The Direct Effects of Endotoxin on the Heart (35082)

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Reports from the literature concerning the actions of endotoxins on the heart are at variance. Results in human patients (1, 2) and some experimental evidence (3) indicate that endotoxins may have a myocardial depressant action while other experimental studies conclude that endotoxins have little or no depressant effect on the heart (4–8).

Because of the peripheral actions of endotoxins (9), large changes occur in the heart rate as well as the preload and afterload of the heart in intact animals, thus rendering an evaluation of the direct effects of endotoxins on the heart difficult. Therefore, a study was designed for this purpose, utilizing an isolated heart preparation, in which the other variables could be controlled. The study represented an improvement over previous investigations in that a physiologic pH was maintained and no anesthetic agent was present in the system, thereby making it possible to relegate any changes to the endotoxin.

Methods. Adult mongrel dogs of either sex were employed. The animals were free of heart worms, intestinal parasites, and respiratory infections and had a minimum hematocrit of 40%.

A plastic canine anesthesia mask was connected to a Fluotec vaporizer and a direct induction was performed using 4 vol % halothane in pure oxygen. After induction, the anesthetic concentration was lowered to 1.5 vol % for maintenance. A midline thoracotomy was performed and a Starling heart–lung preparation instituted (10). Following ligation of the brachiocephalic and left subclavian arteries, the halothane was removed from the respiratory gas mixture. After the heart–lung preparation was established, a small incision was made in the pericardial sac and left auricle. Through this opening a catheter tip manometer (SF-1 Statham Instrument Co., Hato Rey, Puerto Rico) was inserted into the left ventricle. Then a source of 5% CO_2 and 95% O_2 was added to the inspiratory gas mixture of pure oxygen. By adjusting the flow rates of this gas source and the pure oxygen, the CO_2 concentration of the inspired mixture was varied from 0 to 5%. The respiratory rate was set at 5–8 breaths/min and the CO_2 concentration was adjusted so as to bring the arterial pCO_2 into a physiologic range for an unanesthetized dog (30–35 mm Hg). This usually resulted in a decreased pH. The arterial pH was adjusted up to a normal range (7.39–7.41) by adding a sufficient quantity of sodium bicarbonate solution, 1 meq/ml, to the venous reservoir. After adjustment of the pCO_2 and pH, the venous return was regulated so as to yield a cardiac output of about 500 ml/min. This was considered zero time and all variables were recorded. Subsequent measurements were taken each quarter hour for 1 hr, then each half hour until 3 hr, at which time the experiments were terminated. The measurements were compared with the values obtained at zero time, which were considered the controls.

The time interval from removal of the anesthetic agent to the recording of variables at zero time was usually about 40 min. This was sufficient time for all of the halothane to be dissipated (11) so that the preparation was entirely free of anesthetic influences.

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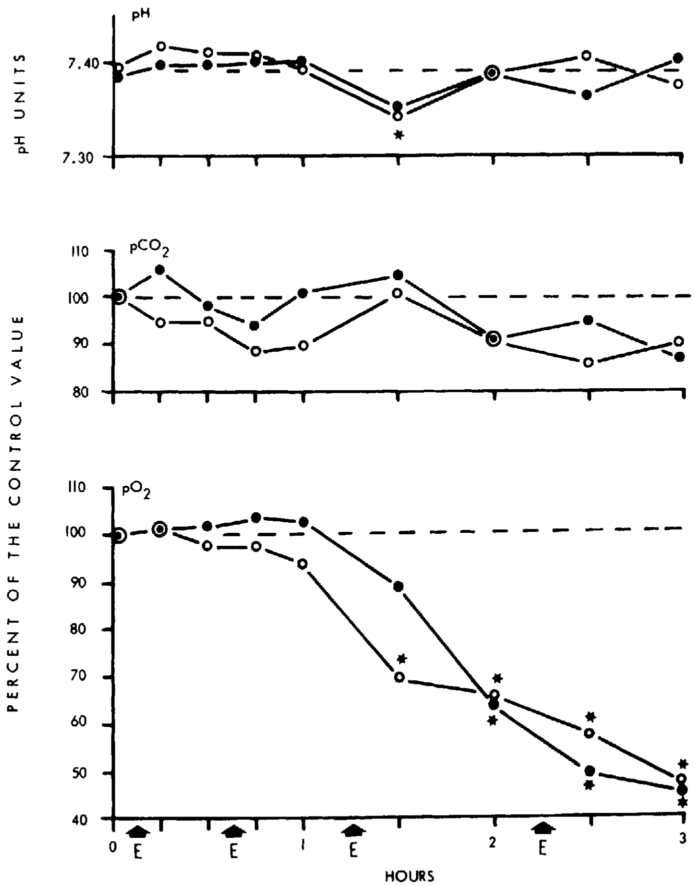

FIG. 1. Shown here are the changes that occurred in arterial pH, pCO_2 and pO_2. Each point represents the mean values for eight animals. The zero time values of these variables for the untreated group (●—)were 7.389 ± 0.014 pH units, 26.7 ± 1.7 mm Hg and 360 ± 30 mm Hg, respectively. The zero time values for the endotoxin-treated group (O—) were 7.394 ± 0.026 pH units, 33.4 ± 2.6 mm Hg and 444 ± 15 mm Hg, respectively. (- - -), the zero time levels. Endotoxin was given in that group at the time intervals marked by arrows. (**), $p < 0.05$ among-groups.

During the 3-hr period, the arterial pH was maintained by adjustment of the arterial pCO_2. This was accomplished by manipulation of the respiratory rate and the concentration of CO_2 in the inspired gas mixture.

Two groups of eight animals each were studied. In one, the untreated group, variables were measured for 3 hr. These included mean arterial, mean right atrial and left ventricular end diastolic pressures, cardiac output, heart rate, reservoir temperature, arterial pH, pCO_2 and pO_2 and the left ventricular maximum *dP/dt*. In the endotoxin-treated group, the same variables were measured. However, 1, 1, 2 and 4 mg/kg total animal body weight of purified *E. coli* endotoxin (Difco Laboratories, Detroit, Michigan) was added to the venous reservoir between the 0 and 0.25; 0.5 and 0.75; 1 and 1.5; and the 2 and 2.5 hr time intervals, respectively.

A Student's paired *t* test was used to detect significant among-group changes from their respective zero time controls. Tests for significant differences between groups were performed with an unpaired *t* test. A *p* value of < 0.05 was considered to be significant. The data are reported in the text and figure descriptions as mean values ± the standard

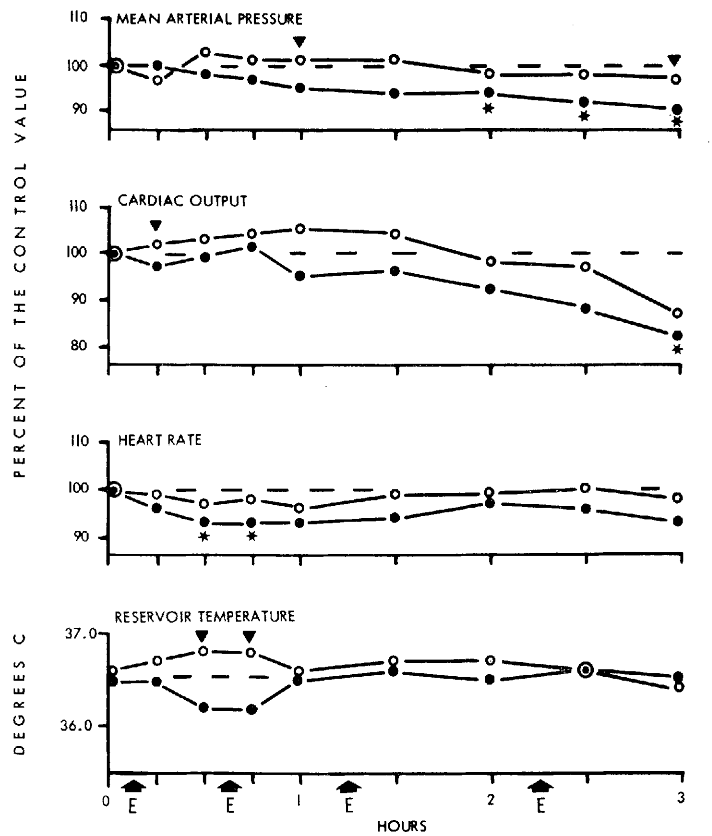

FIG. 2. Shown here are the changes that occurred in mean arterial pressure, cardiac output, heart rate, and reservoir temperature. Each point represents the mean values for eight animals. The zero time values of these variables for the untreated (●—) group were 78 ± 3 mm Hg, 498 ± 8 ml/min, 130 ± 7 beats/min, and 36.5 ± 0.2°, respectively. The zero time values for the endotoxin-treated (O—) group were 81 ± 3 mm Hg, 506 ± 7 ml/min, 131 ± 6 beats/min, and 36.6 ± 0.2°, respectively. (- - -) the zero time levels. Endotoxin was given in that group at the time intervals marked by arrows. (**), $p < 0.05$ among groups; and (▼) $p < 0.05$ between groups.

error of the mean.

Results. The measurements recorded at zero time were considered to be the control values for the untreated and the endotoxin-treated groups.

The changes that occurred in the arterial blood gases and pH are shown in Fig. 1. The pCO_2 did not change significantly from the zero time value in either group. Only one change ($p<0.05$) occurred in the pH, that being a decrease at 1.5 hr in the endotoxin group. The pO_2 decreased ($p<0.05$) from 2 hr onward in the untreated group and from 1.5 hr in the endotoxin-treated group. With all three of these variables, significant between-group differences were not observed.

Figure 2 shows the changes that occurred in mean arterial pressure, cardiac output, heart rate, and reservoir temperature. In the heart–lung preparation, since the heart is denervated, heart rate can be affected only by temperature, or external agents. Because temperature was held constant mechanically, heart rate should not change. The two decreases ($p<0.05$) in heart rate in the untreated group at 0.5 and 0.75 hr were due, however, to a fall in reservoir temperature during several of the experiments in that group, subsequent to a malfunctioning of the constant temperature device. Otherwise heart

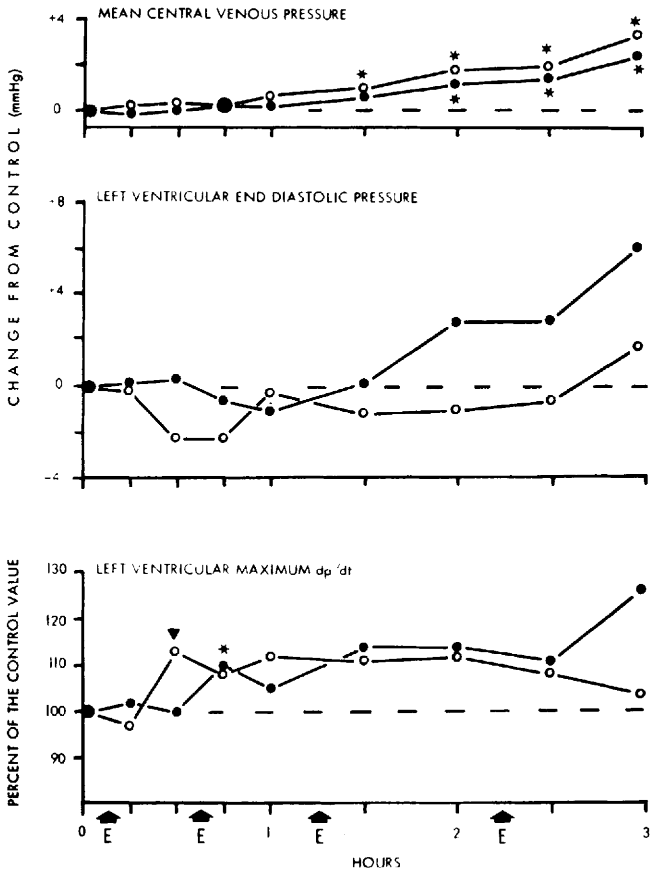

FIG. 3. Shown here are the changes that occurred in the mean central venous and left ventricular end diastolic pressures (mm Hg change from control) and left ventricular maximum *dP/dt*. The zero time values of these variables for the untreated (●—) group were + 1.5 ± 0.4 mm Hg, + 5.2 ± 2.6 mm Hg, and 1206 ± 62 mm Hg/sec, respectively. The zero time values for the endotoxin-treated group (O—) were +2.2 ± 0.3 mm Hg, +8.5 ± 1.1 mm Hg, and 1076 ± 60 mm Hg/sec, respectively. (- - -), zero time levels. Endotoxin was given in that group at the time intervals marked by arrows. (**), $p < 0.05$ among groups, and (▼) $p < 0.05$ between groups.

rate did not change significantly in either group and between-group significant differences in this variable were not observed. The mean arterial pressure decreased ($p<0.05$) in the untreated group from 2 hr on, but did not show a signficant change from the zero time value in the endotoxin-treated group. Between group differences ($p<0.05$) occurred at 1 and 3 hr. The cardiac output in the untreated group decreased below the zero time value from 1 hr onward, this decrease becoming significant by 3 hr. The cardiac output of the endotoxin-treated group did not change appreciably from the zero time value. One between-group difference ($p<0.05$) occurred at 0.25 hr.

The data for central venous and left ventricular end diastolic pressures and the ventricular maximum *dP/dt* are shown in Fig. 3. The central venous pressure in the untreated group was elevated ($p<0.05$) from 2 hr on, while that of the endotoxin-treated group increased ($p<0.05$) from 1.5 hr until the end of the experiment. Significant changes from the zero time values were not observed in the left ventricular end diastolic pressures of either group. Only one change ($p<0.05$) was seen in the ventricular maximum *dP/dt*. This increase occurred at 0.75 hr in the untreated group. With all three of these variables, there was only one between-group difference ($p < 0.05$), that being the 0.5 hr ventricular dP/dt.

Discussion. Previous experimental studies relating to the effect of endotoxin on the heart have all had one factor in common; that being the presence of anesthetic agents (3–8). Several of these studies have been in intact animals (3–5, 8). Three of the intact animal studies resulted in the conclusion (4, 5, 8), on the basis of ventricular function curves, that endotoxin had no depressant effects on the heart. The fourth (3) evaluated myocardial contractility with the isometric time–tension index method and found it to be decreased. Of the studies performed on isolated hearts (6, 7) one did not report any quantitative data but only stated that endotoxin exerted no detrimental effects on the rabbit heart (6). The other study, in which a canine heart–lung preparation was utilized, reported that the animals given endotoxin lasted only half as long as the controls. However this was due to the pulmonary effects of the toxin; the heart response to an increased work load was not altered and thus it was concluded that the endotoxin had minimal direct effects on the heart (7).

In the present studies the direct effects of endotoxin, on an isolated heart, were evaluated in the absence of an anesthetic agent, while maintaining the pH at physiologic levels. The results indicate that endotoxin has no direct negative inotropic effects on cardiac function.

Because of denervation, the heart–lung preparation represents a failing heart (12). This was evident in the present study by the early elevation of right atrial and left ventricular end diastolic pressures, and an early decline in cardiac output and mean arterial pressure in the untreated group. The decline in cardiac output resulted from a diminution of stroke volume, since heart rate was constant. The decreased stroke volume produced an increased ventricular end systolic volume and since venous return was unchanged, ventricular end diastolic pressure was elevated. Peripheral resistance was held constant, therefore the decline in cardiac output resulted in a decreased arterial pressure.

In the endotoxin-treated group, ventricular end diastolic pressure did not increase until later and in fact actually declined slightly in the early stages of the experiment. It appears that the endotoxin delayed the onset of failure. For this reason, the decline in cardiac output in this group occurred at a later time period in the experiment, and arterial pressure was maintained longer. In this group, the rise in right atrial pressure was not due to cardiac failure but probably to an increase in pulmonary vascular resistance caused by the endotoxin (13).

Since peripheral resistance, venous return, and heart rate were constant, the ventricular maximum dP/dt was a good index of myocardial contractile force. However a discrepancy arises in that the changes in this variable were practically identical for both groups. The contractile force appeared to be slightly elevated in both groups. In the untreated group, the apparent slight elevation of the contractile force was probably due to the elevated end diastolic volume which placed a greater stretch on the myocardial fibers.

Since the pulmonary vascular constriction phenomenon of endotoxin is quantitatively greater on the pulmonary venous side (13) there probably resulted an alveolar capillary edema. This led to the progressive decline in arterial pO_2 in the endotoxin-treated group. A similar phenomenon that resulted in the untreated group was most likely due to left heart failure.

These results support the conclusions of previous investigators that endotoxin has no detrimental action on cardiac mechanics, and oppose the idea that endotoxins are direct cardiac depressants. Although there were no significant differences, between the two groups, in the variables indicative of the cardiac contractile status, the onsets of the deterioration in cardiac output and therefore mean arterial pressure and the rise in ventricular end diastolic pressure were, in fact, delayed in the endotoxin-treated group. This is not sufficient evidence to conclude that endotoxins possess a positive inotropic action. It is unlikely that the endotoxin caused catecholamine release from cardiac sympathetic nerve endings since no simultaneous increases in heart rate were noted. If the endotoxin possesses any direct cardiac supportive activity, it is extremely weak and perhaps was only indicated in this study, as opposed to previous investigations (3–8), because of the absence of an anesthetic agent, most of which are cardiac depressants and would easily override such a weak effect.

Since endotoxins have been shown to increase the vascular reactivity to catecholamines (14), it is possible that a similar action of endotoxins could occur for the cardiac sensitivity to catecholamines already in the system and that this could be an explanation for the delay of the onset of failure noted here rather than a direct effect of the endotoxins themselves.

Summary. The direct effects of gram-negative bacterial endotoxin on the heart were studied, using a Starling heart–lung preparation. The technique was modified so as to have a preparation that was anesthetic free and had a physiologic pH. The data show that endotoxin does not have a depressant action on the heart but that it did delay the onset of cardiac failure in this preparation. Such a phenomenon may be due to a weak supportive action of endotoxin on the heart which can only be detected in the absence of anesthetics, since anesthetics generally depress the heart. A possible explanation for such a phenomenon is offered.

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