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Interstitial Fluid Pressure in Intestinal Submucosa of Dogs in Endotoxin Shock.* (27140)

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The loss of fluids from vessels has been shown to be associated with changes in lymph flow and interstitial fluid pressure(1,2). Aust *et al.*(3) found a significant sequestration of plasma albumin labeled with I^{131} in the intestine of the dog 5-7 minutes following administration of a lethal dose of *E. coli* endotoxin. Ballin and Meyer(4) have shown an increase in lymph flow rate from the small intestine after endotoxin and more recently Alican and Hardy(5) observed an increase in the thoracic lymph flow early after endotoxin, which was primarily attributed to an increase in hepatic lymph flow. This was followed by a decline and a secondary rise which was chiefly accounted for by an increase in the intestinal lymph flow. It therefore seemed desirable to measure tissue pressure in the intestinal submucosa during endotoxin shock. In addition, since portal hypertension occurs during the initial stages of endotoxin shock (6), tissue pressures were measured during a 10-minute period of obstructive elevation of the portal venous pressure in order that comparisons might be made.

Method. Adult dogs were fasted 18-24 hours, then anesthetized by intravenous administration of sodium pentobarbital. The procedure for measuring tissue pressure was modified after that of McMaster(1,2) and Hinshaw *et al.*(7). A #24 or 27 gauge needle filled with saline was inserted into the intestinal submucosa, connected to a Statham strain gauge *via* a polyethylene catheter and the pressure was recorded on a Sanborn recorder. Pressure within the system was elevated 3 to 10 cm of saline for a short period (0.5 to 1 sec.) and the pressure decay slope was followed until a plateau occurred which was accepted as the tissue pressure (P_{tissue}) in mm of Hg when referred to a zero catheter at atmospheric pressure. Successive values agreed within 0.5 mm of Hg. Pressure in the portal vein (P_{pv}) was also recorded by cannulating the splenic vein following splenectomy.

Tissue and portal pressures were measured in 12 dogs, prior and subsequent to intravenous administration of *E. coli*† endotoxin (1 mg/kg) and in another 12 dogs, before, during, and after obstructive elevation of the portal pressure. Portal pressure was mechanically increased by utilizing a screw-clamp fitted with an extension or by using a long ligature of umbilical tape placed about the vein and passed through a plastic tube which could be depressed against the vessel.

Results. The average tissue pressure in the intestinal submucosa at various times following administration of endotoxin and obstructive elevation of the portal pressure, plus and minus the standard error of the

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† *E. coli* endotoxin was obtained from Difco Labs.

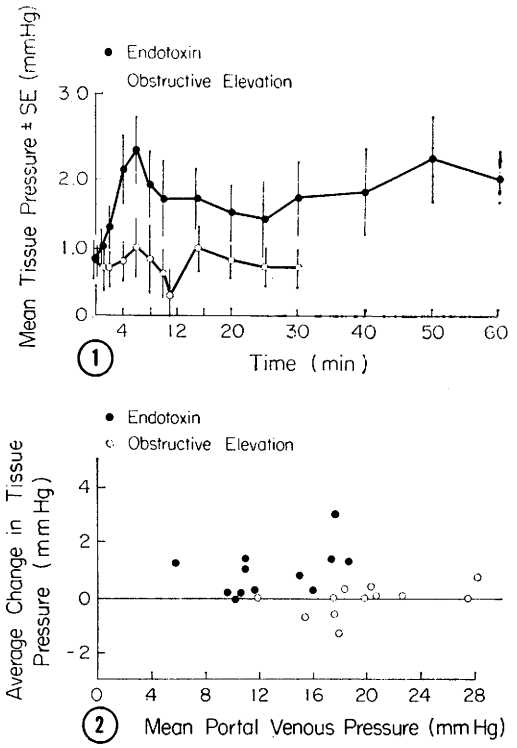

FIG. 1. Submucosal tissue pressure (atmospheric pressure taken as 0 pressure) ± stand. error (SE) at various times following administration of endotoxin also during and after obstructive elevation of portal venous pressure.

FIG. 2. Relationship between avg change in submucosal tissue pressure and mean portal venous pressure for a 10-min. period of obstructive elevation of portal venous pressure and for a similar period following administration of endotoxin.

mean are plotted in Fig. 1. A parametric statistical evaluation of these data by using the *t* test indicates that the submucosal tissue pressure following endotoxin is significantly (p-values ≤ 0.05) different from the initial value at 4, 6, 50, and 60 minutes. Average tissue pressure during the first 10 minutes of endotoxin shock is significantly different from the mean values during 10 minutes of obstructive elevation of the venous pressure only at the 4-minute observation. A statistical analysis utilizing the non-parametric sign test (in which the frequency of positive and negative changes is used as a basis of evaluating the significance of directional alterations in a given parameter(8)) indicates a significant increase in tissue pressure during the portal hypertensive phase of and during the later stages of endotoxin shock (p-value <0.01). However, when this test is applied to the data during mechanical elevation of the portal pressure, the change in tissue pressure is not significant.

Averages for the change in tissue pressure and mean portal vein pressure were determined for each experiment during the 10 minutes of partial portal occlusion and a similar period following endotoxin and are presented in Fig. 2. The results from these determinations appear to come from 2 different populations. That is, the average change in submucosal tissue pressure is less for an equal or greater rise in portal vein pressure during partial occlusion of the portal vein than during an equal period of portal hypertension following administration of endotoxin.

Discussion. Results tend to show that during the portal hypertensive period of endotoxin shock the submucosal tissue pressure is increased more than during an equal or greater rise of portal pressure by partial mechanical obstruction. Such a manifestation may denote greater losses of intravascular fluids following endotoxin. The rise in weight of an isolated loop of small intestine per mm of Hg rise in portal venous pressure has been shown to be 4 to 5 times greater during 10 minutes of portal hypertension following endotoxin than for a like period of obstructive elevation of the portal pressure (9).

The average rise in tissue pressure for the first 10 minutes after endotoxin is only 1.0 ± 0.22 mm Hg. This change is, however, significantly different from the obstructive elevation response ($p<0.001$) despite the fact that the P_{pv} was higher in the latter case. Thus it is apparent that endotoxin promotes increased interstitial tissue pressure in the intestine. Data will be presented later(10) which indicate that increased venular resistance may account for this finding.

It will be noted that there was an average of -0.1 ± 0.15 change in tissue pressure during obstructive elevation of the portal venous pressure. In several individual instances there were falls which may be significant. A possible reason for such a result is the veno-arteriolar response, described by Selkurt(11),

Selkurt and Johnson(12) and Meyer(13), which occurs during obstructive elevation of pressure in the portal vein. An arteriolar constriction occurs which may lower intestinal capillary pressure despite the elevation in venous pressure. Intestinal blood flow rates fall on the average about 40 per cent (14) and the venules and veins dilate, indicating that the capillary to large vein pressure drop will necessarily be considerably reduced. The capillary pressure may actually be elevated more after endotoxin than during mechanical portal obstruction, thus allowing for the possibility of a mechanical hydrostatic pressure mechanism for accumulation of tissue fluid seen after endotoxin by Aust *et al.* (3). This may be particularly important during the later stages of endotoxin shock when the localized areas of venous constriction become more numerous and more severe and are associated with a marked submucosal arteriolar dilatation(10). Haddy(15) has pointed out that the arteriolar dilatation and venous constriction in the dog forelimb, which was produced by the intraarterial infusion of histamine, may elevate the capillary hydrostatic pressure, and that this mechanism can account for histamine edema.

Summary. 1) The tissue pressure in the intestinal submucosa of the dog is significantly increased during the portal hypertensive phase and during the later stages following administration of a 1 mg/kg dose of *E. coli* endotoxin. 2) The change in submucosal tissue pressure is less for an equal or greater rise in portal vein pressure due to obstructive elevation of this pressure than during the portal hypertensive period of endotoxin shock.

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Action of l-Leucine on Plasma Insulin Effect and Glucose Uptake of the Diaphragm and Adipose Tissue. (27141)

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The mechanism by which l-leucine produces hypoglycemia in children(1) and in patients with pancreatic islet cell tumors(2) is not quite clear. Cochrane *et al.*(3) have very recently found peripheral effects to which the hypoglycemic action could be attributed and Grumbach and Kaplan(4) and Johnson, Herring and Field(5) impute the hypoglycemia to stimulant action on the Langerhans islet cells. We have studied the action of l-leucine, after intravenous injection, on the plasma insulin effect and glucose uptake by the diaphragm and epididymal fat of the same animal, as well as the effect of leucine added *in vitro* on glucose uptake by both tissues.

Methods. Animals. Male rats from our colony, weighing 120-130 g, were used; females with the same characteristics to estimate the plasma insulin effect with the iso-