## Respiratory Effects of Increased Air Flow Resistance in Dogs.* (23469)

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Following description of pneumotachographic technics by Silverman *et al.*(1) numerous investigators have studied the effects of resistance to air flow on patterns of breathing. Recently Zechman *et al.*(2) has shown that the primary effect of resistance to air flow is a reduction in air flow velocity and an increase in the duration of the impeded phase resulting in a reduction of pulmonary ventilation, a rise in alveolar $CO_2$ pressure and a fall in oxygen saturations. It was thought worthwhile to continue the study of impedances to air flow in anesthetized animals where greater impedances could be imposed and more extensive blood studies could be made.

*Methods.* Twenty-two mongrel dogs were used in these experiments. Weights ranged from 11 to 16 kg. It was not considered desirable to do all of the tests on each dog because of the great stress imposed on the individual animal. The number of dogs used in each series is indicated on each figure and table. Dogs were anesthetized by intraperitoneal injection of 55 mg of Dial in Urethane (Ciba)/kg body weight. A tracheal cannula containing a wire cloth flowmeter capsule for recording respiratory flow patterns and intratracheal pressures was inserted in the trachea. Various size orifices were inserted in the capsule. The capsule assembly added no significant volume to the respiratory dead space. Differential pressures across the flowmeter capsule were linear with flow within the range of values obtained. Thus tidal volume could be determined by planimetering the areas of the recordings and from these values pulmonary ventilation was calculated. Maximum inspiratory flow of air into the trachea could also be measured. A photograph of the assembly is shown in Fig. 1. Blood pressure was recorded by Statham transducers attached to polyethylene catheters 2 mm inside diameter. The free end of one of these catheters was inserted well up into the femoral artery. Blood samples were also drawn through this catheter. Blood samples were analyzed for oxygen content, oxygen capacity and carbon dioxide content by use of a Van Slyke manometric gas analyzer(3) and pH was measured with Cambridge Instrument Co. research type glass electrode. Blood samples were drawn anaerobically in 5 ml syringes and analyses made at once. Total hemoglobin was determined by converting hemoglobin in the samples to met-cyanhemoglobin and reading the concentration on an Evelyn photoelectric colorimeter. The factor of 1.35 was used to calculate total hemoglobin oxygen capacity. Femoral artery blood pressure, tracheal pressure and velocity of air flow into and out of the trachea were recorded simultaneously on a Miller Oscillograph. Recordings were made before and after orifices of various sizes were inserted in the tracheal cannula. Each dog breathed with an open tracheal cannula for 12 minutes and then an orifice was inserted. Breathing continued through it for 12 minutes and then recovery was permitted through an open cannula for

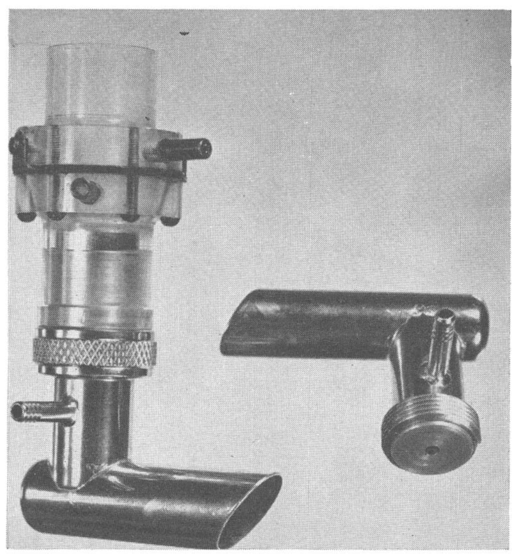

FIG. 1. Tracheal cannula and flow meter assembly showing position of plate orifices.

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12 minutes before the next sized orifice was used. The results reported are from determinations made between the 11th and 12th minute. In preliminary tests it was found that orifices greater than 5 mm in diameter had little effect upon the factors under study. Pressure-flow characteristics were determined for each orifice using each respiratory gas used in experiments. Consideration was given to the fact that respiratory gases varied in density which in turn would affect the resistance of each orifice. However, this was found not significant enough to influence results. Four orifices were used each being 1 mm in thickness and having diameters of 1.5, 1.9, 2.3, 3.2 mm respectively.

*Results.* Mean values for various pressures and respiratory factors are plotted in Fig. 2 and 3. Points on the abscissas are shown as the reciprocals of the areas of the various orifices used, the open tracheal cannula being considered normal (N). Plotting points as reciprocal of the areas is somewhat arbitrary for flow through orifices of these dimensions cannot accurately be expressed so simply. These graphs are used solely to illustrate the relative manner in which different factors vary relatively with varying obstruction to breathing.

Table I shows how arterial oxygen saturation and $CO_2$ pressures change with obstruction to breathing. It will be noted that only when very small orifices are used to obstruct breathing does arterial oxygen saturation fall to a low level. Fig. 4 shows the effect of the

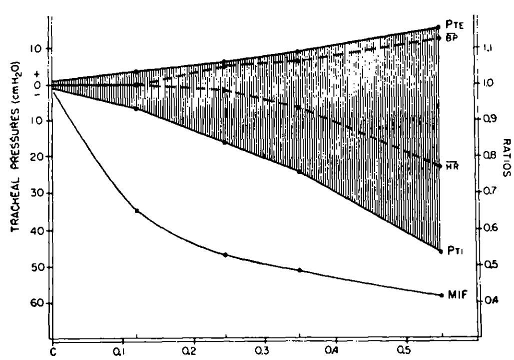


FIG. 2. Influence of air flow impedance on tracheal air flow and pressure, arterial blood pressure and heart rate.

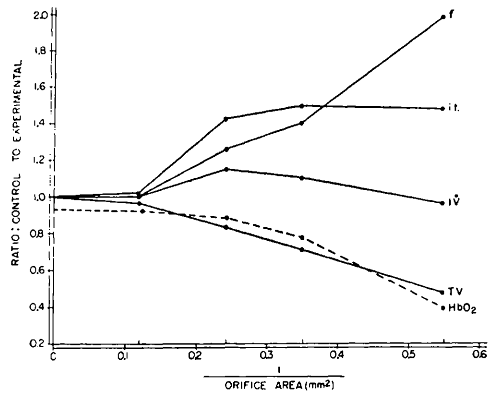


FIG. 3. Influence of air flow impedance on respiratory frequency, inspiratory time, minute volume, tidal volume and arterial oxygen saturation.

various orifices on the oxygen and carbon dioxide pressures. The tracheal pressure relations obtained are shown in Fig. 2. PTE represents average maximum positive tracheal pressures recorded during expiration in cm $H_2O$ and PTI represents average maximum negative pressures recorded during inspiration. BP represents average maximum systolic blood pressures recorded and HR represents average heart rate recorded. MIF represents average maximum instantaneous flow of air into the trachea on inspiration. The latter 3 factors are expressed in ratios, relating the values obtained while dogs were breathing through resistances to the control values while breathing through an open trachea. Thus each dog was his own control and average values can be shown in a single figure which expresses the results in a summary manner.

It should be kept in mind that in these experiments resistance to breathing was the same for inspiration as for expiration and

TABLE I. Summary of Oxygen Saturation and $pCO_2$ Values for Arterial Blood of 10 Dogs after Breathing through Various Size Orifices for 12 Min.

| Orifice area | % Hb $O_2$ | $pCO_2$, mm Hg |
|---|---|---|
| Open trachea | 93 ± 2.6* | 44 ± 3.0* |
| 25 mm$^2$ | 93 ± 4.0 | 44 ± 3.2 |
| 8.3 | 92 ± 3.6 | 45 ± 3.0 |
| 4.1 | 89 ± 7.6 | 51 ± 6.2 |
| 2.8 | 78 ± 14.0 | 59 ± 9.7 |
| 1.9 | 39 ± 23.4 | 69 ± 10.9 |

* ± S.D.

TABLE II. Tidal Air, Breathing Rates and Maximum Tracheal Pressures (Avg for 6 Dogs Breathing through 1.9 mm Diameter Orifice).

| | Maximum tracheal pressures | | | |
|---|---|---|---|---|
| | Inspir., cm $H_2O$ | Expir., cm $H_2O$ | Tidal air, ml | Breathing rate/min. |
| Control (open trachea) | .1 | .7 | 164 | 16 |
| Breathing air | 19.2 | 6.3 | 122 | 21 |
| " 100% $O_2$ | 17.0 | 5.1 | 147 | 11 |
| " 5.6% $CO_2$ (in oxygen) | 20.9 | 7.8 | 129 | 21 |

also that pressure-flow relations are not linear. Of course the tidal volume must be moved twice in each breathing cycle, once with negative pressure and once with positive pressure, and the tidal volume must be moved within a limited time if alveolar ventilation is to be maintained at an adequate level. It would appear that this is accomplished almost entirely by an increased frequency of breathing (see f, Fig. 3). A point was finally reached, however, with the smallest orifice when pulmonary ventilation (see IV, Fig. 3) was inadequate to maintain proper alveolar $pO_2$ and $pCO_2$ levels and respiratory failure ensued. It is interesting to note that this orifice with an area of 1.8 mm$^2$ was less than one-hundredth the area of the trachea. The relative length of time of inspiration during the breathing cycle increased when small orifices were inserted but this is of little advantage to the animals since the tidal volume must be moved in and out of the lungs in each cycle against similar resistances. Also shown in Fig. 3 are other respiratory factors

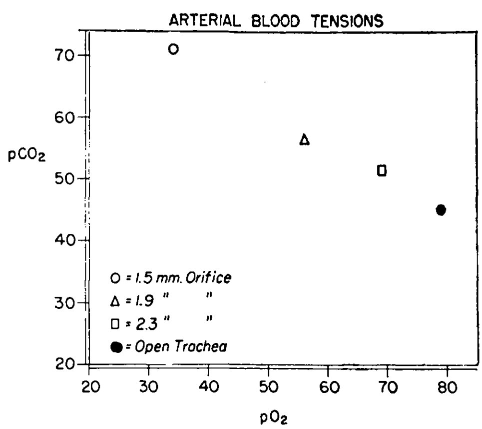


FIG. 4. Effect of different plate orifices on arterial oxygen and carbon dioxide tensions.

which are influenced by breathing through the orifices of various sizes: i.t. represents relative length of time of the breathing cycle taken by inspiration; IV, pulmonary ventilation or minute volume; TV, tidal volume for each inspiration; $HbO_2$, percentage oxygen saturation of arterial hemoglobin. These are mean values obtained on 7 dogs, each dog was his own control (C) and 1.0 is the control value for the resting condition with each dog breathing through a wide open trachea. It can be seen that oxygen saturation values decreased in proportion to decreases in tidal volume.

To gain a better understanding of the control of respiration when increased air flow resistance is encountered, a separate experimental series was conducted. Each dog was used as his own control, *i.e.*, recordings were made on each dog while it was breathing through an open trachea, then a 1.9 mm diameter orifice was inserted in the tracheal cannula and subsequent measurements were made while each dog breathed gas mixtures as indicated. Only one orifice was used in order to reduce total stress of breathing to a minimum.

The results are summarized in Tables II and III. Breathing 5.6% $CO_2$ in oxygen produced the highest tracheal pressures and breathing 100% oxygen the lowest, but the differences are small. The more striking ef-

TABLE III. Average Arterial Gas Tensions in 6 Dogs Breathing through 1.9 mm Diameter Orifice.

| | Hb $O_2$ (%) | p $CO_2$ (mm Hg) |
|---|---|---|
| Control | 90 | 43 |
| Breathing air | 77 | 51 |
| " 100% $O_2$ | 99 | 58 |
| " 5.6% $CO_2$ (in oxygen) | 97 | 65 |

fects obtained were on breathing rate. There was a pronounced decrease in breathing rate while dogs were breathing 100% oxygen.

It was stated(2) that increased air flow resistance in humans resulted in a decreased respiratory frequency. In the human studies, unlike these on dogs, the level of resistance was not sufficient to produce hypoxia. The decreased frequency of dogs breathing 100% oxygen seems to indicate that increased air flow resistance *per se* decreases breathing rate, but if severe enough to cause hypoxia, an increase in rate is initiated. The pause between expiration and inspiration in the normal dog is retained while breathing oxygen through resistances, but is lost while breathing air in an hypoxic state. Hypoxia eliminates or greatly reduces the respiratory pause.

*Conclusions.* 1. When tracheal air flow is so impeded as to produce pronounced changes in inspiratory and expiratory pressures, breathing rates increase, minute volumes may remain relatively uniform and tidal volumes decrease inversely with the pressure differences. 2. Two factors are involved in the accommodation to this respiratory stress: (a) Increasing carbon dioxide tensions act as primary stimuli to more forced inspiration and expiration; (b) Decreasing oxygen tensions act as stimuli to more rapid breathing by reducing the time of the expiratory phase of the breathing cycle.

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## Presence of a Carcinogenic Substance in Hens' Eggs. (23470)

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It was shown previously that hens' eggs contain a substance that stimulates growth and sex development. Chicks maintained on a diet made up of eggs and wheat bran grew faster and became sexually mature earlier than the control chicks of the same breed and age maintained on a Purina broiler mash diet. The females became productive relatively early and the males developed very large combs, wattles and spurs. Females maintained on the above diet for over 2 years developed cancer of the ovary(1). Recently Menge, Lillie and Denton(2) reported the presence in egg yolk of a growth stimulating factor. The authors state that the latter is destroyed by heat, since ashes of yolk are without any effect upon growth. In the experiments carried out by the author(1) the eggs used in the diet were autoclaved for at least 30 minutes at 15 lb pressure. It is possible, however, that the growth-promoting factor in this case is the same as that reported by Menge and his co-workers; the moist heat of the autoclave may not be as destructive as ashing. There is also the possibility that these are 2 different substances, since the egg diet stimulated sex development in addition to growth. More work will have to be done in order to identify the growth-stimulating substance or substances in eggs. Since chicks were the only animals used in the study of the growth-stimulating action of eggs, the question arose whether animals other than birds would be affected in their growth by a diet containing eggs and to what extent such a diet might influence the development of malignant tumors. These were the bases for a new series of experiments in which mice were used. The present is a report of the first series of experiments carried out with "A" strain mice.

*Methods.* Sixteen mice (8 males and 8 females caged separately) were placed on a Rockland rat diet supplemented with eggs.