Evaluation of Extravascular Thermal Volume in the Lung in Dogs with Endotoxin-Induced Shock by Double Indicator Dilution Method using Heat and Sodium Ions

Masahiro TAGAWA, Shozo OKANO, Yasushi HARA, Hiroyasu EJIMA, Shigekatsu MOTOYOSHI, Norimoto URAKAWA, Kiyonori FURUKAWA, Masahiko ONDA, and Ryo OGAWA

Division of Veterinary Surgery, 1Veterinary Internal Medicine and 2Veterinary Pharmacology, Nippon Veterinary and Animal Science University, I-7-1 Kyonan-cho, Musashino, Tokyo, 180. 3First Department of Surgery and 4Department of Anesthesiology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113, Japan

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ABSTRACT. Accuracy assessment was undertaken under varying hemodynamic conditions for a lung water volume measurement device which is based on the principle of a double indicator dilution method using heat and sodium ions. Changes in extravascular thermal volume were investigated in dogs with endotoxin-induced shock. The isoproterenol- or propranolol-induced changes in hemodynamics had no effect on the measurement. This confirmed the high accuracy of this measuring method. The measurement revealed a tendency for the extravascular thermal volume to gradually increase (p<0.05) during endotoxin shock. This confirmed the gradual progression of pulmonary edema during endotoxin shock.—KEY WORDS: dog, endotoxin shock, extravascular thermal volume, hemodynamics, pulmonary edema.


Endotoxin shock induced by infection with gram-negative bacteria involves various organs such as liver, lung and kidney and progresses into lethal prognosis [4, 5]. It is therefore regarded as one of a number of serious problems not only in the field of human medicine but also in the field of veterinary medicine. Pulmonary edema resulting from the hyperpermeability of the pulmonary vessels represents the entity of acute and severe respiratory insufficiency which appears during the course of endotoxin shock [2, 3, 17]. Regular monitoring of the pulmonary water volume is necessary in understanding the pathology of endotoxin shock and in evaluating the effect of treatment. The development of measuring methods has been attempted.

Direct measurement of the pulmonary water volume has been achieved by the method proposed by Pearce et al. [16]. Since removed lungs are used, the method cannot be used for investigation of the changes with time nor can it be applied in the actual clinical field. Noble and Severinghans [14] and Lewis and Elings [11] have developed a computer assisted double indicator dilution method using heat and an indicator (pigment). This made clinical application possible. Since there had been a problem with accuracy [7], a double indicator dilution measuring device using sodium ions instead of pigment as a nondiffusible indicator has been developed [8, 10]. However there has been little study on whether measurement by this method was influenced by the changes in cardiac output, heart rate, blood pressure or other hemodynamic parameters. Measurement of the extravascular thermal volume in endotoxin shock has not been undertaken so far.

This study was designed to investigate the time changes in pulmonary extravascular water volume during shock by the double indicator dilution method with heat and sodium ions and to determine the influence of hemodynamic changes on measurement by this method. The clinical significance of this measuring method was also assessed.

MATERIALS AND METHODS

Experiment 1: Influence of hemodynamic changes on extravascular thermal volume
1. Principle of double indicator dilution method

A commercial pulmonary water volume measuring device (Nihon Koden, Model MTV-1100, Tokyo) was used in this experiment as an instrument to be used for the double indicator dilution method. This device is based on the concept of the indicator dilution method proposed by Hamilton [6]. In this method, two kinds of indicators are used; a diffusible indicator (heat) which penetrates the walls of pulmonary capillaries and spreads into the pulmonary interstitial spaces and a nondiffusible indicator which does not spread extravascularly. The indicators are infused via the central vein and are detected on the arterial side after circulation in the lung. The cardiac output and mean circulation times are
calculated from the two dilution curves. While sodium ions is detected without spreading extravascularly from pulmonary capillary walls, detection of heat is delayed, because it is released and diffused extravascularly while passing through the lung and then recovered. Thus, the mean circulation time for heat is longer than that for sodium ions. By utilizing this time lag, the extravascular thermal volume is automatically calculated with a lung water computer by the formulæ shown in Fig. 1.

2. Experimental dogs and conditions

Five filaria-free, almost perfectly healthy beagles were used. They weighed 8–13 kg (mean 10.6 kg). After inducing general anesthesia with atropine sulfate (0.05 mg/kg, i.m.) and pentobarbital sodium (25 mg/kg, i.v.), the dogs were endotracheally intubated and were then immobilized with pancuronium bromide (0.1 mg/kg, i.v.). The respiration was regulated with room air so as to maintain PaCO₂ at 30–40 mmHg. The dogs were placed in a lateral recumbent position. A lung water volume measurement catheter (Nihon Koden, HE-2900) was inserted from the femoral artery into the aorta and a 5 Fr. Swan-Ganz catheter from the femoral vein into the pulmonary artery. Both of them were indwelt and fixed.

By means of the above-mentioned pulmonary water volume measurement device, the pulmonary extravascular water volume was measured by rapidly infusing 3 ml of 3% NaCl at 0°C through the 5 Fr. Swan-Ganz catheter from the central vein side. In Experiment 1, the effect of hemodynamic changes on the pulmonary water volume was examined with appropriate infusion of two kinds of drugs that affected the blood circulation. Following measurement of the pulmonary water volume prior to administration, a β-activator, isoproterenol (Proctanol L, Nikken Chemical Co., Tokyo) for increasing the cardiac output and a β-blocker, propranolol (Inderal, Sumitomo Pharmaceutical Co., Tokyo) for reducing the cardiac output were administered at appropriate doses, and the pulmonary water volume was measured under different hemodynamic conditions. Since respiration has a considerable effect, measurement was performed by momentarily stopping the controlled respiration. The same measurement procedure was repeated three times under each set of hemodynamic-altered conditions, and the mean value was used to represent the measurement data.

Experiments 2: Changes in extravascular thermal volume during endotoxin shock

Seven filaria-free, almost perfectly healthy beagles were used. They weigh 7–13 kg (mean 9.6 kg). The method of anesthesia and the experimental conditions were the same as in Experiment 1. However, anesthetics and a muscle relaxant were used as necessary to maintain the depth of anesthesia and to stabilize the hemodynamics.

Endotoxin (E. coli 055: B5, Difco, Michigan, U.S.A.) was diluted with 0.9% saline to a total volume of 10 ml and injected 3 mg/kg body weight via the antebraochiocephalic vein over five minutes to produce a model of endotoxin shock.

The hemodynamic parameters measured were the heart rate (HR), cardiac output (CO), mean aortic pressure (MAOP), mean pulmonary arterial pressure (MPAP), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) and extravascular thermal volume (ETV). These were measured before, and one, three and six hours after administration of the endotoxin.

The measurement data were expressed as the mean ± SD, and were statistically analyzed by paired t-test.

RESULTS

1. Effect of hemodynamic changes on extravascular thermal volume

\[ ETV = V_T - V_w = F(t_r - t_{w*}) = CO(t_r - t_{w*}) \times 1000/50 (ml) \]

\[ ETV : \text{Extravascular thermal volume} \]
\[ F : \text{Blood flow (ml/sec)} \]
\[ CO : \text{Cardiac output (1/min)} \]
\[ t_r : \text{Thermal indicator mean transit time (sec)} \]
\[ t_{w*} : \text{Na indicator mean transit time (sec)} \]
EXTRAVASCULAR THERMAL VOLUME IN ENDOTOXIN SHOCK

Table 1. Hemodynamic changes following administration of endotoxin

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>60 min</th>
<th>180 min</th>
<th>360 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR(\text{bpm)})</td>
<td>138.5±28.0</td>
<td>171.9±26.9(\text{(a)})</td>
<td>179.0±23.2(\text{(a)})</td>
<td>165.6±25.3(\text{(a)})</td>
</tr>
<tr>
<td>MAOP(\text{mmHg)})</td>
<td>110.8±15.9</td>
<td>56.0±13.5(\text{(a)})</td>
<td>64.2±9.1(\text{(a)})</td>
<td>90.5±15.4(\text{(a)})</td>
</tr>
<tr>
<td>MPAP(\text{mmHg)})</td>
<td>12.1±2.6</td>
<td>8.0±1.8(\text{(a)})</td>
<td>9.2±3.0(\text{(a)})</td>
<td>13.5±7.3</td>
</tr>
<tr>
<td>CO(\text{(l/min)})</td>
<td>2.2±0.7</td>
<td>1.0±0.3(\text{(a)})</td>
<td>1.2±0.3(\text{(a)})</td>
<td>1.1±0.3(\text{(a)})</td>
</tr>
<tr>
<td>SVR(\text{(dyne-s-cm}^{-2}\text{)})</td>
<td>459.1±1789</td>
<td>5075±3238 (\text{(a)})</td>
<td>4666±1451</td>
<td>6867±1640(\text{(a)})</td>
</tr>
<tr>
<td>PVR(\text{(dyne-s-cm}^{-2}\text{)})</td>
<td>484±154</td>
<td>733±315(\text{(a)})</td>
<td>716±256(\text{(a)})</td>
<td>1198±629(\text{(a)})</td>
</tr>
</tbody>
</table>

a) HR: Heart rate, b) MAOP: Mean aortic pressure, c) MPAP: Mean pulmonary arterial pressure, d) CO: Cardiac output, e) SVR: Systemic vascular resistance, f) PVR: Pulmonary vascular resistance, g) p<0.01 vs Pre.

![Fig. 2. Hemodynamic changes after administration of drugs.](image)

![Fig. 3. Changes in extravascular thermal volume after administration of drugs.](image)

![Fig. 4. Changes in extravascular thermal volume after administration of endotoxin. \(\star\): p<0.05 vs Pre](image)

Figure 2 shows the changes in hemodynamics after administration of the \(\beta\)-activator and \(\beta\)-blocker. Administration of these drugs induced marked changes in HR, MAOP and CO. CO in particular changed significantly. The value which was 1.73±0.28 l/min in the control was increased to approximately double (3.17±0.57 l/min) by administering isoproterenol and was decreased to approximately 60% (1.09±0.16 l/min) of the control value by administering propranolol. ETVI was 8.18±0.96 ml/kg in the control. After the administration of isoproterenol, the value was 8.58±1.64 ml/kg. After the administration of propranolol, it was 7.93±0.92 ml/kg, in other words, there was almost no difference. When the changes in ETV are shown as a ratios to the control value, the increases after the administration of isoproterenol and propranolol were 103.2±6.9% and 101.7±6.9%, respectively. The ETV measured values with the hemodynamic changes were almost perfectly stable (Fig. 3). 2. Changes in pulmonary extravascular water volume during endotoxin shock

The hemodynamic changes induced by the administration of the endotoxin are shown in Table 1. Marked changes began to appear 60 min after the administration of the endotoxin, demonstrating that the dogs were in a state of shock.

ETV tended to gradually increase with time, as shown in Fig. 4. A significant increase (p<0.05) was demonstrated at 360 min after administration of the endotoxin, compared to the pre-endotoxin level.

**DISCUSSION**

The double indicator dilution method, one of the
methods used for measuring the pulmonary extravascular water volume is dependent on blood flow. The volume of blood circulation is considered to affect the measurement [8, 12, 13, 15, 18]. Considering the occurrence of hemodynamic changes during endotoxin shock, the reliability of the measuring method under varying hemodynamic conditions was assessed and the changes in pulmonary extravascular water volume during endotoxin shock were investigated in this experiment. No significant changes were detected in the pulmonary extravascular water volume, when the volumes were compared before and after induction of blood flow changes by administering isoproterenol which has positive inotropic and chronotropic actions on the heart and propranolol which as a negative action on the heart. It was confirmed that the pulmonary extravascular water volume was not influenced by CO changes of this magnitude. This suggested that the double indicator dilution method could be applied to measurement of the pulmonary extravascular water volume under varying hemodynamic conditions induced by endotoxin shock. The pulmonary extravascular water volume in normal dogs determined in a series of experiments was 7.75±1.06 ml/kg. This almost exactly agreed with the results of earlier investigators [1, 9].

In the endotoxin-treated dogs examined in Experiment 2, CO at the time of measuring the pulmonary extravascular water volume during endotoxin-induced shock was approximately 1.0 l/min. This was almost equal to the value obtained with propranolol. This finding suggests that the measurement data obtained are sufficiently reliable as indicating the value of pulmonary extravascular water volume at any time during measurement. It is known, however, that decreased vascular beds in the lung affect the measurement values and lead to readings lower than actual value. In endotoxin shock, a change in pulmonary vascular beds in addition to the depression of hemodynamics (such as blood pressure and cardiac output) are induced. Endotoxin injection causes agglutination of leukocytes and platelets. It is, therefore, presumed that the blood supply to distal vessels of the lung is not fully maintained. Senryo [19] have reported that if effective vascular beds are decreased, the pulmonary extravascular water volume is also decreased. When these are all taken into consideration, the pulmonary extravascular water volume measured after endotoxin injection in this study is likely to be underestimated, compared to the estimable actual level. On examining the changes in pulmonary extravascular water volume after endotoxin injection, the value tended to increase with time. This suggested the advance of pulmonary edema from its condition in the early phase of endotoxin shock. The pathological aspect of endotoxin shock produced in this experiment was not described, but autopsy of dogs sacrificed by euthanasia revealed histological evidence of pulmonary edema. This seemed to indicate that pulmonary edema is an important factor in the pathology of endotoxin shock and that monitoring of the water volume in the lung is important in the management of endotoxin shock.

REFERENCES