

Mechanisms of Blood Flow and Fluid Exchange in Microvessels:

Hemorrhagic Hypotension Model

*Benjamin W. Zweifach, Ph.D.**

SEVERE BLOOD LOSS sets into motion a train of compensatory adjustments which are temporarily life-saving, but do so at the expense of the peripheral circulation. The adjustments are at best marginal, and with time the circulatory insufficiency at the tissue level becomes self-destructive. The syndrome is thus characterized by an insidious undermining of the entire circulation whose etiology is difficult to pinpoint and which, if allowed to progress, becomes unresponsive to the mechanical restoration of the blood originally lost. The effects of a low-flow state throughout the body are many and complex. It is generally accepted that the ultimate failure of the circulation is peripheral in origin and that in essence the microcirculation has lost its ability to contribute actively to circulatory adjustments in accord with tissue needs. The precise mechanisms, however, are not well documented or understood.

Basically the deterioration of the circulation is brought about by a disparity between central and peripheral regulation in the face of the marginal perfusion of blood through the tissues. As perfusion falls below the metabolic needs of the parenchymal cells, the decisive element is the stagnant hypoxia and its attendant effect on cell metabolism. In considering the effects of stagnant hypoxia, emphasis has been placed on parenchymal cell damage, but not enough consideration has been given to the fact that the same degree of hypoperfusion will serve to override local compensatory regulation by a sustained relaxation of microvascular smooth muscle. Just as in the case of any other organ system, the intrinsic behavior of the microcirculation will become increasingly less effective be-

cause the stagnant hypoxia undermines the capacity of its smooth muscle to respond and eventually may also damage vascular endothelium.

General Considerations

The term "microcirculation" has been used in a general framework covering its activities in all tissues. There are, however, substantial regional differences in the extent to which flow is curtailed during shock, with organs such as the heart, brain, and lungs being preferentially spared.¹ It is only when the systemic driving pressure falls below 45–50 mm Hg following hemorrhage that even these tissues begin to show signs of irreparable damage.

With the ineffectiveness of volume-replacement therapy following protracted hypotension, the clinician is caught on the horns of a dilemma. The obvious and immediate cause of the tissue ischemia is the intense constriction of the arterioles and precapillaries. Unless this can be modified, adequate tissue perfusion is not possible. On the other hand, the arteriolar vasoconstriction is an essential aspect of the central control of blood pressure and unless peripheral resistance is maintained, the cardiac output during shock will be unable to sustain systemic blood pressure at an effective level. For this reason the mechanical effects of volume replacement with blood or with plasma expanders are by themselves sufficient during the initial phase, since they permit more adequate filling of the heart, improved cardiac output and, thereby, lessen the extent to which the peripheral resistance has to be increased to buttress the arterial pressure.

In assessing the relative importance of the intrinsic mechanisms underlying the disruption of local tissue perfusion during the shock

* AMES-Bioengineering, University of California, San Diego, La Jolla, California 92037.

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state, a singularly critical feature would be the extent to which the terminal vascular bed has retained its capacity to contribute to the maintenance of blood volume through a balance of transcapillary fluid exchange. The constitutive equation governing this phenomenon rests upon the Starling concept, which in essence is based on the opposing interaction of the hydrostatic pressure of the blood and the colloid osmotic pressure of the plasma proteins. It can readily be appreciated that both the pressure relationships within the microcirculatory exchange vessels and the colloid osmotic pressures of the blood and tissue compartments may be thrown out of balance during shock. Until recently, there was a dearth of objective evidence on this all-important aspect of balanced transcapillary fluid exchange. It is the purpose of this presentation to bring together the current status of our information on the basic mechanisms concerned with the translocation of fluid, using the response to hemorrhagic hypotension as a model.

Methods

A brief discussion of the methodology needs to be included as a frame of reference, since it would be both premature and misleading to generalize freely from particular experimental models. The present article is based on experiments carried out on anesthetized cats, rats, and rabbits. Similar studies have been made on dogs, but because of their atypical splanchnic pathology following hemorrhage, these data are not discussed in detail here. Circulatory insufficiency is induced by a single bleeding of about 40 per cent of the estimated blood volume, carried out over a period of 20 minutes. The animal is then allowed to recover spontaneously. Central mean blood pressure (P_A) rises from its initial low point of between 40 and 50 mm Hg to near normal. In the face of such a large volume deficit, the P_A then falls progressively over a period of 3–4 hours and, unless the condition is relieved by blood replacement, fatal collapse of the circulation occurs (see fig. 1).

This method² was used to avoid the repeated small infusions involved in other procedures to maintain the blood pressure at

an arbitrary level, since this would make it difficult to interpret changes in the colloid osmotic pressure of the plasma and in the hematocrit. The method has the further advantage of allowing compensatory and decompensatory mechanisms to develop in each animal in accord with its own capabilities.

Data on the microcirculation deal, for the most part, with the intestinal mesentery of the cat, rat, and rabbit. Where relevant, the data on the dog refer to the omental circulation. Micropressures were recorded by an electronic servo-null procedure modified by Intaglietta³ after that developed by Wiederhielm *et al.*⁴ Blood flow was recorded on the basis of erythrocyte velocity measurements using cross-correlation techniques to estimate the transit time between two accurately spaced diodes.⁵ Vessel diameters were continuously recorded by an electronic image shearing technique at a magnification of 900–1000 \times .

Systemic vs. Local Disturbances

The adjustment of the peripheral circulation to hemorrhage involves separate local and remote mechanisms which potentially have diametrically opposed objectives in terms of homeostasis. Local regulatory phenomena under normal circumstances are designed to sustain the metabolic needs of the tissue and, in the face of a reduced central pressure during hemorrhagic hypotension, would act primarily to increase tissue perfusion. Such mechanisms include adjustments of the number of capillaries, exchange surface area, and capillary pressure via changes in vasomotor behavior in the immediate precapillary vessels. There is some evidence for active adjustment of postcapillary resistance under such conditions, and much is made of the ratio of pre- to postcapillary resistances,⁶ but specific data in a dynamic, *in-vivo* framework are not available. In addition, an ascending reaction which involves dilation of the feeding arterioles and normally leads to the delivery of an increased volume blood develops. Some studies^{7,8} suggest that this response may be mediated through a sharp reduction in tissue P_{O₂}.

Within the tissue proper, the physical transport and distribution of blood is the result

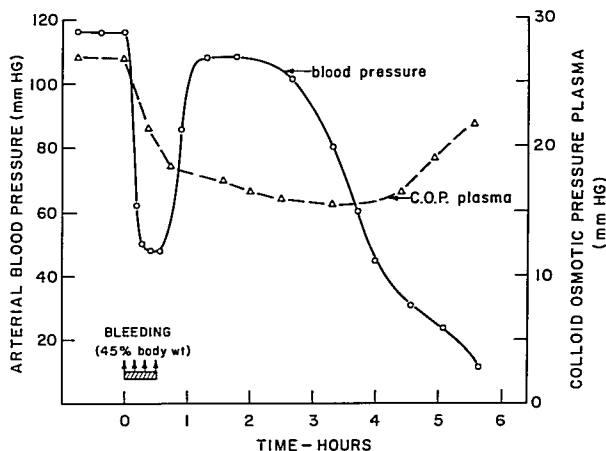


FIG. 1. Hemorrhagic shock in the cat. The plot shows the time course of the change in blood pressure with a single large bleeding. Note that on the average (based on 23 cats), the mean systemic pressure falls progressively for a period of 2 to 3 hours, and unless blood replacement measures are instituted, 85 per cent of the animals die within six hours. Also plotted is the change in plasma colloid osmotic pressure (hemodilution) in such animals. Note that hemodilution occurs rapidly and is near maximal by 40-50 minutes after the bleeding. The π_{pl} shows a continuous trend towards plasma concentration during the final 60-90 minutes.

of a number of interdependent mechanisms. Obviously, a key factor is the tone of the arterial inflow vessels just proximal to the microvascular bed. These small arteries or arterioles (60-75 μ wide) are under the influence of both the nervous system and local environmental factors. Following hemorrhage, these vessels become narrowed as part of the remotely controlled systemic effort to bolster central arterial pressure, and they remain in the constricted state throughout the hypotensive phase of the syndrome. The vasoconstriction is sufficient to reduce blood flow by more than 60-70 per cent and to lower the driving pressure in the microcirculation proper by 30-40 per cent. This pattern does not develop uniformly in all tissues. Organs such as the brain, heart, and lungs are spared this ischemic, vasoconstriction-dependent response.

Other local regulatory mechanisms are involved distal to the feeding arterioles. A type of autoregulation, believed to be myo-

genic in origin,⁹ is characteristic of the terminal arterioles (metarterioles) and pre-capillaries.¹⁰ When the hypotensive episode is prolonged, such autoregulation becomes less and less evident. After 3-4 hours the microvasculature responds in a purely passive manner to changes in arterial pressure. The apparent viscosity of the blood increases because of erythrocyte aggregation¹¹ and margination of leukocytes. The reduced volume flow through the microcirculatory bed gives the tissue an overall ischemic appearance throughout the syndrome. However, the selective capillary perfusion and the impaired venous outflow initially present are replaced during the terminal stages of hemorrhagic shock by an erratic circulation which is clearly ineffective locally and results in a further decrease in venous return through the peripheral sequestration of blood in the venular vessels.

The functional deterioration of the terminal vascular bed becomes more apparent after

blood volume replacement when as a consequence of the resulting dilation of the arteriolar and precapillary vessels, pressure and flow remain well above normal control conditions even though mean central pressure is only 80–90 mm Hg. Impairment of these intrinsic regulatory mechanisms makes it difficult for the microvessels to adjust tissue blood flow in accord with local conditions and is eventually reflected by diminished return to the heart and inability to maintain overall circulatory efficiency.

The reduction in flow through the tissues following hemorrhage is thus the result of a persistent narrowing of the small inflow arteries and large arterioles. Within the capillary network proper and in the postcapillaries, which are simple endothelial channels, blood transport is only passively influenced by physical factors such as the caliber of the vessels, their branching, and the pressure difference across the bed. It is generally agreed that the true capillaries are noncontractile in a regulatory sense.¹² There is some evidence that the endothelial cells may swell, presumably due to changes in ion transport into the cell. The capillaries are narrower (4–7 μ) than the erythrocytes in some organs, *e.g.*, in the retina of the eye, and in skeletal and cardiac muscle, and in a small percentage of vessels in the mesentery. Here, even a slight narrowing (0.5–1.0 μ) due to endothelial swelling will produce a substantial increase in the resistance to flow (r^4). In most tissues, where the capillaries are 7–9 μ in diameter, slight changes in endothelial cell disposition or thickness will have a proportionately lesser effect on the blood flow through these channels. Table 1 lists the principal disturbances at the microcirculatory level which lead to failure of tissue perfusion and circulatory collapse. These disturbances are discussed in detail below.

Microcirculatory Defects

In the face of such a severe disruption in tissue perfusion during hemorrhagic shock, it has long been suspected that the low-flow state tends to undermine one of the most basic functions of the microvasculature,

that of maintaining fluid balance between the blood and tissue compartments. Current concepts of capillary exchange of fluid are based on the Starling balance of hydrostatic and osmotic forces.¹³ The Starling constitutive equation for transcapillary fluid exchange (\dot{m}) is usually written as

$$\dot{m} = K_F[(P_c - P_t) - (\pi_{pi} - \pi_t)] \quad (1)$$

where K_F = the filtration coefficient of the vessel wall, reflecting the permeability to water; P_c = the average capillary pressure; P_t = tissue hydrostatic pressure; π_{pi} = the colloid osmotic pressure of the blood plasma; π_t = the colloid osmotic pressure of the interstitial compartment. The net driving pressure favoring filtration is $P_c - P_t$, and the net colloid osmotic pressure favoring fluid absorption is $\pi_{pi} - \pi_t$. The effectiveness of fluid-exchange mechanics during hemorrhage can best be appreciated by systematically examining the separate facets of the Starling equation. There are very few objective data in the literature defining the status of these aspects, with the possible exception of π_{pi} values, which can be estimated from measurements of plasma protein concentrations.¹⁴

In an operational sense, the conventional version of the Starling equilibrium is incorrect. Equation 1 assumes that the system is a closed one, *i.e.*, all of the fluid that is filtered is returned to the capillary network by absorption. Actually, under steady-state conditions, there is a continuous movement of fluid from the interstitium into the terminal lymphatic capillaries. It has been assumed that this volume of lymph fluid is so small compared with the transcapillary flux that it can be neglected for all practical purposes. Recent studies,¹⁵ however, suggest that not only is the amount of fluid filtered in the microcirculatory network much less than previously estimated, but that under steady-state conditions the volume of lymph flow and the transcapillary filtration rate are equal. A revised Starling relationship to take this into account would be

$$\dot{m} = K_F[(P_c - P_t) - (\pi_{pi} - \pi_t)] - K_L(P_t - P_L) \quad (2)$$

where K_L = the filtration coefficient of the lymphatic endothelial barrier, and P_L = the pressure in the terminal lymphatics. The pressure in the terminal lymphatics, when measured directly, was found to range from 1 to 2 mm Hg.¹⁶ K_F is presumably quite high in view of the high permeability of the lymphatics to plasma proteins.¹⁷ Although direct measurement would not have been possible, it is presumed that the concentrations of protein in the terminal lymphatics (π_L) and in the interstitium (π_i) are the same. In order to account for the movement of fluid from the interstitium into the lymph, there must be a pressure difference between P_i and P_L . It is not clear whether this differential is osmotic or hydrostatic; both may be involved.¹⁸ For example, with increased transcapillary flux in the direction of filtration, π_i will be reduced and water would tend to move from the interstitium into the lymphatic capillaries until the two protein concentrations, π_i and π_L , were again equal.¹⁹ Another possibility involves the effect of an increased volume of capillary filtrate on tissue pressure (P_i). The end result would depend upon the compliance of the interstitial gel, but the data in this regard are based primarily on *in-vitro* analogs or on indirect measurements of limb volume. Claims have been advanced for both low²⁰ and high²¹ interstitial compliance. It should be kept in mind that only a small pressure difference (1–2 cm H₂O) would suffice to shift the necessary volumes of fluid. Direct measurements with micropipettes indicate that a positive pressure of as little as 1 cm H₂O is sufficient to open or to close the valve leaflets of the larger lymph channels into which the terminal vessels drain.

CAPILLARY PRESSURE (P_c)

Under normal conditions, the pressure drop across the microvascular bed is 8–10 mm Hg, the actual driving pressure being about 28–32 mm Hg on the arterial side and 18–22 mm Hg on the venous side. It should be pointed out that there is good evidence²² that the capillary vessels on the venous side of the microcirculation have a higher permeability coefficient (on the average 3×)

TABLE I. Microcirculatory Derangements in Low-flow States

Reduced volume flow
Nonselective distribution of blood
Nutritional shunting (O ₂ extraction down)
Transcapillary fluid exchange unbalanced
Lymph drainage reduced
No local autoregulation—terminal vascular bed passive
Venular stasis
Permeability of capillary barrier impaired

than vessels on the arterial side. The system is thus structured to maintain a uniform loss of fluid by filtration along the length of the capillary vessels, the gradual fall in pressure being counterbalanced by the higher hydrodynamic conductivity of the vessel barrier. Conditions which interfere with flow and pressure relationships on the postcapillary, venular side would tend to favor filtration throughout the system. Capillary pressure as measured by direct intubation with a micropipette is, on the average, 4–5 mm Hg above the level of the plasma colloid osmotic pressure. Venular or postcapillary pressures are about equivalent to π_p . The determining factor favoring filtration or absorption would thus appear to be the concentration of plasma proteins in the interstitial compartment. Under normal conditions, the amount of protein in the interstitium is comparatively small (about 10–20 per cent of that in the plasma). With the marked reduction of lymph flow during shock, protein will tend to accumulate and will reduce accordingly the absorption of fluid from the tissue.

It has been assumed that with the development of shock, capillary pressure (P_c) falls in accord with the reduction in arterial pressure (P_A). As shown in figure 2, this has not been found to be the case, since the trend for P_c to fall is countered by local regulatory mechanisms. Thus, in the splanchnic mesentery, direct recording of micropressures shows that even when P_A is reduced by as much as 50 per cent, P_c is readjusted to within 10 per cent of control levels. After several hours of hypotension, P_c becomes much more variable and cannot be stabilized. It is at this stage that capillary flow becomes erratic. In some portions of

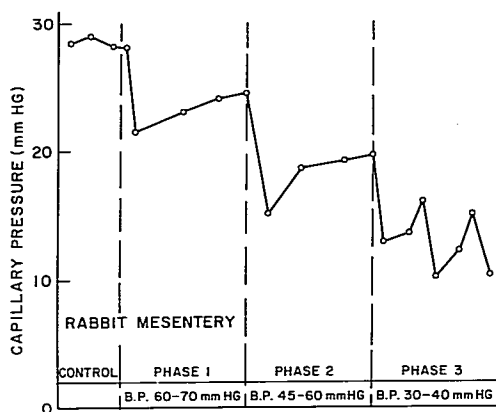


FIG. 2. Local regulation of capillary pressure after hemorrhage. Direct measurement of capillary pressure in the mid-portion of the network of the mesentery during hemorrhage. The P_c shows a tendency to maintain a given level immediately after hemorrhage and then falls to a lower level (phase 2) when the systemic pressure develops a continuous downward course. During the final stages, when capillary blood flow is erratic, P_c becomes erratic also. (Based on 19 continuous records.)

the network, venular outflow is almost at a standstill. When the systemic mean pressure remains below 45 mm Hg, P_c falls to near venous levels (14–18 mm Hg) due in large part to the almost complete closure of the terminal arterioles.

PLASMA COLLOID OSMOTIC PRESSURE (π_{pl})

With the onset of hypotension, there is a fairly rapid reduction in plasma colloid osmotic pressure (π_{pl}) from 26–30 mm Hg to as low as 12–15 mm Hg. Throughout the greater portion of the hypotensive period, π_{pl} remains at this low level, but after several hours (2.5 to 4 hours depending upon the PA), the colloid osmotic pressure of the plasma begins a continued upward trend (fig. 1). This increase appears to be related to the loss of intravascular fluid, as evidenced by a comparable rise in the hematocrit at this time. It is interesting that this secondary shift of fluid out of the vascular compartment occurs at a time when the blood volume is already drastically reduced. Since the hemodilution process involves about a 10–15 per cent change in π_{pl} , this reversal towards normal levels during the later stage of the syndrome represents a corresponding reduction of the circulating blood volume.

Not much information exists regarding the specific tissues from which the fluid is sequestered during hemodilution. The splanchnic viscera have been found to be the major tissue contributing fluid. This was clearly shown in animals subjected to subtotal resection of the gastrointestinal tract.²³ The splanchnic viscera have been implicated for the most part in the decompensatory phase of the shock syndrome as a site for the release of toxins and the sequestration of blood.²⁴ These tissues obviously have an important compensatory function as well.

The term “hemoconcentration,” as applied to traumatic and septic shock, has been used clinically on the basis of changes in the erythrocyte hematocrit. When, in addition, plasma colloid osmotic pressure is followed, fluid shifts can be seen to pass through several phases. Initially, there is a rapid hemodilution in which both plasma colloid osmotic pressure and hematocrit show identical courses. Hemodilution then slows considerably, and after 50–60 minutes, π_{pl} plateaus out and remains 20–25 per cent below normal. When hypotension persists for more than 2–3 hours, π_{pl} begins to increase again. During this reversal, the erythrocyte hematocrit shows a similar course, indicating that the phenomenon is due to transcapillary fluid shifts.

During the terminal phases of the hemorrhagic shock syndrome, the hematocrit and plasma colloid osmotic pressure show opposing trends, probably because of a regional loss of plasma through increased capillary permeability.

TISSUE FACTORS (P_t , π_t)

The general attrition characteristic of the shock syndrome leads to a distortion of extravascular factors which contributes significantly to the inability of the microcirculation to maintain balanced fluid exchange. There is still a good deal of uncertainty regarding the source and the physiologic significance of "tissue pressure." The work of Guyton²⁵ with implanted capsules and that of Scholander and Hargens²⁶ and Snashall *et al.*²⁷ with the cotton wick procedure suggest that the interstitial gel is under subatmospheric pressures as low as minus 6–8 mm Hg. Recent studies^{28,29} have shown that tissue pressures measured with subcutaneously implanted cotton wicks initially were between –1 and –2 mm Hg, and following hemorrhage fell to as low as –10 mm Hg. The validity of this method for estimating tissue pressure has been challenged, but from a purely physical point of view there is little doubt that such a phenomenon is possible. For example, it has been found³⁰ that negative pressures develop in hyaluronic acid gels when they are dehydrated (analogous to the absorption of tissue fluid during hemodilution).

The basic question in dispute is the amount of mobile or free water in the interstitial gel.²⁹ Aside from major differences in the various tissues, time-dependent or pathophysiologic variations undoubtedly exist so that *in-vitro* measurements of swelling of tissues such as skin³¹ cannot be accepted as representing *in-situ* conditions. A small volume of fluid can be removed from gels with a pressure differential of as little as 1–2 cm H₂O; beyond this point, water can be shifted with great difficulty only by using applied pressures beyond the range believed to be present in biologic systems of this kind. The ability of gels to swell has been equated with the movement of fluid between

blood and tissue compartments. Such analogues do not take into account the time factors involved—days for imbibition to reach equilibrium and seconds or fractions of seconds for transepillary flux to reach equilibrium conditions. Some investigators³¹ believe the factor influencing fluid movement in the interstitium proper is the colloid osmotic pressure generated by the large hyaluronic acid molecules and the plasma proteins. Still unresolved is the precise significance of hydrostatic pressure in a multicompartmental gel and its relationship to the movement of fluid into and out of the blood capillary network.

Thus, during the initial phase of the syndrome, fluid absorption from the tissue is favored by capillary ischemia and an intermittency associated with precapillary vasomotion. With time, however, capillary ischemia is replaced by an overall slowed flow involving most of the capillaries. During this changeover, P_c rises and approaches near-normal levels. The combined effect of an elevated P_c and a greater surface area for exchange, together with a low plasma protein level (20–25 per cent below normal) is a small but sustained net filtration. Another factor contributing to the extravascular loss of fluid may be the uptake of water by the parenchymal cells after several hours of stagnant hypoxia.³²

A comparison of the changes in capillary pressure with those in colloid osmotic pressure under the influence of acute hemorrhage is shown in figure 3. It is obvious that in the mesentery the average P_c is slightly higher than π_{pi} under normal conditions. With blood loss, average capillary pressures are proportionately lower than the corresponding colloid osmotic pressures. On this basis alone, one would estimate a moderate bias in favor of filtration under control conditions and fluid absorption following hemorrhage. Obviously, other factors must be taken into consideration, in particular the distribution of pressures within the network. Such an analysis must also take into account extravascular factors (P_t and π_t). However, the fact that P_c and π_{pi} values are clustered about the ideal line of balance again points to the importance of the remaining elements in the Starling constitutive equation governing fluid movement through the capillary wall.

The impaired functional status of the microcirculation becomes much more apparent following blood replacement. Except for a few areas where vascular stasis developed earlier, the positive effect of the increased blood volume, the elevated cardiac output, and the near-normal blood pressure is mirrored in the microcirculation by a plethoric flow through all available channels. This is in large part due to precapillary dilation of such extent that with a PA of only 80–85 mm Hg, capillary pressures averaged as high as 40–45 mm Hg. Because of the large volume of infused blood with a normal protein content, the π_{pl} is brought within the normal range (–10 per cent). There is, however, no indication of any local adjustment either to restrict blood flow or to bring capillary and venular pressures down to normal levels for at least 3–4 hours.

TERMINAL LYMPHATICS

As indicated in Equation 2, one of the parameters which must be taken into account in analyses of transepillary fluid exchange is the colloid osmotic pressure of the interstitial compartment. The small concentration of plasma proteins which permeates the microcirculatory barrier presumably remains reasonably constant under normal conditions. There are no measurements of the colloid osmotic pressure in the interstitium. Estimates of π_i have been made on the basis of the protein content of lymph samples taken from the major lymph ducts,³³ but these are undoubtedly not accurate since, as pointed out, the lymph fluid becomes concentrated during its passage along the terminal lymphatics.

Several possible interpretations have been advanced to account for the formation of lymph fluid. The conventional one is that a considerable volume of fluid is filtered across the microcirculatory network into the interstitial compartment and that about 80–90 per cent of this fluid is absorbed on the venous side of the capillary bed. This would leave an excess of about 10–20 per cent which is then handled by the lymphatic drainage. The above explanation is based on a comparatively high filtration coefficient, as established by plethysmographic and isogravimetric procedures. Recent work³⁴ has

questioned the validity of such high filtration coefficients and suggests that they may be as much as 10× higher than is actually the case. An alternative interpretation³⁵ would be that under steady-state conditions, there is a slow, steady filtration across the entire capillary network and that the volume of fluid filtered represents the volume which enters the lymphatic capillaries and is drained away. According to this point of view, the net flux in the direction of transepillary filtration sets up a gradient in the interstitium which results in the continuous movement of fluid into the terminal lymphatic capillaries. As discussed in another section, this force can either be hydrostatic or osmotic, with a differential only as small as 1–2 cm H₂O needed.

Lymph fluid is transported from the terminal lymphatic capillaries into the collecting channels, which are made up of a series of closed segments bounded by proximal and distal valve leaflets. The walls of these initial collecting channels are thicker and in many tissues contain smooth muscle, as manifest by their spontaneous contractions. Pressure in these successive intervalve segments of the collecting lymphatics becomes higher until a P_L of 10–12 cm H₂O is reached before they empty into the largest lymph vessels (200–250 μ) in the tissue proper.³⁶ Microinjection studies with dye-tagged albumin solutions indicate a marked difference in the permeability of the lymphatic capillaries and the collecting lymph channels.³⁷ Protein diffuses freely from the lymphatic terminal capillaries into the interstitium, but is retained within the larger collecting channels, while low-molecular-weight dyes permeate both of these lymph vessel barriers.

It can be appreciated that the lymph fluid, during its slow convective transport through the series of collecting channels, is under a substantial positive pressure. These two circumstances create a situation which should favor fluid filtration across the lymphatic barrier back into the interstitium proper. It is proposed that in this way the potential lymph fluid is gradually concentrated, depending upon the actual lymphatic pressure and the rate of lymph flow.

Actual lymph flow has been measured by collecting fluid from the major lymphatic

ducts, or regionally from the appropriate effluent duct (e.g., hind limb, kidney). The volume of peripheral lymph during hemorrhagic shock falls abruptly to extremely low levels.³⁸ Direct measurements of lymphatic capillary pressures (P_L) during this stage show that P_L falls from control values of 1 to 3 cm H₂O to as low as zero or even 2-3 cm H₂O below atmospheric pressure. A further indication of the progressive impairment of the microcirculation with protracted hypotension is seen in the fact that P_L values rise to as high as 5-8 cm H₂O after blood replacement during the terminal or so-called "irreversible" phase of hemorrhagic shock.

It has been found that the protein concentration of lymph fluid collected from the large lymph ducts becomes proportionately smaller as the rate of transcapillary filtration is increased, and conversely, lymph has a higher concentration of protein as filtration is reduced. It is this continuous removal of fluid and protein from the interstitium that is essential for achieving a steady-state fluid balance between the blood and tissue compartments under normal conditions. Unfortunately, there is no acceptable way to determine the extent to which the fluid leaving the tissue has been concentrated during its movement along the collecting channels of the lymphatic system. It would be a gross oversimplification to assume that lymph duct values are a true reflection of the interstitial fluid composition. During shock, not only is the total lymph flow markedly reduced, but under many conditions even the A:G ratio of the lymph proteins is changed.

Because of the high permeability of the lymphatic endothelium,³⁹ it is believed that colloids, such as plasma proteins, are evenly distributed so that osmotic forces in the tissue proper and the lymphatic capillaries are the same. This leaves some type of hydrostatic gradient as the probable mechanism under steady-state conditions for the movement of interstitial fluid into the terminal lymphatics.

Tissue protein is continuously removed by the lymph in relation to the fluid filtered from the capillaries. The precise concentration of protein will depend upon the rate of transcapillary filtration, as opposed to the rate of influx into the lymphatic capillaries.

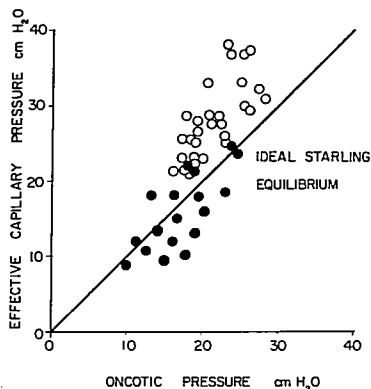


FIG. 3. A plot comparing P_e and its associated π_{av} in different animals subjected to hemorrhage. The open circles are controls and the solid circles the values after hemorrhage. Note that the controls and post-hemorrhage ratios form discrete clusters on either side of the idealized line of equality. See text for discussion.

Some positive gradient must be responsible for the movement of interstitial fluid into the terminal lymphatics. Such a driving force can arise either in the interstitium proper (via a net positive hydrostatic pressure) or as a consequence of some form of active pumping (based on the spontaneous contractile behavior of the collecting valve containing lymphatic channels). Reconstructions of the relative number and size of blood capillaries versus lymphatic capillaries per unit tissue mass indicate that the surface area for exchange is almost 100 per cent greater for the terminal lymphatics in tissues such as the mesentery or omentum. Only a comparatively small gradient or pressure difference is needed to transfer the volume of fluid involved in such exchange.

The other alternative would be the contraction of the collecting lymphatics (either active or passive) to set up essentially a pumping action. Baez⁴⁰ and others⁴¹ have shown that the muscular lymph channels undergo periodic spontaneous narrowing during the early phases of hemorrhagic hypotension coincident with periods of hemodilu-

tion. This activity then falls off rapidly and after 1–2 hours, no vasomotion of the lymphatic channels is observed. Here again, only a small differential is needed to move the interstitial fluid into the terminal lymphatics and up the series of lymphatic valves.

It has been assumed that tissue pressure and the protein concentration in the interstitial compartment are reciprocally related so that an increase in one is matched by a comparable decrease in the other factor. The flaw in this line of reasoning is that there is no evidence that tissue compliance (and thereby tissue pressure) will result in a change in tissue pressure with the volume of fluid shifted by an increased or a decreased filtration across the blood capillaries. Likewise, the extent to which tissue protein will be concentrated or diluted by transcapillary fluid movement remains purely conjectural, inasmuch as the actual volumes involved under these conditions are not known.

Therapeutic Implications

The inability of local regulatory mechanisms to provide active support to tissue perfusion is perhaps the single most serious consequence of protracted oligemia. It basically derives from the fact that the stagnant hypoxia has damaged the smooth muscle motor effector unit. Such damage may range from simple depletion of amine transmitter stores to interference with ion regulation and a shift in resting membrane potential. In addition, with restoration of blood flow by blood replacement, microvascular smooth muscle is programmed to respond to local environmental factors and will remain relaxed until the effects of anaerobic metabolism on the tissue parenchyma have been fully remedied.

Present therapy for patients in shock is directed towards a mechanical improvement in venous return to the heart, thereby, through elevation of systemic pressure, to open up the peripheral circulation. Provided the syndrome has not accrued too excessive a metabolic debt, the improved tissue perfusion should allow for a recovery of cell metabolism and permit vascular regulatory mechanisms to become operative again. It can be appreciated that when as a consequence of

protracted hypotension such a defect is widespread, there would be a continuous and substantial trend for net filtration and an unremitting undermining of the effective circulating blood volume. What is needed are measurements or indices which reflect the extent of the peripheral circulatory insufficiency in particular tissues or areas (e.g., venous blood from different regions).

With restoration of blood volume by transfusion, the mechanical elevation of systemic pressure will increase peripheral blood flow, but in individuals suffering from protracted hypotension this is accompanied by an abnormal ratio of pre- to postcapillary resistances and, in turn, by atypical P_e values. In the context of the present discussion on fluid exchange, it can be seen that a balanced Starling relationship will depend not only on appropriate P_e levels but on the surface area available for exchange. All of the observations in animals and in man indicate that fluid replacement measures do not necessarily restore peripheral or nutritional flow. This defect has not been explored in sufficient detail to warrant other than an approximation as to its origins.

Among the important physical factors which influence blood flow, the properties of the blood itself represent an important consideration at the capillary level. Not only is the actual hematocrit an important rheologic factor, but the deformability of the erythrocytes⁴² and the extent of aggregation at the low shear rates which are present during shock⁴³ have the potential to contribute to the disturbed pressure-flow relationship. The end result will thus depend upon the extent to which these many factors are involved and will be reflected in various degree in different tissues because of peculiarities of pattern, branching, distribution of smooth muscle, neurohumoral control, etc. No definitive therapy for the correction of such specific defects exists.

Another complication of sustained hypoxia is the possible impairment of capillary permeability in key organs. Although an overt increase in permeability is not seen in most organs, even a modest change would become a formidable handicap under the marginal conditions which prevail during shock. In tissues which have suffered such damage,

the restoration of blood flow and the associated increase in hydrostatic pressure would lead to excessive filtration and an increased loss of plasma proteins into the interstitial compartment. It would be anticipated that tissues which are flexible in terms of volume flow regulation (heart, skeletal muscle) would be less vulnerable to the exacerbating effects of changes in the flow properties of blood. In some sites, such as the intestinal tract, the local microcirculation may be compromised by short-circuiting (physiologic shunting). Still others, such as the skin and kidneys, have extensive vascular beds over and above their own nutritional needs and are subservient to central functions such as temperature control and excretory homeostasis. They should, therefore, be less susceptible to simple mechanical disruption of capillary flow and its attendant impact on cellular integrity.

Many reports¹⁴ emphasize the susceptibility of organs such as the heart, liver, and intestinal tract to stagnant hypoxia. In a similar context, the coronary circulation and the myocardial cells have been cited as primary targets for "toxic" materials during various forms of shock. The work of Fine and collaborators²¹ has emphasized endotoxemia and an attendant suppression of the functional capacity of the reticuloendothelial system to handle such materials as a key factor contributing to the inability of the cardiovascular system to be restored by blood replacement measures alone.

That there are as many concepts of the etiology of shock as there are experimental models points to the syndrome as a disease with a broad spectrum of contributing factors which are difficult to recognize, but must be singled out before therapeutic measures can be directed towards their resolution.

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