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THE REGULATION OF LYMPHATIC PUMPING

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ABSTRACT

An important functional property of lymphatic vessels is their ability to pump fluid. To quantitate this activity in vivo, *sheep mesenteric lymphatic segments were isolated from all lymph input and provided with lymph plasma or saline from a reservoir. Lymphatic pumping was controlled by transmural pressure with increases in pressure resulting in elevated fluid pumping followed by reductions in flow at high intraluminal pressures. With lymph input to the vessels denied, but with blood and nerve supply left intact, the pumping activity could be altered with systemic physiological perturbations including a major blood loss and the intravenous infusion of endotoxin. In each case, it was clear that the modulation of lymphatic pumping resulted from the direct effects of the test procedure on the 'lymph pump' and not from effects on vascular parameters or lymph formation.*

Our concept of the lymphatic vessel has changed considerably in the past few years. It was originally thought that these vessels were passive conduits, relying totally on extrinsic forces to compress the vessel and propel lymph back to the bloodstream. The recognition, however, that the lymphatic vessel has smooth muscle in its wall and is capable of contracting has led to the notion that contractions of these vessels provide a major part of the force responsible for lymph movement. The regulation of this activity has been thought to reside within the properties of the smooth muscle with the degree and rate of distension of the vessel wall regulating the frequency and force of contractions. However, it has been established that the lymphatic vessel has a nerve supply and can respond to a variety of humoral agents *in vivo* (1,2). Whether these factors alter lymphatic contractile activity *in vivo* has not been previously established. In this paper, we review experiments from our laboratory that suggest that nerves or humoral agents may modulate lymphatic pumping in pathophysiological states.

EXPERIMENTAL PROTOCOL

Since either changes in lymphatic pumping or changes in lymph formation may lead to altered flow rates monitored from indwelling catheters, we have utilized a model system that permits the analysis of systemic physiologic perturbations on lymphatic pumping without the complication of variable lymph inputs (3,4).

A segment of sheep mesenteric lymphatic was isolated from lymph input by placing a catheter in the direction of flow close to the point where it emerges from the terminal mesenteric node and inserting a second catheter downstream from the node (10 to 15 cm) against the direc-

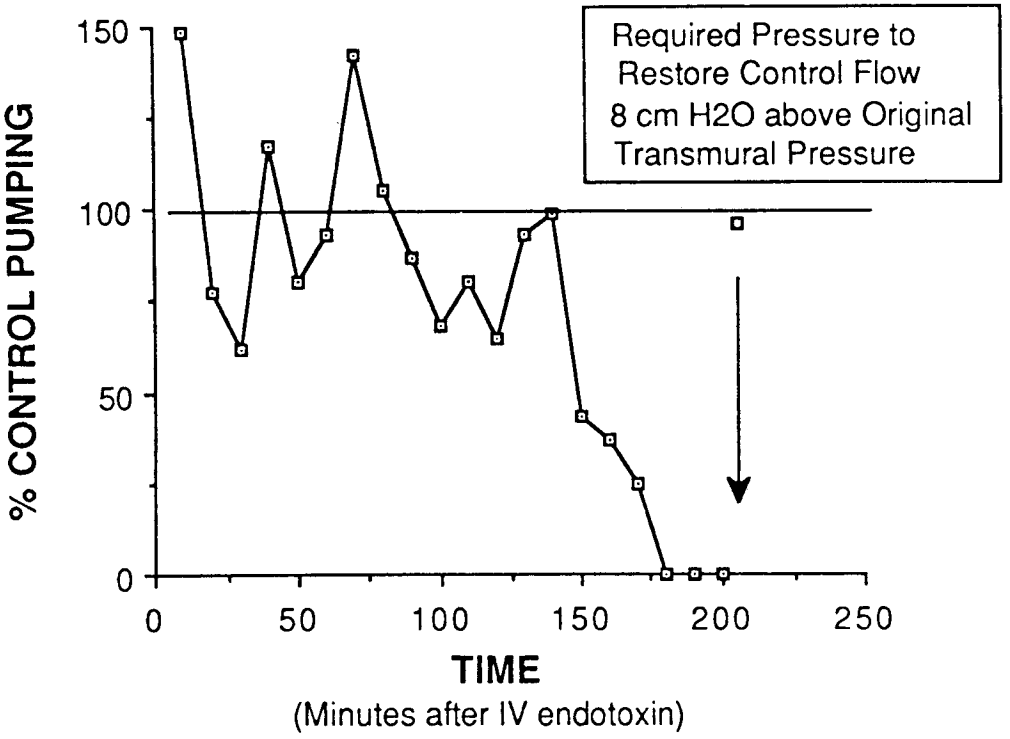

Fig. 1. The effects of lymph (from an animal that had received endotoxin) on lymphatic pumping. Lymph was allowed to flow from a donor animal into the reservoir of the 'isolated duct preparation' in a second sheep. After establishing a transmural pressure/fluid pumping curve in the recipient animal, the pressure was set at a level that maintained flow at approximately 70% of maximum. After a 1 hour control period, 33.0μg/kg endotoxin (055:B5) was infused intravenously into the donor animal. As can be seen in the Figure, lymphatic pumping became irregular in the recipient with periods of increased and periods of decreased pumping relative to the control. However, at 160 minutes post-endotoxin, pumping declined to 0. This pattern was observed in all animals although the time taken to reach complete suppression of pumping was variable. In this example, control flows could be re-established by elevating the transmural pressure 8cm H_2O above the level originally chosen for the experiment. This finding indicated that some lymph-borne factor decreased the sensitivity of the vessel to transmural pressure stimulation.

tion of flow. All of the tributary vessels were tied off so that there was no lymph flow through the duct. A fluid reservoir containing saline or lymph provided the only input to the vessel. By raising the height of both the reservoir and the outflow catheter, the transmural distending pressure could be increased to the point where the vessel was triggered to contract and propel fluid. Flow could occur only if the lymphatic vessel contracted and propelled its contents in the direction allowed by the valves provided that the heights of the reservoir and outflow catheters were set equal to each other (i.e., no net driving pressure). The nerve and blood supply to the lymphatic was left intact. This model will be re-

ferred to as the 'isolated duct preparation.'

RESULTS

We observed that phlebotomy of 25% (based on total blood volume) resulted in up to 6 fold increases in fluid propulsion by these vessels over a 6-hour period (3). If a greater percentage of the blood was removed (50% of the blood volume), fluid pumping declined.

With the systemic administration of endotoxin, the opposite effect was observed. Endotoxin suppressed fluid propulsion (4). Endotoxin itself had no direct effect on contractile activity when added to the reservoir fluid suggesting that it had to interact with the host to produce this effect.

It was clear, therefore, that physiologic perturbations could alter lymphatic pumping independent of vascular changes and filtration forces. However, these results did not provide any information on whether these effects were mediated by neurogenic or humoral mechanisms. We have recently modified the 'isolated duct preparation' such that the lymph in the reservoir was provided from an indwelling catheter in a second sheep. In these experiments, endotoxin was administered to the donor animal and the pumping of the mesenteric vessel in the recipient sheep monitored. Our results indicate that the administration of endotoxin to the donor sheep resulted in inhibition of lymphatic pumping in the recipient animal (one example illustrated in *Fig. 1*). Comparing the transmural pressure/fluid pumping curve generated with control lymph in the reservoir, with that produced with lymph from 'endotoxin' animals, revealed that the latter samples shifted the curve to the right. To put it another way, in order to generate the same level of pumping activity with the 'endotoxin' lymph, greater transmural distending pressures had to be applied to the vessel. This is, we believe, the first evidence that endogenously produced humoral factors can modulate lymphatic pumping *in vivo*.

CONCLUSIONS

With a transmural pressure applied to the duct to initiate and maintain fluid pumping, certain degrees of hemorrhage resulted in stimulation of the 'lymph pump' whereas the infusion of endotoxin suppressed fluid propulsion. These results indicate that physiologic perturbations alter lymphatic pumping activity independent of any effects on filtration forces. While the nature of this activity is unknown at present, we have some evidence that, at least in the case of the endotoxin experiments, humoral factors may play an important role in regulating lymphatic contractile activity. The consequences of altered lymphatic pumping in these pathophysiologic states is unknown. Possibly, the endotoxin-induced decreased sensitivity of the lymphatic vessel to transmural pressure stimuli contributes to the edema associated with sepsis and inflammation by reducing the ability of the lymphatics to remove extravasated protein from the tissues. In contrast, it is tempting to speculate that stimulation of the lymph pump following hemorrhage, facilitates the return to the bloodstream of the contents of the lymphatic circulatory system and possibly the lymph-accessible fluid and protein in the interstitium as well.

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