# POSTURAL DRAINAGE OF RESPIRATORY TRACT FLUID IN PHOSGENE-INDUCED PULMONARY OEDEMA

BY ELDON M. BOYD AND WILLIAM F. PERRY*

*From the Department of Pharmacology, Queen's University, Kingston, Ontario, Canada*

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Cats and dogs were given phosgene by inhalation at a dose in the range of the LD50. During the hour or two before death, the volume output of respiratory tract fluid increased some 30-fold in half the animals and its lipid and sodium chloride contents were similar to those of blood plasma. Postural pulmonary drainage did not augment the volume output of respiratory tract fluid nor consistently affect chemical or histological measurements upon the lungs and chemical measurements upon respiratory tract fluid and blood. Postural pulmonary drainage did not increase the survival rate of intact rats exposed to phosgene. The ability of the animals to excrete such large volumes of respiratory tract fluid appeared to be due to a marked reserve capacity of the ciliary drainage mechanism which was evidently not affected by the dose of phosgene given to these animals.

IN a previous communication Boyd and Perry (1960) reported a sixty fold increase in the volume output of respiratory tract fluid just before death in the late symptomatic period of pulmonary oedema induced by inhalation of phosgene in rabbits. The sodium, chloride, and lipid levels of this respiratory tract fluid were insignificantly different from those of the animal's blood plasma. It appeared possible that the presence of such huge amounts of plasma-like fluid might tax the capacity of the lungs to eliminate it and that death might be the result of failure to remove the fluid from the respiratory airway. It was found that postural pulmonary drainage did not augment the output of respiratory tract fluid in cats or dogs treated with phosgene nor increase the survival rate in albino rats so treated. The results indicate that the ciliary mechanism for the elimination of respiratory tract fluid has tremendous reserve capacity.

## METHODS

Techniques employed were similar to those reported by Boyd and Perry (1960). The animals were exposed to an estimated LD50 of phosgene (Spector, 1956) by the static method in a chamber of 400 litres capacity. The initial concentration of phosgene was varied between 0·10 and 0·30 mg./litre, depending upon the relative humidity of the laboratory air and the number and weight of animals exposed at one time. The half life of phosgene varied with the relative humidity of air inside the sealed chamber; at 25 per cent relative humidity, for example, the half life of these concentrations of phosgene averaged 10 min. The exposure time was 30 min. Identical exposures were used for each group of animals subsequently divided into equal numbers and posturally drained at angles of 0°, 30°, or 50° with the horizontal.

* Present address: Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada.

Experiments were made upon 57 cats exposed to phosgene and upon 12 controls not exposed. At intervals of up to 17 hr. after exposure, they were anaesthetized with urethane and arranged for the collection of respiratory tract fluid after the technique of Boyd (1954). Equal numbers of animals were assembled, for this purpose, on tilt tables with the long axis of the body held, head downward, at angles of 0° (prone upon the belly), 30°, and 50° with the horizontal. Similar experiments were made upon 24 dogs, half exposed and half not exposed to phosgene. One hundred and twenty-six albino rats, with 30 controls, were similarly treated except that they were not operated upon for the collection of respiratory tract fluid but rather maintained in straight jackets under sedation with urethane at the same angles of postural pulmonary drainage.

The observations and measurements noted below were made by methods described by Boyd and Perry (1960). Statistical methods were those of Croxton (1953).

## Results

Exposure to phosgene increased the output of respiratory tract fluid, particularly in the hour or two before death. Postural pulmonary drainage did not produce a further increase in the volume output of this fluid as shown by results summarized in Fig. 1. Not included in data averaged in Fig. 1 are two cats arranged in the prone (0°) position in which, during the hour before death, the volume output of respiratory tract fluid reached values $1\frac{1}{2}$ and $2\frac{1}{2}$ thousand-fold the normal output. In confirmation of

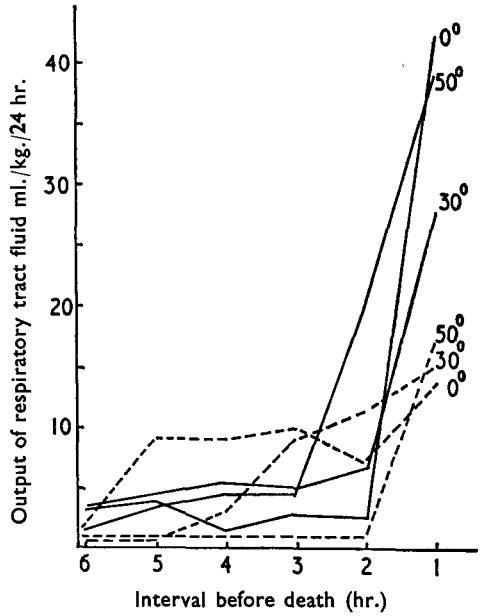


FIG. 1. The mean volume output of respiratory tract fluid in cats (solid lines) and dogs (broken lines) exposed to phosgene and arranged for postural pulmonary drainage at angles of 0°, 30° and 50° with the horizontal.

the findings of Boyd and Ronan (1942), postural pulmonary drainage also had no effect upon the volume output of respiratory tract fluid in control cats and dogs not exposed to phosgene.

The mean ± standard deviation hours survival during which respiratory tract fluid was collected was 37·1 ± 13·9 in control cats and 8·1 ±3·8 in cats exposed to phosgene. Corresponding figures in dogs were 20·5 ± 12·2 and 9·8 ± 7·3. In neither cats nor dogs was survival time related to the angle of postural pulmonary drainage. In albino rats exposed to phosgene but not arranged for collection of respiratory tract fluid, there were 23 per cent survivors at 24 hr. in animals held at 0°, 17 per cent at 30°, and 30 per cent at 50° with no deaths at corresponding angles in the controls not given phosgene. No evidence was obtained, therefore, that postural pulmonary drainage increased the rate of survival of animals exposed to lethal doses of phosgene.

TABLE I

THE HISTOPATHOLOGY OF THE LUNGS IN CATS AND DOGS AT DEATH FROM PHOSGENE INHALATION*

| Measurement | Angle of drainage | | |
|---|---|---|---|
| | 0° | 30° | 50° |
| **Cats** | | | |
| Oedema | 2·8 ± 1·0 | 2·3 ± 1·0 | 2·5 ± 1·2 |
| Congestion | 1·4 ± 1·4 | 0·7 ± 1·2 | 1·6 ± 1·5 |
| Emphysema | 2·0 ± 1·1 | 1·9 ± 1·6 | 1·0 ± 1·1† |
| Atelectasis | 0·0 ± 0·0 | 0·1 ± 0·3 | 0·4 ± 0·7 |
| Haemorrhage | 0·6 ± 0·8 | 0·2 ± 0·6 | 0·7 ± 0·8 |
| Contracted arteries | 0·4 ± 0·7 | 0·5 ± 1·2 | 0·5 ± 1·0 |
| **Dogs** | | | |
| Oedema | 4·0 ± 0·0 | 1·5 ± 0·5† | |
| Congestion | 4·0 ± 0·0 | 4·0 ± 0·1 | |
| Emphysema | 2·0 ± 0·5 | 2·5 ± 1·5 | |
| Atelectasis | 0·0 ± 0·0 | 0·0 ± 0·0 | |
| Haemorrhage | 3·0 ± 1·0 | 3·0 ± 1·0 | |
| Contracted arteries | 0·0 ± 0·0 | 0·0 ± 0·0 | |

* The results are expressed as mean ± standard deviation arbitrary (1+ to 4+) units. Means in animals drained at 30° or 50° which differed at P = 0·05 or less from means in animals drained at 0°, by a *t* test, are indicated thus: †.

As shown by results summarized in Table I, postural pulmonary drainage had no consistent effect upon the histopathologic appearance of the lungs at autopsy. The lumen of the trachea, bronchi, and bronchioles often contained an exudate but the lining mucosa appeared normal.

Postural pulmonary drainage had no consistently significant effect upon the sodium, chloride, and lipid content of respiratory tract fluid in control animals or in animals exposed to phosgene. Data supporting this conclusion are presented in Table II. In over half of the animals there occurred a pre-mortem gush or marked increase in the output of respiratory tract fluid. This group corresponded to the rabbits of Group III in the report of Boyd and Perry (1960). The incidence of all animals with a pre-mortem gush was 55 per cent in animals held at 0°, 52 per cent at 30°, and 62 per cent at 50°. In animals with a pre-mortem gush, the composition of respiratory tract fluid was almost identical to that of blood plasma.

## TABLE II

### MEASUREMENTS UPON RESPIRATORY TRACT FLUID*

| Measurement | Controls | Phosgene-treated; angle of drainage | | |
|---|---|---|---|---|
| | | 0° | 30° | 50° |
| **Cats** | | | | |
| Sodium | 59 ± 35 | 219 ± 244 | 159 ± 120† | 175 ± 106† |
| Chloride | 74 ± 44 | 280 ± 151† | 190 ± 163† | 270 ± 119† |
| Total lipid | 60 ± 4 | 221 ± 119† | 272 ± 69† | 155 ± 61† |
| Neutral fat | 12 ± 7 | 52 ± 51† | 103 ± 84† | 62 ± 56† |
| Total fatty acids | 33 ± 8 | 130 ± 74† | 180 ± 56† | 104 ± 54† |
| Total cholesterol | 19 ± 8 | 61 ± 29† | 60 ± 36† | 32 ± 11†S |
| Ester cholesterol | 12 ± 2 | 39 ± 26† | 40 ± 23† | 20 ± 9† |
| Free cholesterol | 7 ± 5 | 22 ± 14† | 20 ± 8† | 12 ± 4† |
| Phospholipid | 22 ± 10 | 82 ± 73† | 81 ± 51† | 48 ± 23† |
| **Dogs** | | | | |
| Sodium | 44 ± 18 | 338 ± 18† | 334 ± 23† | |
| Chloride | 59 ± 21 | 381 ± 16† | 352 ± 57† | |
| Total lipid | 197 ± 49 | 332 ± 41† | 279 ± 62 | |
| Neutral fat | 53 ± 31 | 50 ± 38 | 91 ± 23 | |
| Total fatty acids | 126 ± 39 | 208 ± 33† | 180 ± 42 | |
| Total cholesterol | 41 ± 15 | 53 ± 11 | 63 ± 10† | |
| Ester cholesterol | 28 ± 19 | 36 ± 16 | 46 ± 7 | |
| Free cholesterol | 13 ± 4 | 17 ± 4 | 17 ± 3 | |
| Phospholipid | 85 ± 37 | 205 ± 18† | 95 ± 35 | |

* The results are expressed as mean ± standard deviation mg./100 ml. of respiratory tract fluid. Means in phosgene-treated animals which differed at P = 0·05 or less from means in controls, by a *t* test, are indicated thus: †. Means in phosgene-treated animals drained at 30° or 50° which correspondingly differed from means in phosgene-treated animals drained at 0° are indicated by S.

## TABLE III

### MEASUREMENTS UPON BLOOD PLASMA*

| Measurement | Units | Controls | Phosgene-treated; angle of drainage | | |
|---|---|---|---|---|---|
| | | | 0° | 30° | 50° |
| **Cats** | | | | | |
| Sodium | mg. | 280 ± 20 | 276 ± 35 | 294 ± 16 | 291 ± 14 |
| Chloride | mg. | 353 ± 26 | 368 ± 58 | 391 ± 24 | 385 ± 29 |
| Total lipid | mg. | 392 ± 56 | 342 ± 81 | 334 ± 90 | 391 ± 117 |
| Neutral fat | mg. | 86 ± 76 | 69 ± 63 | 88 ± 54 | 73 ± 44 |
| Total fatty acids | mg. | 242 ± 74 | 200 ± 59 | 203 ± 63 | 226 ± 61 |
| Total cholesterol | mg. | 92 ± 31 | 88 ± 40 | 85 ± 27 | 105 ± 51 |
| Ester cholesterol | mg. | 58 ± 29 | 51 ± 29 | 52 ± 20 | 66 ± 39 |
| Free cholesterol | mg. | 34 ± 12 | 37 ± 19 | 33 ± 12 | 39 ± 15 |
| Phospholipid | mg. | 167 ± 41 | 151 ± 25 | 126 ± 51† | 169 ± 70 |
| Haemoglobin | g. | 11·5 ± 1·9 | 13·9 ± 3·3† | 13·8 ± 2·6† | 14·1 ± 4·0 |
| Haematocrit | ml. | 31·2 ± 3·6 | 38·3 ± 9·5† | 33·8 ± 6·7 | 41·4 ± 11·5† |
| **Dogs** | | | | | |
| Sodium | mg. | 283 ± 24 | 262 ± 35 | 288 ± 35 | |
| Chloride | mg. | 350 ± 10 | 353 ± 9 | 369 ± 19 | |
| Total lipid | mg. | 590 ± 152 | 430 ± 83† | 616 ± 150 | |
| Neutral fat | mg. | 182 ± 74 | 94 ± 22† | 136 ± 69 | |
| Total fatty acids | mg. | 386 ± 105 | 273 ± 60† | 369 ± 99 | |
| Total cholesterol | mg. | 110 ± 29 | 77 ± 7† | 144 ± 30S | |
| Ester cholesterol | mg. | 59 ± 19 | 48 ± 10 | 69 ± 28 | |
| Free cholesterol | mg. | 51 ± 19 | 29 ± 4† | 75 ± 29S | |
| Phospholipid | mg. | 258 ± 78 | 227 ± 47 | 291 ± 94 | |
| Haemoglobin | g. | 14·5 ± 0·5 | 29·3 ± 8·8† | 16·3 ± 6·9 | |
| Haematocrit | ml. | 37·0 ± 3·0 | 75·0 ± 14·0† | 45·3 ± 17·6 | |

* The results are expressed as mean ± standard deviation units/100 ml. of blood plasma, excepting haemoglobin and haematocrit which are per 100 ml. of whole blood. Means in phosgene-treated animals which differed at P = 0·05 or less from means in controls, by a *t* test, are indicated thus: †. Means in phosgene-treated animals drained at 30° or 50° which correspondingly differed from means in phosgene-treated animals drained at 0° are indicated by S.

Measurements upon blood and blood plasma are summarized in Table III. In phosgene poisoning there occurred an increase in the hematocrit and in the concentration of haemoglobin. When this was marked, as in dogs held at 0° angles, the concentration of plasma lipids was sometimes reduced. Postural pulmonary drainage did not consistently affect the results.

TABLE IV

MEASUREMENTS UPON THE LUNGS AND TRACHEA*

| Measurement | Units | Controls | Phosgene-treated; angle of drainage | | |
|---|---|---|---|---|---|
| | | | 0° | 30° | 50° |
| **Cats** | | | | | |
| Periphery, water .. | g./100 g. wet wt. | 77·7 ± 1·10 | 86·1 ± 2·6† | 85·3 ± 2·4† | 84·2 ± 2·0† |
| Periphery, chloride | mg./g. dry wt. | 10·6 ± 1·4 | 19·9 ± 2·8† | 18·5 ± 3·1† | 17·4 ± 2·9†S |
| Periphery, iron .. | µg./g. dry wt. | 561 ± 65 | 483 ± 232 | 496 ± 198 | 503 ± 162 |
| Hilus, water .. | g./100 g. wet wt. | 76·5 ± 1·8 | 85·2 ± 2·2† | 84·1 ± 2·7† | 83·3 ± 2·5† |
| Hilus, iron .. | µg./g. dry wt. | 425 ± 42 | 370 ± 169 | 472 ± 169 | 423 ± 165 |
| Trachea, water .. | g./100 g. wet wt. | 69·5 ± 2·9 | 73·1 ± 4·5† | 75·2 ± 4·0† | 70·5 ± 4·3 |
| Trachea, iron .. | µg./g. dry wt. | 124 ± 43 | 112 ± 62 | 121 ± 48 | 125 ± 40 |
| **Dogs** | | | | | |
| Periphery, water .. | g./100 g. wet wt. | 78·7 ± 0·9 | 84·3 ± 0·3† | 81·7 ± 2·8 | |
| Periphery, chloride | mg./g. dry wt. | 9·4 ± 0·8 | 16·9 ± 1·5† | 12·4 ± 3·3S | |
| Periphery, iron .. | µg./g. dry wt. | 852 ± 176 | 789 ± 29 | 648 ± 154 | |
| Hilus, water .. | g./100 g. wet wt. | 77·3 ± 1·3 | 82·5 ± 1·4† | 80·5 ± 2·7 | |
| Hilus, iron .. | µg./g. dry wt. | 723 ± 302 | 737 ± 63 | 640 ± 68 | |
| Trachea, water .. | g./100 g. wet wt. | 69·9 ± 3·0 | 69·6 ± 1·8 | 70·0 ± 1·8 | |
| Trachea, iron .. | µg./g. dry wt. | 104 ± 91 | 100 ± 20 | 88 ± 10 | |
| **Albino Rats** | | | | | |
| Lung, water .. | g./100 g. wet wt. | 79·4 ± 2·8 | 83·2 ± 3·7† | 83·2 ± 1·5† | 84·0 ± 1·5† |
| Lung, chloride .. | mg./g. dry wt. | 10·5 ± 2·0 | 15·1 ± 1·8† | 12·4 ± 3·0 | 13·4 ± 1·6† |
| Lung, iron .. | µg./g. dry wt. | 864 ± 327 | 698 ± 131† | 548 ± 261† | 772 ± 215 |

* The results are expressed as mean ± standard deviation. Means in phosgene-treated animals which differed at P = 0·05 or less from means in controls, by a *t* test, are indicated thus: †. Means in phosgene-treated animals drained at 30° or 50° which correspondingly differed from means in phosgene-treated animals drained at 0° are indicated by S.

Finally, measurements upon the lung periphery, hilus, and trachea are summarised in Table IV. In phosgene-induced pulmonary oedema, levels of water and chloride were consistently increased while levels of iron tended to decrease. There was some evidence of a tendency for these changes to be less marked in animals arranged at 30° and 50° angles. In a separate experiment, it was found that control albino rats held at these angles for 72 hr. had lower levels of whole lung water and chloride and higher levels of iron than had albino rats held at a 0° angle. It may be concluded, therefore, that changes in the chemical composition of the lungs induced by inhalation of phosgene were not affected by postural pulmonary drainage.

## DISCUSSION

Insofar as indicated by the measurements used, the course of phosgene intoxication in cats, dogs, and rats was essentially similar to that in rabbits reported by Boyd and Perry (1960). In half of the cats and dogs, there occurred a pre-mortem gush or marked increase in the volume output of

respiratory tract fluid. The sodium, chloride, and lipid contents of this gushed respiratory tract fluid were similar to those of blood plasma. Cameron and Courtice (1946) found the protein content of respiratory tract fluid drained from the lungs after death from phosgene to be similar to that of blood plasma in rabbits, dogs, and goats.

At death, the alveolar portions of the lungs were oedematous, congested, and emphysematous, with areas of atelectasis, hemorrhage, and contracted arteries and with an increase in the levels of water and chloride. The trachea and bronchi were normal in microscopic appearance. The hematocrit and concentration of blood haemoglobin were increased, particularly in dogs in which plasma lipid content was sometimes depressed. Cameron and Courtice (1946) reported a fall in plasma protein concentration in dogs exposed to phosgene. While plasma transfusions temporarily relieve the haemoconcentration, they increase the pulmonary oedema and are detrimental (Courtice and Foss, 1946).

Postural pulmonary drainage did not augment the output of respiratory tract fluid nor survival rate and had no consistent effect upon other measured signs of phosgene poisoning in the animals used. During the pre-mortem gush, the volume output of respiratory tract fluid averaged some thirty fold the normal output, indicating a very high reserve capacity of the lungs to excrete respiratory tract fluid. The most important single mechanism for the excretion of respiratory tract fluid appears to be ciliary action (Boyd, 1954). There was no histological evidence of damage to the cilia of the bronchi and trachea in the cats and dogs used in this study of phosgene intoxication. When the cilia are destroyed by inhalation of ammmonia gas or steam, excretion is retarded and the output of respiratory tract fluid is increased by postural pulmonary drainage (Boyd, Perry and Stevens, 1944).

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## References

Boyd, E. M. (1954). *Pharmacol. Rev.*, **6**, 521–542.
Boyd, E. M. and Perry, W. F. (1960). *J. Pharm. Pharmacol.*, **12**, 726–732.
Boyd, E. M., Perry, W. F. and Stevens, M. E. T. (1944). *Amer. J. Physiol.*, **140**, 467–473.
Boyd, E. M. and Ronan, A. (1942). *Ibid.*, **135**, 383–386.
Cameron, S. R. and Courtice, F. C. (1946). *J. Physiol.*, **105**, 175–185.
Courtice, F. C. and Foss, G. L. (1946). *Lancet*, **2**, 670–671.
Croxton, F. E. (1953). *Elementary Statistics with Applications in Medicine*, New York: Prentice-Hall Inc.
Spector, W. S. (1956). *Handbook of Toxicology*, Volume I, *Acute Toxicities of Solids, Liquids and Gases to Laboratory Animals*, Philadelphia: W. B. Saunders Company.