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ESTIMATION OF LYMPH FLOW BY RELATING LYMPHATIC PUMP FUNCTION TO PASSIVE FLOW CURVES

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ABSTRACT

Active pumping in postnodal lymphatic vessels is an important factor influencing lymph flow. However, the output of the lymphatic pump also depends on the rate of flow into the pump. This arrangement is similar to the blood circulation where cardiac output depends on the rate of blood flow through the veins into the heart (venous return) and on the pumping characteristics of the heart itself (cardiac function curves). One common way to analyze the blood circulation rate is to interrelate venous return and cardiac function curves. In this study, we used a similar technique to analyze lymph flow. We used lymphatic flow vs. outflow pressure (passive flow) relationships for nonpumping lymphatics to represent the inflow of lymph to the lymphatic pump. We used data on the pumping characteristics of postnodal lymphatic vessels to generate relationships between lymphatic pump outflow and pump inflow pressure (pump function curves), and then interrelated these curves. The results were not only similar to previously measured lymph flow data obtained from experimental animals, but also support the observation that under normal circumstances lymph flow is periodic and in surges (active pumping) but in edematogenic states lymph flows more continuously (i.e., passively).

Studies with isolated segments of postnodal lymphatic vessels (lymphangions) have confirmed that lymphatics actively pump fluid (1,2). This pumping action is due to the rhythmic contraction of the lymphatic vessel smooth muscle. When the intramural muscle contracts, fluid is forced forward through the lymphatic, and when the muscle relaxes, fluid flows into the lymphatic. Retrograde flow is prevented by closure of one-way valves. Several investigators have shown that the lymphatic stroke volume and contraction frequency both increase when the lymphatic filling pressure rises to 10cm H_2O (1,2). Greater pumping theoretically helps the lymphatics adjust to increases in fluid load just as increases in pumping help the heart accommodate to increases in venous return. Thus Starling's "law of the heart" may also apply to lymphatic vascular dynamics.

Active lymphatic pumping, however, is not the only determinant of lymph flow. We have analyzed the lung lymphatic system in terms of the relationship between lymph flow rate (Q_L) and lymphatic vascular outflow pressure (P_O) (3-5). In anesthetized, acutely operated animals, Q_L decreased linearly with increases in P_O. Because there was no active lymphatic pumping in these anesthetized animals, we deduced that the linear Q_L vs P_O relationships reflected the passive flow of lymph from the tissues to the postnodal lymphatics. These relationships are similar to "venous return curves" which reflect the passive flow of blood from the veins to the heart.

Considerable disagreement persists about the role of active lymphatic pumping in the regulation of lymph flow (6). This controversy is similar to the issue of the role of the heart and/or the peripheral circulation in regulating cardiac output. In 1955, Guyton (7) helped clarify the interaction between the heart and the peripheral circulation when he plotted cardiac function and venous return curves on the same graph. In this study, we have used a similar technique to analyze flow from lymphatic vessels. The results conform to data from experiments in animals.

MATERIALS AND METHODS

Lymphatic "Pump Function" Curves

For analysis, we needed to know the relationship between lymphatic pump output and inflow pressure (filling pressure) to the lymphatic, Although there are no published data on this relationship, many investigators have examined the lymphatic pump using parameters often used to describe cardiac function (8-10). We previously used these data to develop a mathematical model of the lymphatic pump (11). In the present study, we used the model to generate "pump function" curves to relate lymphatic pump output to pump inflow pressure.

Our model, which we previously described in detail (11), represents the pumping activity in a 5 lymphangion-long segment of postnodal lymphatic *(Fig. 1)*. For the present study, we set the inflow pressure (P_{in}) and outflow pressure (P_O) to a particular segment. We then ran simulations to estimate the pump output. Initially we set P_O equal to 2cm H_2O and then had the model estimate the pump output for P_{in} from 0.2 to 2.0cm H_2O. Then, we set P_O equal to 3.0cm H_2O and had the model estimate the pump output for P_{in} from 0.2 to 3.0cm H_2O. We repeated this procedure for each P_O up to 21cm H_2O. For each P_O, we plotted the pump output vs P_{in}. The result was a series of 20 lymphatic pump function curves corresponding to outflow pressures of 2 to 21cm H_2O.

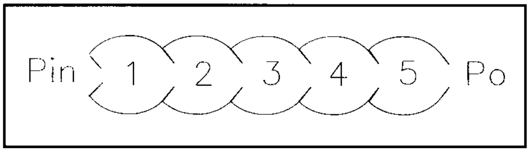

Fig. 1. A schematic multisegmented (5 lymphangion) lymphatic pump. P_{in}=fluid inflow; P_O=outflow pressure.

Passive Lymph Flow to the Pump

We used linear flow vs. P_{in} relationships to represent the passive flow of lymph from the tissue spaces to the lymphatic pump. To represent the flow under baseline conditions, we used Flow=135-27 P_{in} and to represent the passive flow of lymph from edematous lungs, we used the relationship of Flow=762-61 P_{in}.

We termed the lymph flow vs. pressure interrelationships "passive flow" lines because the data were obtained in anesthetized animals (3-5). The postnodal lymphatic vessels cannulated in these animals did not actively pump lymph. This finding was not surprising because lymphatic pumping is typically suppressed in anesthetized, acutely operated animals. However, we are not certain that active pumping was entirely suppressed in the prenodal lymphatics within the lung. Thus the "passive flow" lines may be slightly influenced by active pumping in prenodal lymphatics.

Lymph Flow Rate Estimates

We plotted the lymphatic pump function curves and the passive flow interrelationships on the same graph, and estimated the lymph flow from the intersection of the pump function and passive flow curves. This technique is similar to the one Guyton used to estimate cardiac output from the intersection of venous return and cardiac function curves (7).

RESULTS

Fig. 2 shows a typical lymphatic pump function curve. For low inflow pressures, the

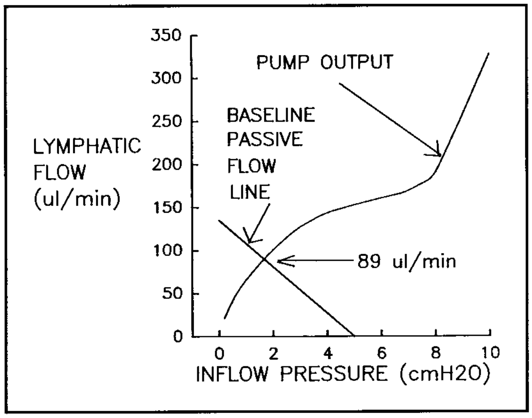

Fig. 2. Lymphatic pump function curve for an outflow pressure of 10cm H_2O with the baseline passive flow line. The two relationships intersect at a flow rate of 89µl/min.

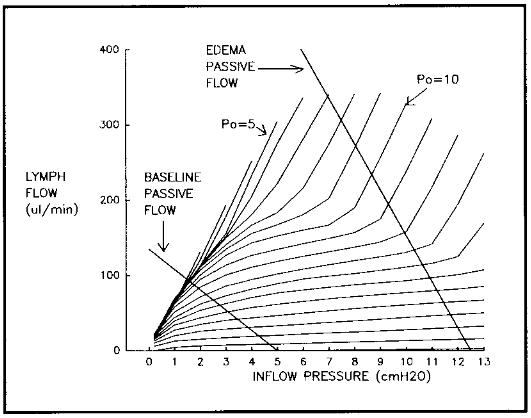

Fig. 3. Lymphatic pump function curves for outflow pressure of 2 to 21cm H_2O. The baseline and edema passive flow lines are also shown. P_O=lymphatic outflow pressure.

stroke volume from lymphangion 1 served to fill lymphangions 2-5. The stroke volume from lymphangion 2 filled lymphangions 3-5. Thus, the output from each lymphangion "primed" the downstream lymphangions and all of the pump output occurred during contraction (systole) of the last lymphangion (lymphangion 5). However, for $P_{in} > 1.0$cm H_2O, the stroke volume from lymphangion 4 overfilled lymphangion 5 and some of the excess fluid "spilled" from the latter lymphangion. Thus, pump output occurred during systole in both lymphangions 4 and 5. At higher P_{in}, more lymphangions were able to eject fluid through the last lymphangion. Consequently, the pump output increased over the entire range of P_{in}.

Fig. 2 also shows the baseline passive flow line. From the intersection of the pump function curve and the passive flow line, we estimated a lymph flow rate of 89µl/min. In *Fig. 3*, we plotted the lymphatic function curves for each P_O and the passive flow lines. We estimated the flow rates corresponding to the intersection of each pump function curve and the baseline passive flow line. Then we plotted these estimated flow rates vs. P_O in *Fig. 4*.

As shown in *Fig. 3*, the pump function curves for P_O from 2-6cm H_2O did not intersect the edema passive flow line. In our initial simulations, we did not allow P_{in} to exceed P_O; however, when we realized that the pump function curves did not cross the edema passive flow line, we repeated some of the simulations. This time we allowed P_{in} to exceed P_O by 1-2cm H_2O *(see dashed lines in Fig. 5)*. *Fig. 6* shows the lymph flow rates estimated for the edema passive flow line and the pump function curves derived from *Fig. 5*.

DISCUSSION

The estimated lymphatic flow vs. outflow pressure relationships *(Figs. 4 and 6)* are similar to the lymph flow rate vs. outflow pressure relationships we reported previously for actively pumping lung lymphatic vessels in awake sheep (11,12). In sheep, there was little decrease in lymph flow for P_O levels of 10-15cm H_2O, but for P_O> 10-15cm H_2O, lymph flow decreased. These findings correspond to the estimated lymph flow rates shown in *Fig. 4*. When we produced edema in sheep, the lymph flow rate decreased linearly for low P_O's and the lymph flow vs. P_O relationship

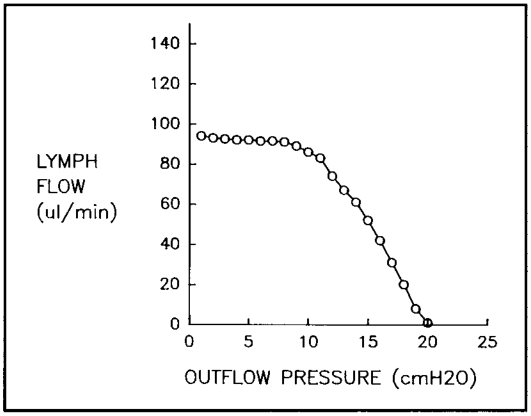

Fig. 4. Lymph flow rates estimated from the intersection of the lymphatic pump function curves and the baseline passive flow line as derived from Fig. 3.

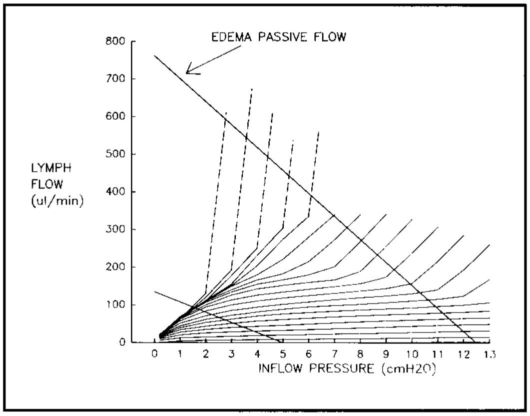

Fig. 5. Lymphatic pump function curves and the edema passive flow line. The dashed lines represent the portion of the pump function curves where inflow pressure exceeded outflow pressure.

was splayed at higher P_O's. These results correspond to the nearly linear decrease in the estimated lymph flow for $P_O > 12$cm H_2O and the splay in the estimated lymph flows for $P_O > 12$cm H_2O as shown in *Fig. 6*.

The similarity between our calculated analysis and the earlier sheep data suggests that the factors which influence lymph flow are accurately represented. For example, for low P_{in} the lymphatic pump function curves for P_O levels of 2 to 10cm H_2O were nearly identical to each other *(Fig. 3)*. Outflow pressure up to 10cm H_2O had little effect on lymph pump output. Consequently, the pump function curves for P_O levels of 2 to 10cm H_2O crossed the baseline passive flow line at almost the same lymph flow rate. This finding accounts for the lymph flow vs. outflow pressure plateau for $P_O < 10$cm H_2O as seen in *Fig. 4* and may account for the plateau of lymph flow data obtained earlier from sheep (11,12). On the other hand, at high lymph flow rates the pump function curves were almost evenly spaced for P_O levels of 2-12cm H_2O *(Fig. 5)*. Consequently, the pump function curves crossed the edema passive flow line at intervals of approximately 40-45µl/min, and account for the nearly linear decrease in the lymph flow for P_O levels of 1-12cm H_2O *(Fig. 6)*. The splay of *Fig. 6* was likely due to the close spacing of the lymphatic pump function curves for P_O levels of 12-21cm H_2O.

Fig. 3 shows that some of the pump function curves from our initial simulations did not reach as high as edema passive flow lines. In other words, fluid flowed into the post nodal lymphatic segment faster than the lymphatic could pump the fluid onward. We extended the pump function curves to higher lymph flow rates by running additional simulations with $P_{in} > P_O$ *(dashed lines in Fig. 5)*, which amounted to causing passive flow through the lymphatic pump. Thus, fluid flowed from the pump almost continuously (i.e., during systole the lymphatic pumped fluid) whereas during diastole, fluid flowed passively through the lymphatic. Passive flow through the pump may explain an unpublished observation we have made in several of our previous studies. Ordinarily, lymph flows from lung or intestinal lymphatic vessels in periodic surges. Each surge seemingly corresponds to a lymphatic contraction. Yet, when we have produced edema, the lymph flows continuously!

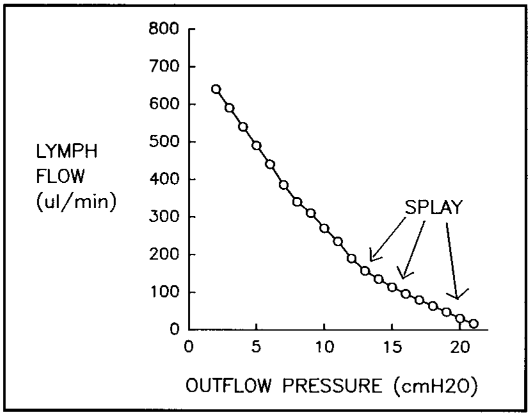

Fig. 6. Lymph flow rates estimated from the intersection of the pump function curves and the edema passive flow line as derived from Fig. 5.

These results signify that the technique Guyton used to analyze blood circulatory dynamics (7) is also applicable to understanding lymphatic circulatory dynamics.

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