# Intestinal Lymph Flow in Dogs after Endotoxin.* (25423)

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Because Gram-negative bacterial endotoxin has been shown(1) to produce portal pressure elevation and intestinal mucosal hemorrhage and edema in dogs, it seemed desirable to measure rate of flow of lymph from the intestine in order to throw additional light on the mechanism of endotoxin shock.

*Method.* Sixteen adult mongrel dogs of from 9 to 24 kg weight were fasted for a period of 18 to 24 hours, then anesthetized with Nembutal administered intravenously. Endotoxin was injected intravenously either before or after investigation of partial occlusion of the portal vein. Twenty-one experiments in which pressure in the portal vein was elevated by obstruction were performed on 13 dogs. In 11 of these animals, endotoxin was subsequently injected. Systemic arterial pressure (carotid) and portal venous pressure were recorded using the method described by Haddy (2) in which the splenic vein was cannulated following splenectomy. A loop of upper ileum 12 to 46 cm in length was isolated and its lymph vessels were tied off near the central lymph gland, similar to the approach used by Renyi-Vamos(3). About one-half hour later the lymph vessels were distended and could be cannulated according to the method of Lee (4). A single lymph vessel was cannulated and lymph collected from this vessel and its collateral connections. The same cannula (28 gauge needle stud with a short polyethylene tube) was used throughout all experiments in order to keep resistance to outflow constant. Lymph flow was measured as $mm^3$ per hour from the tip of the cannula. The average drop was measured to be 18.4 $mm^3$. Mechanical elevation of pressure in the portal vein was accomplished by one of two methods after a portion of the portal vein about 4-5 cm below the liver was freed from all surrounding tissue. Either a screw-clamp fitted with an extension or a long ligature of umbilical tape was placed around the portal vein. The ligature was then passed through a plastic tube, and partial occlusion was achieved by depressing the tube against the vein, similar to the method described by Selkurt and Alexander(5). The clamp or ligature was placed downstream from the tip of the cannula monitoring the portal venous pressure. The results of elevating the portal vein pressure were the same with both methods.

*Results.* Since pressure in the portal vein usually becomes elevated for about 10 minutes following administration of endotoxin, it seemed desirable to apply equal or greater pressures mechanically for the same period. Time average values were calculated for all parameters measured during this period under both circumstances. Time averages of the pressure data were also computed at specific intervals for 30 minutes following the onset of each experimental condition (Fig. 4). Average control lymph flow rates were 1.53 $mm^3$/min for the obstructive portal venous pressure study and 1.50 $mm^3$/min for the endotoxin investigation. Mean lymph flow rates were calculated at various times after conditions were changed. Times of maximal lymph flow and time to first drop of lymph following injection of endotoxin or elevation of venous pressure were noted. Fractions of a drop on the cannula tip at time of change in experimental conditions were removed. The results are presented in Figs. 1 to 4.

In Fig. 1 the average percentage change in lymph flow was calculated in each experiment and plotted as a function of average portal vein pressure. The method of least squares was used to determine the best fitting line from the observations made during portal vein obstruction. The correlation coefficient in this case was $+0.76$ ($p<0.001$). For the endotoxin effect $r = +0.16$ ($p>0.56$) and the

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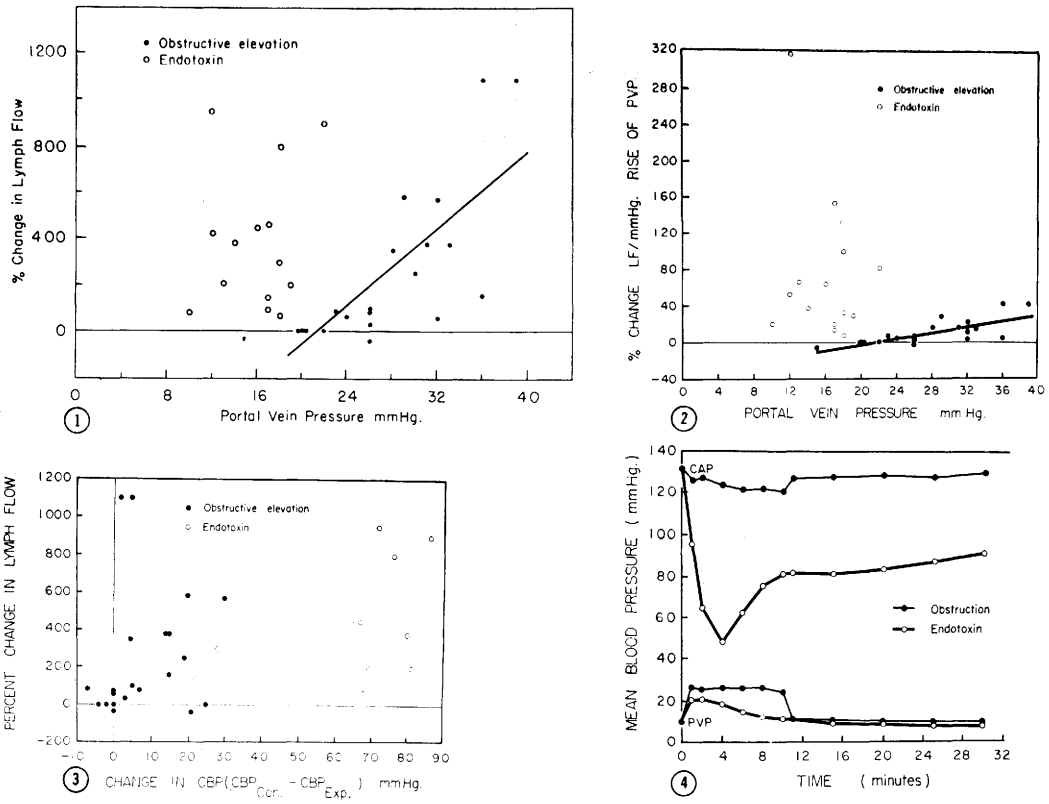


FIG. 1. Relation between percent change in lymph flow and portal vein pressure.

FIG. 2. Percent change in lymph flow (LF)/mm rise of pressure in portal vein (PV) as a function of portal vein pressure (PVP).

FIG. 3. Percent change in lymph flow (LF) *vs* change in carotid blood pressure (CBP).

FIG. 4. Composite graph of pressure tracings under obstructive elevation of portal vein pressure (PVP) and effect of 1 mg/kg (i.v.) *E. coli* endotoxin upon portal vein and carotid artery pressures (CAP).

lymph flow increase was therefore not significantly related to the magnitude of the portal pressure.

In Fig. 2 average percentage change in lymph flow/mm rise of portal venous pressure was calculated in each experiment and plotted as a function of average portal vein pressure. The correlation coefficient in this case was $+0.76$ ($p<0.001$). For the endotoxin effect $r = -0.21$ ($p>0.56$).

When the percentage change in lymph flow is related to the change in arterial pressure (Fig. 3), there appears to be some correlation after endotoxin between fall in arterial pressure and lymph flow rate, but not in the case of portal vein obstruction.

In Fig. 4 average pressure changes are compared in the two studies. Average initial pressure in the portal vein was 9.2 mm Hg, in the occlusion studies and 9.7 mm Hg in the endotoxin experiments. Average portal vein pressure rise during the 10 minutes of mechanical elevation was 16.7 mm Hg while with endotoxin injection it was 6.8 mm Hg. Nevertheless the lymph flow increased 389% after endotoxin injection and only 249% after obstructive elevation on the average in these experiments.

*Discussion.* Aust and others(6) found a significant sequestration of plasma albumen labeled with $I^{131}$ in the intestine of the dog, 5-7 minutes after administration of *E. coli* endotoxin. According to Heidenhain(7) and Starling(8) ligation of the portal vein, which produces an increase in pressure in the capillaries of the small intestines, resulted in an increase in lymph flow from the intestines. In our findings there appears to be a linear rela-

tion between mean portal vein pressure and the change in lymph flow after partial occlusion of the portal vein (Fig. 1). However, there is not a similar correlation between the increased venous pressure and the change in lymph flow produced after administration of endotoxin. Our data indicate that intestinal lymph flow per unit rise in portal venous pressure increases as the absolute magnitude of the portal pressure by obstructive elevation becomes larger (Fig. 2). This indicates that lymph flow rate is probably not a simple linear function of the ultrafiltration rate, assuming that filtration area and permeability constants do not change. This finding does not necessarily conflict with the conclusion of Pappenheimer and Soto-Rivera(9) that tissue fluid filtration rate is a linear function of pressure above colloid osmotic pressure because lymph flow rate depends upon rate of reabsorption as well as upon rates of ultrafiltration of tissue fluid. Fig. 2 also shows that the correlation between the parameters studied exists for the obstructive elevation experiments but not in the case of endotoxin. Factors other than the elevated portal venous pressure appear to be responsible in major part for the increase in lymph flow after endotoxin.

When the weight of a loop of small intestine was measured in another study(10) under the same experimental conditions, the average percent change in weight/mm rise in portal vein pressure was found to be 0.27 for obstructive elevation and 0.95 after endotoxin. This finding also indicates that in their action upon the intestine there are different mechanisms for the effects of simple obstructive portal pressure elevation and those of endotoxin administration.

It has been suggested that histamine may possibly play a role in the physiological disturbances produced by endotoxin(11). Ráskova and Vanecek felt that they had proved that *Shigella shigae* endotoxin liberated histamine from the tissues(12). It seems likely that some chemical effect of endotoxin, perhaps histamine liberation, is acting on structures other than those causing portal vein pressure elevation, evoking the great increase in rate of lymph flow.

*Summary.* 1. There is a marked increase in intestinal lymph flow of the dog following injection of *E. coli* endotoxin, and also after partial obstruction of the portal vein. 2. The magnitude of the rise in lymph flow after endotoxin is not significantly correlated with the rise in portal venous pressure. But there is a highly significant correlation between the absolute portal venous pressure level during obstructive elevation and the percentage change in lymph flow. There is a similarly significant correlation between the percentage change in lymph flow per unit rise in portal pressure and the absolute level of portal vein pressure. 3. The increased lymph flow after injection of endotoxin can not be accounted for on the basis of the elevation in portal venous pressure but perhaps is due to the action of substances liberated by some chemical effect of endotoxin which influence lymph flow through some mechanism other than one acting through rise in portal venous pressure.

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