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HEMODYNAMICS IN EXPERIMENTAL ENDOTOXIN SHOCK WITH CONTINUOUS ADMINISTRATION

BY

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ABSTRACT

Experimental endotoxin shock was induced with 4 mg/kg of purified endotoxin by continuous infusion instead of bolus injection in order to simulate the clinical condition. Abrupt decrease in the mean artery pressure and transient increase in the pulmonary artery pressure, which were usually seen in the initial stage accompanying the bolus injection of endotoxin, did not occur with continuous infusion.

The superior mesenteric fraction rate of cardiac output (CO) in our study showed an increase, which was different from the small intestinal fraction rate of CO shown by Okada *et al.* by the micro-sphere method (MS method) accompanying the bolus injection of endotoxin.

These effects might be caused by the difference in the injection method and endotoxin dose. Measurements of the cardiac output, common carotid artery flow, renal artery flow and superior mesenteric artery flow proved that the largest reduction was observed in the renal blood flow.

Key words: Experimental endotoxin shock, renal blood flow, superior mesenteric blood flow, β-glucuronidase

INTRODUCTION

Recently endotoxin shock has often been investigated because of its uniqueness. Treatment is difficult and often results in multiple organ failure. The pathology of endotoxin shock is very unique and has not yet been solved completely. The clinical manifestation of endotoxin shock is affected by many factors and is extremely complex.

Experimental study of endotoxin shock by using purified gram-negative endotoxin has been often done (Okada *et al.* [1], Okada *et al.* [2]). Many differences have been noted, however, between the experimental endotoxin shock and clinical endotoxin shock. For example, the hyperdynamic stage has been reported mostly in clinical septic shock but rarely in the experimental endotoxin shock (Ishiyama, [3]). Clinical endotoxin shock takes place when the increase in the extrinsic or intrinsic endotoxin exceeds its disposition by the reticuloendothelial system and the protecting factors in the serum. Only a small amount of serum endotoxin is usually detected until the cause is removed.

On the other hand, a large amount of endotoxin is injected as bolus to produce the experimental endotoxin shock.

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Great variations are seen in the effect of endotoxin depending on the dose, injection method and species of the purified endotoxin. Chemical mediators such as catecholamines, histamine or serotonin, lysosomal enzymes such as β-glucuronidase and toxic factors such as myocardial depressant factor (MDF) are released directly or secondarily by the purified endotoxin, thereby changing the hemodynamics in shock.

This study was aimed at investigating the circulatory changes caused by 4 mg/kg of purified endotoxin continuously infused for an hour. Such a continuous injection method has been rarely reported. This method can simulate the clinical conditions fairly well except that the amount of the serum endotoxin is large.

METHOD

Six dogs were anesthetized with 20 mg/kg of secobarbital i.v. and intubated. Under controlled ventilation $Paco_2$ was adjusted to 35±5 mmHg and Pao_2 to 90±10 mmHg.

Catheters were inserted into the right femoral artery for blood pressure line, left femoral vein for venous line (Ringer's lactate solution 5 ml/kg) and right brachial vein for endotoxin infusion.

The Swan-Ganz catheter was inserted into the pulmonary artery via the right femoral vein for the measurements of the pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP) and cardiac output (CO) by the thermodilution method. Electromagnetic flowmeter probes were fixed to the right common carotid artery, left renal artery, superior mesenteric artery and right femoral artery.

After a suitable control period, 4 mg/kg of endotoxin (Difco: E. coli, 0111: B4) was infused continuously for an hour. Measurements were done as shown in Fig. 1.

RESULTS

I. Changes in heart rate (Fig. 2)

The heart rate changed from the control value of 150±22 beat/min to 132±12 at the 180-minute point. Heart rate showed a tendency to decrease though not significantly.

II. Changes in artery pressure (AP) (Fig. 2, Fig. 5)

The mean AP was 120±7.8 mmHg during the control period and decreased significantly to 89.7±2.3 mmHg at the 30-minute point. But the initial sudden fall was not seen.

Then mean AP fell to the lowest level at the 60-minute point. After the endotoxin infusion was stopped it rose slightly but was significantly low at the 180-minute point.

III. Changes in mean PAP and PCWP (Fig. 3, Fig. 5)

The mean PAP was 19.5±2.4 mmHg during the control period and remained unchanged after the endotoxin infusion. The initial abrupt increase in PAP was

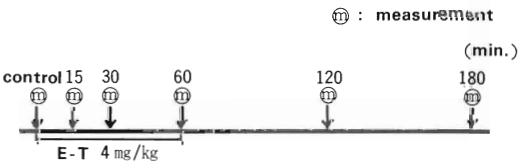

Fig. 1. Time Schedule of Experiment.

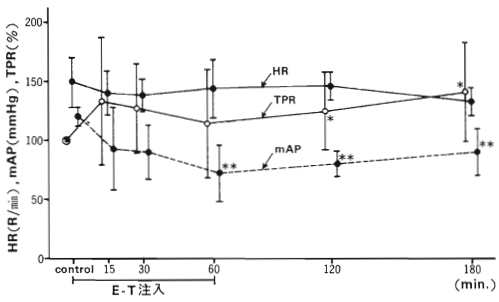

Fig. 2. Changes in Heart Rate, TPR and mAP.

Table 1. Changes in Hemodynamics, β-glucuronidase and Hb

	control	15 min	30 min	60 min	120 min	180 min
HR (R/min)	150.0±22.1	139.7±19.1	138.2±24.2	142.3±23.4	145.7±12.1	132.8±11.6
mAP (mmHg)	120.0±7.8	92.5±35.3	* 89.7±23.0	** 71.7±24.0	** 79.7±11.2	** 89.8±20.4
mPAP (mmHg)	19.5±2.4	20.3±5.7	19.2±3.4	17.8±3.4	18.7±3.5	20.5±3.1
PCWP (mmHg)	9.2±1.5	11.2±4.3	9.2±1.9	9.8±2.4	9.0±2.8	* 12.0±2.5
TPR (%)	100	132.6±53.5	126.8±37.5	113.8±45.8	* 125.1±33.4	* 140.5±42.4
PVR (%)	100	* 177.9±109.0	** 171.2±48.4	** 148.9±45.7	** 178.9±49.4	* 168.7±41.1
CI (ℓ/m²)	2.9±0.8	*** 1.6±0.4	** 1.7±0.4	** 1.5±0.4	** 1.6±0.5	** 1.5±0.5
CCAF (%)	100	* 66.7±30.2	75.8±31.7	84.0±23.7	94.8±12.2	76.7±32.4
SMAF (%)	100	77.7±39.2	79.7±32.2	** 59.5±28.2	** 64.3±21.2	* 66.5±26.7
RAF (%)	100	* 54.3±36.8	** 42.2±37.2	*** 37.8±25.7	*** 32.0±14.4	*** 40.5±22.2
FAF (%)	100	* 66.2±28.9	*** 51.3±19.5	*** 40.5±20.1	*** 51.3±15.9	** 53.3±33.8
CCFR (%)	6.7±3.6	7.8±4.9	8.5±5.9	10.0±3.9	11.4±6.7	9.8±7.4
SMFR (%)	10.8±3.2	15.3±10.9	15.6±11.1	16.0±17.2	13.7±8.9	14.0±8.2
RFR (%)	4.8±1.1	4.2±3.0	3.1±2.7	3.1±1.6	* 2.5±0.4	3.3±1.0
FFR (%)	2.0±1.9	4.8±5.7	1.4±0.8	1.1±0.7	1.6±1.2	1.6±1.5
Hb (g/dl)	12.5±2.1		13.1±2.0		14.3±2.1	
β-glucuronidase (μg/dl)	3752±1760		6609±3346		9928±5288	

HR : heart rate. mAP : mean artery pressure. mPAP : mean pulmonary artery pressure. PCWP : pulmonary capillary wedge pressure. TPR : total peripheral resistance. PVR : pulmonary vascular resistance. CI : cardiac index. CCAF : common carotid artery flow. SMAF : superior mesenteric artery flow. RAF: renal artery flow. FAF : femoral artery flow. CCFR : common carotid fraction rate of CO. SMFR : superior mesenteric fraction rate of CO. RFR : renal fraction rate of CO. FFR : femoral fraction rate of CO. Hb : hemoglobin.
*: statistically significant $P<0.05$ **: statistically significant $P<0.01$
***: statistically significant $P<0.001$

not seen. The PCWP increased from 9.2±1.5 mmHg of the control value to 12.0±2.5 mmHg at the 180-minute point.

IV. Changes in total peripheral resistance (TPR) and pulmonary vascular resistance (PVR) (Fig. 2, 3)

The TPR and PVR are shown by the percentage change of the control values. The TPR showed a control value of 5905±1553 dyne/cm² and increased significantly to 140.5±42.4% at the 180-minute point.

The PVR increased significantly at the

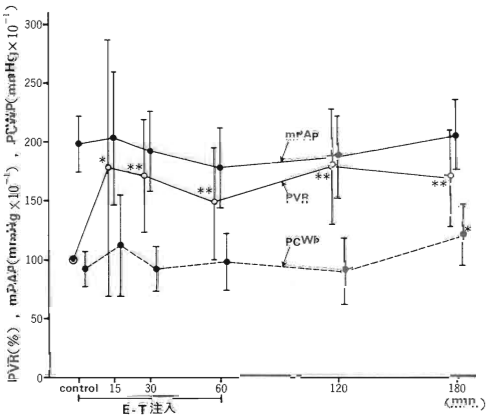

Fig. 3. Changes in mPAP, PVR and PCWP.

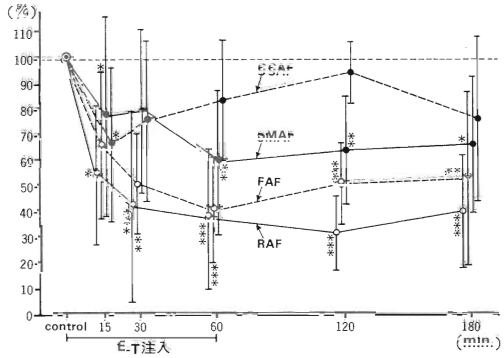

Fig. 4. Changes in Visceral Blood Flow.

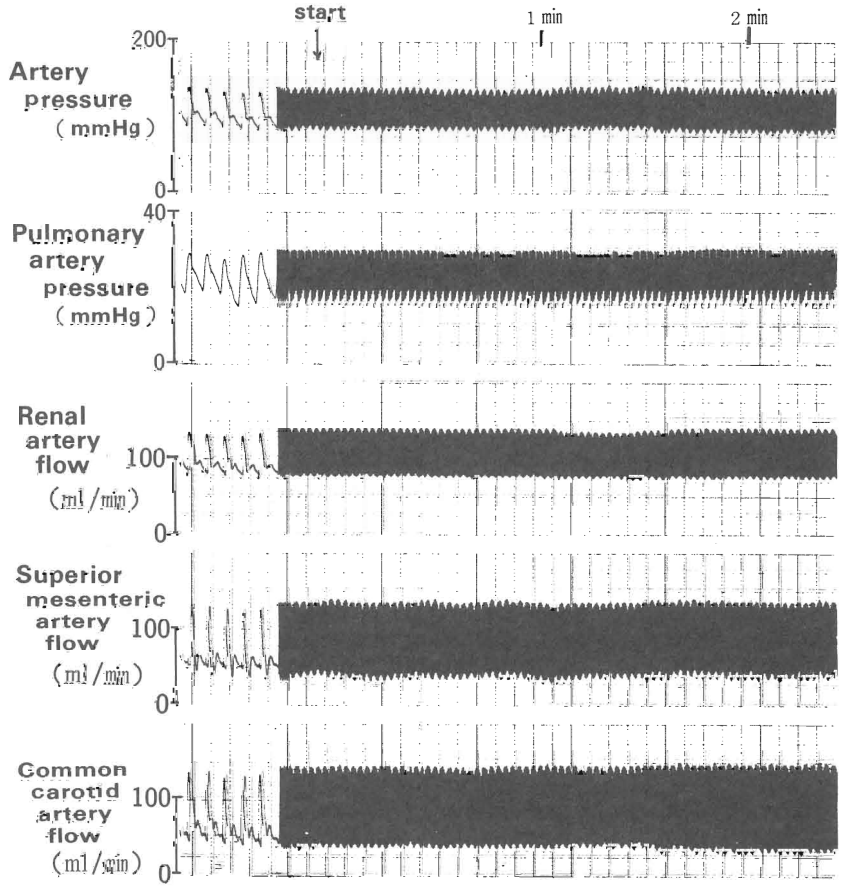

Fig. 5. Initial Responses to Continuous Infusion of Endotoxin in mAP, mPAP, RAF, SMAF and CCAF. Initial abrupt change was not seen.

30-minute point and maintained this level.

V. Changes in visceral blood flow (Fig. 4, Fig. 5)

The cardiac index was 2.9 ± 0.8 l/m^2 during the control period and decreased significantly at the 15-minute point and remained at this low level during the experiment.

Each visceral blood flow is shown by the percentage change of the control value. The initial abrupt decrease was not seen.

The common carotid artery flow fell significantly at the 15-minute point and remained at this low level until the end of the experiment.

The superior mesenteric artery flow fell later than the renal artery flow. The changes in the femoral artery flow, which was similar to that of the renal artery flow, remained at this low level during the experiment.

VI. Changes in the fraction rate of CO

The common carotid fraction rate of CO was $6.7 \pm 3.6\%$ during the control period and had a tendency to increase slightly. The renal fraction rate had a tendency to decrease with endotoxin infusion. The value at the 120-minute point was $2.5 \pm 0.4\%$, which decreased significantly from 4.8 to 1.1% during the control period.

The superior mesenteric fraction rate tended to increase from $10.8 \pm 3.2\%$ during the control period to $14.0 \pm 8.2\%$ at the 180-minute point. The femoral fraction rate of CO increased from $2.0 \pm 1.9\%$ during the control period to $4.8 \pm 5.7\%$ at the 15-minute point and fell up to the 180-minute point.

Discussion

The gram-negative endotoxin is said to injure each organ directly or indirectly and make the pathophysiology of endotoxin shock complex. In addition, complements, chemical mediators and lysosomal enzymes play important roles in the development of the shock. Endotoxin activates the alternative pathway of the complements and also probably the classical pathway.

Activated complements damage the cell membrane and induce cellular destruction.

Anaphylatoxin composed of activated complements releases the histamine from the mast cell. Activated complements release the lysosomal enzymes from the leucocytes and aggregate the platelets (Hans J. Muller [4]). Serotonin is released from the platelet and constricts small intestine and smooth muscle of the vessel. On the other hand, serotonin facilitates the secondary aggregation of the platelets and so the abnormality in the coagulation system is triggered. At the same time serotonin triggers the release of thromboxan A_2 and prostacycline from the platelet or vessel membrane (Robert R. G. [5], Gine B. K. [6], Kenneth M. M. *et al.* [7]). The former is thought to be one of the causes of the increment in pulmonary artery pressure in the initial stage. Endotoxin damages the cell directly in endotoxin shock, thus it may be different in pathophysiology from the hemorrhagic shock and cardiogenic shock.

In endotoxin shock, the initial blood pooling in the peripheral vessel induces probably the decrease in cardiac output by the decrease in the venous return (Yoshitake *et al.* [8]). Cardiac output was decreased significantly by the decreased stroke volume throughout this study. The mean AP also maintained a low level. The changes in TPR was small but increased significantly after the 120-minute point. These changes are different from the clinical septic shock usually

accompanied by a high cardiac output and low vascular resistance. Many reports on experimental endotoxin shock, however, have shown increased TPR and absence of the hyperdynamic stage. Hinshaw ([9], [10]) reported that TPR decreased in the eviscerated dog. The pooling in the visceral organs is supposed to cause an increase in TPR in the dog.

The mean PAP was unchanged despite the decrease of CO and mean AP. PVR maintained a high level in this study. The transient increase in PAP has been shown by many reports (Kuida [10], Hinshaw [11]) and may be caused by the clots of the platelets and leucocytes. But a sudden rise in PAP was not seen in this study. Therefore, our results may be caused by the decrease in the intravascular blood volume in the pulmonary circulation induced by the decrease in the venous return accompanied by the pooling in the systemic circulation.

We used a continuous administration of 4 mg/kg endotoxin. It seems likely to be near the clinical condition. In our study the initial sudden fall of mean AP and organic blood flow was not seen.

Each blood flow decreased gradually until the end of the endotoxin administration. Dedichen [12] reported the observation that the injection of a minimal dose (0.1 mg/kg) produced a typical sudden fall in blood pressure but a larger second dose (1.0 mg/kg) after partial recovery produced almost no reaction at all and an additional endotoxin dose in late endotoxin shock was without any observable hemodynamic effects. He said that his observation is well explained by an allergic mechanism, which might be applied to our study using the continuous infusion method.

As regards the blood distribution, Okada *et al.* [1] and Yamaguchi *et al.* [13] presented reports on the Micro Sphere method ([1], [13]). Okada *et al.* administered 3 mg/kg endotoxin and Yamaguchi *et al.* 1 mg/kg endotoxin as bolus. The two reports differ in the cerebral fraction rate of CO. The cerebral fraction rate of CO by Okada *et al.* was shown to decrease but that by Yamaguchi *et al.* was shown to increase at the 60-minute point. Our calculated common carotid fraction rate of CO was increased.

Okada said that the cerebral blood flow is not favored by the blood centralization in endotoxin shock. But we think that the decrease in the cerebral blood flow might be induced by the large dose of endotoxin by the bolus injection.

In our study the superior mesenteric fraction rate of CO increased at the 60-minute point and then decreased gradually. It does not agree to the preceeding two reports in which the small intestine fraction rate of CO was shown to decrease at the 60-minute point.

We estimate that continuous administration may cause a different response from that by the bolus injection of endotoxin. We also estimate that the centralization of blood may be seen in the early stage in endotoxin shock in the same way as is seen in hemorrhagic shock.

The decrease in the renal flow was significant at the 15-minute point and the decrease in the renal fraction rate of CO was significant at the 120-minute point. Dedichen showed that the decrease in the renal flow and the increase in the renal vascular resistance were maximum in all the arteries. Gillenwater *et al.* [14] proved that the persistent renal vascular constriction was due to the catecholamine release during systemic hypotension since the local infusion of phentolamine blocked the renal vasoconstriction. They also showed that renal dysfunction

was blocked by phentolamine during the initial 30 minutes. They said that the principal effect of endotoxin on the kidney is hemodynamic and not nephrotic. We guessed that the renal flow is sacrificed mostly in endotoxin shock in the same way as in hemorrhagic shock. In fact, renal dysfunction has been seen mostly among the patients proved positive by the Limulus test at our ICU (Nakagawa *et al.* [15]). It suggests that early care of renal flow is necessary.

The β-glucuronidase has been said to be a useful index of shock as one of lysosomal enzymes (Ogawa *et al.* [16], [17]). The lysosomal enzymes in shock have been said to come from the pancreas or the small intestine (Clement H. G. [18], Aaron J. *et al.* [19]). They may be the main components of the myocardial depressant factor (MDF). Lysosomal enzymes injure each organ directly and the shock stage develops. In our study the average value of β-glucuronidase increased, though not significantly. It suggests that the visceral damage is yet small since the decrease in the β-glucuronidase was insignificant accompanied by the relative maintenance in the flow of common carotid and superior mesenteric artery.

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