

# Pulmonary Extravascular Water Volume during Halothane-Oxygen Anesthesia in Dogs

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Pulmonary extravascular water volumes in eight dogs were measured using the double indicator injection technique. No significant change in water volume was found from the start (phase 1 mean =  $108 \pm SE 7$  ml) to the end (phase 2 mean =  $92 \pm SE 9$  ml) of three hours of halothane-oxygen anesthesia with mechanical ventilation at a constant pressure and rate. Total extravascular pulmonary water volumes (mean =  $176 \pm SE 12.5$  ml) were also measured by weighing after sacrificing the animals. The relationship between the results of the two methods of measuring pulmonary water and the factors determining changes in volume are discussed. (Key words: Lung water; Pulmonary extravascular water; Pulmonary circulation; Venous admixture; General Anesthesia; Pulmonary transit times.)

A VARIETY of clinical states<sup>1</sup> lead to increased volumes of water in the pulmonary extravascular tissues without the development of frank pulmonary edema and often accompanied by deterioration of pulmonary function. Hydrostatic, mechanical, and osmotic pressure differences exerted across the alveolar-capillary interspace<sup>2</sup> determine the exchange of pulmonary water. This balance of forces may be disturbed by many different factors, all of which have a "common" clinical expression as pulmonary interstitial edema.

We have seen this condition recently in three patients in the early postoperative period, and wondered whether general anesthesia could be contributory. Furthermore, if in-

creased pulmonary water volume regularly accompanied anesthesia, it might be concerned in the etiology of the decreased arterial oxygen tension that has been reported.<sup>3,4</sup> Therefore, we determined the pulmonary extravascular water volumes in dogs during uncomplicated general anesthesia with mechanical ventilation.

## Methods

### GENERAL METHODS

In eight dogs (six male and two female) of mixed breeds (weight, mean  $28.2 \pm SE 0.5$  kg) anesthesia was induced with intravenous thiopental sodium (Pentothal) (15 mg/kg) and the trachea intubated. The dogs were secured in the supine position and anesthesia was maintained with halothane (Fluothane) (0.5–1.0 per cent) in oxygen from a calibrated vaporizer (Drager Vapor) via a circle absorber system. Intravenous gallamine triethiodide (Flaxedil) was administered intermittently (mean total dose = 100 mg).

The lungs were ventilated mechanically (Bird Mark IV) to obtain an end-tidal carbon dioxide tension of approximately 35 torr (Godard Capnograph) and the respiratory rate and volume (8 ml/kg approximately) were not altered thereafter. The inspired oxygen tension was measured with a calibrated paramagnetic analyzer (Beckman D2).

Through an incision in the neck a carotid artery (15-ga Jelco) and a jugular vein (6-inch Intracath, o.d. 0.06 inches) were cannulated. A double-lumen (Courmand, 9 Fr.) cardiac catheter was inserted in another neck vein and positioned so that pulmonary arterial pressure could be observed from the distal lumen and right ventricular pressure from the proximal lumen. These pressures, together with that of the carotid artery, were transduced (Statham P23 strain gauges) and recorded on

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a Gilson Polygraph. After securing hemostasis the animals were heparinized (10,000 units IV). Body temperature was measured with a rectal thermistor probe and maintained with heating pads (mean temperature =  $38.3 \pm SE$  0.3 C).

The above preparations occupied approximately an hour, following which arterial blood and mixed venous blood were sampled for measurement of oxygen and carbon dioxide tensions, oxygen content, pH, hemoglobin, hematocrit, and the first measurements (phase 1) of pulmonary extravascular water volume and cardiac output obtained with the double injection technique (see below).

Three hours later the above measurements were repeated (phase 2). Immediately following this, the chest was opened and the lungs removed after clamping the hila, for determination of lung water volume by weighing. The positions of the cardiac catheter openings were confirmed.

#### MEASUREMENT OF PULMONARY EXTRAVASCULAR WATER VOLUME (P.E.W.V.)

Two methods for measuring the P.E.W.V. were used. The first employed the double indicator injection technique. Details of and rationale for this method have been discussed by others,<sup>5,6</sup> but the principles are as follows. An indicator confined to the vascular space (indocyanine green) is injected rapidly into a central vein and the concentration time curve of the indicator in a peripheral artery recorded. From this curve, after correction for recirculation, the cardiac output and mean transit time ( $\bar{t}_H$ ) may be calculated, and hence, the central blood volume included between the site of injection and the site of sampling may be obtained by multiplication. If a second indicator that is freely diffusible at the pulmonary capillaries (tritiated water) is injected simultaneously, a second concentration time curve is obtained and longer mean transit time ( $\bar{t}_V$ ) calculated. Cardiac output is the same in both instances, and therefore the volume of distribution calculated for the freely-diffusible indicator is larger and includes the central blood volume and pulmonary extravascular water volume. The latter volume may then be obtained by subtraction ( $\Delta V$ ).

In using this technique we injected 1 ml of a mixture of 5 mg indocyanine green and 100  $\mu$ c tritiated water rapidly into a jugular vein. Simultaneously, carotid arterial blood was pumped (Sigmamotor 60–80 ml/min) into a timed, rotating rack so that a sample of approximately 1 ml was obtained each second for 30 seconds.

The second technique<sup>7</sup> used for measuring whole-lung water volume (T.V.) was to sacrifice the animals by opening the chest, rapidly clamp both hila, and remove the lungs. The lungs were trimmed of large vessels and bronchi, weighed, and homogenized in an electric blender; three weighed samples were removed for estimating the blood content by the acid hematin method and the remainder was dried to a constant volume in an oven at 100 C.

#### ANALYTIC METHODS

Blood gas tensions and pH were measured with a Corning microelectrode system. The sample for arterial oxygen tension ( $P_{aO_2}$ ) was analyzed immediately after withdrawal and corrected only for temperature and the blood-gas electrode differences. The remaining samples were immersed in ice water before analysis and corrected for both time and temperature differences.<sup>8,9</sup> Composition of calibrating gases was determined (Scholander's technique).<sup>10</sup>

Saturation and hemoglobin content were measured spectrophotometrically (Instrumentation Laboratory CO-Oximeter) and the oxygen content was calculated from these measurements together with the addition of dissolved oxygen.

For the measurement of whole blood content of indocyanine green a 0.4-ml blood sample was diluted with 0.8 ml of isotonic saline solution and centrifuged at 1,500 rpm for ten minutes. The optical density of the supernatant was measured at 805  $m\mu$  spectrophotometrically and the indocyanine green concentration obtained from a calibration line prepared for each experimental phase.

The tritiated water concentration was determined by liquid scintillation counting (Packard 3000 series). A 0.2-ml sample was pipetted into 20 ml of liquid scintillant (scintillant composition: P.P.O. 25 g, dimethyl P.O.P.O.P. 2.5 g, Triton 2 l, and toluene to

5 l). The vial was capped, centrifuged for ten minutes at 2,000 rpm and left in the refrigerated counting racks overnight at 4 C to minimize the background count. The recorded counts were converted to concentrations of radioactive water in  $\mu\text{c/l}$  with a calibration line prepared for each phase. The counting efficiency for this technique was approximately 15 per cent (a reasonable figure for this low-energy  $\beta$ -emitter).

For the estimation of pulmonary tissue whole-blood content, the weighed samples of homogenized lung were mixed with 10 ml of 0.01 N HCl to convert the hemoglobin to acid hematin. The samples were filtered and the optical density read at 540  $m\mu$  in a spectrophotometer. The acid hematin concentrations were determined with a calibration line prepared from whole-blood standards treated similarly.

#### CALCULATIONS

Alveolar oxygen tension ( $P_{A_{O_2}}$ ) was calculated from:

$$P_{A_{O_2}} = P_{I_{O_2}} - P_{H_2O} - P_{a_{CO_2}}$$

where the  $P_{I_{O_2}}$  was obtained from the paramagnetic oxygen analyzer.  $P_{H_2O}$  is the saturated vapor tension at body temperature and  $P_{a_{CO_2}}$  is assumed equal to  $P_{a_{CO_2}}$ .

The alveolar-arterial oxygen difference [ $P(A - a)O_2D$ ] was calculated by subtraction and the percentage venous admixture ( $\dot{Q}_s/\dot{Q}_t\%$ ) obtained from:

$$\dot{Q}_s/\dot{Q}_t\% = \frac{P(A - a)O_2D \times \alpha}{P(A - a)O_2D \times \alpha + C(a - \bar{v})O_2D}$$

where  $\alpha$  the solubility coefficient of oxygen = 0.0031 and  $C(a - \bar{v})O_2D$  is the arterio-mixed venous oxygen content difference.

The whole-blood concentrations of indocyanine green were converted to recovery ratios ( $R_B$ ) by dividing each value by the concentration of the dye injected. These recovery ratios were then plotted against time on semilogarithmic paper, and the slope of the exponential washout determined to correct for recirculation and to allow the area under the curve, extrapolated to infinity, to be calculated ( $\int_0^\infty R_B(t)dt$ ). These calculations are illustrated in figure 1.

The cardiac output ( $\dot{Q}_t$ ) was calculated from:

$$\dot{Q}_t = \frac{1}{\int_0^\infty R_B(t)dt}$$

The mean transit time ( $\bar{t}_B$ ) was calculated from:

$$\bar{t}_B = \frac{\int_0^\infty n \cdot R_B(t)dt}{\int_0^\infty R_B(t)dt} - (\text{catheter delay time})$$

where  $n$  is the sample number.

The distribution volume for the dye ( $V_B$ ) is then given by:

$$V_B = \dot{Q}_t \cdot \bar{t}_B$$

The data from the tritiated water analysis were treated similarly and the transit time ( $\bar{t}_w$ ) and volume of distribution ( $V_w$ ) for the water indicator calculated.

The extravascular volume of water distribution ( $\Delta V$ ) was then calculated:

$$\Delta V = V_w - V_B$$

From the wet and dry lung weights total pulmonary water volume (T.V.) was calculated after subtraction of the volume of contained blood.

Calculations and statistical analysis with Student's  $t$  tests for paired data were facilitated by programs written for a desk calculator.

#### Results

The two experimental phases were separated by a mean time of  $181 \pm SE 3.9$  min. Table 1 shows the experimental conditions. The inspired halothane concentration (mean, 3.55 torr) and  $P_{a_{CO_2}}$  (mean, 43 torr) were unchanged between phases 1 and 2. The rectal temperature increased 0.5 C and hemoglobin concentration, systemic blood pressure and  $C(a - \bar{v})O_2D$  also increased slightly between phases. There was a small decrease in  $pH_a$  (from mean 7.340 to 7.310), indicating slight metabolic acidosis. None of the above changes was statistically significant. The only sign of deterioration evident was the significant ( $P < 0.001$ ) decrease of the  $P_{a_{O_2}}$  (mean, phase 1 = 541, phase 2 = 511 torr).

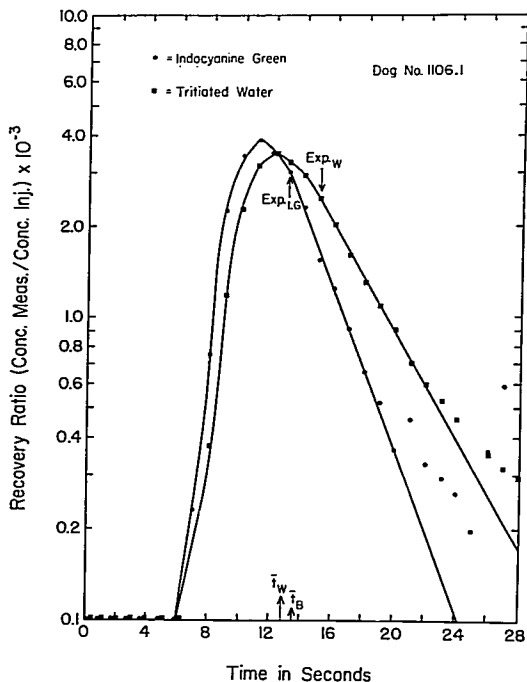


FIG. 1. Representative data obtained from the double injection technique. Curves are fitted to the points and the best exponential washout slopes chosen. The points marked Exp.<sub>w</sub> and Exp.<sub>lg</sub> are the beginnings of the exponential extrapolations used for calculating the area under the curves for tritiated water and indocyanine green, respectively. The calculated mean transit times for these curves are indicated on the abscissa for tritiated water ( $\bar{t}_w$ ) and indocyanine green ( $\bar{t}_n$ ).

That the condition of the animals was well maintained is further supported by the derived data in table 2. There were small changes, not significant statistically, in cardiac output, oxygen consumption, venous admixture and central blood volume. The increased mean transit times for both blood and water reflect the decreased cardiac output during phase 2. A significant ( $P < 0.001$ ) increase in  $P(A-a) O_2D$  occurred (mean, phase 1 = 128, phase 2 = 156 torr), but this was not related consistently to either an increased venous admixture or a decreased  $P\bar{V}O_2$  (table 1).

The excess volumes of distribution of water ( $\Delta V$ ) in phase 1 (mean = 108  $\pm$  SE 7 ml)

and in phase 2 (mean = 92  $\pm$  SE 9 ml) were not statistically significant, but decreases occurred in six of the eight animals. From the lung-weighting technique a mean total pulmonary water (T.W.) of 176  $\pm$  SE 12 ml was obtained; thus, the mean water content of these dogs' lungs was 78  $\pm$  SE 1.2 per cent of the wet lung weight or 3.8  $\pm$  SE 0.2 ml/g dry lung.

### Discussion

An increased alveolar-arterial oxygen tension difference has been reported to occur during general anesthesia and has been shown to

TABLE I. General Conditions:  
Means  $\pm$  SE of Eight Dogs

	Phase 1	Phase 2
Rectal temperature (C)	38.1 $\pm 0.3$	38.6 $\pm 0.3$
P <sub>i</sub> halothane (torr)	3.6 $\pm 0.1$	3.5 $\pm 0.1$
Hb <sub>a</sub> (g/100 ml)	11.48 $\pm 0.4$	11.84 $\pm 0.4$
Systemic blood pressure (mean, torr)	114 $\pm 5$	122.5 $\pm 4$
Pulmonary blood pressure (mean, torr)	10.6 $\pm 1.2$	10.4 $\pm 0.8$
Pulmonary pulse pressure (mean, torr)	8.0 $\pm 1.1$	9.6 $\pm 1.1$
Paco <sub>2</sub> (torr)	42.8 $\pm 1.6$	43.3 $\pm 2.0$
PaO <sub>2</sub> (torr)	541 $\pm 10$	511* $\pm 9$
P $\bar{v}$ O <sub>2</sub> (torr)	49.3 $\pm 2.6$	43.5 $\pm 2.9$
C(a - $\bar{v}$ )O <sub>2</sub> D (ml/100 ml)	5.2 $\pm 0.3$	5.6 $\pm 0.5$
pH <sub>a</sub> (units)	7.340 $\pm 0.021$	7.310 $\pm 0.023$

\* Difference between phases significant at 0.001 level.

result from both intra- and extrapulmonary factors.<sup>2,4</sup> In both man and animals progressive intrapulmonary changes may be minimized by mechanical ventilation with large tidal volumes independent of PaCO<sub>2</sub> changes.<sup>11</sup> The present studies confirm this observation, no consistent increases in venous admixture percentage were observed between phases 1 (7.4 per cent) and 2 (8.2 per cent). The P (A-a) O<sub>2</sub>D, while greater than that measured in conscious man, was comparable to values previously observed in anesthetized dogs. The significant increase of P (A-a) O<sub>2</sub>D observed between phases 1 (128 torr) and 2 (156 torr) was attributable partly to the increased C

(a- $\bar{v}$ ) O<sub>2</sub>D reflected in the decreased P $\bar{v}$ O<sub>2</sub> (mean, phase 1 = 49.3, phase 2 = 43.5 torr) and partly to changes in venous admixture percentage, but not consistently to either.

Therefore, in the context of these studies, the measurements of pulmonary water represent changes accompanying a steady state of anesthesia in the absence of serious deteriorations of arterial oxygenation.

The values of total pulmonary water (T.W.) obtained by weighing (mean, 3.80 ml/kg body weight) are comparable to the values of 3.73<sup>12</sup> and 3.5<sup>13</sup> ml/kg found in dogs by other investigators. Exposure to a total of four hours of anesthesia, therefore, did not result in a gross change in this volume, which includes both intra- and extracellular extravascular water.

The mean values of P.E.W.V. obtained with the double indicator technique ( $\Delta V$ ) did not change significantly from phase 1 (108 ml) to phase 2 (92 ml), but the interpretation of this measurement was more complex. The errors inherent in this technique are considerable, but 85 per cent of duplicate measurements have been shown to differ by less than 15 per cent.<sup>12</sup>

The ratio of  $\Delta V/T.W.$  indicates that the double injection technique measured 53 per cent of the total water present in these studies. Others have shown that this fraction remains constant and that the volume of water measured in the extravascular space with the double indicator technique is related linearly to the total pulmonary water volume over a wide range, including severe pulmonary edema.<sup>12</sup>

The reason for the discrepancy between the water volumes measured by the two techniques has not been established. That the radioactive water was not "lost" (*i.e.*, via the respired gases) is indicated by the sum of the recovery ratios for this indicator, which had a mean value of 101 per cent of that for the intravascular indicator. However, the water volume measured with the double injection technique is that volume associated with perfused pulmonary capillaries and, therefore, compared with the weighing technique will not include unperfused alveoli or areas of the

lung supplied by bronchial vessels. Furthermore, while tritiated water is freely diffusible and  $\Delta V$  may be expected to indicate both intra- and extracellular water from the capillary endothelial cells, across the pulmonary interstitial space and including the alveolar cells and lining layers, the exact boundaries remain to be defined.

Changes in  $\Delta V$  may be due either to hemodynamic alterations in the area of lung being perfused or to actual changes in P.E.W.V. In these studies the cardiac output, pulmonary arterial pressure and pulmonary arterial pulse pressure (table 1) did not change between phases. While the pulmonary venous pressure was not measured, it was unlikely to have altered significantly without a change in pulmonary arterial pressure,<sup>14</sup> and with constant ventilatory pressures no changes in the distribution of the ventilation/perfusion zones would be expected; therefore, the area of perfused lung probably was unchanged.

Thus, the constancy of the  $\Delta V$  indicates that the volume of extravascular pulmonary water in perfused areas of the pulmonary circulation was not altered during three hours of general anesthesia with mechanical ventilation. The onset of mechanical ventilation is accompanied by a reduction in  $\Delta V$ <sup>2</sup> and the tendency for  $\Delta V$  to decrease (in six of eight dogs) was perhaps due to this.

There are many circumstances<sup>15</sup> in which this satisfactory state may be disturbed. Thus, in sepsis and other forms of "shock," heart failure, fat embolism, and even certain neurologic lesions, the lungs are often characterized by an interstitial edema histologically. Clinical observations include decreased  $Pa_{O_2}$ , "wet"-sounding lungs on auscultation, and generalized fluffy opacities radiographically. It seems probable that anesthesia and resuscitation measures exacerbate some of these disturbances, either by hemodynamic alterations (including changes in plasma oncotic pressure) or by more subtle influences, such as decreased lymphatic drainage, changes in endothelial permeability, or interference with processes responsible for maintenance of normal alveolar and interstitial tissue architecture. The investigation of these complex interactions

TABLE 2. Derived Data: Means  $\pm$  SE of Eight Dogs

	Phase 1	Phase 2
Cardiac output ( $Q_c$ , l/min)	2.840 $\pm 0.143$	2.396 $\pm 0.197$
Oxygen consumption ( $\dot{V}O_2$ , ml/min STPD)	145 $\pm 8$	130 $\pm 12$
Alveolar-arterial $PO_2$ difference [ $P(A - a)O_2$ , torr]	128 $\pm 9$	156* $\pm 10$
Venous admixture ( $Q_v/Q_t$ , %)	7.4 $\pm 1.0$	8.2 $\pm 0.9$
Mean transit time (blood) ( $t_b$ , sec)	11.9 $\pm 0.6$	13.5 $\pm 0.7$
Mean transit time (water) ( $t_w$ , sec)	14.2 $\pm 0.6$	15.8 $\pm 0.9$
Central blood volume ( $V_b$ , ml)	555 $\pm 27$	528 $\pm 37$
Excess water volume ( $\Delta V$ , ml)	108 $\pm 7$	92 $\pm 9$
Total pulmonary water† (T.W., ml)	—	176 $\pm 12.5$
T.W./g dry lung† (ml/g)	—	3.8 $\pm 0.2$
$\Delta V/T.W.$ † (%)	—	53.1 $\pm 4.9$

\* Difference between phases significant at 0.001 level.

† Means from six animals.

$\Delta V$  from double indicator injection and T.W. from lung-weighting techniques.

should prove fruitful for the understanding and management of many clinical situations which presently are puzzling.

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### Pediatrics

**CHILDHOOD ASTHMA** Sixteen children, 8 to 14 years old, with symptomatic childhood bronchial asthma resulting in forced expiratory volumes at one second ( $FEV_1$ ) of less than 65 per cent of vital capacity, were studied.  $FEV_1$  and expiratory peak flow rate (EPFR) were evaluated 5, 15, and 30 minutes after inhalation of 2.5 mg of isoproterenol aerosol. Three test cycles were performed, with five-minute intervals between the 30-minute pulmonary function test and the next inhalation of isoproterenol. The results indicate that  $FEV_1$  increased an average of 57 per cent after the first dose and an average of 79 per cent 15 minutes after the third dose. EPFR increased 31 per cent after the first dose and 54 per cent after the third dose, with peak values occurring at the 5- or the 15-minute test. Heart rate changes showed marked individual variations, with increases of 10 to 60 beats/min, but bore no correlation to the increase in pulmonary function. Repeat doses of isoproterenol aerosol at 35-minute intervals resulted in significantly better  $FEV_1$  and EPFR than a single inhalation. Subsequent inhalations result in further improvement because the initial inhalation has decreased airway obstruction to permit further penetration of the aerosol into the smaller airways. (Featherby, E. A., Weng, T. R., and Levison, H.: *Measurement of Response to Isoprenaline in Asthmatic Children*, *Arch. Dis. Child.* 44: 382 (June) 1969.)