Anesthesiology
57:103-110, 1982

Influence of Ventilation on Response to Fluid Load in Dogs: Body Water and Albumin Distribution

Bryan E. Marshall, M.D., F.R.C.P., Arnold J. Berry, M.D.,† Carol Marshall, Ph.D.,‡ Ralph T. Geer, M.D.,§*

Beagle dogs were sedated with intravenous pentobarbital ventilated for 46 h with either spontaneous ventilation (SV), controlled ventilation (CV), or controlled ventilation with 10 cmH_2O end-expiratory pressure (CV + PEEP). Throughout the study period saline (0.45 per cent with added KCl) was infused at 120 ml/h. The influence of ventilatory mode on the accumulation and organ distribution of body water during continuous fluid loading was determined. Five animals were studied with each ventilatory mode. In all groups body weight increased, but with SV weight increase began only after 28 h and increased by 7.2 per cent of body weight by 46 h. With CV the weight increase was continuous and was 9.2 per cent of initial body weight at 46 h. With CV + PEEP the increase was earlier and greater reaching 22 per cent by 46 h. Radioisotopic analysis of total body water, extracellular water, and plasma and erythrocyte water demonstrated that the body weight increase was due to water retention principally in the extracellular compartment.

Postmortem analysis of the major body organs for water and albumin distribution demonstrated increased water in the muscle and subcutaneous tissue of the CV + PEEP group that accounted for the total difference in water retention compared to the SV or CV animals. Organ extravascular albumin content varied relatively little between ventilatory modes.

Ventilation with increased mean intrathoracic pressure was accompanied by marked and prolonged fluid retention. In these otherwise healthy dogs the water accumulation was confined to sites that appeared unlikely to interfere with organ function. (Key words: Fluid balance: body weight; distribution. Protein: albumin. Ventilation: controlled; positive end-expiratory pressure; spontaneous.)

CONSTANCY of extracellular fluid volume contributes to circulatory stability and results from mechanisms that govern renal sodium excretion.[1] Salt and water elimination vary in response to changes in the activity of volume-sensitive receptors in several organs, but the vascular filling that is "perceived" by the volume receptors can be misled by some therapeutic maneuvers so as to distort the homeostatic outcome. In particular, acute experiments have shown that increased intrathoracic pressure, associated with ventilatory support, alters cardiac and great vessel transmural pressures with retention of sodium chloride and water.[2,3] Increased body weight in patients undergoing respiratory intensive care has been attributed to this mechanism[4] but controlled observations under prolonged experimental conditions have not been reported.

In the present studies a constant salt and water load was imposed on healthy sedated dogs. The time course, extent, and sites of water accumulation were then observed when the animals were either allowed to breathe spontaneously or were subjected to mechanical ventilation with or without 10 cmH_2O PEEP for 46 h.

Materials and Methods

A total of 15 female beagle dogs were studied. Some 3-7 days prior to study each animal was anesthetized and a heparin-filled Silastic® catheter was secured in the left atrium through a thoracotomy incision. Postoperatively prophylactic antibiotics were administered four times per day for 5 days and food and water were provided *ad libidum*.

At the onset of the study each animal was anesthetized with 30 mg/kg pentobarbital intravenously and the trachea intubated with a sterile tube. A Foley catheter was secured in the urinary bladder, cannulae inserted in a carotid artery, internal jugular vein and the inferior vena cava, and a Swan-Ganz catheter advanced into a main pulmonary artery. Catheter patency was maintained by continuous infusion of heparinized saline at 0.3 ml/min. Throughout the study a solution of 0.45 per cent NaCl with 20 mEq KCl/l was administered intravenously at 2.0 ml/min. During the control period (period I) all dogs breathed spontaneously until cardiovascular conditions were constant for three consecutive measurements during a 30-min period. Thereafter, each dog was randomly assigned to one of three ventilatory modes that were maintained for the rest of the study. These modes were spontaneous ventilation (SV), controlled ventilation (CV), or controlled ventilation with 10 cmH_2O positive end-expiratory pressure (CV + PEEP). Controlled ventilation was provided with an Emerson ventilator and positive end-expiratory pressure with a 10 cmH_2O Boehringer PEEP valve. The respiratory gases were humidified air supplemented with oxygen as necessary to maintain arterial oxygen tension greater than 60 mmHg. With controlled ventilation a tidal volume of 15 ml/kg body weight was selected and respiratory rate adjusted to maintain normocarbia. The dogs were maintained on a metabolic balance in the prone position during measurement periods but otherwise were rotated to

* Professor of Anesthesia.

† Research Fellow.

‡ Assistant Research Professor.

§ Associate Professor of Anesthesia and Medicine.

Received from the Department of Anesthesiology, University of Pennsylvania Medical School, Philadelphia, Pennsylvania 19104. Accepted for publication January 11, 1982. Supported in part by USPHS Research Grants 5701-GM-00215 from the National Institute of General Medical Science and by R01-HL16916 from the National Heart, Lung and Blood Institute.

Address reprint requests to Dr. Bryan E. Marshall.

0003-3022/82/0800/0103 $01.20 © The American Society of Anesthesiologists, Inc.

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/57/2/103/305559/0000542-198208000-00007.pdf by guest on 22 January 2022

left or right lateral or supine positions at hourly intervals. At these same intervals the lungs were hyperinflated to 30 mmHg three successive times and secretions aspirated as necessary. The measurements reported here were performed at five intervals during the 46-h study. The control period is designated period I and ended at zero time. Period II was three hours after beginning the assigned ventilatory mode. Period III was at 26 h, period IV at 29 h, and period V at 46 h, respectively.

At each measurement period the body weight, vascular pressure, arterial blood-gas tensions, hematocrit, plasma oncotic pressure, and plasma total proteins were recorded.

At periods II and III, whole body extracellular water space was measured by standard techniques.[5] For this purpose an equilibrium was established by a constant infusion of ^{14}C-inulin beginning three hours earlier. At each measurement period the ^{14}C-activity per milliliter of plasma water was measured. The corresponding total body content of ^{14}C-inulin was measured by discontinuing the infusion and measuring the total ^{14}C-inulin activity in urine collected during the subsequent 12 h.

At period III total body water was estimated from the equilibrium concentration of plasma deuterium divided by the volume of deuterated water injected three hours previously, corrected for urinary losses.[5] Blood removed for analysis was replaced with an equal volume of compatible filtered blood from a donor animal.

Following a final equilibration with double strength ^{14}C-inulin during period V, the animals were killed in the following manner. A mid-sternal thoracotomy was performed and a noose arranged around the base of the heart. One milliliter of albumin freshly labeled with technetium (^{99m}Tc) was injected intravenously followed by 100 IU of heparin. Arterial blood samples were obtained precisely 5 and 10 min later for calculations of plasma water volume from the ^{99m}Tc activity,[5] and the erythrocyte volume. A final blood sample was withdrawn and the circulation was arrested by tightening the noose and the inulin infusion discontinued. For the animals breathing spontaneously respiration was supported manually with an Ambu bag throughout this period.

The hematocrit and hemoglobin content were measured in the final blood sample, together with the water content of its plasma and erythrocytes. The ^{99m}Tc-albumin gamma activity and the ^{14}C-inulin beta activity (corrected for quenching) were counted. Plasma samples were analyzed for total protein by refractometry and for albumin by radial immunodiffusion assay.

The abdominal and thoracic organs were removed, samples of muscle obtained from all major tissue masses, non-fatty subcutaneous material (see below) collected, and the entire shaved skin removed. Each tissue was then subjected to separate analysis.

Analysis of Organs

For calculation of the total organ water and albumin content and to allow separation of the various intra- and extravascular and intra- and extracellular compartments the organs were analyzed as described below.

Organs were excised and washed with saline and gently dried with tissue paper. The intestines were opened and washed free of contents, and to reduce self-digestion, they were contained in a plastic bag submerged in ice water. Muscle samples were obtained from all major muscle masses and were not washed. The material identified as subcutaneous requires special mention for this refers to the non-fat almost translucent light brown tissue that was observed subcutaneously in all animals but was particularly evident in the CV + PEEP group. This tissue was gelatinous when first exposed at autopsy, but rapidly (1–5 min) became liquified and flowed out of the tissues. The liquified material could not be collected without contamination with spilled blood and, therefore, samples of the gelatinous material were collected immediately after cutting into the tissue and no attempt was made to collect the entire mass.

Each organ was weighed and homogenized in a Waring® blender. A weighed sample (approximately 5 g) of this crude homogenate was combined with 25 ml of distilled water and homogenized for 15 min with a Willens Polytron high speed homogenizer; the sample was cooled with a jacket of ice water. Three weighed samples (approximately 2 ml) were removed for counting the emissions from ^{99m}Tc albumin in a gamma spectrometer (Intertechnique Model CG-4000) and the tissue plasma content calculated. The remaining homogenate was allowed to stand overnight in a cold room at 4° C. The following day the homogenates were mixed thoroughly and aliquots removed for analysis as follows: (1) Approximately 15 ml of homogenate were weighed, freeze-dried (Virtis Freeze Dryer) and reweighed to obtain the total water content. (2) The remainder of the homogenate was centrifuged at 30,000 *g* for 60 min (International B-20 Centrifuge). A thin layer of lipid at the surface was removed and this supernatant decanted. The beta emissions associated with ^{14}C-inulin were counted in a scintillation spectrometer (Intertechnique Model SL-30). Correction factors for quenching were obtained by adding known quantities of ^{14}C-inulin to additional samples as internal standards. After allowing for the added water and plasma content, the tissue interstitial water volume was calculated. A 5-ml sample of supernatant was weighed, freeze-dried, and reweighed, to obtain the water content. The hemoglobin content of the supernatant was measured spectrophotometrically.[6] For skeletal muscle and heart muscle the myoglobin content also was measured[7] and the hemoglobin measurement corrected ap-

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/57/2/103/305559/0000542-198208000-00007.pdf by guest on 22 January 2022

propriately. The erythrocyte volume of each organ was then calculated. Albumin content was measured by radial immunodiffusion assay.[8] From these analyses the total water and albumin content of each organ was derived and separated into the various intra- and extravascular and intra- and extracellular compartments. The equations used for these calculations are shown in the Appendix.

These data were initially analyzed statistically by two-way analysis of variance comparing the effects of ventilatory mode and of time. Differences between means were examined with Tukey's specific comparison test with significance at $P < 0.05$. Other statistical tests are identified where necessary.

Results

General

The mean body weight of the 15 female beagle dogs was 10.26 ± 0.55 g at period I. Body temperature was 36.7 ± 0.6° C after the surgical preparation, but by period II had increased to 37.7 ± 0.7° C, and thereafter did not change significantly in the three groups. Arterial oxygen tension was maintained with variable amounts of oxygen added to the inspired gas mixture; there were no significant differences between groups and the overall mean arterial oxygen tension was 97.5 ± 12 mmHg. End-tidal carbon dioxide concentration was monitored continuously and ventilatory requirements adjusted appropriately; for the ventilated animals the overall mean arterial carbon dioxide tension was 36.0 ± 2 mmHg. For the five animals respiring spontaneously the mean arterial carbon dioxide tensions were 35.7 ± 2.3, 39.2 ± 2.8, and 39.4 ± 3 mmHg in periods II, IV, and V, respectively. Arterial *p*H did not change significantly with time and was not different between groups; the overall mean value was 7.342 ± 0.024 units.

Intrathoracic pressure was systematically different between the three ventilatory modes with mean esophageal pressure values of −1.7 + 0.33 mmHg during SV, −0.26 ± 0.3 mmHg for CV, and +3.7 ± 0.4 mmHg for CV + PEEP. No further changes of esophageal pressure occurred with time once the ventilatory mode had been established.

For the remainder of the general data the significant changes are discussed below.¶ For the five animals maintained on spontaneous ventilation the initial body weight (period I = 10.4 ± 0.7 g) was increased significantly only at period V (to 11.2 ± 0.8 g). Large vessel hematocrit (period I = 38.6 ± 1.5%) did not change significantly, although plasma protein and plasma oncotic pressure decreased throughout the study to reach values at period V that were only 75 per cent and 65 per cent, respectively, of those at period I (plasma protein = 5.4 ± 0.1 g/dl, oncotic pressure = 16.7 ± 0.4 mmHg). For all ventilatory modes 68 ± 5 per cent of the changes in total plasma protein was due to decreased albumin. Small, but statistically significant, decreases in systemic arterial pressure occurred from 150 ± 4 mmHg at period I to 132 ± 6 mmHg by period V, but no other significant changes of central venous pressure, transmural pulmonary artery or left atrial pressure occurred.

Results from the CV group were similar to SV. Body weight (period I = 9.8 ± 0.5 g) increased throughout but was significantly different only at period V (to 10.7 ± 0.7 g). Hematocrit was unchanged (period I = 36.1 ± 0.6 per cent), while total plasma protein and plasma oncotic pressure decreased progressively and significantly throughout the study from 5.5 ± 0.2 g/dl and 16.3 ± 0.9 mmHg at period I to 4.2 ± 0.3 g/dl and 11 ± 1.2 mmHg at period V, respectively. A modest decrease in transmural pulmonary artery pressure at period V was the only statistically significant change of the hemodynamic measurements. Comparing the CV group with the SV group reveals essentially no difference at each time interval.

In contrast, the changes observed with CV + PEEP were more marked. In these animals body weight (period I = 10.6 + 1.5 kg) was increased significantly at period IV (to 12.2 ± 1.4 kg) and by period V (to 12.9 ± 1.4 kg) had increased by 22 per cent. These changes were significantly greater than in the other two ventilatory modes. Plasma oncotic pressure and total plasma protein decreased progressively and significantly from 16.6 ± 1.6 mmHg and 5.3 ± 0.49 g/dl in period I to 9.0 ± 0.7 mmHg and 3.6 + 0.29 g/dl by period V, respectively. In this group hematocrit also decreased significantly from 36.2 ± 3.8 per cent in period I to 27.6 ± 3.5 per cent in period V. Systemic arterial pressure demonstrated a small decrease by period V, while transmural pulmonary artery and left atrial pressures did not change. Central venous pressure was increased significantly as a result of PEEP, but this difference was not present if calculated as a transmural pressure. Inferior vena-caval pressure was also measured in all animals and showed no significant increases with time in any of the groups.

Whole Body Water Compartments

The measured values for the whole body water compartments are shown in table 1. Total body water mea-

¶ See NAPS Document No. 03971 for 8 pages of supplementary material. Order from ASIS/NAPS, c/o Microfiche Publications, P. O. Box 3513, Grand Central Station, New York, NY 10017. Remit in advance for each NAPS accession number. Institutions and organizations may use purchase orders when ordering, however, there is a billing charge for this service. Make checks payable to Microfiche Publications. Photocopies are $5.00. Microfiche are $3.00 each. Outside the United States and Canada, postage is $3.00 for a photocopy or $1.00 for a fiche.

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/57/2/103/305559/0000542-198208000-00007.pdf by guest on 22 January 2022

TABLE 1. Body Water Measurements (n = 5)

	Spontaneous Ventilation	Controlled Ventilation	Controlled Ventilation + PEEP
Total body water (deuterium) period III (ml)	7,584 ± 483	7,569 ± 525	7,953 ± 746
Extracellular water (inulin) period II (ml)	2,927 ± 167	3,076 ± 273	3,154 ± 445
Extracellular water (inulin) period IV (ml)	2,930 ± 131	3,839 ± 283*	4,199 ± 513*
Plasma water (albumin) period V (ml)	547 ± 45	551 ± 58	650 ± 57†
Erythrocyte water period V (ml)	182 ± 30	174 ± 21	166 ± 25

Values are means ± SEM.
* Indicates period IV extracellular water significantly ($P < 0.05$) different from period II by paired Student *t* test within groups.
† Indicates plasma water value significantly ($P < 0.05$) different from other plasma volumes by unpaired Student *t* test, between groups. No other differences significant.

sured at period III was not significantly different between groups and amounted to 71 per cent, 72 per cent, and 68 per cent, respectively, of the body weight at that time. The extracellular water volume measured with ^{14}C-inulin at period II was approximately 3,000 ml in all three groups. At period IV extracellular water volume had increased significantly in both the CV group and the CV + PEEP group, but not in the SV group. Total plasma water measured at period V in the CV + PEEP group was significantly greater than either in the CV or SV groups. Total erythrocyte water was not different between the groups.

From these basic measurements, a number of additional body water compartment values were derived for each of the periods and these values are summarized in figure 1.

The total erythrocyte volume calculated at period V was assumed constant throughout the study. Plasma water volumes were unchanged throughout the SV and CV but increased significantly from 443 ± 48 ml in period I to 650 ± 57 ml by period V with CV + PEEP.

Examination of the data for extracellular water volume at periods II and IV suggested that most of the gain in body weight could be accounted for by accumulation of extracellular water. A linear regression of changes in extracellular water volume with changes of body weight produced the equation:

$$\text{Gain Extracellular Water (ml)} = 1.114\ (\text{Weight Gain g}) - 103.$$

The correlation coefficient (r = 0.84) was significant ($P < 0.01$). Using this relationship the extracellular water for period V was calculated for each of the animals using the weight gain between periods IV and V.

From these volumes of extracellular water at each period, the plasma water volume was subtracted and the interstitial water volumes derived. The initial volumes of interstitial water at period I (SV = 2,396 ± 174 ml, CV = 2,430 ± 307 ml, and CV + PEEP = 2,425 ± 463 ml) were not significantly different. All the volumes increased significantly by period V, but whereas for SV the only significant increase was at the final period (2,284 ± 184 ml), the increases for CV and CV + PEEP were progressive throughout the study, significant at periods IV (CV = 3,292 ± 294 ml and CV + PEEP = 3,651 ± 502 ml) and V (CV = 3,551 ± 345 ml and CV ± PEEP = 4,086 ± 549 ml), and significantly greater than the changes occurring with SV.

Total intracellular water was calculated as the difference between total water and extracellular water volume. There was a tendency for extravascular cell water volumes to increase with time, especially with CV + PEEP, but none of the changes were significant.

ORGAN BLOOD, WATER AND ALBUMIN

The mean data for each of the organs is summarized in table 2 for SV, CV, CV + PEEP, respectively; all the values are extravascular. The water content of the organ in ml/g dry blood free tissue is shown in the first three columns of table 2. For the SV and CV modes, the water content of the skin was significantly less than the other organs, and that of intestine, heart, and lung significantly greater than liver or muscle, while subcutaneous tissue contained 5–10 times more water. For the CV + PEEP mode of table 2, skin contained less and subcutaneous contained more water than other tissues, but now muscle joins intestines, heart, and lung in containing significantly more water than liver. Comparing the values for each organ between ventilatory modes, the water content of subcutaneous tissue, muscle, and large intestine in the CV + PEEP mode was significantly greater than either SV or CV modes. No other organ water content differences were significant.

Interstitial water volume as per cent of the total extravascular water volume did not differ between ventilatory modes. The general pattern therefore is represented by the results for the SV group where the values for lung (55.2 ± 4.0 per cent), skin (45.7 ± 7.2 per cent), intestine (46.7 ± 2.3 per cent), and liver (41.8 ± 6.2 per cent) were greater than those for subcutaneous tissue (36 ± 10.0 per cent), heart (28.9 ± 2.4 per cent), or muscle (20.9 ± 2.6 per cent).

The last three columns of table 2 display the organ albumin data normalized as extravascular albumin/g dry

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/57/2/103/305559/0000542-198208000-00007.pdf by guest on 22 January 2022

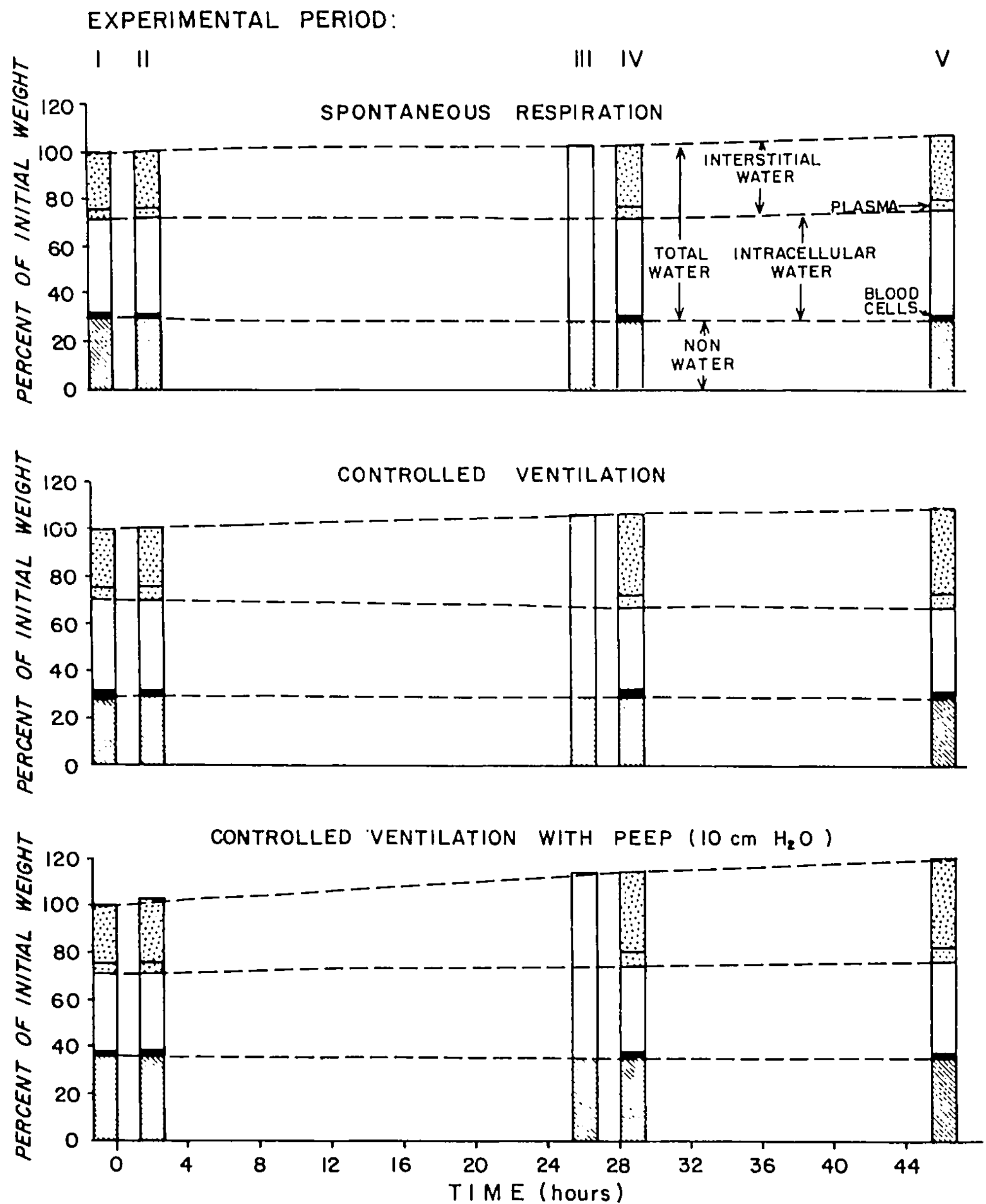

FIG. 1. Water Compartments: Mean changes are shown for each of the three ventilation modes throughout the study period. Total body weight is indicated by the height of each column. At period III total body water was measured and is shown as a clear area while the non-water weight is cross-hatched. For the remaining experimental periods non-water weight is assumed the same as in period III (cross-hatched) and the total water volume is subdivided into intracellular (including red cell water shown as solid black and the rest shown clear) and interstitial (stippled with the smaller subdivision indicating plasma and the larger the extravascular volume) water.

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/57/2/103/305559/0000542-198208000-00007.pdf by guest on 22 January 2022

blood free organ. The pattern was similar for all three ventilatory modes with subcutaneous tissue containing significantly more than any other organ, lung containing more than all organs except subcutaneous, and all the remaining organs containing albumin in the range 3–8 mg/g dry blood free tissue. There were no significant differences for each organ between the different ventilatory modes.

Whole body albumin distribution was calculated from the product of organ albumin content and organ weight with the contributions of muscle and subcutaneous tissues estimated as follows. Muscle normally constitutes approximately 43 per cent of the body weight in dogs, and therefore a lower limit to muscle mass was calculated as this fraction of the initial body weight. The gel-like subcutaneous tissue was estimated as 1 per cent of body weight for SV and CV modes and as 2 per cent of body weight for CV + PEEP modes. All of these estimates are conservative; in the case of muscle they do not include changes in muscle mass with time and for the subcutaneous tissue on two occasions the liquid collected in the CV + PEEP modes exceeded 400 ml (*i.e.*, greater than 3 per cent). Using these estimates the total albumin content of muscle and subcutaneous tissues were calculated. For the SV mode the total body albumin was 21.54 ± 1.83 g, of which 35.6 per cent was intravascular. The muscle contained 35.6 per cent, subcutaneous tissue 5.4 per cent, and the other organs 23.4 per cent (with 15.6

TABLE 2. Extravascular Organ Water and Albumin (n = 5)

Organ	Water Content (ml/g dry)			Albumin Content (mg/g dry)		
	SV	CV	CV + PEEP	SV	CV	CV + PEEP
Liver	2.1 ± 0.2	2.1 ± 0.1	2.5 ± 0.1	5.0 ± 2.0	3.2 ± 1.0	3.4 ± 0.6
Skin	1.1 ± 0.2	1.6 ± 0.2	1.2 ± 0.1	6.7 ± 2.2	8.1 ± 1.7	5.4 ± 0.9
Stomach	3.0 ± 0.3	2.7 ± 0.3	4.1 ± 0.4	6.6 ± 1.3	7.0 ± 1.3	5.9 ± 1.4
Small intestine	2.9 ± 0.3	2.7 ± 0.3	3.2 ± 0.3	5.6 ± 1.5	4.9 ± 1.2	5.7 ± 2.1
Large intestine	3.6 ± 0.2	3.6 ± 0.3	4.5 ± 0.1	7.2 ± 1.5	6.3 ± 0.9	4.6 ± 0.7
Heart	3.5 ± 0.1	3.4 ± 0.1	3.7 ± 0.1	7.8 ± 1.5	6.5 ± 0.6	6.1 ± 0.6
Lung	4.2 ± 0.5	4.4 ± 0.3	3.9 ± 0.4	35.2 ± 5.5	35.0 ± 6.3	27.9 ± 2.3
Subcutaneous	23.4 ± 2.6	23.1 ± 3.5	31.6 ± 3.8	157 ± 14	138 ± 11	144 ± 29
Muscle	2.7 ± 0.4	2.6 ± 0.3	3.6 ± 0.2	7.0 ± 1.1	4.1 ± 0.4	8.6 ± 1.9

Values are means ± SE.

per cent contributed by skin). There were no significant differences from this pattern of distribution for the CV and CV + PEEP modes.

Discussion

These beagle dogs were subjected to a constant fluid load during 46 h of intensive care with three different ventilatory modes. With an infusion rate of 138 ml/min the total fluid volume administered was approximately six liters, primarily as 0.45 per cent NaCl with 20 mEq/l KCl. This infusion rate was selected as being sufficiently large to constitute a stress and yet one for which previous experiments had established the ability of the kidney to maintain equilibrium for at least several hours.[9–12] Against this background of fluid infusion the influences of different types of ventilation on fluid retention are compared with greater sensitivity, and subtle changes in the organ distribution of water and albumin are enhanced. It is not intended that a clinical counterpart be sought for such large volumes of infusion, rather, this model is designed to test the vulnerability of homeostatic responses and to identify some of the tissue sites associated with sequestration of water.

The principal conclusions from this study in dogs are: (1) prolonged sedation with respiratory intensive care is associated with retention of water, but the rapidity and extent of water accumulation depends on the ventilatory management; (2) water accumulates in interstitial sites particularly of muscle and subcutaneous tissue; and (3) body albumin content is distributed principally in extravascular sites with characteristic contents in each organ and the retention of water results in a generalized dilution. These conclusions are discussed further below.

Several studies of short duration (approximately six hours) have previously reported that fluid retention occurs in response to positive pressure ventilation.[2,3] The present studies have confirmed these observations, and in addition, have demonstrated that for CV and CV + PEEP the initial rate of fluid retention continues approximately constant for at least 46 h. With SV fluid retention did not occur until after 28 h of sedation and respiratory intensive care.

As to the mechanism underlying these changes in total body water it suffices here to state that the principal cause is retention of salt and water by the kidney as a result of humoral and neurogenic mediators apparently regulated by changes of effective intravascular volume.[13] Increased intrathoracic pressure associated with the use of PEEP and to a lesser extent CV alone reduce the intrathoracic end-expiratory transmural distending pressures and initiate homeostatic responses as if the animal had become hypovolemic. The basis for the late fluid retention in the SV group is perhaps similar to other types of stress response[14] or reflects an inability to sustain diuresis indefinitely.

In all groups, hemodynamics and respiratory functions were maintained satisfactorily. It follows that retained water was sequestered in tissue sites that did not interfere with vital function. The muscle and subcutaneous tissues were identified as the most significant reservoirs for accumulating water. Because muscle mass is large, small increases in tissue water represent large overall accumulations, and even if the increase in muscle tissue is sufficient to interfere with functions, this is unlikely to be critical in the respiratory intensive care setting unless it reduces the ability to ventilate when mechanical assistance is discontinued. Water accumulation in subcutaneous tissue was evident particularly in the CV + PEEP group. This tissue is able to sustain large increments of water with apparently no interference in vital functions. This change from gel to sol state when the tissue is exposed is apparently due to the absence of chemical bonding between the mucopolysaccharide molecules.[15]

Albumin accounts for approximately 80 per cent of the plasma oncotic pressure initially measured; and in tissues, albumin contributes an even greater proportion of the total interstitial oncotic pressure. As the study progressed the plasma oncotic pressure decreased with

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/57/2/103/305559/0000542-198208000-00007.pdf by guest on 22 January 2022

the plasma albumin concentration, and the final value was reduced by approximately 40 per cent of the initial value. This latter decrease is attributable to reduced synthesis, metabolic consumption, redistribution, and dilution of albumin. No nutritional supplement of amino acids was administered throughout this study, but these observations again emphasize the importance of such considerations.

The total quantity of body albumin was not altered by the different ventilatory modes. These values do not include albumin contained in fat, skeleton, kidneys, spleen, and pancreas, but their albumin content appears to be small.[16] The total quantity of albumin measured, approximately 2 g/kg, was similar to that of Rossing *et al.*[17] but as a result of the progressive reduction of albumin during the course of the study was almost half that measured in healthy rabbits[18] and man.[19] The intravascular albumin in the four cited studies and in the present one was approximately 35 per cent of the total. The total quantity and the intra- and extravascular distributions were not altered by the different ventilatory modes. Albumin is a critical factor in Starling's equation for the balance of forces governing water exchange between plasma and tissue and as a first hypothesis it might be expected that the tissues containing the most albumin would be capable of sequestering the most water. Extravascular albumin accounts for 65 per cent of the total and most of this is contained in skin and muscle. The hypothesis expressed above concerning albumin and sites of water sequestration is therefore seen to be inconsistent. If the quantity of albumin in the organ was the only determinant, then water should have accumulated in skin as well as muscle, while if albumin concentration was the determinant, pulmonary edema might have been expected to occur as well as water retention in subcutaneous tissue (table 2). Other factors are clearly important in determining whether a specific organ accumulates excess water. Capillary permeability, kinetics of albumin exchange, lymph flow, and heterogeneity of the interstitial space have been considered in detail only for the lung.[20]

Several recent studies[21-23] have emphasized the importance of normal levels of plasma protein in determining lymph flow and the general capacity to resist edema. The present studies have demonstrated magnitudes of water changes that differ both between organs and ventilatory modes. Taken together these observations suggest that the pattern of distribution and quantity of whole body albumin are important components of the homeostatic response.

The authors acknowledge the technical expertise of Research Specialist Barbara Ewing, B.A., and Research Technicians Lisa Litvin, B.S., and Sharon Suer, B.S. The continuous around-the-clock intensive care for these animals was provided by the following veterinary and undergraduate students: Kathleen Boldy, Noam Zelman, Carol Landefled, Mary Sommer, Christopher Ficke, and Leisa (Marshall) Clark.

References

1. Skorecki KL, Brenner MB: Body fluid homeostasis in man: A contemporary review. Am J Med 70:77-88, 1981
2. Kumar A, Pontoppidan H, Baratz RA, Laver MB: Inappropriate response to increased plasma ADH during mechanical ventilation in acute respiratory failure. ANESTHESIOLOGY 40:215-221, 1974
3. Hall SV, Johnson EB, Hedley-Whyte J: Renal hemodynamics and function with continuous positive pressure ventilation in dogs. ANESTHESIOLOGY 41:452-461, 1974
4. Sladen A, Laver MB, Pontoppidan H: Pulmonary complications and water retention in prolonged mechanical ventilation. N Engl J Med 279:448-453, 1968
5. Blahd WH: Radioisotope techniques, Clinical Disorders of Fluid and Electrolyte Metabolism. Edited by Maxwell MH, Kleeman CR. New York, McGraw Hill Company, 1981, pp 399-412
6. Pearce MC, Yamashita BA, Beasell J: Measurement of pulmonary edema. Circ Res 16:482-488, 1965
7. Fairbanks VF: Hemoglobin, hemoglobin derivatives and myoglobin, Fundamentals of Clinical Chemistry. Edited by Tietz NW. Philadelphia, WB Saunder, 1967, pp 450-455
8. Mancini G, Carbonara AO, Heremans JR: Immunological quantitation of antigens by single radial immunodiffusion. Immunochemistry 2:235-254, 1965
9. Ypersele CV, Bodart P, Dardenne A: General techniques in clinical nephrology, Nephrology. Edited by Hamburger J, Crosnier J, Grunfeld JP. New York, John Wiley and Sons, 1979, pp 112-118
10. Strauss MB, Davis RK, Rosenbaum JD, Rossmeils EC: Production of increased renal sodium excretion by the hypotonic expansion of extracellular fluid volume in recumbent subjects. J Clin Invest 51:80-86, 1952
11. Atherton JC, Hai MA, Thomas S: Effects of water diuresis and osmotic (mannitol) diuresis on urinary solute excretion by the conscious rat. J Physiol (Lond) 197:395-410, 1968
12. Rector FC, Gieson GV, Kiil F, Seldin DW: Influence of expansion of extracellular volume on tubular reabsorption of sodium independent of changes in glomerular filtration rate and aldosterone activity. J Clin Invest 43:341-348, 1964
13. Priebe HJ, Heimann JC, Hedley-Whyte J: Mechanisms of renal dysfunction during positive end-expiratory pressure ventilation. J Appl Physiol 50:643-649, 1981
14. Moore FD: Metabolic Care of the Surgical Patient. Philadelphia, WB Saunders Co., 1959
15. Guyton AC, Taylor AE, Granger HJ: Circulatory Physiology II: Dynamics and Control of the Body Fluids. Philadelphia, WB Saunders Co., 1975, pp 53-70
16. Rothschild MA, Oratz M, Schreiber SS: Serum albumin. Am J Dig Dis 14:711-744, 1969
17. Rossing N: The normal metabolism of ^{131}I-labelled albumin in man. Clin Sci 33:593-602, 1967
18. Matthews CME: Effects of plasmapheresis on albumin pools in rabbits. J Clin Invest 40:603-610, 1961
19. Rothschild MA, Oratz M, Schreiber SS: Albumin Synthesis, Part I. N Engl J Med 286:748-757, 1972
20. Staub NC: Pulmonary edema. Physiol Rev 54:678-811, 1974
21. Harms BA, Kramer CC, Bodai BI, Demling RH: Effect of hypoproteinemia on pulmonary and soft tissue edema formation. Crit Care Med 9:503-508, 1981
22. Beattie HW, Evans G, Garnett ES, Regoeczi E, Webber CE, Wong KL: Albumin and water fluxes during cardiopulmonary bypass. J Thorac Cardiovasc Surg 67:926-931, 1974
23. Brace RA, Power GG: Thoracic duct lymph flow and protein flux dynamics: Responses to intravascular saline. Am J Physiol 240:R282-R288, 1981

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/57/2/103/305559/0000542-198208000-00007.pdf by guest on 22 January 2022

APPENDIX

Organ Calculations and Equations

Organ Water Volume (O_w) ml

$$O_w = \frac{\text{Organ Weight}}{\text{Sample Weight}} [(\text{Homogenate Weight}) H_{fw} - 25]$$

Organ Erythrocyte Water (O_{EW}) ml

$$O_{EW} = \frac{\text{Organ Weight}}{\text{Sample Weight}} \frac{(\text{Homogenate Weight}) H_{fw}, S_{Hb}, B_{Ht}, E_{fw}}{S_{fw} B_{Hb}}$$

and

$$E_{fw} = \frac{B_{fw} - P_{fw}(1 - B_{Ht})}{B_{Ht}}$$

Organ Plasma Water (O_{PW}) ml

$$O_{PW} = \frac{\text{Organ Weight}}{\text{Sample Weight}} \frac{(\text{Homogenate Weight}) H_\lambda P_{fw}}{P_\lambda}$$

Organ Interstitial Water Volume (O_{IW}) ml

$$O_{IW} = \frac{\text{Organ Weight}}{\text{Sample Weight}} \times \frac{(\text{Homogenate Weight}) H_{fw} \cdot P_{fw} \cdot S_{\beta H}}{S_{fw} P_{\beta H}} - O_{Pw}$$

Total Organ Albumin—mg

$$\text{Total Organ Albumin} = \frac{\text{Organ Weight}}{\text{Sample Weight}} \frac{(\text{Homogenate Weight}) H_{fw} S_A}{S_{fw}}$$

Organ Plasma Albumin—mg

$$\text{Organ Plasma Albumin} = \frac{P_A \cdot O_{PW}}{P_{fw}}$$

From these primary measurements other values can be derived:

Organ extravascular albumin

= (Total Organ Albumin) − (Organ Plasma Albumin)

Organ albumin interstitial concentration

= Organ extravascular albumin ÷ O_{IW}

All the values may be expressed as whole organ quantities or normalized per g of dry or wet organ weight.

Organ Calculations

In the equations below, the following symbols are used:

Symbol	Definition
H_{fw}	= Homogenate water fraction (ml/g)
B_{fw}, E_{fw}, S_{fw}, P_{fw}	= Whole blood, Erythrocyte, Supernatant and Plasma Water fraction (ml/ml)
S_{Hb} and B_{Hb}	= Supernatant and Whole blood hemoglobin (g/ml)
B_{Ht}	= Whole blood, large vessel hematocrit (per cent)
H_λ	= Homogenate gamma counts ^{99m}Tc-albumin (cts/g)
P_λ	= Plasma gamma counts ^{99m}Tc-albumin (cts/ml)
$S_{\beta H}$ and $P_{\beta H}$	= Supernatant and plasma beta counts from ^{14}C − Inulin (cts/ml)
P_A and S_A	= Plasma and supernatant albumin concentration (mg/ml)
H_D	= Homogenate Dry/Wet Weight (mg/g)
P_D	= Plasma Dry/Wet Weight (mg/ml)

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/57/2/103/305559/0000542-198208000-00007.pdf by guest on 22 January 2022