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The Effect of Endotoxin on General and Coronary Haemodynamics and Metabolism, and its Relation in Certain Infectious Diseases.

by

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Abstract

Shock occurs in gram-negative septicaemia, dengue, and other infections: to understand the situation better, a study was made of the effects of endotoxin on the general and coronary circulation of intact animals. Cardiac output (Fick), coronary flow (N₂O Fick), vascular pressures, glucose lactate, pyruvate, non-esterified fatty acid (NEFA), and C₁₄ palmitate levels, were measured before and after the injection of Serratia marcescens endotoxin into healthy anaesthetized dogs.

Cardiac output, vascular pressures, and cardiac work fell precipitously. Coronary blood flow, myocardial O₂ consumption, and cardiac efficiency decreased by 50%.

Whole-body glucose, lactate, pyruvate, and NEFA increased, but no change occurred in the myocardial extraction of these substances. The myocardial oxidation of C₁₄ palmitate increased.

The general haemodynamic changes are similar to those occurring in patients; it is suggested that the changes in the coronary circulation seen in animals may also occur in the clinical situation. Other animal studies with a histamine releaser (Tween 20), gave results similar to those of endotoxin. Anaphylotoxins may then also be relevant to the "shock" state of certain infections.

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Many diseases can be complicated by shock. Among them are gram-negative septicaemias, endotoxaemia (as in contaminated blood transfusion) and certain virus diseases, especially those due to the dengue (arbovirus) groups. Little was known about the effects of endotoxin on other than the simplest circulatory parameters; accordingly a study was made of general and coronary haemodynamics and metabolism, using dogs as subjects, and the endotoxin of *Serratia marcescens* (*B. prodigiosus*) as the test toxin.

Materials and Methods

The animals (20 in number) were premedicated with morphine sulphate (3 mg/kg subcutaneously) and anaesthetised one hour later by an intravenous injection of dial-urethane-pentobarbital* (0.25 mg/kg). Small incisions were made into the superficial neck veins and through them cardiac catheters were placed in a main pulmonary artery and into the coronary sinus. Needles were placed percutaneously in each femoral artery, and a manifold system was set up which allowed the frequent sampling of blood for O_2 , CO_2 , N_2O , and various biochemical measurements, as well as rapid repeated measurement of vascular pressures. Cardiac output was measured by the Fick principle, or by dye-cur-

ve, and coronary flow by the N_2O (Fick saturation) method. The turnover of radioactive material was estimated by continually infusing C_{14} -labelled palmitate and sampling from a femoral artery, pulmonary artery, and coronary sinus.

On completion of the control studies, endotoxin (*Serratia marcescens*) was injected intravenously in a dose of 1.5 mg/kg body weight. The measurements described above were then repeated.

Each animal always acted as his own control, statistical evaluation of the differences between the group means (control and experimental) was done by Student's 't' test. Statistical significance was accepted at the 5% level.

Results

The endotoxin caused a rapid decrease in systemic and right atrial pressures, which continued throughout the study period, and was accompanied by a doubling of heart rate. The pulmonary arterial pressure increased transiently, but then fell below control values.

The principal changes in general and coronary haemodynamics are summarized in Table 1, and show a marked decrease in cardiac output and left ventricular work. There is an increase in systemic vascular resistance. The same trends were found

* Contains Dial 100 mg/ml, monoethylurea and Urethane each 400 mg/ml, Pentobarbitone 60 mg/ml used as 1 : 1 diluent.

in the figures for right ventricular work and total pulmonary resistance.

There was a marked decrease in coronary flow; as systemic pressure fell to the same degree, coronary vascular resistance was unchanged. There was an increase in cardiac oxygen extraction (Δ arterial - coronary sinus O_2). This compensated for the decreased coronary flow, so that cardiac oxygen consumption (the product of coronary flow and cardiac oxygen extraction) showed only an insignificant change.

Biochemical changes

Glucose values in the femoral artery increased from 75 ± 18 mg% to 85 ± 19 mg%, a significant change. Similar trends were seen in the glucose content of the coronary sinus blood, but no change was found in the cardiac extraction of glucose. Non-esterified fatty acid (NEFA) levels also increased in both the artery and coronary sinus, with an increase in cardiac NEFA extraction. No significant change was found in pyruvate values, either in the artery or the coronary sinus. Lactate values in the femoral artery increased from 6.2 ± 2.4 mg% to 11 ± 3.5 mg%, with corresponding changes in the coronary sinus values, but without any significant change in cardiac lactate extraction values.

The behaviour of radio-active palmitate is shown in figure 1, which contrasts the effect of endotoxin

against a control study for time alone. The figure shows a significant increase in C_{14} palmitate extraction and oxidation, together with a transient decrease in efflux from the myocardium.

Discussion

The experimental results shown for general haemodynamics are not very unlike those recorded in humans suffering from haemorrhagic fever (Entwisle and Hale, 1957) and the decrease in systemic pressure and cardiac output is reasonably in accord with clinical observations in children suffering from dengue haemorrhagic fever (Wong Hock Boon et al., 1973).

Accordingly it is not unreasonable to predict that some of the changes in coronary flow and myocardial metabolism noted in the animal study could also occur in humans.

If this is so, then the marked decline in coronary flow and cardiac efficiency would undoubtedly contribute to the death rate observed in dengue haemorrhagic fever, and other forms of septic shock, and certainly would accord with the evidence of myocarditis noted in arbovirus infections (Obeyesekere and Hermon, 1972).

In the clinical situation of dengue haemorrhagic fever, anaemia, thrombocytopenia, and hyponatraemia are all usual clinical components. None of these would however greatly alter the deductions concerning

cardiac haemodynamics and metabolism now presented, since essentially similar findings have been reported in haemorrhagic shock (Edwards et al., 1953) or in hypovolaemic hyponatraemic situations (Maxwell, 1966). The biochemical changes in endotoxin shock are also similar to those found in hyponatraemic hypovolaemic situations. It seems clear from the present study that not only is there a marked decrease in mechanical efficiency, but that this is paralleled by the biochemical evidence of an apparent increase in C_{14} palmitate oxidation in the face of a marked decline in left ventricular work, and maintenance of total cardiac oxygen consumption at near control values. Since the data (cardiac O_2 consumption and C_{14} palmitate oxidation) were obtained by independent methods, there is a suggestion that myocardial metabolism shifts from an aerobic to a relatively anaerobic form.

It has been claimed recently (Bokisch et al., 1973) that anaphylotoxins derived from the activation of complement, may be related to the shock-state of dengue haemorrhagic fever. We can support this thesis in

that other histamine releasers e.g. Tween 20, cause exactly the same changes in experimental animals as does endotoxin (Burnell and Maxwell, 1974).

The experimental studies now described have not guided us to any specific method of treatment. The general principles of volume replacement (with blood or saline fluids) apply. The studies have suggested that underestimation of blood sequestration is often present in septic shock and that this may apply also in the clinical situation.

Summary

In intact anaesthetized dogs, endotoxin (*S. marcescens*) caused a marked decrease in systemic pressure, cardiac output, coronary flow, and cardiac efficiency. Glucose, lactate and NEFA values increased both in the systemic artery and coronary sinus, but no change was found in the cardiac extraction of these substrates. Radioactive palmitate showed an increase in cardiac efflux and oxidation. It is suggested that a similar change may exist in the clinical situation of endotoxin shock.

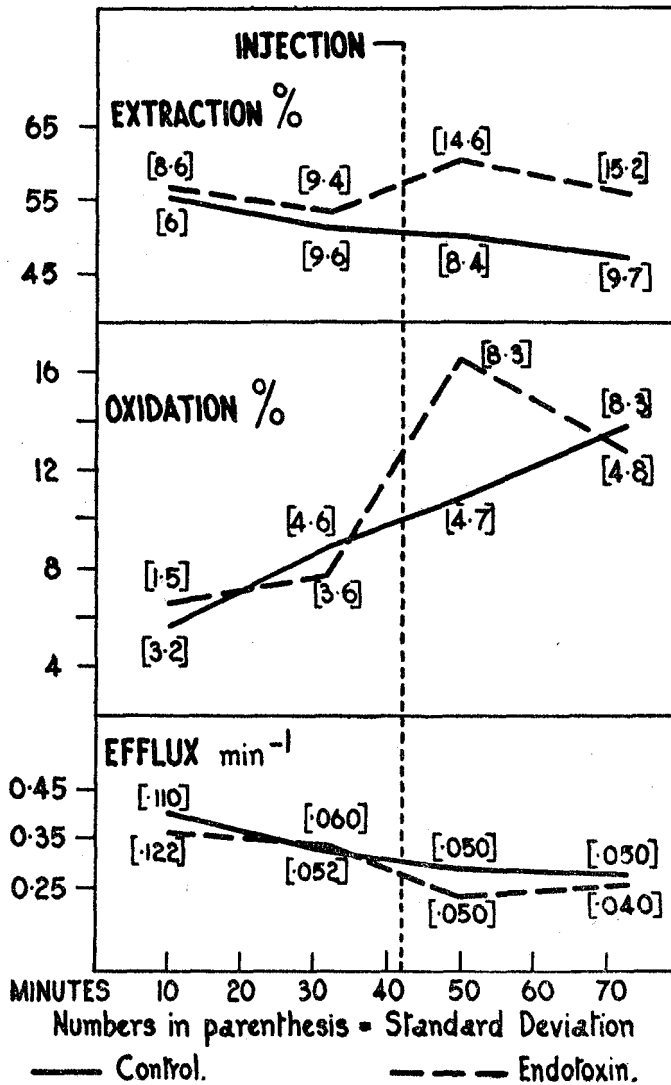
TABLE 1 : *Endotoxin Study. Changes in General and Coronary Haemodynamics.*

FACTOR	CONTROL	EXPERIMENTAL
Cardiac output (L/minute)	3.3 ± 1.4	1.75 ± 0.8*
Heart rate/minute	76 ± 12	159 ± 28*
Femoral arterial pressure (mean, mm, Hg)	134 ± 21	101 ± 29*
Left ventricular work (kg/M/minute)	6.1 ± 3.2	2.4 ± 1.8*
Total peripheral resistance (c.g.s. units)	3200 ± 1160	4600 ± 1470*
Coronary blood flow (ml/100 gm heart/minute)	86 ± 9	61 ± 9*
Coronary vascular resistance (arbitrary units)	1.5 ± 0.24	1.6 ± 0.4
Δ arterial - coronary sinus O ₂ (vols%)	8.6 ± 1.8	13.9 ± 2.4*
Cardiac O ₂ consumption (ml/100 gm heart/minute)	7.4 ± 1.9	8.5 ± 2.1
Cardiac CO ₂ production (ml/100 gm heart/minute)	6.2 ± 1.5	6.4 ± 2.0
Index of Efficiency (L.V. work + cardiac O ₂ consumption)	0.8 ± 0.5	0.3 ± 0.2*

Figures are group means with S.D.

* = statistically significant change from control values

FIG. 1 : *Endotoxin Study. Comparison of metabolism of C14-labelled palmitate with control.*



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