Upsala J Med Sci 93: 193–200, 1988

Aspects of the Blood-lymph-barrier in Shock

G. Arturson

Burn Centre, University Hospital, Uppsala, Sweden

INTRODUCTION

The blood-lymph-barrier includes the endothelial cells and basement membrane of the capillary wall on one side, the terminal lymphatic cells on the other side and in between the interstitial space.

THE CAPILLARY WALL

In the fifties and sixties, the focus of studies of the blood-to-lymph pathway was on the properties on the capillary wall. In the early studies on capillary permeability in shock, measurements were made either of the changes of haematocrit of the blood or of the disappearance from the blood stream of different test substances. The first investigation aimed to characterize the functional ultrastructure of the blood-lymph-barrier in haemorrhagic shock was published by Arturson and Thorén in 1964 (3). They used dextran as a test substance in bleeding experiments in dogs (Lamson technique). The molecular weights of the dextran molecules in collected lymph and in plasma were determined and the lymph/plasma concentration ratio (C_L/C_P) of varying molecular sizes was calculated. This ratio for a wide range of molecular sizes will show the sieving characteristics or permeability of the capillary membrane. It was concluded that capillary permeability does not change significantly during or after two hour hypotensive periods (arterial blood pressure 35 or 50 mm Hg) if the PaO_2 was kept within normal range (Fig. 1). The lymph flow decreased to very low values during the hypotensive periods. Studies of the blood-lymph-barrier in traumatic shock following e.g. thermal injury, showed quite different results compared with simple haemorrhagic shock. Increased microvascular permeability was observed in thermally damaged tissue, but also to some extent generally in tissues remote from the trauma in extensive burns (Fig. 2).

In order to investigate quantitatively the acute oedema formation associated with increased microvascular permeability, the 'dextran sieving' data were compared with results obtained using a pletysmographic technique applied to a thermal trauma on cat hind part (2). When, in this way, the magnitude of the filtration coefficient and the rate of transcapillary net movement of fluid were known, data were available to permit an approximative calculation of the magnitude of the force that would be required for this fluid exchange (Fig. 3). During the initial period after the trauma, the effective driving force required to explain the fluid loss to the tissue would amount to 250-300 mm Hg. The changes of the osmolality in plasma of the venous blood drained from the thermally damaged tissue observed during the first 10 minutes after the trauma, corresponded to osmotic forces up to 300 mm Hg. These figures are in the same range as the driving force calculated indirectly.

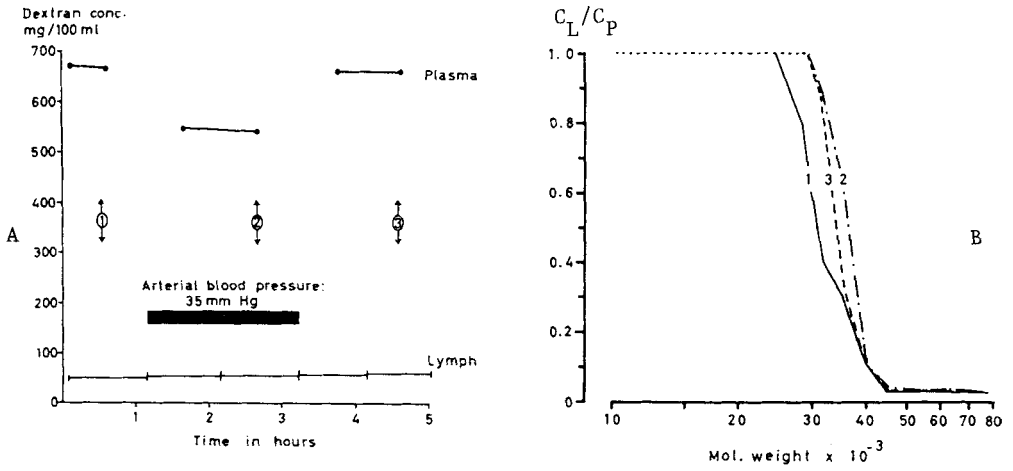

Fig. 1 A Total dextran concentration in plasma and lymph from a paw before, during, and after a two hour hypotensive period of 35 mm Hg. The dextran concentration in plasma is decreased during the shock period, while the concentration in lymph is more or less unchanged. At 1,2, and 3 the molecular weight distribution of the dextran in samples of blood and lymph was determined and the lymph/plasma dextran concentration ratio (C_L/C_P) for different molecular sizes calculated. B The C_L/C_P ratio is unchanged for molecular weights >40,000 and slightly increased for molecules <40,000.

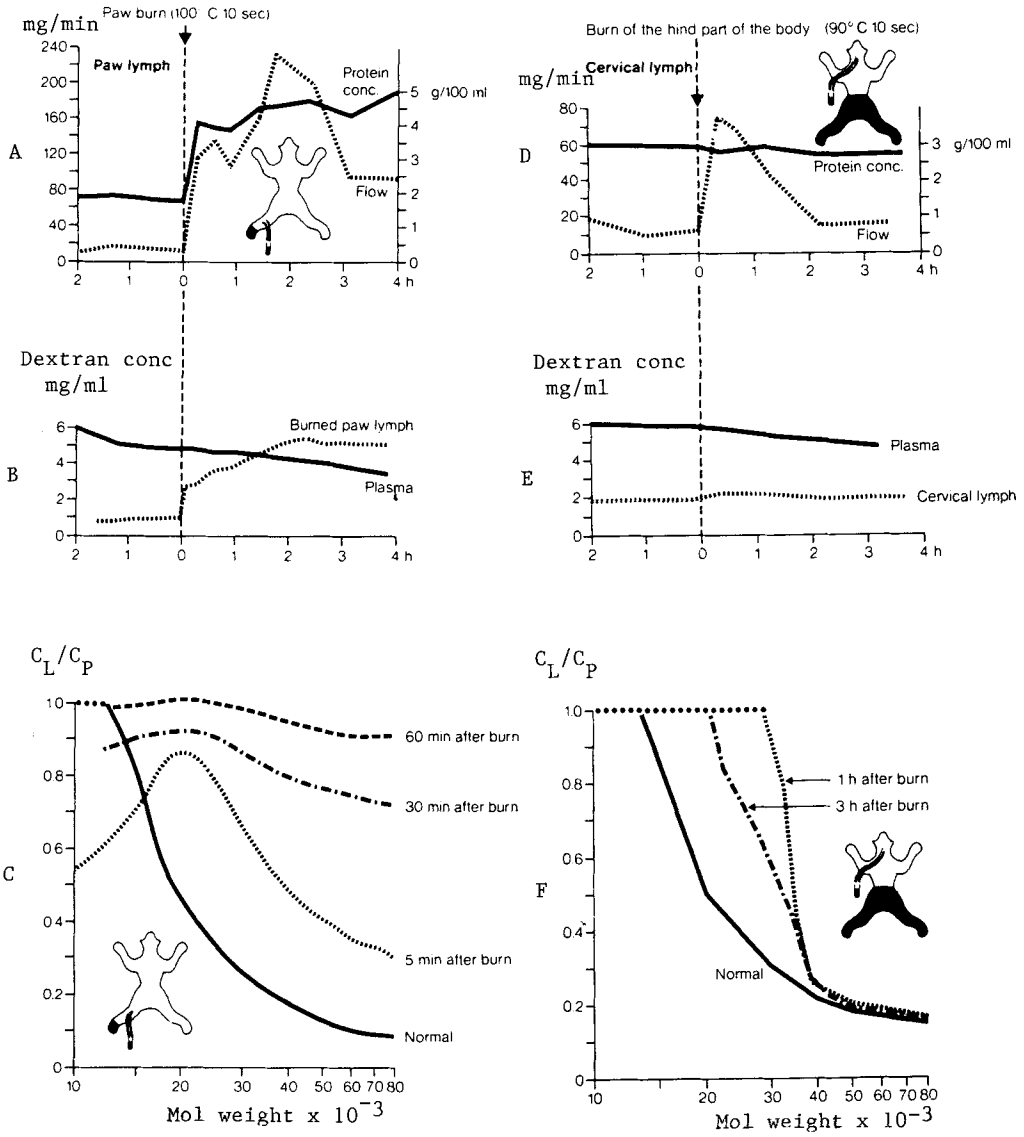

Fig. 2 A Lymph flow and protein concentration of lymph drained from a dog paw with a second degree burn. B Total dextran concentration in burned paw lymph increased above that of plasma. C The lymph/plasma dextran concentration ratio (C_L/C_P) increased rapidly after scalding and was about the same (1.0) for all molecular sizes about 60 minutes after the burn. D Lymph flow and protein concentration of lymph drained from non-burned areas of a dog with major burn on the hind part of the body. E Total dextran concentration in cervical lymph and plasma. F The increase of the C_L/C_P ratio for different molecular sizes occurs concomitantly with an increased lymph flow and indicates a sligth increase of permeability of the blood-lymph-barrier in non-burned areas.

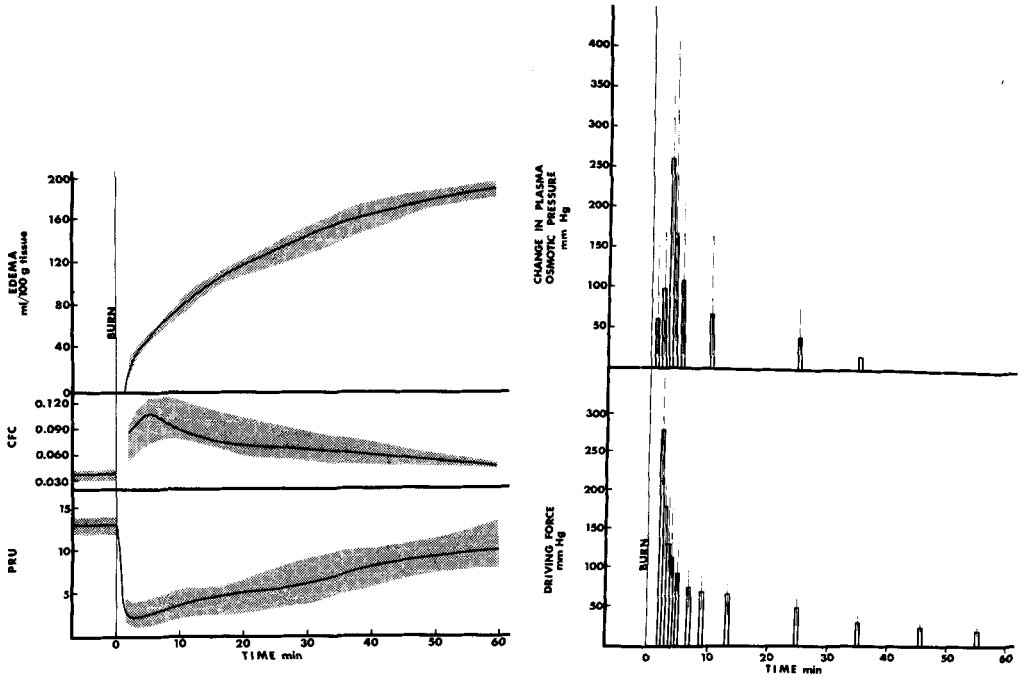

Fig. 3 Left: The effects of second degree burns on resistance vessels (PRU) on capillary filtration coefficient (CFC) and on net transcapillary movement (oedema) in cat hind paw. Solid lines represent means of five experiments, shaded areas range of individual experiments. There is a pronounced dilatation of resistance vessels and a very rapid oedema formation, especially in the early phase after burning. A moderate increase of CFC occurs, but this is much less than expected from the rapid transcapillary fluid movement.

Right: Lower diagram: The magnitude of the transcapillary driving force for fluid transfer in burns as calculated from the data on CFC and the rate of oedema formation given in Fig. 3 left. Mean values and range of individual experiments indicated. Upper diagram: Change above control level of plasma osmotic pressure in venous blood drained from burned tissue. Mean values of ten experiments and range of individual observations indicated. The results suggest that the main factor responsible for burn oedema in the early phase is a temporary increase of extravascular osmotic activity.

THE INTERSTITIUM

All these studies around 1964 focused the interest towards the role of the interstitial space and the involvement of lymphatic collecting ducts in shock. At that time, the compliance of the interstitial space was unknown and some misconceptions concerning the lymphatic circulatory system existed, e.g. that the volume of lymph formed is very small, that the lymphatic vessel is a passive conduit etc.

The increased attention that the interstitium has received in the last two decades has resulted in greater understanding of microvascular exchange. The introduction of various new techniques, e.g. micropuncture, wick-in-needle, computer simulation, etc., have contributed to this.

The interstitium, previously thought to be only a well-mixed storage chamber for fluid and solutes, is today recognized to have important physiochemical characteristics, such as 'self-regulation' due to oncotic buffering and protein washdown and mechanisms that govern the rate of transport of materials from blood to lymph. At present, the most widely accepted model of the heterogenous, complex interstitium is (a) free-fluid channels that may or may not contain mobile hydrophilic macromolecules, (b) a gel space with high electrical charge densities due to the presence of hyaluronate and/or proteoglycans packed in a meshwork of collagenous fibres, and (c) cells. The interstitium behaves as a gel-exclusion chromatography column with respect to its effect on blood-to-lymph transport of macromolecules.

Under normal conditions, the interstitial fluid pressure in human skin is slightly negative, mean -3.1 mm Hg (range -5 to -0.5 mm Hg) (8). It has been argued that a lymphatic 'suction pump' may be responsible for this negative interstitial pressure (1). In thermally damaged tissue, the interstitial pressure drops to very low values (around -150 to -200 mm Hg) immediately following the trauma (7), which is in accordance with the driving force calculated by Arturson and Mellander in 1964 (2). The reasons for this very low negative pressure are unclear. An increased extravascular osmotic activity due to rapid degradation of hyaluronate and collagenous fibres might play a role. It is of importance to realize that the burn shock is not only due to plasma leakage caused by increased microvascular permeability, but also to a very rapid initial suction of fluid out into the interstitium.

Computer simulations of microvascular exchange following thermal injury have shown that extensive burns are characterized by (a) a local, protein rich oedema caused by changes in both the circulatory system and the interstitial space and (b) a general, protein poor oedema caused by typical changes in the circulatory state variables (4).

THE LYMPHATIC VESSELS

It has been shown in the last decade that the lymphatic vessel participates in the regulation of interstitial dynamics through its ability to contract and propel fluid and protein from the extravascular tissues back to the blood stream. The 'lymph pump' appears to be regulated by local physiological forces as well as neurogenic and humoral factors (5).

Under normal circumstances in man, lymph is returned to the circulation over a 24 hour period in volumes comparable to the intravascular pool. The mass of interstitial protein is similarly large. About 50 per cent of the total circulating plasma protein escapes into the interstitium daily and is carried away by the lymphatics.

In a model system for assessing lymphatic pumping in vivo Johnston and co-workers (6) have recently shown that a 25 per cent blood loss resulted in increased activity of the lymph pump: up to six times more fluid was propelled through the 'isolated' lymph vessel than in similar preparations in sheep that were not bled (Fig. 4). Following very severe bleeds (50 per cent of the blood volume) both lymph flow and fluid pumping were depressed. The recognition that changes in lymph pumping and lymph flow are dependent on the degree of blood loss, may help to explain the extremely variable reports of lymph flow changes in the literature.

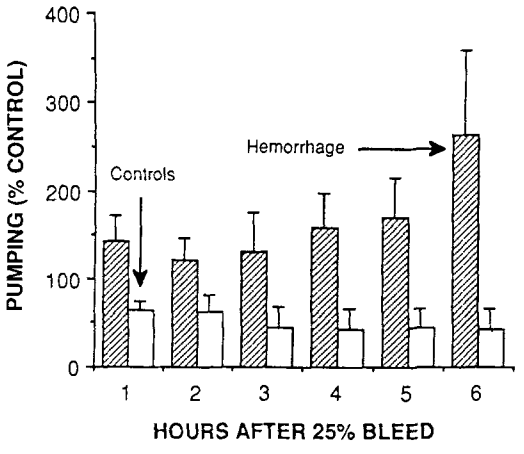

Fig. 4 Effects of hemorrhage on pumping activity in anesthetized sheep. 17.5 ml/kg b.w. or 25 per cent of the blood volume was removed from the arterial line assuming a blood volume of 70 ml/kg b.w. Each bar represents the mean ± S.E.M. of the volumes pumped over a one-hour period expressed as a percentage of the volume pumped during a one-hour control period (external control non-bled animals) or immediately preceding a 25 per cent bleed (hemorrhaged group). The cross-hatched bars illustrate the data from eight sheep in the hemorrhaged group. The open bars represent the data from the five animals in the non-bled group. Using an analysis of variance, there was a significant difference between the two groups ($P<0.01$). The data have been taken by permission from Johnston et al. (6).

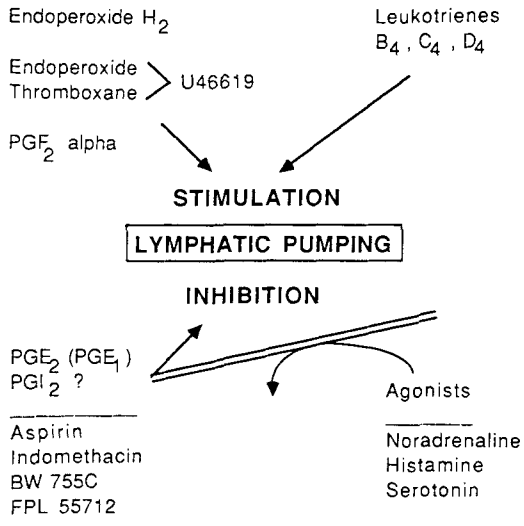

Fig. 5 Effects of various arachidonic acid metabolites and inhibitors on lymphatic vessel contractility. Permission from Johnston et al. (6).

It seems most likely that the autonomous nervous system with noradrenaline as the principal mediator, will turn out to be an important regulatory factor. Other possibilities include metabolic of arachidonic acid metabolism (Fig. 5).

In septic shock, accumulation of extravascular fluid occurs due to increased microvascular permeability. The enhanced transvascular flux of protein and fluid simply overwhelms the lymphatic transport capabilities. Furthermore, recent studies by Johnston et al. (6) have shown that intravenous administration of endotoxin suppressed fluid propulsion in the lymphatics (Fig. 6). Fluid pumping declined as lymph flows increased. Similar results were obtained after intradermal injections of E. coli in the rabbit, which produced large increases in vascular permeability, but the clearance of extravascular albumin from these sites was decreased, even less than that from control skin sites.

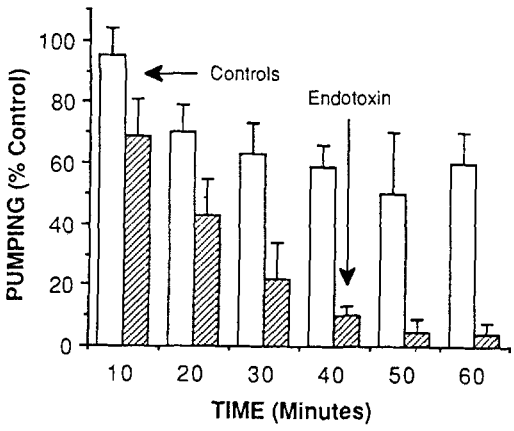

Fig. 6 Effects of endotoxin on pumping activity in anesthetized sheep. Each bar represents the mean ± S.E.M. of the volumes pumped over ten-minute intervals expressed as a percentage of the average volume pumped during a one hour control period immediately preceding the intravenous infusion of 3.3 μg/kg endotoxin (E. coli -055:B5). The cross-hatched bars illustrate the data from the five sheep in the endotoxin group and the open bars represent the data from the five control sheep. Even though there was a decline in pumping activity in the control group due to the effects of the anesthetic, there was a significant difference between the two groups ($P < 0.02$). The data have been taken by permission from Johnston et al. (6).

CONCLUSION

The microvascular exchange system, the circulation, the tissue space, and the lymphatics, is highly interactive, nonlinear, and complex. Stabilization of the interstitium occurs through autoregulation (control of interstitial fluid volume). Lymphatic vessels participate in the regulation of interstitial dynamics through their ability to contract and propel fluid and protein from the extravascular tissues back to the blood stream. Considering the large reservoir of fluid and protein in the interstitium and lymph, stimulation of the 'lymph pumps' following moderate haemorrhage might help to re-expand the vascular space. If, however, the haemorrhage is very severe (> 50 per cent of blood volume), lymph flows and fluid pumping are depressed and hypovolemic shock develops.

Endotoxins cause tissue oedema, not only by an enhanced flux of fluid and protein from the vasculature, but also by the suppression of lymphatic pumping. The clearance of extravascular protein from tissues is even less than normal and septic shock develops very rapidly.

REFERENCES

1. Adair, T.H. & Guyton, A.C.: Lymph formation and its modification in the lymphatic system. In: Experimental biology of the lymphatic circulation (ed. M.G. Johnston) pp. 13-44. Elsevier Science Publishers, B.V., 1985.

2. Arturson, G. & Mellander, S.: Acute changes in capillary filtration and diffusion in experimental burn injury. Acta Physiol Scand 62: 457-463, 1964.

3. Arturson, G. & Thorén, L.: Capillary permeability in haemorrhagic shock. Studies of the blood-lymph barrier with dextran as a test substance. Acta Chir Scand 129: 345-351, 1964.

4. Arturson, G., Hedlund, A., Groth, T. & Zaar, B.: Potential use of computer simulation in treatment of burns with special regard to oedema formation. Scand J Plast Reconstr Surg 18: 39-48, 1984.

5. Johnston, M.G.: Involvement of lymphatic collecting ducts in the physiology and pathophysiology of lymph flow. In: Experimental biology of the lymphatic circulation (ed. M.G. Johnston) pp. 81-120. Elsevier Science Publishers, 1985.

6. Johnston, M.G., Elias, R.M., Hayashi, A. & Nelson, W.: Role of the lymphatic circulatory system in shock. J Burn Care Rehab 8: 469-474, 1987.

7. Lund, T., Wiig, H., Reed, R.K. & Aukland, K.: A "new" mechanism for edema generation. Strongly negative interstitial fluid pressure causes rapid fluid flow into thermally injured skin. Acta Physiol Scand 129/3: 433-435, 1987.

8. Reed, R.K. & Wiig, H.: Compliance of the interstitial space in rats. I. Studies on hindlimb skeletal muscle. Acta Physiol Scand 113: 297-305, 1981.

Address for reprints:

Gösta Arturson
Burn Centre
University Hospital
S-751 85 Uppsala
Sweden