Baroreflex Participation of Cardiovascular Response to E. coli Endotoxin

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Abstract The purpose of this experiment was to evaluate the effects of the arterial baroreceptor buffering capacity on cardiovascular parameters during hypotension caused by E. coli endotoxin in anesthetized dogs. In the control group, mean blood pressure and cardiac output fell significantly from 104±10 mmHg to 63±7 mmHg and 1.17±0.16 l/min to 0.67±0.08 l/min, respectively, 60 min after intravenous injection of endotoxin (1 mg/kg). Central venous pressure also decreased significantly after the injection. Total peripheral resistance and portal vein pressure increased significantly immediately after the injection, and then returned toward baseline levels. The time course of changes in these five cardiovascular parameters after the injection of endotoxin was the same as that in dogs with sino-aortic denervation. Following the injection of endotoxin, stroke volume and left ventricular dP/dt fell significantly in both control and denervated dogs; however, these decreases in the denervated group were significantly greater. These findings suggest that the arterial baroreceptors may play a role in the poor compensatory response to hypotension induced by endotoxin, at least, in the cases of mean blood pressure, cardiac output, total peripheral resistance, central venous pressure, and portal vein pressure.

Key words: E. coli endotoxin, hypotension, baroreceptors, sino-aortic denervation, cardiovascular response.

The physiological function of the cardiovascular system in correcting hypotension and maintaining systemic blood pressure at a steady level has been documented. Removal of the baroreceptor reflex reduces tolerance to acute hemorrhagic hypotension because vasoconstriction triggered by baroreceptors via the sympathetic nervous system is lacking (CHIEN, 1967; KORNER, 1971). There are

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conflicting reports about the participation of the baroreceptor reflex system in endotoxic hypotension (Trank and Visscher, 1962; Blattbarg and Levy, 1969; Halinen et al., 1977). Halinen et al. (1977) reported that peripheral sympathetic nerve discharges increase reflexly during their 15-min observation periods after the injection of endotoxin, as in the case of acute hemorrhagic hypotension but they did not report what happened later. Trank and Visscher (1962) found that carotid sinus baroreceptor mechanisms do not function normally when endotoxin was present for longer observation periods of over 30 min. Koyama and Manning (1985) reported that hypotension caused by endotoxin occurred in parallel with a decrease in efferent splanchnic nerve activity, and Koyama (1986) showed that an intravenous injection of endotoxin causes a hypotensive effect simultaneous with a reduction in spontaneous renal sympathetic nerve activity. Changes in arterial blood pressure and renal sympathetic responses to repetitive stimulation of medullary pressor regions are reduced significantly by endotoxin. Discharges evoked in renal sympathetic nerves by medullary stimulation with a single shock and twin pulses are reduced. Therefore, endotoxin causes a central depressed sympathetic outflow from medullary pressor regions to efferent sympathetic nerves. In previous reports (Koyama et al., 1982b, 1983; Koyama, 1984), we showed that the hypotensive effect of endotoxin is mediated by the stimulation of central α-adrenoceptors leading to inhibition of the brain stem sympathetic pathway, which may be a component of the baroreflex circuit. Whether or not the buffering capacity of arterial baroreceptors affects various cardiovascular parameters during hypotension caused by E. coli endotoxin has not yet been studied. In this study, we have investigated these parameters during endotoxic hypotension before and after baroreceptor denervation.

METHODS

Twenty mongrel dogs of either sex weighing 7–14 kg were anesthetized with sodium pentobarbital (25 mg/kg, i.v.). More anesthetic was given when needed. The trachea was intubated and the animals were mechanically ventilated with room air delivered from a Harvard respirator. The ventilation rate (12–18 cycles/min) and tidal volume (15–20 ml/kg) were adjusted to maintain an arterial blood $P\text{O}_2$ level of 100–110 mmHg and a $P\text{CO}_2$ level of 28–36 mmHg. Animals were paralyzed with an intravenous injection of gallamine triethiodide (2 mg/kg) to avoid cardiovascular effects secondary to muscle activity. Body temperature was measured with a thermistor inserted into the rectum and maintained at 36 ± 1°C by the use of a heating lamp. Polyethylene tubes were placed in the lower aorta through the femoral artery and in the femoral vein for measurement of mean blood pressure (MBP) and intravenous injection of endotoxin, respectively. Arterial blood pressure was monitored by a pressure transducer (Nihon Kohden, MPU-0.5A) and the heart rate (HR) was measured on a cardiotachometer (Nihon Kohden, AT 600G) triggered by a lead II electrocardiogram. Cardiac output (CO) was measured by...
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thermal dilution from a flow-directed Swan-Granz catheter (F47) with a thermister tip in the main pulmonary artery, introduced via the femoral vein, using a cardiac output computer (Nihon Kohden, EQ611V and AH611V). In this step, 3 ml of a physiological saline at room temperature was injected into the right atrium. CO was measured twice and averaged. Thermodilution curves were checked periodically to see if they were exponential. Central venous pressure (CVP) was measured simultaneously through the Swan-Ganz catheter connected to a pressure transducer (Nihon Kohden, MPU-0.5A). Total peripheral resistance (TPR) and stroke volume (SV) were calculated by the following formulae:

\[
\text{TPR (dyn s/cm}^5\text{)} = (\text{MBP (mmHg)} - \text{CVP (mmHg)}) \times 79.9 / \text{CO (ml/min)}
\]

\[
\text{SV (ml/beats)} = \text{CO (ml/min)} / \text{HR (beats/min)}
\]

A polyethylene tube was placed in the left ventricle through the left common carotid artery. Left ventricular pressure (LVP) was monitored by a pressure transducer (Nihon Kohden, MPU-0.5A) and differentiated to obtain LV dP/dt as an index of cardiac contractility by means of a pressure processor (Nihon Kohden, EQ-600G). Another polyethylene tube was placed in the main portal vein to measure portal vein pressure (PVP) via the splenic vein, after upper median laparotomy. The incised wound on the abdomen was closed by a layer to layer suture.

Through an upper median cervical incision, bilateral sino-aortic denervation (SAD) was performed by carefully isolating and severing the carotid sinus and aortic nerves on both sides under a dissecting microscope. The aortic nerves were separated from the vagi after identification of the aortic nerves between the nodose ganglion and the superior laryngeal nerve. In some dogs, we severed the glossopharyngeal nerve as it passed through the jugular foramen, or we cut all tissue strands in the region surrounded by the nodose ganglion, vagal nerve, cervical sympathetic trunk, and superior laryngeal nerve. The denervation was verified when the blood pressure and heart rate did not change after bilateral carotid occlusion and by the lack of a reflex inhibitory response of the heart rate to a pressor dose (1–2 \( \mu \text{g/kg, i.v.} \)) of norepinephrine. A sham operation on the upper cervical region was performed in all control animals.

*E. coli* endotoxin (Difco Lab.; 0111, B4) was freshly prepared as a suspension in a physiological saline. Each parameter was allowed to stabilize for at least 30 min before the injection. Endotoxin was injected intravenously at a dose of 1 mg/kg for 15 s; parameters were measured for the next 60 min. All values are reported as means ± S.E. Comparisons between the control value before and at various times after the injection were made using the Student's t-test for paired data or unpaired data. When multiple comparisons were made within groups, a one-way analysis of variance was done. Comparisons involving more than one group were analyzed using the appropriate analysis of variance technique. "p" values of less than 0.05 were considered significant.
RESULTS

Steady state baseline values for the cardiovascular parameters in the control and in the SAD group are shown in Table 1. Differences between the baseline values of parameters in the control group and in the SAD group before sino-aortic denervation were not significant. However, there were significant differences between the baseline values of MBP, HR, and TPR before and after sino-aortic denervation in the SAD group.

Figure 1 shows the time course of changes in MBP sampled at regular intervals after the injection of endotoxin. In the control group, MBP fell from $104 \pm 10$ mmHg to $85 \pm 6$ mmHg at 5 min and $90 \pm 4$ mmHg at 10 min after the injection. Thereafter a progressive and significant decline in MBP followed, to $63 \pm 7$ mmHg at 60 min. In the SAD group, MBP fell significantly, from $124 \pm 9$ mmHg to $77 \pm 11$ mmHg at 60 min. Changes in MBP over time were similar in both groups. In the control group, HR fell insignificantly from $157 \pm 7$ beats/min after the injection of endotoxin, followed by a gradual recovery such that in 60 min HR had advanced to $165 \pm 6$ beats/min. The Basal level of HR in the SAD group was $182 \pm 9$ beats/min, which was significantly higher than that in the control group. When endotoxin was administered intravenously in the SAD group, HR initially remained unchanged but a slight increase occurred after 40 min and continued until the end of the experiment, but this was not significant: 60 min after the injection of endotoxin HR was $195 \pm 5$ beats/min (Fig. 1).

In the control group, CO significantly decreased from $1.17 \pm 0.16$ l/min to

<table>
<thead>
<tr>
<th>Table 1. Baseline values of cardiovascular parameters.</th>
<th>Control group ($N=6$)</th>
<th>SAD group ($N=6$)</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After sham operation</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>112 ± 8</td>
<td>104 ± 10</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>148 ± 10</td>
<td>157 ± 7</td>
</tr>
<tr>
<td>CO (/min)</td>
<td>1.19 ± 0.18</td>
<td>1.17 ± 0.16</td>
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<tr>
<td>TPR (dyn\·s/cm²)</td>
<td>7,520 ± 528</td>
<td>7,854 ± 615</td>
</tr>
<tr>
<td>SV (ml/beats)</td>
<td>8.0 ± 1.2</td>
<td>7.4 ± 1.4</td>
</tr>
<tr>
<td>LV dP/dt (mmHg/s)</td>
<td>4,530 ± 510</td>
<td>4,240 ± 410</td>
</tr>
<tr>
<td>PVP (mmHg)</td>
<td>8.7 ± 1.8</td>
<td>10.9 ± 1.1</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>4.8 ± 2.1</td>
<td>5.3 ± 1.4</td>
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All values are mean ± S.E.M. MBP = mean blood pressure, HR = heart rate, CO = cardiac output, TPR = total peripheral resistance, SV = stroke volume, LV dP/dt = left ventricular dP/dt, PVP = portal venous pressure, CVP = central venous pressure, SAD = sino-aortic denervation. The asterisk (*) indicates a significant difference ($p < 0.05$) between the control and SAD groups.

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0.69 ± 0.10 l/min 10 min after the injection; and in the SAD group, from 1.28 ± 0.19 l/min to 0.65 ± 0.05 l/min. These decreased levels of CO in both groups continued throughout the experiment, and were 0.67 ± 0.08 l/min in the control group and 0.61 ± 0.07 l/min in the SAD group at 60 min. The changes over time in CO in the two groups were similar (Fig. 2). Figure 2 also shows the time course of the changes in TPR in both groups. In the control group, TPR significantly increased during the first 10 min after the injection of endotoxin, and then gradually returned toward the baseline level. The time course in both groups was similar, but levels of TPR over time in the SAD group were higher than in the control group.

SV fell significantly from 7.4 ± 1.4 ml/min to 5.8 ± 0.8 ml/min 10 min after the injection (Fig. 3). The level remained low until the end of the experiment. In the SAD group, the decreases in SV after the injection were significantly larger at each time we measured SV compared to the control group. Figure 3 also shows the time course of changes in LV dP/dt in both groups. Following the injection of endotoxin in the control group, LV dP/dt decreased; for at 60 min, it was 3,138 ± 451 mmHg/s. In the SAD group, LV dP/dt also decreased significantly; at 60 min, it was 2,340 ± 281 mmHg/s. The pattern of changes in LV dP/dt in both groups was...
similar, but this parameter was significantly lower in the SAD group from 40 min after the injection of endotoxin until the end of the experiment.

Following the injection of endotoxin, CVP continued to decrease, in the control group until the end of the experiment, but not significantly (Fig. 4). The time course of changes in CVP in both groups were similar. Intravenous injection of endotoxin caused significant increases in PVP (from 10.9 ± 1.1 mmHg of the preendotoxin level to 17.3 ± 1.7 mmHg 5 min after the injection of endotoxin) followed by a return toward the preendotoxin level in both groups, whose time course of changes were similar, as shown in Fig. 4.

DISCUSSION

In this experiment, *E. coli* endotoxin caused progressive decreases in MBP, CO, SV, LV dP/dt, and CVP, and temporary increases in TPR and PVP followed by a return toward baseline levels, which confirms the findings of a previous report (GILBERT, 1960). In general, it would be expected that a decrease in systemic blood pressure would reduce afferent nerve impulses from the arterial baroreceptors to
medullary blood pressure regulatory circuits, which in turn enhance sympathetic outflow, causing an elevation of the total resistance for maintaining arterial blood pressure at a steady level (CHIEN, 1967; KORNER, 1971). However, in this study, the
time course pattern of changes in TPR following injection of endotoxin did not differ significantly between the control group and the SAD group and decreases in MBP in both groups were also similar. Therefore, the present findings indicate that activation of the baroreceptor-sympathetic reflex system leading to peripheral vasoconstriction is depressed in endotoxic hypotension. TRANK and VISSCHER (1962) observed a relationship between the stepwise alteration of carotid sinus pressure and the carotid sinus nerve discharge firing rate during endotoxic hypotension. Thus, for a given level of pressure within the carotid sinus, there would be an increased mean frequency of discharge from the baroreceptors, leading to a reflex inhibition of efferent sympathetic nerve activity. They concluded, in agreement with the present findings, that the baroreceptor-reflex systems play a role in the poor compensatory response to hypotension induced by endotoxin. CHIEN et al. (1966), also, indicated by the quantitative examination of arterial blood pressure-cardiac output relationships that sympathetic activity in endotoxin shock is not as effective as in hemorrhagic shock. Recently, we reported (KOYAMA et al. 1982b, 1983; KOYAMA and MANNING, 1985) that preganglionic splanchnic nerve activity following the intravenous injection of endotoxin decreased simultaneously with a fall in systemic arterial blood pressure, indicating that hypotension due to E. coli endotoxin was at least partly independent from the baroreceptor-reflex compensatory mechanisms. Furthermore, decreases in blood pressure, renal vascular resistance, and peripheral sympathetic activity following the intravenous injection of endotoxin are abated by intracisternal pretreatment with either phentolamine or prazosin, an α-adrenoceptor blockade (KOYAMA et al., 1982a; KOYAMA, 1984; KOYAMA and MANNING, 1985). These findings suggest that E. coli endotoxin acts on central autonomic blood pressure regulatory circuits, by stimulating the central α1-adrenoceptors, thus leading to the inhibition of brain-stem sympathetic pathways and causing cardiovascular depression. KOYAMA (1986) showed by a neurophysiological approach that endotoxic hypotension results from a central neural abnormality leading to a depressed sympathetic transmission from the medullary pressor regions into the brain-stem to efferent sympathetic nerves.

Additional findings of this study showed that levels of HR and TPR in the SAD group, for each time throughout the experiment, were significantly higher than that in the control group. These results were dependent on near maximal increases in the basal level of sympathetic tone following the sino-aortic denervation. Thus, these higher levels of HR together with elevated TPR in the SAD group may be associated with further decreases in SV over time after the injection of endotoxin. Greater decreases in LV dP/dt in the SAD group than in the control group also occurred from 40 min after the injection of endotoxin and continued until the end of the experiment (Fig. 3). These differences in LV dP/dt between both groups may, however, be associated with the following two possibilities. One is that high basal levels of sympathetic tone in the SAD group result in an increase in afterload to the heart, causing reductions of myocardial contractile force. Another possibility is that a direct inotropic effect of circulating catecholamines to the myocardium following
administration of endotoxin may be less in the SAD group than that in the control group; because the sino-aortic denervation may eliminate increases in circulating catecholamines sympathetically released by the baroreceptor reflex during endotoxic hypotension. However, the present result did not show any direct evidence for supporting these possibilities. Basal levels of sympathetic tone in the sino-aortic denervated dogs may have been near maximal, making it difficult to detect exact contributions of the baroreceptor-reflex system on myocardial functions in endotoxic hypotension. Therefore, further experiments need to be evaluated by the carotid baroreceptor isolation technique which allows us to control basal sympathetic tone to near normal levels and thus allows us to assess the influence of the baroreceptor reflex under conditions in which small changes in cardiovascular variables might be appreciated in endotoxic hypotension.

REFERENCES


