Effect of Norepinephrine and Fluid Administration on Pulmonary Extravascular Water Volume in Dogs

By James H. Ellis, Jr., and John F. Murray

ABSTRACT

The effects of norepinephrine-induced vasoconstriction on pulmonary extravascular water volume (PEWV) and central volume were studied before and after intravenous volume expansion with 5% dextrose and water (20 ml/kg body weight). PEWV was measured by double isotope dilution and gravimetric analysis and assessed by electron photomicrography. Comparisons were made with saline-treated control dogs. Thirty-six dogs were studied after they had been anesthetized with sodium pentobarbital. PEWV determined by indicator dilution increased during norepinephrine infusion, especially after volume expansion; in contrast, PEWV in control dogs was constant despite similar increases in pulmonary arterial and left atrial pressures. However, measurements of PEWV by gravimetric analysis and inspection of electron photomicrographs failed to reveal extravascular accumulation of water in vasoconstricted dogs. Thus, it was concluded that the increased PEWV measured by indicator dilution in norepinephrine-treated dogs compared with that in saline-treated dogs reflects more complete perfusion of pulmonary capillaries and access of the diffusible indicator to additional lung tissues and spaces. Improved capillary filling presumably is attributable to peripheral vasoconstriction and redistribution of blood into the thorax. PEWV determined by gravimetric analysis in dogs that had had open-chest procedures for lung biopsy and electron photomicrography was significantly less than that in dogs with their chests closed throughout the experiments. Although the mechanism for the water loss is unknown, the difference must be recognized when the results from various types of experiments are compared.

We have noticed that pulmonary edema can develop during the first few days of hospitalization in patients (1) who have systemic arterial hypotension, which often requires pressor agents such as norepinephrine, and (2) who are treated with intravenous fluids but not in large volumes, usually < 2 liters/day. We reasoned that two mechanisms, operating in concert, might cause fluid to extravasate into the lungs in this clinical setting. (1) Peripheral vasocostriction, owing either to stress-induced adrenergic responses or to infusion of vasoconstrictor drugs, would shift blood into the lungs and fill most of the available blood vessels. (2) Under these newly established conditions, the blood vessels of the body would be unable to accommodate as much additional volume as they ordinarily can, because the peripheral vasculature is contracted. Thus, intravenous administration of fluid in volumes in excess of a greatly limited reservoir capacity leads to congestion in the lungs and development of pulmonary edema. This theory assumes that the lungs are the most vulnerable site for fluid accumulation owing to changes in one or more of the factors that affect fluid formation or removal: (1) an increase in transmural hydrostatic pressure from the effects of adrenergic stimulation, (2) an increase in filtration from expansion of capillary surface area secondary to dilatation and recruitment, (3) an increase in permeability from the effects of circulating substances, and (4) a decrease in lymphatic drainage. To test our hypothesis, we studied the effects of fluid administration on pulmonary extravascular water volume (PEWV) in the presence and the absence of peripheral vasoconstriction.

Methods

Studies of PEWV were carried out in 36 mongrel dogs weighing between 14.3 and 22.5 kg. The basic protocol, illustrated in Figure 1, was the same throughout the study, but three different techniques were used to measure or detect PEWV: (1) multiple indicator dilution method, (2) gravimetric analysis of the lungs, and (3) electron microscopy of the lungs. After the dogs had been...
anesthetized with sodium pentobarbital, they were intubated and ventilated with a Harvard respirator using a tidal volume of 12 ml/kg body weight and adjusting respiratory rate to set arterial Pco2 at about 40 mm Hg. Thereafter, minute volume was constant. Cannulas for infusion were placed in a femoral vein and a cephalic vein and in the superior vena cava via the external jugular vein; a cannula for sampling and pressure measurements was inserted in a femoral artery. At intervals throughout each study and 2 minutes before each set of measurements, the dog’s lungs were inflated twice and held briefly at an airway pressure of 25 cm H2O to prevent formation of atelectasis. After the dogs had been allowed to stabilize, data were recorded and specimens were obtained. The initial measurements constituted period 1 and were considered to have been made at time 0 (Fig. 1). Five minutes later, an intravenous infusion of either norepinephrine diluted in saline (norepinephrine dogs) or plain saline (control dogs) was started through the cephalic vein using a Harvard constant-infusion pump. The rate of norepinephrine administration was increased from 0.1 to 0.4 µg/kg body weight min⁻¹ as necessary to achieve an increase in mean femoral artery pressure of 15–20 mm Hg above the initial value. Once the desired pressure had been reached and observed to be constant, the infusion was continued at the same rate for the remainder of the experiment. Control dogs received normal saline at a rate of 0.5 ml/min to approximate the volume of fluid given to the norepinephrine dogs. Twenty minutes after the constant infusion was begun and while it was being continued, the measurements of period 2 were obtained. Ten minutes after completion of period 2, fluid loading with 5% dextrose in water was carried out through the femoral vein. Each dog received 20 ml/kg body weight during a 10-minute interval; 2 minutes later, period 3 measurements were obtained.

Intravascular pressures were recorded using suitable transducers and a Beckman recorder. Arterial Po2, Pco2, and pH were analyzed with appropriate electrodes and a Beckman model 160 gas analyzer. The electrodes were calibrated with gases of known partial pressures just before each set of determinations. The hemoglobin concentration was determined colorimetrically, and the hematocrit ratio was obtained after centrifugation for 30 minutes at 2,000 g.

Group 1: PEWV Determined by Multiple Indicator Dilution (Closed Chest).—Besides the preliminary procedures just described, the 24 dogs in group 1 (14 norepinephrine dogs and 10 control dogs) had catheters positioned in the left atrium (via the left carotid artery), the pulmonary artery (via the right external jugular vein), and the right atrium (via the left external jugular vein) under fluoroscopic guidance. Multiple indicator dilution curves were obtained after injections into the right atrium of a mixture of 125I-labeled human albumin (7.5–10 µc), tritiated water (THO, 18–25 µc), and indocyanine green dye (3.75–5.0 mg) in a 1.5–2.0-ml aliquot. The injectate was preloaded into the injection catheter and flushed in as a bolus with 10 ml of normal saline. Blood was withdrawn from the femoral artery first through a Gilson densitometer and then into a multisyringe collection device. The moment of injection was recorded with a Honeywell Visicorder that also provided a helpful visual display of the injection of the indocyanine green dilution curve; when recirculation of the dye was clearly evident, withdrawal of blood was stopped.

The collection apparatus contained 29 5.0-ml glass syringes connected in series by one-way stopcocks to a common channel. The channel and the dead space of the syringes were prefilled with heparinized saline. The barrel of each syringe was raised in sequence during a 1-second interval by a rotating cam shaft system that was powered by an electric motor. After each syringe had been filled, its stopcock was turned to isolate the sample. The average sample size was 2.2 ml. At the end of each measurement period, the amount of blood withdrawn during the sampling procedures was replaced by an equivalent volume of 6% dextran in saline.

Because the collection device added an increment of dead-space volume as the syringes were loaded, the concentration of isotoxopes was reduced proportionately and the actual withdrawal time was prolonged. These aberrations could be corrected mathematically, because (1) the dead-space volume between successive samples (Y) was identical for all samples and was filled with heparinized saline and (2) the withdrawn volume (X) and the withdrawal rate were also identical for all samples. The corrected concentration of any sample (Ccor) could be related to the measured concentration (Cm) by a statement of conservation of mass: Cm • X = Ccor • (X – Y) or Ccor = Cm (1/[1 – Y/X]), which corrects the sample indicator concentrations. Similarly, each sample was delayed in time by the amount Y/X, because the withdrawal rate was constant. The corrected time for any sample (Tcor) could be obtained by multiplication of the measured time for collection (Tm) by (1 – Y/X); the corrected value represents the actual time of appearance of each sample when there is no progressive increase in dead space. Because the withdrawal rate and the ratio of dead-space volume to withdrawal volume (Y/X) were constants, the total time was prolonged by the same fraction, (1 – Y/X). Thus, calculation of the corrected mean transit time of the curve (Tm) in terms of the measured mean transit time (Tm) could be obtained by the following relationship: Tm = (1 – Y/X)Tm.

A 0.5-ml sample of whole blood from each specimen and six to ten samples of suitably diluted injectate (for
Cardiac output was calculated in the usual manner using the corrected values for the concentrations of the two isotopes. PEWV was computed according to the method of Chinard and Enns (1) as modified by Goresky and associates (2) to obtain a composite mean transit time value ($t_{comp}$) for the passage of an intravascular label consisting of red blood cells and plasma. Because only plasma was labeled in our experiments, we calculated the mean transit time for red blood cells ($t_{RBC}$) by combining Eqs. 6 and 7 of Goresky and co-workers (2) and using a lung wet weight ($g$)–body weight (kg) ratio of 9.52 (from data obtained in eight normal dogs studied in our laboratory). Accordingly,

$$t_{RBC} = t_{Air} - \frac{1.47Q + 0.021}{9.52Q(1 - Hct)},$$

where $Q$ is expressed in ml/sec kg$^{-1}$ body weight (the same units as in Eq. 3), and $t_{Air}$ is the mean transit time of the $^{125}$I plasma label. Once $t_{RBC}$ is derived, $t_{comp}$ can be computed from Eq. 9 of Goresky and associates:

$$t_{comp} = \frac{\alpha Hct}{\rho} + \frac{\beta (1 - Hct)}{\rho} t_{Air},$$

where $\alpha$ is the water content of red cells (0.70 g H$_2$O/ml cells), $\beta$ is the water content of plasma (normally 0.93 ml H$_2$O/ml plasma$^1$), and $\rho$ is the water content of whole blood ($\rho = \alpha Hct + \beta (1 - Hct)$). Accordingly, PEWV, relative to the water content of the blood, is

$$PEWV = Q(t_{THO} - t_{comp}).$$

The values of $t_{comp}$ derived from Eqs. 1 and 2 differ from the measured values of $t_{Air}$ by only a few percent (mean = 1.8% in norepinephrine dogs and 1.4% in saline dogs). However, the use of $\rho$ in Eq. 3 transforms the flow of blood into the flow of water (the appropriate reference) and provides a common basis for comparing PEWV values obtained by indicator dilution and gravimetric methods of analysis.

"Central volume" was calculated as the product of the mean cardiac output from the $^{131}$I and THO curves and $t_{comp}$; the latter was used to correct for differences between the transit times of red blood cells and plasma through the pulmonary circulation. All transit times were corrected for the delay caused by the catheter and the densitometer.

Group 2: PEWV Determined by Gravimetric Analysis.—In 18 dogs (8 norepinephrine dogs and 10 control dogs) PEWV was determined by gravimetric analysis according to the usual procedures and protocol described earlier had been completed. Ten of the 18 dogs were also included with group 1 dogs because the entire series of group 1 measurements was performed before the lungs were obtained for gravimetric studies. Gravimetric analysis of PEWV was performed according to the method of Pearce and co-workers (3). Heparin (10,000 units) was used as an anticoagulant, and $^{125}$I-albumin was used to label the plasma volume; the isotope was injected as part of period 3 studies in the 10 dogs that were included in both groups 1 and 2 and was given separately to the 8 other dogs that did not have multiple indicator dilution curves performed. After a 10-minute equilibration period, a blood specimen was obtained for $^{125}$I and hemoglobin determinations. Cardiac arrest was then produced by injecting concentrated KCl into the left atrium. The chest was quickly opened, and both lungs were removed.

Superficial blood was gently wiped off, and the lungs were inspected and weighed. Both lungs were minced in a blender that contained about 200 ml of distilled water to facilitate homogenization. The $^{125}$I concentration of the total weighed homogenate and the hemoglobin concentration of the supernatant fluid of a centrifuged aliquot of the homogenate were determined by gamma counting and colorimetry, respectively. The homogenate was then dehydrated in an oven at 80°C until a stable weight was obtained (usually 2-3 days). The water content of the lungs, exclusive of the amount of water contained in the residual blood, was calculated by the method of Pearce and associates (3).

The plasma volume component of the residual volume of blood in the lungs was computed from the $^{131}$I counts in the lung homogenate; accordingly, any leak of the label from the vascular compartment into the interstitial spaces of the lung during the course of the experiment would result in falsely elevated values. Some movement of $^{131}$I into the extravascular space must have occurred in those group 1 dogs that also had gravimetric measurements; however, the effect of this phenomenon appeared to be negligible under the conditions of our experiments for the following reasons. (1) PEWV values did not differ between those dogs that received $^{131}$I in period 1 and those that did not. (2) Residual blood plasma volumes computed from the lung hemoglobin concentration and the hematocrit did not differ from the plasma volumes measured with $^{125}$I ($P > 0.5$).

Group 3: PEWV Determined by Electron Microscopy (Open Chest).—In eight dogs, four of which were also included in group 1 (one norepinephrine dog and three saline dogs), immediately after period 3 measurements had been made, the chest was opened by a sternum-splitting incision, and one lobe of the right lung was obtained for electron microscopic studies. The dog was then killed by an injection of KCl after which ligatures that had been placed around the lung hilas were tightened, and the lungs were removed, weighed, and inspected. Total lung water, excluding the tissue submitted for electron microscopy, was measured, and its partition between blood and pulmonary tissue was determined by the method described earlier.

The biopsies were prepared by direct osmium fixation (2% osmium buffered with veronal acetate to pH 7.4), fixed for 90 minutes, dehydrated with acetone, and embedded in araldite. Numerous random sections were prepared. Electron photomicrographs were inspected for

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$^1$Because the 0.07 ml solids/ml plasma will be diluted by the same proportion as $Hct$ when plasma volume is expanded by infusion of dextrose and water, the effect on $\beta$ can be calculated.
evidence of extravascular fluid accumulation in the lung: distention of the peribronchovascular space, flattening of capillary endothelium (indicative of capillary distention), widening of the interstitial space in the thick portion of the interalveolar septum, separation of collagenous fibrils, protein accumulation (dilatation of pinocytotic vesicles), and fragmentation of erythrocytes or other cells (4).

Statistical Methods.—Within-group comparisons (either norepinephrine or saline dogs) were made using each dog as its own control; the significance of the changes was analyzed by the paired Student’s t-test. Between-group comparisons (norepinephrine vs. saline dogs) were made using the unpaired Student’s t-test of (1) the absolute values during any given experimental period and (2) the changes from one period to the next (e.g., changes from period 1 to period 2 or from period 2 to period 3).

Results

Group 1.—Means ± SE and the statistical significance of the changes in the measurements in control and norepinephrine dogs are presented in Table 1. The initial (period 1) findings were similar except that central volume was slightly but significantly higher (P < 0.05) in control dogs than it was in norepinephrine dogs. There were no significant changes in the control dogs during infusion of low volumes of saline (period 2); in contrast, the cardiac index, mean systemic arterial blood pressure, central volume, PEWV, and hematocrit increased significantly in norepinephrine dogs (Table 1). After the fluid load (period 3), all variables in the control group changed significantly except PEWV and mean systemic arterial blood pressure. All variables including PEWV and systemic arterial blood pressure changed significantly in the norepinephrine dogs in period 3 compared with period 2; in addition, the changes in cardiac output (P < 0.05), central volume (P < 0.01), and PEWV (P < 0.001) were of greater magnitude in norepinephrine dogs than they were in control dogs.

Group 2.—The results of the gravimetric analysis of PEWV are presented in Table 2. Despite the large differences in PEWV between control and norepinephrine dogs when the double isotope dilution method was used, no significant difference was observed when the gravimetric analysis was employed. This finding held whether the results were expressed per kilogram of body weight, as fractional water content, or as milliliters of water per gram dry weight.

Group 3.—There was no evidence on inspection of electron photomicrographs (Fig. 2) of accumulation of extravascular fluid in the lung (e.g., flattening of capillary endothelium, widening of interstitial spaces, separation of fibrils, accumulation of protein, and cellular fragmentation). There was also no apparent difference between norepinephrine and control dogs.

Gravimetric analysis of the bulk of the lungs that remained after the specimens for microscopy had been removed also failed to reveal differences between norepinephrine and control dogs (Table 2). However, it is of interest that fractional PEWV

<p>| TABLE 1 |</p>
<table>
<thead>
<tr>
<th>Within-Group Changes in Hemodynamic, Blood Gas, and Pulmonary Extravascular Water Volume (PEWV) Measurements in Group 1 Dogs Given Either Saline (n = 10) or Norepinephrine (n = 14)</th>
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<tr>
<td>Cardiac index (ml/kg min⁻¹)</td>
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<td>Femoral arterial pressure (mm Hg)</td>
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<td>Pulmonary arterial pres- sure (mm Hg)</td>
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<td>Arterial pH</td>
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<td>PEWV (ml/kg)</td>
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<td>Central volume (ml/kg)</td>
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<td>Hematocrit (%)</td>
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All values are means ± SE. *P values refer to significance of changes from one period to the next.

†P < 0.05.
and PEWV/dry weight values were significantly lower ($P < 0.025$) in group 3 (open-chest, control) than they were in group 2 (closed-chest, control) dogs.

**Discussion**

This study was designed primarily to examine a hypothesis about the mechanisms of pulmonary edema formation in seriously ill patients. The results in group 1 using the multiple indicator dilution technique appeared to support our theory that the combination of peripheral vasoconstriction and fluid administration leads to the extravasation of fluid into the lungs. But the results of the experiments in groups 2 and 3 failed to confirm the impression that norepinephrine-treated dogs accumulated more PEWV than did nonvasoconstricted control dogs. Two important conclusions can be derived from the experimental data. (1) The multiple indicator dilution method is not a sensitive way of detecting "early" (i.e., mild) pulmonary edema, because it does not differentiate between an increase in the extent of the vascular bed that is being perfused and an actual accumulation of extravascular fluid. (2) Norepinephrine, in doses sufficient to produce a moderate increase in mean systemic arterial blood pressure (16 mm Hg), causes a redistribution of blood from the vessels of peripheral tissues into those of the lungs; moreover, this effect is considerably magnified if total intravascular volume is expanded by the administration of fluid (dextrose/water).

**Double Indicator Dilution Method.**—Measurement of PEWV by the double indicator dilution method depends on the principle that as a freely diffusible indicator (e.g., THO) flows through pulmonary capillaries it diffuses into and equilibrates with water in the extravascular space and then diffuses back into the bloodstream; in contrast, the intravascular indicator, labeled plasma or red blood cells, remains confined to the vascular space as it flows through the lungs. Derivation of $t_{comp}$ provides a reference intravascular label by adjusting for differences in transit times through the lung of red blood cells and plasma. If recovery of the diffusible and nondiffusible isotopes is complete at the sampling site, the difference between the mean transit times of the composite reference curve and the THO curve can be used to compute the extravascular volume of distribution of the diffusible indicator, i.e., PEWV. Our criterion for satisfactory recovery was that cardiac outputs calculated from the THO and $^{125}$I curves had to agree within $\pm 10\%$, otherwise the data were rejected. The initial values of PEWV in the norepinephrine and control dogs (both 3.2 ml/kg body weight) are in reasonable agreement with data reported by other investigators (5, 6) using similar techniques (3.6 and 3.5 ml/kg body weight, respectively$^2$). These authors and others (7) have emphasized that extravascular water in a given region of lung will not be detected unless blood perfuses that region and THO has access to its tissues and spaces. This phenomenon accounts for the finding in our control dogs that the final measurement of PEWV by the indicator dilution technique was 69% of the value obtained by gravimetric analysis (Fig. 3). The "missing" water can be accounted for by the fact that not all pulmonary capillaries are being perfused under resting (anesthetized) conditions, and

$^2$The values shown were corrected by multiplying the authors’ data by 0.83, the water content of normal blood; the values would be slightly lower if the results had been calculated according to Eqs. 1 and 2.

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Representative electron photomicrograph from a norepinephrine-treated dog. CAP = pulmonary capillary, RBC = red blood cells, PL = platelet, AS = alveolar space, C = collagen fibrils, EL = elastic fibrils, EP, = type 1 alveolar epithelial cell, and EN = endothelial cell. The pulmonary capillary and the interalveolar septum (and their constituents) show no abnormalities, and there is no evidence of excess fluid accumulation. Horizontal bar = 1 μm.

the water in some lung tissues (airways, walls of large blood vessels, peribronchial and perivascular spaces and contents) is not “in reach” of a diffusible substance that perfuses pulmonary capillaries. By exercising dogs, Goresky and co-workers (2) showed that increasing the number of blood vessels being perfused results in an increase in PEWV toward an asymptote as progressively more lung is “exposed” to the diffusible indicator. An increase in PEWV, therefore, can result from either an
water (period 3), arterial \( P_{O_2} \) and \( P_{CO_2} \) increased and pH decreased in both groups. Because tidal volume and respiratory frequency were held constant throughout the experiments, the increase in \( P_O_2 \) can be accounted for by the increase in cardiac output (less venous admixture effect) and an improvement in the matching of ventilation and perfusion (caused by the increase in pulmonary arterial pressure). The same mechanisms should decrease both alveolar dead space and \( P_{CO_2} \) (unless regions developed in the lung that were ventilated but not perfused at all); thus, the observed rise in \( P_{CO_2} \) was probably caused by increased \( CO_2 \) production, part of which was consequent to the metabolic acidosis that accompanied the dextrose infusion.

**Effects of Open Vs. Closed Chests.**—We are unaware of previous investigations concerning the effects of opening the chest on PEWV; however, it is of interest that Pearce and co-workers (3), who used an open-chest preparation, reported PEWV values determined by isotope dilution (2.78 ml/kg body weight) and gravimetric analysis (3.93 ml/kg body weight) that are considerably lower than those from our study and the studies of others (4, 5) using closed-chest preparations. How opening the chest serves to reduce PEWV is not known but might include one or more of the following: (1) desiccation of the lung, (2) increased removal of PEWV by lymphatics, and (3) decreased PEWV formation. If these mechanisms are operating, the factor of time should contribute to the magnitude of the changes. The lower values for PEWV in the studies of Pearce et al. (3) in which the chest was opened for prolonged periods compared with those in our study in which the chest was opened for < 10 minutes support such a time-dependent effect.

In summary, these investigations do not answer the question of whether seriously ill patients who are vasoconstricted from endogenous or exogenous adrenergic stimuli are predisposed to the development of pulmonary edema owing to redistribution of their vascular volumes. If the phenomenon that we have identified in anesthetized dogs occurs in man, it would suggest that the congested lungs of vasoconstricted patients may be more vulnerable to the effects of any given additional factor(s) that increases fluid filtration.

**Acknowledgment**

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Effects of Open Vs. Closed Chests.—We are unaware of previous investigations concerning the effects of opening the chest on PEWW; however, it is of interest that Pearce and co-workers (3), who used an open-chest preparation, reported PEWW values determined by isotope dilution (2.78 ml/kg body weight) and gravimetric analysis (3.93 ml/kg body weight) that are considerably lower than those from our study and the studies of others (4, 5) using closed-chest preparations. How opening the chest serves to reduce PEWW is not known but might include one or more of the following: (1) desiccation of the lung, (2) increased removal of PEWW by lymphatics, and (3) decreased PEWW formation. If these mechanisms are operating, the factor of time should contribute to the magnitude of the changes. The lower values for PEWW in the studies of Pearce et al. (3) in which the chest was opened for prolonged periods compared with those in our study in which the chest was opened for < 10 minutes support such a time-dependent effect.

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