Comparison of Extravascular Lung Water Volume with Radiographic Findings in Dogs with Experimentally Increased Permeability Pulmonary Edema

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ABSTRACT. The relationship between extravascular lung water volume (ELWV) and chest radiographical findings was studied in general-anaesthetized beagles. The dogs were experimentally injected with oleic acid to increase pulmonary vascular permeability. When the ELWV value in the dogs increased more than approximately 37% from the control value, their chest radiographs began to show signs of pulmonary edema. At this time, the chest X-ray density increased to 10% above the control level. PaO2 decreased, and PaCO2 increased after the administration of oleic acid. This clearly showed that the pulmonary gas exchange function was reduced following increasing ELWV. This comparison showed that probably the thermal-sodium double indicator dilution measurement of ELWV can detect slight hyperpermeability pulmonary edema that does not show on chest radiographs. The chest radiograph was therefore not suitable for the detection of slight pulmonary edema, because it did not show any changes in the early stages in hyperpermeability pulmonary edema.—KEY WORDS: canine, chest radiography, extravascular lung water volume, oleic acid, pulmonary edema.


Pulmonary edema is a pathologic state in which there is abnormal extravascular water storage in the lung [23]. Extravascular water means the presence of fluid in the interstitium and air spaces in the lung. This fluid is normally removed by the lymphatic system, pulmonary vascular resorption and discharge into the tracheal space [20]. However, when the fluid which extravasates from the capillary parietes to the interstitium increases, and its increase exceeds removal capacity, the fluid accumulates in the interstitium and the alveolus, and is called pulmonary edema. Pulmonary edema is generally divided into 3 groups: hydrostatic pulmonary edema, hyperpermeability pulmonary edema and others [14].

Pulmonary edema is mainly diagnosed by chest radiographic findings, clinical signs and the results of blood gas analysis. In humans, various methods have been devised to establish a quantitative diagnosis for pulmonary edema [21]. One of them, the double indicator dilution method (DIDM) is established [13] and is currently the only practical technique for the measurement of pulmonary edema in vivo [12, 13].

Oleic acid, a kind of fatty acid, was used to experimentally produce a model of hyperpermeability pulmonary edema in animals. Intravenous injection of it induces pulmonary edema by injuring pulmonary endothelial cells [1, 5, 7]. Kawanae [11] reported the relationship among extravascular lung water volume (ELWV), chest radiographic findings and hemodynamic parameters in mongrel dogs with permeability increased pulmonary edema caused by intravenous injection of 0.1 mg/kg oleic acid. The lung edema produced by the injection of 0.1 mg/kg oleic acid in our preliminary experiments was hyperacuta edema with severe hemorrhage in the lung. To our knowledge, there is no report indicating whether such hyperacute and severe pulmonary edema with severe hemorrhage corresponds to slight or moderate pulmonary edema, or not.

In the study, the relationships among ELWV measured by thermal-sodium DIDDM, chest radiographic findings and blood gas analysis were studied in dogs with slight or moderate hyperpermeability pulmonary edema caused by the experimental injection of 0.02 or 0.04 mg/kg oleic acid.

MATERIALS AND METHODS

Experimental animals: Eight adult beagles which were regarded as clinically normal from results of physical examination and general blood and blood chemical examinations, were used. They weighed 10–18 (mean 12.1) kg and were 1–2 years of age. These eight beagles were randomly divided into 2 groups, A and B.

Anesthesia: After inducing general anesthesia with 0.03 nil/kg of atropine sulfate (i.m.), 0.03 ml/kg of fluntrazepam (i.v.) and 25 mg/kg of pentobarbital sodium (i.v.), they were endotracheally intubated and then paralysed with 0.05 mg/kg of vecuronium bromide (i.v.). Additional sodium pentobarbital (5 mg/kg) and vecuronium bromide (0.05 mg/kg) were administered every 30 min. Following tracheal intubation, they were mechanically ventilated with a ventilator (KV-2N, Kimuraikakiki, Tokyo) at a fractional inspired oxygen concentration (FiO2)of 1.0 and a frequency of 16 breaths/min to achieve an arterial carbon dioxide tension (PaCO2) of 35–45 mmHg. A solution of heparin (100 U/kg) was given intravenously every 30 min.

Preparation for monitoring: The anesthetized dogs were placed in dorsal recumbency, and a thermodilution catheter (5F, TC-504, Viggo-Spectramed Co., Surrey, England) was inserted from the left jugular vein into the pulmonary artery for pressure monitoring with a polype...
graph (360 system, Nihondenki Sanei, Tokyo). Then a lung water catheter (5F HE-2900, Electro Catheter Co., New Jersey, U.S.A.) was inserted 20-25 cm from the femoral artery into the abdominal aorta. After PaCO₂ was stable at 35 to 45 mmHg, the dogs were given 0.02 ml/kg oleic acid through the thermodilution catheter in group A, and 0.04 ml/kg in group B.

Measurement of extravascular lung water volume (ELWV) and cardiac output (CO): The ELWV and CO were measured with the Lung Water Computer (MTV 1100, Nihon Kohden Ltd., Tokyo) by heat-sodium DlDM [9, 10, 22], after 3 ml of ice-cold 3% saline solution was rapidly injected into the right atrium through the thermodilution catheter. The average of 3 consecutive measurements was regarded as the true reading. To avoid distortion of the dilution curve, respiration was stopped during the measurement of ELWV.

Blood gas analysis: Blood gas tensions and arterial blood pH (pH) were analyzed by using the auto blood gas analyzer system (IL-1306, Instrumentation Lab. Co., Milano, Italy) and corrected for blood temperature and hemoglobin concentration.

Chest radiography and its evaluation: Chest radiography was carried out at maximum inspiration in dorsal recumbency. Chest radiographic findings before and after the injection of oleic acid were compared. The observers were unaware of the time after the injection of oleic acid when the radiograph was taken, to make their assessments as fair as possible.

The chest X-ray density was evaluated by processing graphic information with a computer based on the method of Kawamae [11] (Fig. 1). In the ventrodorsal aspect, the density was analyzed and compared with results obtained with a Benoa durometer (Sakatascisakusyo, Tokyo) at the same time as the index of density was measured with the Image Command system (4198, Ratoc System Engineering Co., Tokyo).

Observation time: The ELWV, CO and blood gasses were measured, and chest radiographs were taken before (0 min) and at 15, 30, 45, 60, 90, 120, 150 and 180 min after the injection of oleic acid. After all measurements, the dogs were euthanized and the gross extent of pulmonary edema was determined by autopsy.

Statistical analysis: The statistical significance of the difference between the two groups was determined by the Mann-Whitney test. The paired t test was used for statistical comparison of the data from before and after the injection of oleic acid, after significant differences were determined by the Friedman test. P values less than 0.05 were considered significant.

RESULTS

ELWV value (Fig. 2): The ELWV value increased to 9.34 ml/kg from 8.09 ml/kg (approximately 15% of the control value) at 60 min after the injection of oleic acid in group A. After 150 min, its increase was only 21% greater than the control value. In contrast, in group B, the ELWV value increased suddenly up to 30 min after the injection of oleic acid, and after 150 min it had increased by more than 50% of the control value.

Chest radiographic findings and the chest X-ray density: In group A, 30 min after the injection of oleic acid, the chest radiographic findings suggested only slight pulmonary edema as the pulmonary vessels were only partially visible, and no later changes were evident (Fig. 3). On the other hand, in group B, the chest radiograph changes began to appear at 60 min after the injection. Up to 180 min the vessels visibility continued to increase and some air

![Fig. 1. The chest X-ray density was evaluated as the mean value for 10 points in the chest radiography according to Kawamae [11].](image)

![Fig. 2. Extravascular lung water volume (ELWV) after 0.02 ml/kg (group A) or 0.04 ml/kg (group B) oleic acid administration. Significant difference (* p<0.05; ** p<0.01) compared with the baseline (0 min) value.](image)
bronchograms appeared on the chest radiography.

The chest X-ray density increased less than 10% in group A, but in group B it had increased significantly (P<0.05) at 60 min after the injection of oleic acid (Fig. 4). When the ELWV value increased by more than 30% of the control value before treatment, the chest X-ray density increased to 10% above the control value.

CO and Blood gas analyses (Fig. 5): In both groups, CO had decreased at 15 min after the injection of oleic acid. In group B especially, the decrease was significant (P<0.05). Up to 60 min, CO recovered temporarily, but again decreased little by little. Arterial oxygen tension (PaO₂) decreased and PaCO₂ increased after the injection of oleic acid in both groups. These findings showed that the function of pulmonary gas exchange was obviously reduced following an increase in ELWV.

Autopsy findings in the lungs: In group A, atelectasis occurred in part of the caudal lobe, especially in the dorsalis, and there was no intratracheal water. In group B, atelectasis formed in almost the entire caudal lobe and partially in accessorius, cranial and medium lobes. There was approximately 10 ml of intratracheal exudate in most dogs in group B. In both groups, the lungs showed edematization.

DISCUSSION

In this study, the value of the extravascular thermal
volume calculated by thermal-sodium DIDM was used as that of ELWV for convenience. It measured the pulmonary extravascular space exactly, so it should be called the extravascular thermal volume.

It is considered that the extravascular thermal volume does not show the real ELWV [8, 13], because there are some problems: for example, heat is diffused by the left heart, bronchi, pulmonary arteries, veins and so on, so that ELWV measurement results in overestimation [8, 13, 15-17].

Pulmonary edema induced by oleic acid has been used as a model of hyperpermeability pulmonary edema induced by aspiration pneumonia, bacterial pneumonia and aspiration of toxicity in the fields of pathologic histology and radiology, among others [2-5, 7-8, 10]. Histopathological findings have shown that pulmonary capillary endothelium and alveolar epithelium cells are damaged. Following leakage of plasma fluid through damaged pulmonary capillaries into the interstitial and alveolar spaces of the lung, perivascular, interstitial and alveolar edema and atelectasis occur [5, 7].

Pistolesi and Giuntini [18] reported an excellent correlation between changes in the chest X-ray density and the ELWV values assessed by DIDM in human cardiogenic pulmonary edema. In cardiogenic pulmonary edema, chest radiographs have been widely used to detect early pulmonary edema, because they show signs of interstitial edema before clinical symptoms develop and the increase in the ELWV value becomes evident [18]. Hirakawa et al. [6] showed that when ELWV increased about 30% from the control value, chest radiographs showed changes in dogs, and were used as a model of acute left ventricular failure and administered overtransfusion. On the other hand, clinical signs such as dyspnea and tachypnea appeared in the early stage of severe hyperpermeability pulmonary edema even though chest radiographs did not show the edema [11]. Hypoxemia, hypocapnia and clinical signs appeared but chest radiographs did not change, and there was a poor correlation between the ELWV values and the radiographic findings [11]. Milne et al. [14] reported that the appearance of air bronchograms was very common in hyperpermeability pulmonary edema but pulmonary blood volume and heart size were normal and no interstitial changes were seen.

The condition of the pulmonary edema produced in this study was considered to be slight (group A) or moderate (group B) pulmonary edema as shown in the autopsy findings. The ELWV value in group A remained a 21% increase over the control value, and chest radiographs showed little change. In group B, when the ELWV value
had increased to approximately 37% over the control value at 60 min after the injection of oleic acid, signs of pulmonary edema began to appear on chest radiographs. These results supported those of previous reports [11, 19]. Snashall et al. [19] said that changes in X-ray density correlated with ELWV, but that density was a poor indicator of the presence of edema in dogs with hyperpermeability pulmonary edema induced by alloxan. They also showed that this correlation was different in various locations in the lung.

Pulmonary blood flow was influenced by factors such as the position of the body, pulmonary vascular resistance, cardiac function and the ventilatory conditions, etc. [11]. In this study, it was so difficult to change the position of the dogs that the chest X-ray density was evaluated only from the ventrodorsal aspect by the method of Kawamadi [11], because changing the position made determination of the correct ELWV values impossible.

The results of this study suggested that this extravascular lung water measurement method could detect slight hyperpermeability pulmonary edema that did not show on chest radiographs. When hyperpermeability pulmonary edema began to show changes on chest radiographs, the ELWV value had increased to approximately 37% over the control value, and at this time pulmonary gas exchange function was obviously reduced.

REFERENCES