log–log relationship was obtained (Fig. 1). Statistical analysis showed that the slopes for the lines, calculated by the method of least squares, were not significantly different, while the separation between the anaesthetized and unanaesthetized groups was highly significant ($P < 0{\cdot}001$) with a "protection factor" for urethane of log 0·104 atm.

The protective action of urethane against high pressure oxygen was tested with carbon dioxide added to the oxygen. The gas mixture used was 2% CO_2/98% O_2. The results obtained are shown in Table 1 (B). It can be seen that addition of carbon dioxide shortened survival times in rats pressurized in oxygen and that under these conditions the protection by urethane was absent at 4 and 5 atm, but still significant at 7 atm.

Also, in contrast to the results in Table 1 (A), at necropsy the lung weights were lighter in anaesthetized than in unanaesthetized rats exposed to high pressures of 2% CO_2/98% O_2, although considerable lung damage had occurred in both groups.

The decrease in protection against oxygen toxicity by urethane when CO_2 was added to hyperbaric oxygen and the difference in the lung weight data [comparing Table 1 (A) and (B)] suggests that the mechanism of damage to respiration caused by pressurization in oxygen may be modified by the addition of CO_2 to oxygen, particularly when rats are exposed to such hyperbaric conditions under anaesthesia. These present results therefore support conclusions drawn from other detailed studies,[8] based on EEG and diaphragmatic EMG recordings, where it was shown that rats ceased breathing due to lung damage and consequent mechanical impedance to air flow when pressurized in oxygen alone, whilst in anaesthetized rats pressurized in oxygen with added carbon dioxide, death was predominantly due to neurogenic respiratory depression.

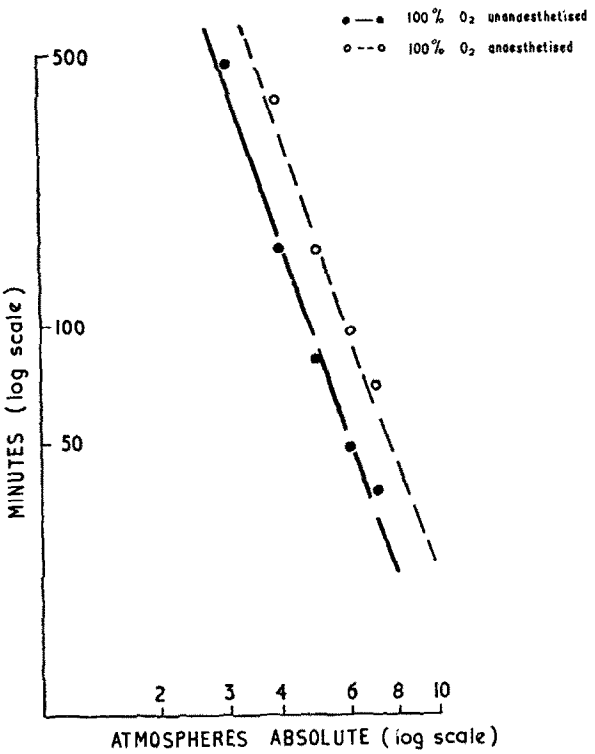

FIG. 1. Survival times for unanaesthetized and urethane anaesthetized rats. Ninety per cent confidence limits are 0·0311 atm. and 0·0219 atm. for control and anaesthetized regression lines respectively.

TABLE 1. SURVIVAL TIMES AND LUNG WET WEIGHTS OF ANAESTHETIZED AND UNANAESTHETIZED RATS EXPOSED TO HIGH PRESSURE OXYGEN OR OXYGEN + 2% CARBON DIOXIDE

O_2 Pressure atm. absolute	Treatment (No. rats)	Survival time (min ± S.E.M.)	*P* value	Lung weight* (g ± S.E.M.)	*P* value
(A)					
3	— (6)	477 ± 44		2·2 ± 0·1	
4	— (6)	158 ± 6	<0·001	1·9 ± 0·2	N.S.
4	urethane (10)	386 ± 34		1·8 ± 0·1	
5	— (6)	82 ± 10	<0·001	2·0 ± 0·1	N.S.
5	urethane (10)	155 ± 9		2·2 ± 0·1	
6	— (6)	48 ± 9	<0·001	2·5 ± 0·2	N.S.
6	urethane (6)	96 ± 7		2·1 ± 0·2	
7	— (6)	38 ± 1	<0·001	2·1 ± 0·2	N.S.
7	urethane (9)	70 ± 4		1·9 ± 0·1	
(B) 2% CO_2/98% O_2					
3	— (6)	296 ± 39		2·4 ± 0·1	
4	— (17)	135 ± 20	N.S.	2·3 ± 0·1	<0·01
4	urethane (9)	118 ± 16		1·7 ± 0·1	
5	— (11)	57 ± 10	N.S.	2·5 ± 0·1	<0·01
5	urethane (12)	63 ± 2		1·9 ± 0·1	
7	— (12)	25 ± 2	<0·02	2·7 ± 0·1	<0·01
7	urethane (11)	34 ± 3		1·8 ± 0·2	

* The lung weights are corrected for body weight variations and are expressed as lung weight per 180 g rat.

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Histidine decarboxylase gastrique et ulcerés experimentaux chez le rat

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BIEN que le mécanisme de formation des ulcères gastriques expérimentaux soit imparfaitement élucidé, on admet généralement que deux facteurs principaux concourent à leur apparition: l'augmentation de la sécrétion acide et les troubles vasomoteurs locaux.[1]

Etant donné que l'histamine de la muqueuse gastrique parait être le médiateur de la sécrétion acide provoquée par divers agents[2] et que, par ailleurs, cette amine semble jouer un role physiologique important dans la régulation de la microcirculation,[3] nous avons voulu vérifier si la production de différents types d'ulcères expérimentaux était liée à des modifications du taux d'histidine décarboxylase dans l'estomac. Une telle relation a été suggérée récemment par Fischer et Snyder[4] qui ont constaté une augmentation marquée du taux de l'enzyme synthétisant l'histamine gastrique chez des rats porteurs d'une anastomose portocave.

Des ulcères gastriques médicamenteux ont été obtenus suivant le protocole de Brodie *et al.*,[5] sur des rats Wistar mâles, de 130–150 g, à jeun depuis 24 h, au moyen d'injections intrapéritonéales de réserpine (8 mg/kg), phénylbutazone (100 mg/kg) ou sérotonine (8 mg/kg). Les animaux ont été sacrifiés 4 h après l'administration de l'agent ulcérogène.

Chez d'autres animaux l'ulcération a été provoquée par mise en contrainte durant 14 h.[6]

A l'issue des expériences les estomacs ont été prélevés et, après examen direct de l'aspect de la muqueuse glandulaire, on a procédé au dosage de l'histidine décarboxylase. L'activité de l'enzyme a été évaluée suivant la méthode de Kobayashi.[7] La partie glandulaire de l'estomac a été homogénéisé dans 5 vol. d'eau puis on a centrifugé cette préparation à basse température (20,000 *g* pendant 10 min). On a alors prélevé une prise aliquote de 1,5 ml du liquide surnageant à laquelle on a ajouté 0,7 ml de solution contenant: 0,12 mM de tampon phosphate pH 7, 40 μM de phosphate de pyridoxal, 32 mμM de DL-histidine à carboxyle ^{14}C Amersham (11,8 mc/mM) et 45 mμM de L histidine. Les incubations ont été pratiquées à 37°, pendant 1 h, au contact de l'air et l'activité enzymatique été rapportée au gramme de tissu frais.