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LYMPH FLOW TRANSIENTS FOLLOWING ELEVATION OF VENOUS PRESSURE IN THE DOG HINDPAW

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ABSTRACT

Lymph flow transients were studied in a dog paw preparation when venous pressure was elevated by 15 and 25mmHg. The lymph flow transients showed a very rapid initial increase which then declined to a steady-state value that was one-half the peak lymph flow response for both pressure changes. Lymph flow increased in the initial 5.3 minutes following venous pressure elevation to 10.4±2.0 and 18.1±4.5 times the normal lymph flow (mean±standard deviation) for the 15 and 25mmHg increases in venous pressure, respectively. However, approximately 9 minutes after attaining the maximal flow rate, the lymph flow declined to only 5.5±0.7 and 9.8±1.8 times the control values. These data demonstrate another condition in which lymph flow is not maintained at the maximal capability. Possible mechanisms causing the observed biphasic lymph flow response to capillary pressure elevation are: 1) changes in Starling forces oppose an increase in capillary pressure; 2) the rate of change in tissue fluid pressure affects lymph flow to a greater extent than does the absolute change in tissue fluid pressure; or, 3) the lymphatics empty upon elevation and refill as the capillaries filter.

In a recent review, the ability of the lymphatics to remove large quantities of capillary filtrate under certain experimental conditions was evaluated relative to edema safety factors (1). That review indicated that lymph flow increased five to ten times above maximal flow observed with elevation of capillary pressure when 1) the endothelium had been damaged by sepsis and burns (2,3) and 2) large amounts of saline were used to expand plasma volume (4). A basic physiological question was posed in this review: Why is it that lymph flow does not attain its maximal potential flow and become a much better edema safety factor under all conditions of increased capillary filtration?

Several years ago, we demonstrated another condition where lymph flow increased immediately after elevating capillary pressure to levels that were higher than that maintained during a prolonged steady-state flow. *Fig. 1* shows the effects of increasing venous outflow pressure (ΔP_v) in a dog paw preparation by 25mmHg on lymph flow (J_L), tissue fluid pressure (P_T), and the change in P_T as a function of time (P_T/t). Lymph flow promptly increased from 3 to 400 µl/min after elevating the venous pressure, but, after ten minutes the lymph flow had declined to a much lower

value of 200 µl/min and remained constant at this level for 20 minutes. When the venous pressure was returned to control values, the lymph flow fell slowly and returned to normal values over a thirty minute time frame. An extended abstract of this study was published (5), but with the renewed interest in factors that cause large increases in the ability of lymph to remove capillary filtrate, we opted to publish this study in its entirety in order that the data would be more readily available.

The present study evaluated lymph flow transients occurring in response to venous outflow pressure increases of 15 and 25mmHg. In two of these experiments, the interstitial fluid pressure was also measured concomitantly using implanted capsules.

MATERIALS AND METHODS

Eight mongrel dogs (18-23kg) of either sex were used in the present study. Five weeks prior to the experiment, a hollow polypropylene semispherical capsule of 20mm diameter containing approximately 100 small holes was implanted into the subcutaneous tissue of the dorsal hindpaw in each of two dogs (4). Four to six weeks were allowed for tissue healing in the dogs with implanted capsules. The dogs were prepared in the same surgical fashion as described below and tissue pressure was measured in the following fashion: A 21 gauge hypodermic needle was connected to a stiff catheter and the needle inserted into the implanted capsule and the pressure monitored (P23BC transducer). Dogs were anesthetized with intravenous sodium pentobarbital (30mg/kg), the trachea intubated and the dog artificially ventilated with room air.

The hindlimb preparation has been described in detail by Chen et al (6). Briefly, dogs were heparinized (5mg/kg, iv), the right cranial tibial artery was cannulated and the hindpaw was perfused with autologous blood from the femoral artery. Two t-tubes were inserted into the perfusion circuit; one was used to monitor the perfusion pressure (Statham P23AC) and the other was connected to an arterial reservoir that was maintained at a hydrostatic level to produce an arterial perfusion pressure of 100mmHg. The lateral saphenous vein was cannulated and connected to a venous reservoir and its pressure monitored (P23BC transducer). The venous pressure could be set at any desired level by simply raising or lowering the venous reservoir height. Other small veins draining the paw were also ligated.

Two lymphatics on each side of the lateral saphenous vein were carefully cannulated using PE 90 tubing. The two catheters were then joined with a Y-connector into a single calibrated piece of PE 90 tubing. Lymph flow was measured at one minute intervals using a ruler placed on catheters that had been calibrated before and after the experimental procedure. Venous pressure was initially set at 5mmHg in each experiment. After lymph flow attained a steady-state value at this pressure, the lymph flow transients were followed after producing a sudden elevation of venous pressure by either 15 or 25mmHg for a 30 minute period. Thereafter, the venous pressure was reduced back to control levels and the off-transient evaluated.

Calculations

For each experimental preparation, the lymph flow was measured for control conditions (LF_c), and at the maximal level obtained following elevation of venous pressure (LF_{max}). The lower steady-state lymph flow attained after the initial rapid transient had dissipated was averaged over a twenty minute period (LF_{ss}). The time course of the transient was analyzed over three time frames, 1) from the control lymph flows to the maximal lymph flow *(labeled 1 in Fig. 1)*, from the maximal lymph flow to the resulting steady state lymph flow *(labeled 2 in Fig. 1)*; the half-time of the lymph flow transient occurring when the venous pressure was decreased *(labeled as 3 in Fig. 1)*, and the total time required for lymph flow to return to control lymph flows *(labeled as 4 in Fig. 1)*. The interstitial pressure was simultaneously measured in 2 dogs and the rate of change of tissue pressure as a function of time was calculated

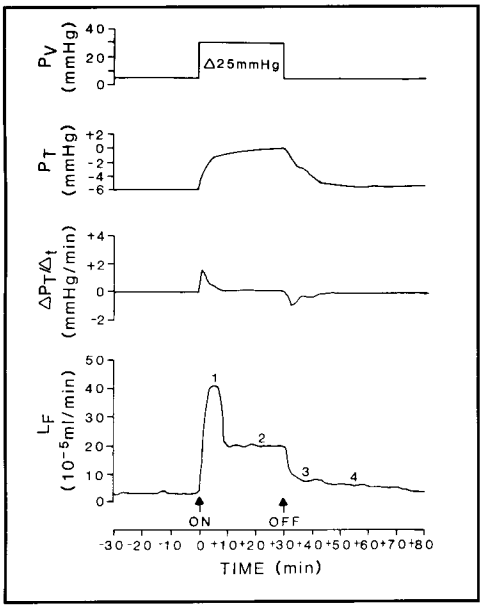

Fig. 1. Effects of elevating venous outflow pressure by 15mmHg (P_v) in a dog paw preparation on lymph flow (LF), tissue fluid pressure (P_T) and the rate of change of tissue fluid pressure ($\Delta P_T/\Delta t$).

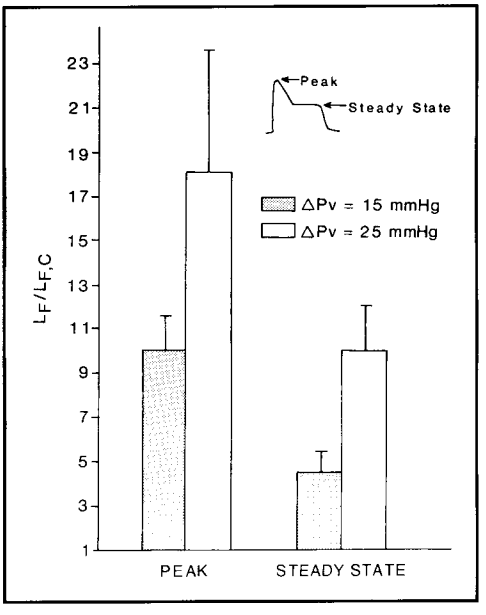

Fig. 2. Comparison of peak lymph flow response to the final steady-state response as defined by the insert following an increase in P_v of 15mmHg (hatched histogram) or 30mmHg (clear histogram) in the hindpaw.

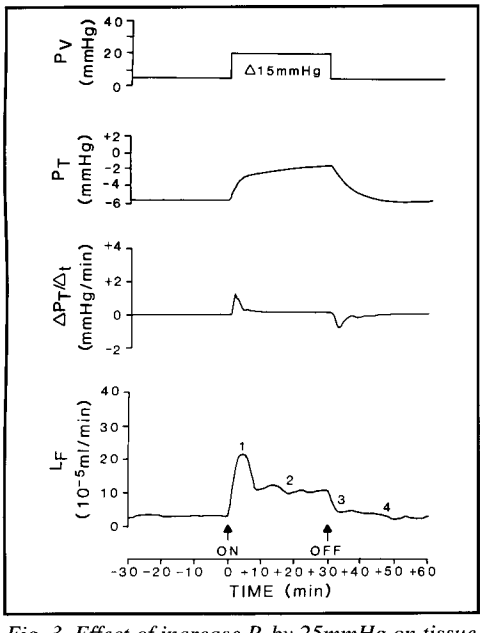

Fig. 3. Effect of increase P_v by 25mmHg on tissue fluid pressure (P_T) rate of change of tissue fluid pressure ($\Delta P_T/\Delta t$) and lymph flow in the dog hindpaw.

as the slope of interstitial pressure transients *(third panel in Fig. 1).*

RESULTS

Table 1 shows the results of these studies. Note that the LF_c was 3.25±1.65 10^{-5} ml/min in control dogs, and lymph flow increased 10 and 18 times after 5.3 minutes attaining a maximum flow of 32.5±11.6 and 63.9±7.9 10^{-5}ml/min for the 15 and 25mmHg increases in venous outflow pressures, respectively. Interestingly, the $t_{1/2}$ of the rise and the total time required to reach the maximal lymph flow was identical for both P_v's, indicating that the mechanism producing this effect after approximately 9 minutes was probably the same in both conditions. After attaining the maximal value, lymph flow then declined to levels only 5 and 10 times the control values for the 15 and 25mmHg increases in venous pressure, respectively. These data indicate that lymph flow transiently increased about 2 fold above those measured when a steady-

TABLE 1
Analysis of Hindpaw Lymph Flow Transients (n=8)
Following Elevations of Venous Pressure (Mean±SD)

	Lymph Flow (10^{-5}ml/min)			$\frac{LF}{LF_c}$		Transient Analysis (min)				Transient Analysis (min)	
						On Transient				Off Transient	
ΔVenous Pressure (mmHg)	Control (LF_c)	Peak (LF_{max})	Steady-State (LF_{ss})	$\frac{LF_{max}}{LF_c}$	$\frac{LF_{ss}}{LF_c}$	$LF_c \rightarrow LF_{max}$ ($t_{1/2}$)	Time (min)	$LF_{max} \rightarrow LF_{ss}$ ($t_{1/2}$)	Time (min)	$LF_{ss} \rightarrow LF_c$ ($t_{1/2}$)	Time (min)
15	3.2 ±1.6	32.5 ±11.6	18.6 ±7.9	10.4 ±2.0	5.5 ±0.7	1.4 ±0.8	5.3 ±1.8	1.8 ±0.9	9.3 ±3.7	1.8 ±0.6	26.0 ±4.7
25	3.3 ±1.7	63.9 ±16.3	35.1 ±9.9	18.1 ±4.5	9.8 ±1.8	1.3 ±0.8	5.3 ±1.5	2.0 ±0.9	8.6 ±2.0	2.1 ±0.5	46.5 ±11.6

Note: LF_c, LF_{max}, and LF_{ss} refers to control lymph flow, maximum lymph flow attained and final steady-state lymph flow after elevation of venous pressure by either 15 or 25mmHg (ΔVenous Pressure), LF_{max}/LF_c and LF_{ss}/LF_c are maximal changes in lymph flow and the steady-state lymph flows relative to control lymph flows. $LF_c \rightarrow LF_{max}$ is the $t_{1/2}$ (seconds) required for the lymph flow to attain a maximum and Time is total time required to attain the maximal lymph flow. $LF_{max} \rightarrow LF_{ss}$ shows the $t_{1/2}$ required to attain the steady-state lymph flow following the maximum and Time is the total time required to attain the steady state. $LF_{ss} \rightarrow LF_c$ is the half time required for the steady-state lymph flow to increase when Venous Pressure is reduced and Time is the total time required to return to control levels.

state had finally been reached. When venous pressure was lowered, the total time for the completion of the off-transient was much longer for the higher venous pressure (46.5 vs. 26.0 minutes) than for the lower venous pressure, likely indicating a larger fluid accumulation occurring in the limb due to the higher capillary pressure.

Interestingly, the $t_{1/2}$ for the rapid portion of the off-transients were almost identical for both venous pressures. This finding indicates that a rapid decrease in venous pressure produces a decreasing lymph flow that is almost equal and opposite to the effect seen with the on-transient! Unfortunately, the entire tissue pressure transients were only measured in two preparations *(Fig. 1 and Fig. 3)*, but it is noteworthy for these two studies that the rate of change of lymph flow was the greatest when P_T was changed maximally. *Fig. 2* shows the lymph flow obtained at peak and steady-state flows for both venous pressures.

DISCUSSION

It is well known that lymph flow plays a vital role in protecting the tissues against excessive fluid accumulation when the capillary pressure is increased or the capillary endothelium is damaged. In fact, the lymph flow usually has an almost infinite gain at capillary pressure within physiological limits, because it removes almost all the excess capillary filtrate, and tissue fluid volume does not notably increase until capillary pressure exceeds 25-30mmHg in many organs (1,4,6-10).

Lymph flow has been shown to be a function of tissue fluid pressure in several organs (4,7). The relationship between lymph flow and tissue fluid pressure is usually sigmoid with lymph flow reaching maximal values of 7 to 10 times normal flow after increasing venous pressure to levels associated with edema formation. However, a recent review indicates that lymph flow

can increase 2 to 3 times further above these levels when the capillary endothelium has been damaged (1). It is clear that the lymphatic system can provide greater transient lymph flows following venous pressure elevation than is maintained during steady-states in our present study. The data, however, do not identify the mechanisms responsible for these findings. On the other hand, damage to capillary endothelium does cause lymph flow to increase to values much greater than that predicted from increasing hydrostatic pressure in normal capillaries, perhaps related to compounds released from damaged endothelium that enable the lymphatic system to become a more efficient pump (11,12).

Both the interstitial pressure and colloid osmotic gradient increase across the capillary wall when venous pressure is elevated. These changes together oppose capillary pressure increase and thereby limit the amount of filtration into the tissues. It is possible that the high maximum lymph flow measured in the present study occurred before the Starling forces had maximally changed and the steady-state lymph flows simply represent a lower transcapillary filtration rate due to the Starling force changes (7,8).

Nonetheless, the LF_{max} appears to be more related to the *rate* of change of tissue pressure rather than to the *absolute* change in tissue pressure for both venous pressure instances, since tissue pressure increased very rapidly (0.5 to 1.0 mmHg/min) while the absolute value of tissue fluid pressure was actually higher during the fall in lymph flow. This rapid rate of change of tissue pressure could increase the pumping ability of the lymphatics, or provide a greater lymphatic filling pressure (i.e., tissue pressure minus lymphatic pressure). However, the maximal lymph flow could also represent an emptying of lymphatic vessels upon venous pressure elevation caused by venous distention. Since the rise to maximal lymph flow and the subsequent decrease to the steady-state had similar time courses, the rise may simply reflect lymphatic emptying while the fall in lymph flow may represent lymphatic refilling as the tissues expand. In any event, if lymph flow had been maintained at the higher level, it would have been a much more effective edema safety factor.

The initial higher lymph flows associated with changing venous outflow pressure is another clear example of lymph flow capabilities that are not always fully realized in various experimental models. Further studies of this nature are needed to explain why high lymph flow values measured under a variety of experimental conditions are not sustained even when interstitial edema is accumulating. Understanding the mechanisms responsible for the present transient phenomenon of lymph flow should lead to a better understanding of how the lymphatics attain and maintain maximal pumping ability when capillary filtration increases.

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