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Lymph Flow Characteristics and Microvascular Exchange: An Analog Computer Simulation

J.L. Bert*, Ph.D., and K.L. Pinder, Ph.D.**

*Department of Pathology and Department of Chemical Engineering, University of British Columbia
**Department of Chemical Engineering, University of British Columbia

Summary

Lymphatic flow characteristics, which include both progressive lymphatic blockage and plateau of lymph flow with increasing interstitial fluid volume, were incorporated into an analog computer simulation of microvascular exchange, and their effects on interstitial fluid volume and protein content were investigated. The steady state and transient response of the microcirculation to changes in the properties of the lymph flow system are reported. The interstitial fluid and protein content is investigated as a function of venous pressure and for changes associated with the lymph flow characteristics. The interstitial protein content is generally more sensitive to changes in the lymph flow properties than is interstitial fluid volume. Properties of lymphatic drainage of tissues as they effect microvascular exchange are discussed.

Introduction

Mathematical models are sometimes useful for predicting the behavior of difficult to measure biological systems. The microcirculation represents a system which can be described by interrelated and non-linear parameters which are difficult to measure. Recent computer simulations of mathematical models of microvascular exchange (*Watson and Grodins*, 1978, *Wiederhielm*, 1979, *Bert and Pinder*, 1982) have proven useful both in interpreting data and demonstrating regulatory mechanisms. In the usual models emphasis has been placed on the properties of the capillary membrane. This structure is pictured as having pores of various sizes through which fluid and proteins move. Experimentally measured selectivity and flows determined from analysis of lymph can be explained reasonably well by the proper selection of a population of pores within the capillary membrane (*Landis and Pappenhiemer*, 1963). Recently, other parts of the overall microvascular exchange system have been receiving increased attention. For example, protein exclusion by tissue components characteristic of the interstitial space has been shown to be important in microvascular exchange (*Bert* et al., 1982). Flow properties of the lymphatic system have also been receiving increased attention. Simplified lymph flow characteristics have been used in the usual exchange models. However, improved understanding of lymph flow characteristics render obsolete the idealized characteristics used previously in microvascular exchange models.

Watson and Grodins (1978), in their digital computer simulation of blood-to-lymph transport, used a constant value of lymph flow, which was appropriate for the limited conditions they were investigating. In the analog computer simulation by *Wiederhielm* (1979), as well as the modification by *Bert and Pinder* (1982), lymph flow was related to interstitial fluid volume. In the present study, lymph flow characteristics were investigated as they affected the overall conditions of microvascular exchange. Lymph flow was set proportional to interstitial fluid volume up to a point where lymph flow reaches a plateau (or saturation) value, similar to that described by other investigators (*Gibson and Gaar*, 1970, *Taylor* et al., 1973, *Mortillaro and Taylor*, 1976). Using this type of relationship, an analog computer simulation of microvascular exchange was used to predict steady state values

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of both interstitial fluid and protein content. In addition, the effects of both increased resistance to flow in the lymphatics, a characteristic feature of lymphedema, and that of increased venous pressure were studied. The transient response of the microcirculation to these perturbations was also examined.

Materials and Methods

A schematic, showing flows, fluid and protein distribution within the various compartments upon which the analog computer simulation is based, appears in Fig. 1. An appendix following the text lists and defines the symbols used in this study. The simulation is based on the skin and muscle content of the normal 70 kg reference man. Equipment and methods used, mathematical analysis of the program, as well as comparison of results predicted by a previous program for normal and a variety of pathological conditions are described in detail elsewhere (*Wiederhielm*, 1979, *Bert and Pinder*, 1982). Several assumptions upon which the program is based, and which are relevant to the lymph flow characteristics are: 1. the content of the circulation is unchanged as a result of material transported to the tissue, 2. proteins are transported across the capillary membrane by leaks, 3. the fluid leaving the interstitial space and draining into the lymphatics is well mixed and represents spatially average conditions in the tissue, and 4. proteins are not concentrated within the lymphatics.

Results

In Fig. 2 is shown for otherwise normal conditions the steady state values of V_T and Q_{PP},

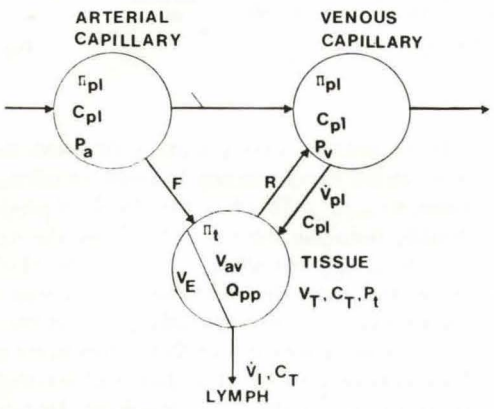

Fig. 1 Four fluid compartments which comprise the microvascular exchange system are shown: arterial and venous capillaries, tissue and lymph. Arrows indicate direction of flows between compartments. A description of terms can be found in the appendix. A more thorough description of terms and equations which relate them can be found in works by *Wiederhielm* (1979) and by *Bert and Pinder* (1982)

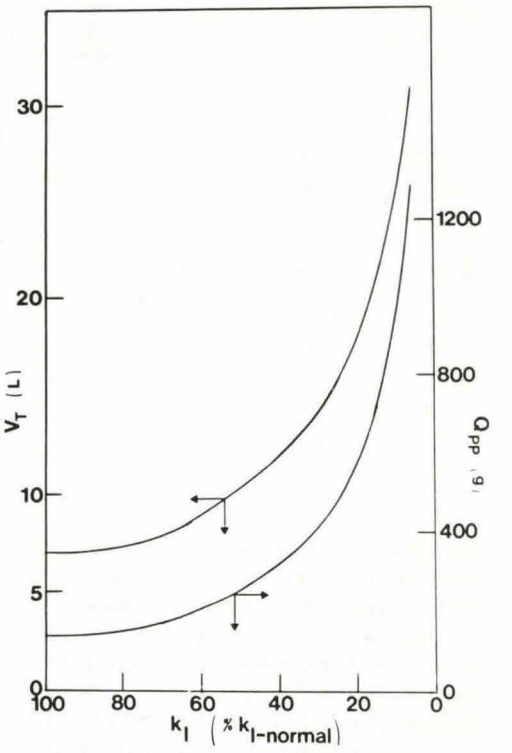

Fig. 2 Steady-state values of total interstitial fluid volume, V_T in liters (L) and interstitial protein content Q_{PP} in grams (g) predicted via the simulation are shown as a function of percentage of normal lymphatic flow rates effected through variation of the proportionality constant k_l, in equation (1) in the text. From left to right the abscissa varies from $k_{l\text{-normal}}$ to zero. The left hand axis corresponds to V_T; the right hand axis to Q_{PP}. A minimum percentage of 6% of normal lymphatic flow, corresponding to 94% lymphatic blockage, could be achieved prior to circuit overloading in the computer

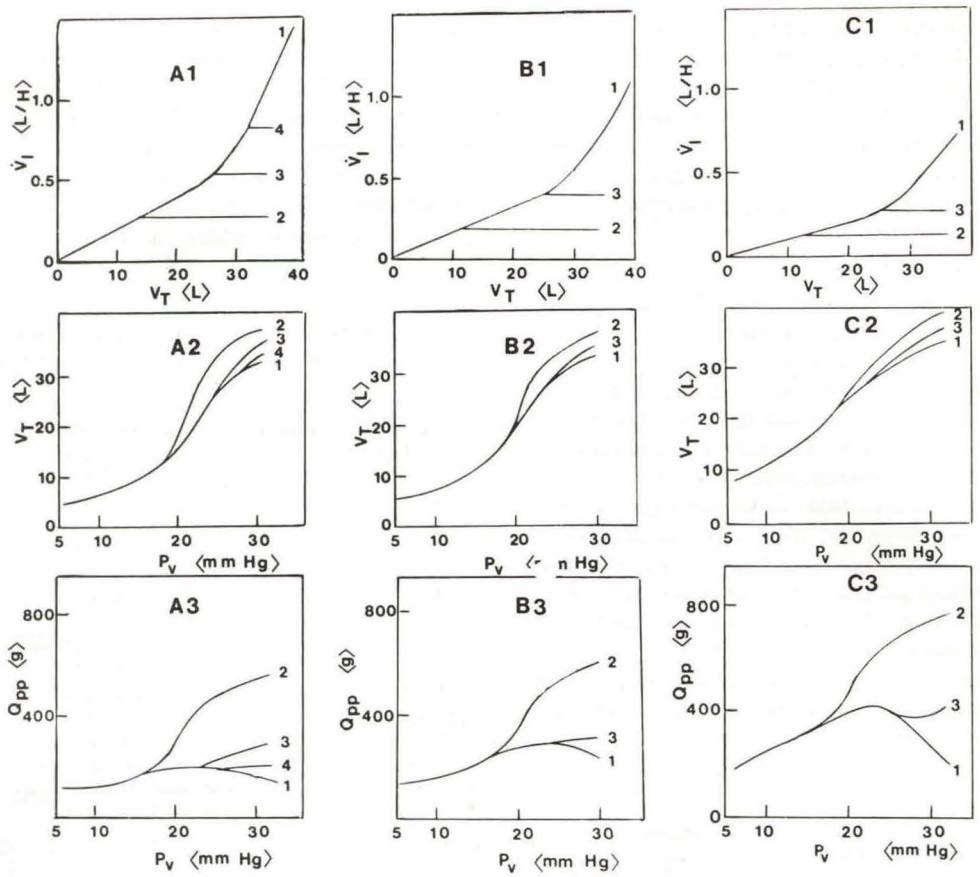

Fig. 3

the interstitial fluid volume and protein content, predicted by the analog computer simulation for increasing lymphatic resistance. Lymphatic flow rate $\dot{V}_l$, is dependent on V_T in a non-linear fashion. In this study $\dot{V}_l$ has been related to V_T by assuming $\dot{V}_l$ is proportional to tissue pressure (*Wiederhielm,* 1979) followed by relating tissue pressure to V_T through a compliance curve. For normal conditions, the $\dot{V}_l$ vs V_T relationship is shown in Fig. 3, Panel A 1, curve 1. This curve contains an initial segment which can be described by:

$$\dot{V}_l = k_l \, V_T \qquad (1)$$

where k_l is a constant of proportionality.

Equations of this form have recently been reviewed (*Aukland and Nicolaysen,* 1981). Increasing resistance to lymphatic flow can be represented by decreasing k_l from its normal value, $k_{l\text{-normal}}$. This has the effect of proportionally reducing the values of $\dot{V}_l$ by the ratio of $k_l/k_{l\text{-normal}}$ for all V_T. *Wiederhielm* (1979) makes the point that for otherwise normal conditions, the proportionally constant between tissue pressure and $\dot{V}_l$ has not been experimentally verified. Our choice of relating $\dot{V}_l$ to V_T suffers the same drawback. However, the large body of experimental and clinical data fit by previous simulations (*Wiederhielm,* 1979, *Bert and Pinder,* 1982) and the rather insensitive effect of k_l on V_T and Q_{PP} near normal conditions, is reassuring. In Fig. 2, the result of decreasing k_l is shown to have a similar effect on both V_T and on Q_{PP}. The progression to high interstitial protein and fluid

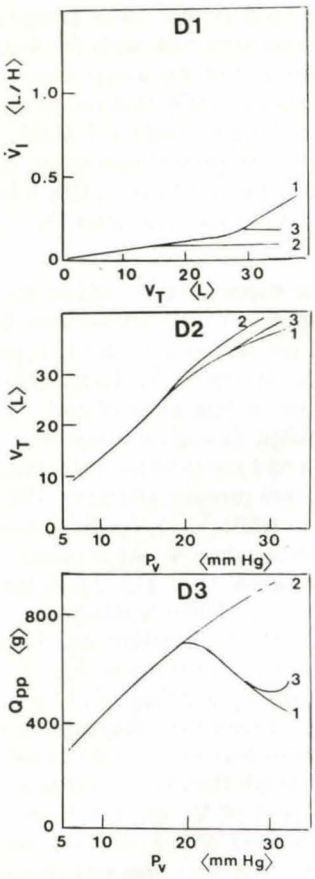

Fig. 3 Panel A shows conditions for normal lymphatic permeability, characterized by $k_{l\text{-normal}}$ in equation (1) in the text. Panels B through D contain conditions for decreasing lymphatic flow rates corresponding to 75%, 50% and 25% of the lymph flow characteristics shown in Panel A. The progression from panels A to D corresponds to increasing lymphatic blockage. In Panels A1 to D1 lymph flow rates, $\dot{V}_l$, in liters per hour (L/H), are shown as a function of interstitial fluid volume, V_T, in liters (L), as follows: curve 1 corresponds to conditions without plateauing, curve 2 corresponds to plateauing at two times normal lymph flow (i.e. normal lymph flow evaluated at P_v = 12 mmHg), curve 3 corresponds to plateauing at four times normal lymph flow and curve 4 corresponds to plateauing at six times normal lymph flow. Shown in Panels A2 to D2 and A3 to D3 are the simulation results of V_T in liters (L) and Qpp in grams (g) for the conditions in panels A1–D1 and as venous pressure, P_v, is varied. In panels A2–D2 and A3–D3, the numbers at the right of each curve correspond to results obtained using the same numbered courve as shown in panels A1–D1

content caused by blockage of the lymphatics is demonstrated in Fig. 2. The computer simulation predicts for steady state and normal hydrostatic pressures that as a greater fraction of the lymphatics become incompetent (i.e. k_l decreases), V_T and Q_{PP} increase. As k_l approaches zero, the values of V_T and Q_{PP} increase rapidly to the point where the computer overloaded.

In each panel of Fig. 3 is shown the simulation results for the effect of venous pressure, P_v, on both V_T, A2–D2, and on Q_{PP}, A3–D3, for $\dot{V}_l$ versus V_T relationships shown in A1–D1. As shown in successive panels progressive lymphatic blockage is achieved by decreasing k_l (in panel B1, $k_l = (3/4)k_{l\text{-normal}}$; in panel C1, $k_l = (1/2)k_{l\text{-normal}}$ and in panel D1, $k_l = (1/4)k_{l\text{-normal}}$). Plateauing is shown to occur when $\dot{V}_l$ reaches a constant value for increasing V_T. Plateau or saturation values of $\dot{V}_l$ were arbitrarily taken as even multiples of $\dot{V}_{l\text{-normal}}$. $\dot{V}_{l\text{-normal}}$, in all cases, was determined at P_v = 12 mmHg. Relationships containing plateau values for $\dot{V}_l$ as shown resulted in changes in V_T or Q_{PP} from values predicted without plateaus. Plateau values of $\dot{V}_l$ which were taken as higher multiples of $\dot{V}_l$ than the highest value shown, resulted in the same curves as predicted without saturation.

Discussion

Lymphedema is caused by the low output failure of the lymphatic system (*Witte and Witte*, 1973) accompanied by an accumulation of both fluid and protein within the tissues. We chose therefore, V_T and Q_{PP} as the two

parameters to be investigated as affected by: 1. changes in k_l, 2. changes in venous pressure, and 3. plateau levels of $\dot{V}_l$. The simulation predicted response of the system to progressive blockage of the lymphatics is shown in Fig. 2. The simulation of complete blockage raises some questions. The simulation is modelled so that fluid can enter the tissue by both filtration and plasma leaks from the circulation (see Fig. 1). Fluid leaves the tissue by reabsorption and via the lymph. The program used in this work allows proteins to enter the tissue only by plasma leaks, and to leave only by the lymphatics. Complete lymphatic blockage eliminates the only exit available for proteins. The only steady state condition that would satisfy this circumstance occurs at zero V_T, corresponding to zero protein leak. One of the descriptive equations upon which the simulation is based, is eliminated for $k_l = 0$ (i.e. total blockage). It is possible that limiting values of V_T and Q_{PP} can be predicted as k_l approaches zero. However, the computer overloaded for values of $k_l < 0.06$ ($k_{l\text{-normal}}$). Therefore, the maximum lymphatic blockage we could model was a 94% reduction of normal lymph flow conditions.

In Fig. 2, the relative increases in both V_T and Q_{PP} caused by changes in k_l, are similar. For a moderate decrease in k_l from normal, the effect on V_T and Q_{PP} is not great. For a decrease in k_l of 50% or more, steady state values of V_T and Q_{PP} increase rapidly at an accelerated rate. Similar trends were noticed by *Wiederhielm* (1979). As k_l is decreased the simulation predicts a many-fold increase in Q_{PP}. This trend results in part from considering the circulation to be an infinite sink with respect to proteins and fluid. The trend is noted, but the absolute values of Q_{PP} may be improbable physiologically.

The transient response of V_T effected by decrease in k_l were also measured. For 94% lymph blockage, the simulation, which is based on the skin and muscle content of man, predicts that it takes approximately 11 days for 50% of the final fluid volume change to be reached and approximately 40 days for 95% of the final fluid volume to be attained. The latter value compares well with the 4–6 weeks for development of the initial acute edema in dogs experimentally induced as a result of excision of lymph vessels and nodes (*Olszewski,* 1973). The present simulation offers no insight into the resultant chronic edema which begins up to one year after the original insult.

It is reasonable to expect that $\dot{V}_l$ will be related to some property of the interstitium. In particular, tissue pressure and V_T are two parameters which may determine $\dot{V}_l$. Tissue pressure and V_T are not independent of each other, but are related through a compliance relationship. To avoid controversy concerning the concept of tissue pressure (*Hargens,* 1981), we have chosen to relate $\dot{V}_l$ to V_T. Realistically, as V_T increases, so does $\dot{V}_l$. As reviewed and discussed by *Taylor* et al. (1973), $\dot{V}_l$ may have a saturation value. Other investigators (*Gibson and Gaar*, 1970, *Mortillaro and Taylor,* 1976) have noted this phenomenon. Fig. 3 shows, the effect on V_T and Q_{PP} of: 1) plateau values of $\dot{V}_l$, 2) lymphatic blockage, and 3) changes in venous pressure. For all values of k_l and for all lymph flow relationships a similarly shaped curve of V_T versus venous pressure, P_v, is obtained, Fig. 3, A2–D2. For all values of k_l, $\dot{V}_l$ saturation does not change the steady state values of V_T by more than 50% from those obtained without $\dot{V}_l$ saturation. As k_l decreases, the effect of a plateau value of $\dot{V}_l$ on V_T decreases; also the value of venous pressure at which the plateau value becomes effective, increases.

In contrast Q_{PP} shows a much greater relative change for similar conditions. In Fig. 3, A3–D3, curve 1 ($\dot{V}_l$ without saturation), Q_{PP} goes through a maximum value as a function of venous pressure. As V_T increases, $\dot{V}_l$ increases and reaches a point where the rate of increase of $\dot{V}_l$ with V_T increases (panels A1–D1). This point is seen to occur approximately at V_T = 27 liters. This rapid increase in $\dot{V}_l$ above V_T = 27 liters, would effectively drain proteins from the interstitium. The maximum value of Q_{PP} as a function of venous pressure can be interpreted as a relative change in the balance be-

tween protein leaking into the tissue, protein present in the tissue, and protein being removed from the tissue.

When plateau values of $\dot{V}_l$ are programmed into the simulation, Q_{PP} changes rapidly, showing a greater effect for lower values of the plateau. In some cases, maximum values of Q_{PP} versus venous pressure still remain. In other cases, particularly for the lower $\dot{V}_l$ plateau values, Q_{PP} increases monotonically with venous pressure.

The greater relative increase in Q_{PP} than in V_T, is consistent with qualitative clinical observations that during lymphatic insufficiency the protein content of the tissue rises. This generally occurs at a $\dot{V}_l$ plateau of 4 times $\dot{V}_{l\text{-normal}}$ or less, but no attempt to further estimate these values based on this simulation shall be made. The lymph flow characteristics described above result in the prediction of conditions which are consistent with the clinical observations as classified by *Foldi* (1977). The results obtained in the absence of $\dot{V}_l$ saturation, are not consistent with these observations.

Analysis of the transient response of the systems shows that it takes a longer time for Q_{PP} to reach steady state than for V_T. The time required to reach steady state after a perturbation of venous pressure, increases for both V_T and Q_{PP}, as k_l decreases or as the plateau value of $\dot{V}_l$ decreases.

Conclusion

Reduction in lymphatic permeability (i.e. lymph blockage) has been shown via an analog computer simulation of a mathematical model of microvascular exchange to result in increases in both interstitial fluid volume and protein content. Lymphatic flow characteristics, which include a plateau level of lymph flow with interstitial fluid volume, are shown to result in overall conditions which are consistent with clinical observations. For increases in lymphatic blockage or decreases in the plateau level of lymph flow, the transient response of the microcirculation is characterized by longer times. These findings demonstrate the important role played by the lymph kinetics on the overall blood-to-lymph transport system and indicate further the need for more accurate quantitation of lymph flow characteristics.

Acknowledgments

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Appendix
Nomenclature

C_{pl}	protein concentration
C_T	tissue protein concentration
P_a	arterial capillary hydrostatic pressure
P_t	tissue hydrostatic pressure
P_v	venous capillary hydrostatic pressure
P_V	venous hydrostatic pressure
π_{pl}	plasma colloid osmotic pressure
π_t	tissue colloid osmotic pressure
F	fluid filtration rate
R	fluid reabsorption rate
$\dot{V}_{pl}$	plasma leak
$\dot{V}_l$	lymphatic flow rate
V_E	interstitial excluded volume
V_{av}	interstitial accessible volume
V_T	total interstitial fluid volume
Q_{PP}	interstitial protein content
k_l	proportionality constant in equation (1) in text
$k_{l\text{-normal}}$	proportionality constant in equation (1) in test, under normal conditions

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Joel L. Bert, Ph.D., Department of Pathology, Faculty of Medicine, 2211 Wesbrook Mall, University of B.C., Vancouver, B.C., V6T 1W5, Canada

K.L. Pinder, Ph.D., Dept. of Chemical Engineering University of B.C. Vancouver, B.C. V6TIW5, Canada