Chapter 4
The Peritoneal Microcirculation in Peritoneal Dialysis

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The peritoneal microcirculation is an intricate microvascular network through which physiological interactions occur between the systemic vasculature and the peritoneal cavity. In peritoneal dialysis these dynamic interactions are of paramount importance in maintaining effective dialysis. The peritoneal microcirculation participates in numerous physiological functions including solute transfer and exchange, regulation of fluid dynamics and ultrafiltration, delivery of nutrients and hormones, delivery of leukocytes to areas of inflammation, and distribution of drugs. Physiological and pathophysiological changes, as well as the process of peritoneal dialysis, may affect many of these microvascular functions. The emphasis of this chapter will be to review available information regarding the peritoneal microcirculation and to integrate this information into a general functional knowledge as it relates to peritoneal dialysis. The chapter will examine: 1) the functional anatomy and blood supply of the peritoneum, 2) components of the peritoneal microvascular network, 3) peritoneal microvascular hemodynamics and the effects of vasoactive agents on the microcirculation, and 4) inflammation in the peritoneal microcirculation with emphasis on leukocyte-endothelial interactions.

Overview of the Functional Anatomy and Blood Supply of the Peritoneum

Functional Anatomy of the Parietal and Visceral Peritoneum

The peritoneum is a large, intricately arranged serous membrane that lines the abdominal wall (parietal peritoneum) and visceral organs of the abdominal cavity (visceral peritoneum). The peritoneal cavity is the potential space between the parietal and visceral layers of peritoneum [1]. The primary purpose of the peritoneum is to provide a smooth surface over which the abdominal viscera may easily move [2]. Normally, the peritoneal cavity contains less than 100 mL of fluid but can accommodate a more than 20-fold increase without patient discomfort [3]. The peritoneal cavity is lined by a layer of mesothelial cells on a connective tissue base that is perfused with blood and lymphatic vessels. Specialized regions of peritoneum, the omenta and mesenteries, are double-layer folds of peritoneum that connect certain viscera to the posterior abdominal wall or to each other. For example, the greater omentum extends from the greater curvature of the stomach to attach to the transverse colon. Specific double-layered peritoneal folds attach solid viscera to the abdominal wall (e.g., the falciform ligament of the liver). The total surface area of the peritoneum in adults approximates the surface area of skin (1–2 m^2) [4]. However, the effective surface of the peritoneal membrane may be below 1 m^2, and can be further reduced as a result of adhesions or prior abdominal surgery [5, 6]. The visceral peritoneum accounts for the majority of the total peritoneal membrane surface area [7, 8]. About 60% of the peritoneal surface can be ascribed to the mesentery of the esophageal-rectal viscera, 15% covers the liver, and 15% is parietal [8]. Considering that most of the surface area is composed of visceral peritoneum, one might intuitively suspect that the contribution of the visceral peritoneum to total peritoneal membrane exchange would predominate over that contribution made by the parietal peritoneum. However, animal studies have suggested that the contribution of the visceral peritoneum to peritoneal exchange is less than would be predicted from the relative anatomical surface area. For example, eviscerated rats exhibit only slight reductions in peritoneal absorption rates for urea, creatinine, glucose, and inulin relative to control animals [9]. Studies in other evisceration animal models have shown similar findings with reductions in peritoneal mass transport of small solutes by only 10–30% [10–14]. In these eviscerated animal models, contact between the dialysate and the parietal peritoneal membrane may be improved, thus

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contributing to these findings. Other conditions may improve transport across the visceral peritoneum. Small solute mass transfer is significantly enhanced with vibration in the intact rat (i.e., with the visceral peritoneum intact), but only marginally improved in the eviscerated animal. With vibration, improved dialysate to visceral membrane contact is thought to occur. Based on these animal studies it has been proposed that the parietal peritoneum can significantly contribute to small solute transport, and that visceral peritoneal transport may be improved when contact is enhanced between visceral peritoneal surfaces and dialysis solutions [15]. The correlation of these animal findings to clinical peritoneal dialysis currently remains speculative, but these results suggest that the relative contribution of the visceral and parietal peritoneum to small solute mass transport may not necessarily correlate to anatomical surface area.

Blood Supply to the Peritoneum

The vascular and lymphatic systems supplying the peritoneal membrane and intraperitoneal organs constitute a complex and efficient system for fluid and solute delivery to the peritoneum. The arterial blood supply to the visceral peritoneum and intraperitoneal organs arises from the coeliac, superior mesenteric, and inferior mesenteric arteries. The arterial blood supply to the parietal peritoneum and underlying musculature arises from the circumflex, iliac, lumbar, intercostal, and epigastric arteries. The veins draining the visceral peritoneum and intraperitoneal organs empty into the portal vein, while the venous system of the parietal peritoneum empties into the systemic veins. A potentially important consequence of this venous vascular arrangement is that drugs and other solutes that are absorbed across the visceral peritoneum are subject to hepatic metabolism. Pharmacological studies have shown intraperitoneal administration of compounds such as atropine, caffeine, glucose, glycine, and progesterone and some intraperitoneally administered vasoactive drugs are subject to metabolism by the liver [16, 17]. Another important example is insulin, which may be absorbed through the portal circulation and a significant portion degraded through first-pass metabolism by the liver [18, 19]. Thus, the pharmacokinetic effects of hepatic first-pass metabolism may play an important role in the systemic availability of some intraperitoneally administered substances.

Summary

In summary, animal studies suggest that the contribution of the visceral and parietal peritoneal membrane to total solute transport may not necessary correlate to anatomical surface area. The importance of contact between peritoneal tissue and dialysis solutions was suggested both in the eviscerated animal model and in studies of the effect of vibration on solute transport in the intact animal model. The general vascular supply to the peritoneum was reviewed and the potential importance of the portal venous drainage was presented.

The Peritoneal Microvascular Network

Peritoneal Microvascular Architecture

The large vessels supplying blood to the visceral peritoneum function primarily as conduits to supply blood to the visceral organs. As the large vessels course through the mesentery they divide and reflect over the bowel surface forming capillary beds, which can presumably participate in transperitoneal solute and fluid exchange. Over 50 years ago, Chambers and Zweifach described the topography of the mesenteric microcirculation [20]. The typical capillary network consists of arterioles, terminal arterioles, precapillary sphincters, arteriovenous anastomoses, throughfare channels, capillaries, postcapillary venules, and venules (Fig. 4.1) [21]. Arterioles and throughfare channels modulate blood flow into the network, while precapillary sphincters regulate blood flow to single capillaries. Arteriovenous anastomoses can divert blood flow from arterioles directly into venules, thereby bypassing capillary networks. The flow through a capillary network can be extremely variable with individual capillary flow starting, stopping, and sometimes reversing direction [22, 23]. In baseline circumstances, only 25–50% of capillaries are perfused. Capillary recruitment increases perfused capillary density and increases surface area for potential exchange processes. Capillary recruitment may occur to meet metabolic demands, as a result of certain vasoactive agents or in response to exposure to peritoneal dialysate [24]. The architecture of the peritoneal microvasculature in animal models has been previously reviewed by Miller [25]. The visceral microvasculature may be visualized on the mesenteric surface and includes abundant arterial and venular arcades that may function to equalize flow during periods of bowel compression. The

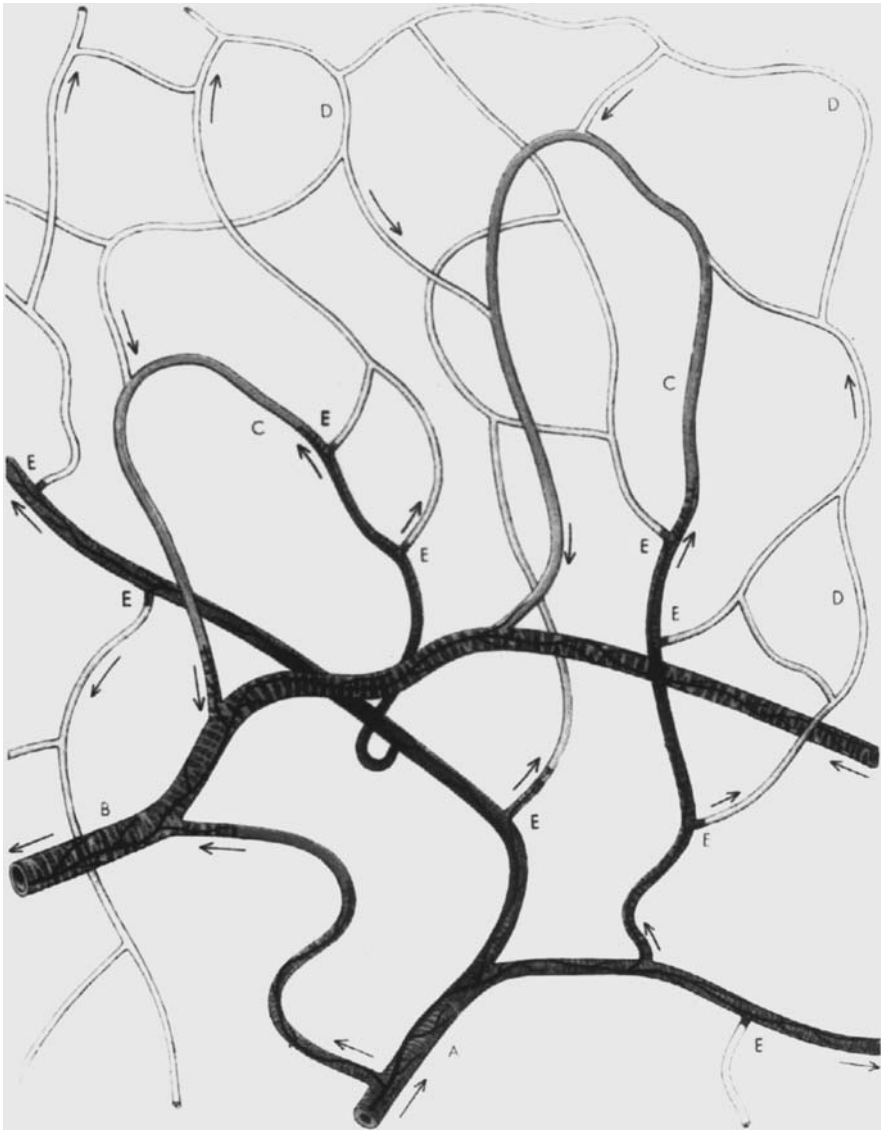

Fig. 4.1 Structural elements of a typical mesenteric microcirculatory bed. A = arteriole, B = venule, C = thoroughfare channel, D = capillary, E = capillary sphincter [21]

parietal microvasculature may be represented by the vascular supply to the cremaster muscle, since this muscle extends from the abdominal wall musculature. Features of the cremaster microcirculation include the absence of short artery to vein anastomoses and the formation of arteriolar and venular arcades from which capillaries may arise [25–27].

Arterioles

The arterioles are the major site of microvascular resistance and regulate flow to capillary beds. Arterioles are lined by endothelial cells resting on a basal lamina surrounded by a layer of smooth muscle cells. Terminal arterioles may participate in the exchange process as they have a discontinuous muscle layer and portions of these vessels are lined only by endothelium and basement membrane. However, the relative contribution to overall peritoneal transport is minimal since the surface area and permeability of these vessels are much less than in capillaries and postcapillary venules. The distal smooth muscle layer of an arteriole may extend to form a ring around the site of capillary origin. This area is termed a precapillary sphincter and regulates flow to single capillaries. Marked arteriolar vasoconstriction can completely close the vascular lumen, resulting in no flow to its capillary distribution [28]. Figure 4.2 illustrates the hemodynamic pressure profiles and demonstrates that the greatest slope for microvascular pressure change occurs in

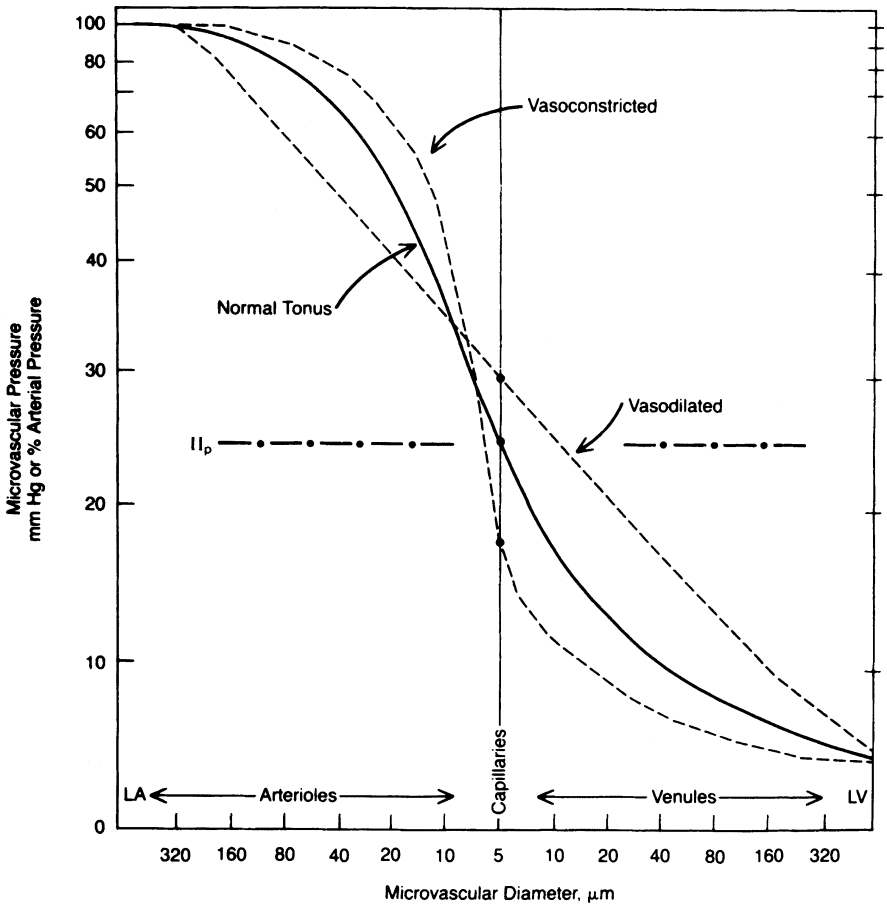

Fig. 4.2 Microvascular pressure profiles as related to microvascular diameter. The dotted lines represent changes in microvascular pressure that occur with vasoconstriction and vasodilation [29]

arterioles 8–40 μm in diameter [29]. This figure also illustrates the pressure changes associated with vasoconstriction and vasodilation and the typical microvessel size gradations for arterioles, capillaries, and venules.

Capillaries

In the peritoneal microvascular network capillaries are the principal sites for solute and fluid exchange [30, 31]. The wall of the capillary is composed of an endothelium and a basal lamina. Capillary size is approximately 5–8 μm, which is large enough to let red blood cells (average diameter 7.5 μm) through, usually one at a time and with some deformity [28]. The capillaries have no smooth muscle and do not vasoactively participate in blood flow regulation. There are three types of capillary endothelium present in the mesenteric area: 1) continuous endothelium as in the peritoneal vessels, 2) fenestrated endothelium as in the intestinal villi, and 3) discontinuous endothelium as found in the liver sinusoids [25]. The properties of peritoneal capillary transport will be reviewed in the following chapter.

Postcapillary Venules

The postcapillary venules participate in fluid and solute exchange, are an important site for microvascular leukocyte adhesion, and may demonstrate dramatic changes in permeability during inflammatory conditions. Small venules that are located just distal to the capillaries are often termed postcapillary venules. Postcapillary venules are generally 10–40 μm in diameter and are composed of endothelial cells resting on a basal lamina surrounded by pericytes with larger venules enclosed by muscular media [32].

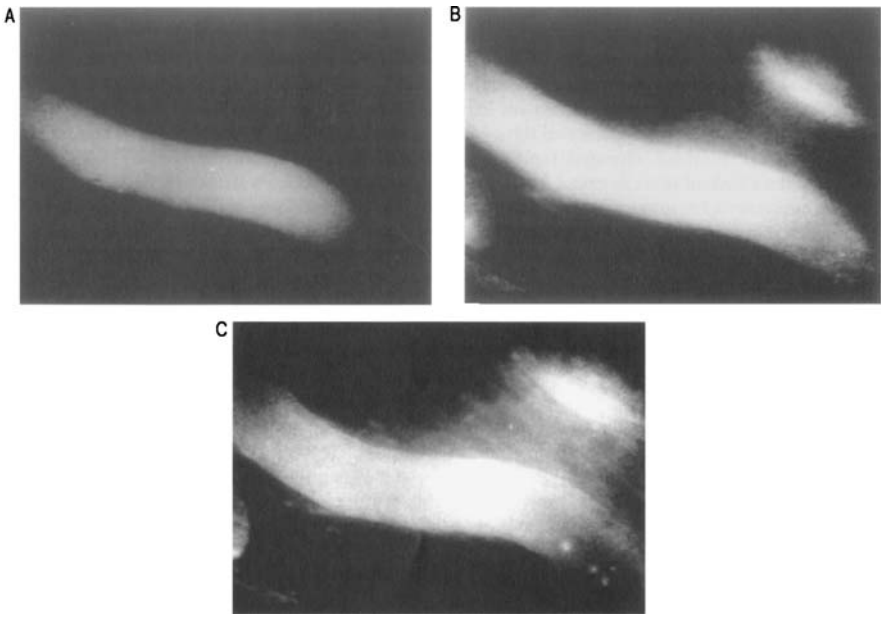

Fig. 4.3 Fluorescence photomicrograph of the mesenteric microcirculation demonstrating the effects of vascular endothelial growth factor (VEGF) on permeability in the rat mesentery. (**a**) No significant leakage of FITC-labeled albumin during basal conditions. (**b**) Superfusion of VEGF (660 pm) induces albumin leakage from the microcirculation after only 10 min of exposure. (**c**) Albumin leakage into the interstitium continues to progress after 20 min of exposure to VEGF. Photomicrograph courtesy of N. Yount, S. Ram, and R. White

Significant changes in microvascular permeability can occur in postcapillary venules. Numerous vasoactive agents, cytokines, and drugs may induce changes in permeability. Histamine, bradykinin, platelet-activating factor, vascular endothelial growth factor (VEGF), certain components of the complement cascade, and drugs such as nitroprusside are examples of agents that can affect mesenteric microvascular permeability [33–40]. For example, Fig. 4.3 demonstrates the effects of vascular permeability factor on albumin permeability in a mesenteric postcapillary venule.

Intravital microscopic studies have demonstrated that the attachment and migration of leukocytes from the vascular space to the extravascular space is localized primarily to postcapillary venules [41–45]. The mechanisms and determinants of intraperitoneal leukocyte migration will be discussed in detail later in this chapter.

Endothelium

The microvascular endothelium has a central regulatory role in microvascular physiology [46–48]. Endothelial-derived substances regulate microvascular hemodynamics, thrombogenesis, fibrinolysis, and leukocyte adhesion. Endothelial cells actively regulate basal vascular tone and vascular reactivity in physiological and pathological conditions, by responding to mechanical forces and neurohumoral mediators with the release of a variety of relaxing and contracting factors. The endothelium-derived relaxing factors include nitric oxide (NO), prostacyclin, and an, as yet elusive, endothelium-derived hyperpolarizing factor (EDHF) [49]. NO is a diffusible, labile gas with a short biological half-life (seconds) [46, 50]. NO is synthesized from L-arginine by a family of enzymes known as nitric oxide synthases (NOS), namely neuronal NOS (nNOS or NOS1), inducible NOS (iNOS or NOS2), and endothelial NOS (eNOS or NOS3). The eNOS is a constitutive, calcium–calmodulin dependent enzyme [50–52]. Once NO is produced in the endothelium it diffuses to the smooth muscle cells and produces smooth muscle relaxation via a cGMP-dependent mechanism [53]. All three NOS isoforms are present in the peritoneal membrane and can be upregulated in response to specific pathophysiologic circumstances [54]. NO production can be inhibited by several exogenous L-arginine analogues such as N^G-monomethyl-L-argine (L-NMMA), N^G-nitro-L-arginine methyl ester (L-NAME), and endogenous arginine analogues such as N^G, N^G-dimethylarginine (ADMA or asymmetrical dimethylarginine) [55–57]. Interestingly, ADMA and other guanidino compounds that inhibit NO production have been shown to accumulate in renal failure [56], although this cannot entirely explain the endothelial dysfunction observed in uremia [58]. Inhibition of NO synthesis produces mesenteric arteriolar vasoconstriction (Fig. 4.4) [59, 60]. This demonstrates that basal levels of NO are important in maintaining normal microvascular tone in the mesenteric microcirculation.

Although NO has generally been considered to be the principal mediator of endothelium-dependent relaxations, evidence is mounting that EDHF is a major determinant of vascular tone, especially in small resistance vessels, like the mesenteric arteries. These vessels control tissue perfusion and thus may be of larger physiological relevance than conductance arteries. The nature of EDHF is still not entirely elucidated [61]. Current evidence suggests that

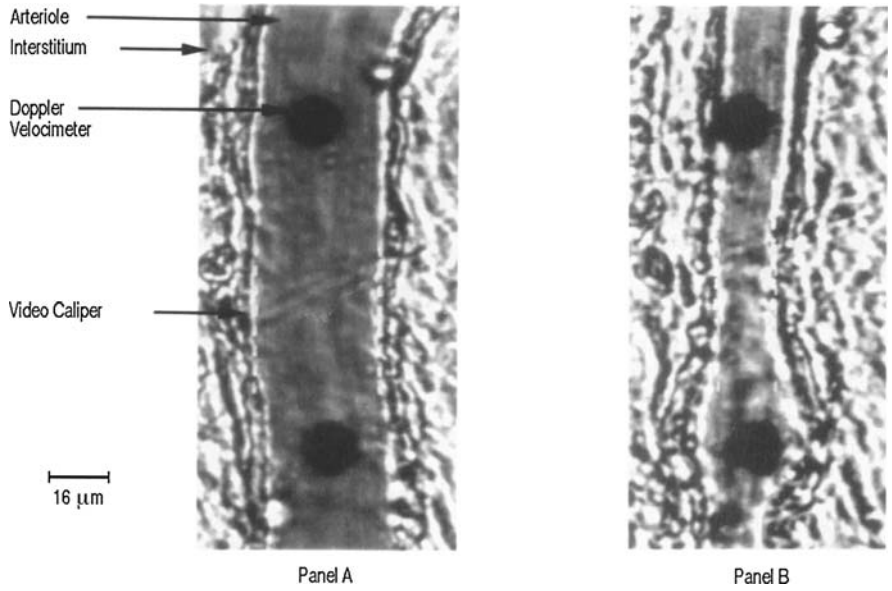

Fig. 4.4 Hemodynamic effect of a nitric oxide synthesis inhibitor (ADMA) on an arteriole in the mesenteric microcirculation in the rat. (**a**) The arteriole during basal conditions with superfusion of a buffer solution. (**b**) ADMA (100 μm) added to the buffer solution induces marked arteriolar vasoconstriction. This demonstrates that basal levels of NO are important in maintaining normal microvascular tone in the mesenteric microcirculation [60]

EDHF-mediated responses are initiated by activation of endothelial K^+ channels with resultant hyperpolarization of endothelial cells. This endothelial hyperpolarization spreads to the underlying smooth muscle layer through myoendothelial gap junctions, or the efflux of K^+ from the endothelial cells elicits hyperpolarization of the adjacent smooth muscle cells. Epoxyeicosatrienoic acids likely have a regulatory role in this pathway. The contribution of EDHF to relaxation is dependent on vessel size, being more prominent in smaller arteries than in larger ones. Although the effect of peritoneal dialysis on the EDHF-mediated responses has not been directly studied, both the uremic state [62] as well as exposure to high glucose concentrations [63] are known to affect EDHF-mediated relaxations. Disturbance of this pathway may thus contribute to altered vascular reactivity in the peritoneal circulation of patients undergoing peritoneal dialysis.

An important constricting factor produced by the endothelium is the potent vasoconstrictor endothelin. The endothelins (ET) are a family of amino acid peptides with diverse and overlapping biological activity. Three isoforms exist: ET-1, ET-2, ET-3 [62–66]. Two human ET receptors have been cloned: ET_A and ET_B. ET_A receptors bind ET-1 > ET-2 > ET-3, whereas ET_B receptors bind these three ET with approximate equal affinity [67–69]. ET-1 is the most potent vasoconstrictor produced by the endothelium and induces sustained, intense vasoconstriction. ET-1 has a short circulating half-life, but the effects may be sustained due to the slow dissociation of the bound peptide from its receptor [66]. In general, ET activates phospholipase C and increases the production of inositol trisphosphate, which mobilizes calcium from the endoplasmic reticulum. ET can also activate calcium channels that allow for the influx of calcium into the cytosol [70]. ET-1 produces vasoconstriction in both mesenteric arterioles and venules [71, 72]. Intravital microscopic observations of mesenteric arterioles have shown that ET-1 can completely arrest blood flow in the microcirculation. ET-1 in small concentrations attached to ET_B may produce mild vasodilation through the release of NO and prostacyclin from endothelial cells, thus forming a potential feedback mechanism [46, 73]. Levels of ET have been shown to be elevated in ESRD, and ET-1 is present in the peritoneal dialysis effluent of PD patients [74]. The relevance of some of these findings as it relates to peritoneal dialysis will be discussed in the next section.

NO and ET also have effects in modulating inflammatory processes. Inhibition of NO production is proinflammatory, as evidenced by an increase in the number of adherent leukocytes in postcapillary venules [75]. ET-1 is a proinflammatory cytokine and in cell culture, ET-1 stimulates neutrophil adhesion to endothelial cell monolayers [76]. ET-1 increases the in vitro endothelial expression of E-selectin [77]. In vivo observations in the mesenteric microcirculation have shown that ET-1 increases leukocyte rolling in postcapillary venules [78].

The endothelium produces both growth promoters and growth inhibitors. An intact endothelium protects the microvascular wall from processes such as intimal hyperplasia, which can occur when the endothelium is disrupted and smooth muscle growth factors are released. NO, heparin sulphates, and transforming growth factor $\beta_1$are inhibitors of vascular smooth muscle proliferation; while angiotensin II, epidermal growth factor, and platelet-derived growth factor contribute to smooth muscle proliferation [46]. ET-1 is known to exert significant proliferative activities on a variety of cell types leading to an accumulation of extracellular matrix. A prospective study in PD patients found that increasing the dwell volume from 1500 to 2500 mL per dwell induced an increase in peritoneal ET-1 synthesis [79]. This volume-induced ET-1 release may contribute to long-term structural alterations in the peritoneal membrane.

Junctional Adhesion Proteins

The tight junction forms an apical intercellular semi-permeable diffusion barrier between endothelial cells [80, 81]. A number of proteins have been described which participate in the formation of the tight junction. Zonula occludens-1 (ZO-1) was the first tight junction protein described and is a peripheral membrane protein located near the plasma membrane [80, 82]. Occludin is another important junctional protein and is transmembrane in location at membrane–membrane sites [83–86]. Occludin appears to be bound near the cytoplasmic membrane to ZO-1. A possible molecular model has ZO-1 bound to spectrin, which is bound to actin [82]. Regulation of occludin has been suggested as a possible mechanism for controlling paracellular permeability [87]. Occludin is more concentrated in arterial junctions than in venous junctions. Kevil and colleagues have shown that arterial endothelial cells express 18-fold more occludin protein than venous endothelial cells. These authors suggest that the arterial and venous endothelial barriers reflect the level of expression of different junctional molecules [88].

In addition to ZO-1 and occludin, many other junctional proteins have been identified. Another cell-to-cell junctional structure is the adherens junction. Adherens junctions are formed by the transmembrane cadherins bound intercellularly to catenins anchored to actin [89–92]. For example, VE-cadherin is a junctional protein localized to the borders between endothelial cells [93]. Kevil et al. have shown that VEGF increases permeability in endothelial monolayers through disorganization of endothelial junctional proteins. The increase in permeability has been related to the rearrangement of endothelial junctional proteins occludin and VE-cadherin [94]. The permeability-enhancing effect of VEGF may also involve the induction of endothelial fenestrations and the functional activation of vesicular-vacuolar organelles in the cytoplasm of endothelial cells. It has been proposed that the increase in microvascular permeability induced by VEGF is an essential step in angiogenesis, allowing the extravasation of blood-borne proteins and the formation of matrix to support the growth of the endothelial cells and the formation of tubes [95]. The relevance of this mechanism for peritoneal dialysis was demonstrated by the observation that VEGF mediates the development of hyperpermeability and angiogenesis in the peritoneal membrane induced by exposure to high glucose concentrations [96].

Basement Membrane

The basement membrane functions as a substratum that acts as a solid support to anchor cells and limits the domain of connective tissue, thus producing distinct cellular compartments [97]. With the exception of large molecules such as plasma proteins, the basement membrane appears to be freely permeable to most solutes [98–102]. This concept is supported by the fact that the restrictive properties of the intestinal capillaries to endogenous macro-molecules are similar to the capillaries found in the mesentery, skin, and skeletal muscle, despite the fact that numerous large fenestrations are present in the intestinal capillary endothelium [103]. It has also been shown that colloidal carbon penetrates the intercellular clefts of continuous capillaries after exposure to histamine, but the transport of the colloidal carbon into the interstitial space is impeded at the basement membrane [104, 105]. These observations imply that the basement membrane may constitute a component of the barrier in the blood to lymph transport of large macromolecules. In addition, the proteoglycans in the basement membrane and interstitial gel matrix create an electrostatic barrier that retards the movement of anionic solutes [106]. These findings suggest that, although the basement membrane is permeable to small solutes, it may provide a significant transport barrier for large macromolecules under conditions of endothelial contraction and/or injury.

Summary

The general architecture of the microvascular network and some important physiological processes occurring in arterioles, capillaries, and postcapillary venules have been reviewed. Arterioles are the major site of microvascular resistance and regulate blood flow to the capillaries. Capillaries are the principal location of solute and fluid exchange. Postcapillary venules are important sites for leukocyte adherence and may show marked changes in permeability under inflammatory conditions. The endothelium is active in the physiological regulation of numerous microvascular processes including microvascular hemodynamics, leukocyte adhesion, and production of growth factors and growth inhibitors. Endothelial adhesion molecules have been described and appear to have important roles in maintenance of tight junctions. The basement membrane appears to be freely permeable to small solutes, but restricts the transport of macromolecules.

Peritoneal Microvascular Hemodynamics

In this section we will first consider the regulation of mesenteric blood flow. Subsequently, the effect of peritoneal microvascular blood flow on solute clearance and ultrafiltration will be discussed. The effect of vasoactive agents on the peritoneal microcirculation will then be considered. Finally, the effect of peritoneal dialysis fluid (PDF) and certain agents with elevated concentrations in renal failure on the microcirculation will be examined.

Regulation of the Mesenteric Circulation (See Also Chapter 9)

The extrinsic control of the mesenteric circulation is mediated by the sympathethic and parasympathethic nervous system and by circulating vasoactive agents, including catecholamines, vasopressin, and angiotensin [107, 108]. There are also intrinsic vascular control mechanisms, that are evidenced by pressure-flow autoregulation, reactive hyperemia, vascular responses to acute venous hypertension, and functional hyperemia [109]. Although myogenic factors have long been considered to be solely responsible for the intrinsic ability of the mesentery to regulate its blood flow, more recent developments indicate that metabolic mechanisms may be of equal importance in this regard. The functional hyperemia after ingestion of a meal is mediated by hormones such as gastrin and cholecystokinin. The purine nucleoside adenosine is a powerful intestinal vasodilator and may be an important metabolic regulator of intestinal autoregulation, although the evidence is controversial [110].

The Impact of Effective Peritoneal Blood Flow on Clearance and Ultrafiltration

Approximately 25% of cardiac output is directed to the splanchnic vascular bed in normal, resting individuals [111]. Excluding the parietal peritoneum, the total abdominal splanchnic blood flow usually exceeds 1200 mL/min at rest [112]. Granger et al. have measured superior mesenteric and peritoneal blood flow during intraperitoneal administration of a commercial peritoneal dialysis fluid (PDF) in anesthetized cats. The PDF significantly increased blood flow to the mesentery, omentum, intestinal serosa, and parietal peritoneum [113]. When considering the overall effective capillary blood flow in the peritoneum, an important question arises. Is the effective blood flow adequate to deliver solutes and fluid such that solute clearance is not primarily blood flow limited?

Due to the heterogeneous nature of peritoneal tissue and its vasculature, it is difficult to precisely measure the effective blood flow in the peritoneal capillary bed. Indirect measures of effective peritoneal blood flow have been made using inert gas (H_2, Xe) washout techniques. Estimates of peritoneal blood flow range between 2.5 and 6.2 mL/min per kg body weight in rabbits to 7.5 mL/min per 100 g body weight in rats [114, 115]. Despite the difficulties in direct measurement of effective blood flow, Nolph et al. have presented indirect evidence that maximum clearance is not primarily blood flow limited [116]. This evidence relies on the interpretation of urea clearance data under conditions of decreased mesenteric blood flow as well as data derived from kinetic modeling. Maximum urea clearances obtained with rapid cycling and predicted clearances at infinite dialysis flow are in the range of 30–40 mL/min. If urea clearances were blood flow limited, a severe restriction in mesenteric blood flow would be expected to reduce urea clearance. However, the results of studies in dogs subjected to circulatory shock have shown that urea clearances remain at 74% of control values despite a 38% reduction in mean arterial pressure [117]. In rabbits, urea clearances are affected when blood flow is reduced to 20% of normal [114, 118]. These findings demonstrate that, despite marked reductions in mesenteric blood flow, only modest decreases in urea clearance occur, suggesting that urea clearance is not primarily blood flow limited. Estimates of effective capillary blood flow have been made using gas diffusion techniques and range between 68 and 82 mL/min. Peritoneal clearances of carbon dioxide are approximately two to three times the maximum urea clearance. Using the ratio of urea clearance to peritoneal blood flow, Aune predicted that a doubling in blood flow would produce less than a 10% increase in urea clearance [114]. However, results obtained using gas diffusion techniques should be viewed with caution since they are based on the assumption that peritoneal gas clearance is equal to effective blood flow. Further studies using intraperitoneal vasodilators and kinetic modeling have also suggested clearance is not blood flow limited [17, 106, 116, 119–123]. However, some authors have suggested that blood flow may be a limiting factor with rapid peritoneal exchanges such as with high flux automated peritoneal dialysis [124].

Kim and colleagues have performed experiments using diffusion chambers attached to the serosal side of the abdominal wall, stomach, caecum, and liver in conjunction with laser Doppler flowmetry to directly evaluate the effect of decreased blood flow on mass transfer of solutes [125, 126]. In these experiments local blood flow beneath a

diffusion chamber was monitored by Doppler flowmetry with simultaneous measurements of the disappearance of a tracer during conditions of baseline control blood flow, 30% of control, and zero blood flow. No significant difference in the rate of mass transfer for mannitol or urea was demonstrated between control blood flow and 30% of control in the abdominal wall. There was a significant reduction in rates of mass transfer with no blood flow. In similar experiments involving the stomach, caecum, and liver there was no difference in the urea mass transfer coefficient for the stomach and caecum when blood flow was reduced to 30% of control. There was a significant decrease in the urea mass transfer coefficient in the liver with reduction of flow to 30% of control. Significant reductions in mass transfer were again demonstrated with zero blood flow. These data demonstrate that reductions of blood flow by approximately 70% do not significantly reduce mass transfer in the parietal and visceral peritoneal areas tested, except in the liver. As noted previously, the relative contribution of a tissue to total transport must take into account the actual tissue surface area available for dialysis solution contact. Since the liver has only a relatively small effective exchange area available, it was concluded that total solute transport in peritoneal dialysis should not be greatly affected during conditions of decreased blood flow.

Rosengren and Rippe studied the effect of peritoneal blood flow on small solute transport in the rat [127]. Peritoneal blood flow reductions were achieved by bleeding the rats to 25% of their blood volume. The resultant reductions in blood pressure and peritoneal blood flow were associated with a significant decrease in the permeability-surface area product for ^{51}Cr-EDTA and glucose. The clearance of albumin fell largely in proportion to the estimated capillary hydrostatic pressure drop. It was concluded that the transperitoneal clearance of small solutes is blood flow limited when peritoneal perfusion is markedly reduced, but to a lower than expected extent, while albumin transport is not blood flow limited [127].

In 20 stable PD patients, effective peritoneal blood flow did not affect peritoneal transfer of small solutes in the first 25 min of the dwell, but appeared to affect transfer rates later in the dwell [128].

Current opinion thus prevails that under physiological conditions, peritoneal blood flow does not limit the transfer of solutes. However, the effective peritoneal blood flow available for transport is only a fraction of the total blood flow through the tissues surrounding the peritoneal cavity, because most of the capillaries are too far from the cavity to be active in the exchange process or they are contained in tissues not in contact with the solution in the cavity. In this respect, it was shown that the use of a surfactant (dioctyl sodium sulfosuccinate) increased the mass transfer rates of mannitol and protein by augmenting the contact area between the peritoneum and the dialysis solution [129].

To evaluate whether ultrafiltration may be limited by effective peritoneal blood flow, Grzegorzewska et al. studied the effects of ultrafiltration and effective peritoneal blood flow during peritoneal dialysis in the rat [130]. When maximum net ultrafiltration rate was obtained with hypertonic solutions, effective peritoneal blood flow was approximately five times greater than net ultrafiltration rate; and under isosmotic conditions effective peritoneal blood flow exceeded net ultrafiltration rate by 57 times. Since there is a great difference between effective peritoneal blood flow and net ultrafiltration rate, it is unlikely that normal peritoneal blood flow significantly limits ultrafiltration during peritoneal dialysis.

Using the same technique of diffusion chambers and laser Doppler flowmetry, the group of Flessner evaluated the effect of blood flow on the hypertonic water flux during periods of control, reduced (50–80%) or no blood flow [131]. With the exception of the liver, marked blood flow reductions had small but insignificant effects on osmotic water transport.

The Effects of Vasoactive Agents on the Peritoneal Microcirculation (See Also Chapter 9)

Numerous endogenous and exogenous vasoactive agents have been shown to modify blood flow in the peritoneal microcirculation. A wide variety of drugs, hormones, neurotransmitters, and mediators of inflammation alter mesenteric vascular resistance. In addition to altering blood flow, some of these agents can also simultaneously affect perfused capillary density and microvascular permeability. For example, bradykinin, glucagon, and histamine increase both blood flow and permeability [33–35]. In contrast, secretin and cholecystokinin infusions increase blood flow but do not alter microvascular permeability to macromolecules [132]. Despite the lack of effect of secretin and cholecystokinin on macromolecular permeability, these agents increase the capillary filtration coefficient. The latter observation suggests that changes in capillary surface area, secondary to capillary recruitment, primarily account for the ability of these agents to increase peritoneal clearances. Using intravital microscopy, the effect of a number of vasodilators on several components of the peritoneal circulation was evaluated [24]. Local application of acetylcholine (10^{-7} to 10^{-5} M), nitroglycerin (10^{-6} to 10^{-4} M), verapamil (10^{-6} to 10^{-4} M), and papaverine (10^{-6} to 10^{-4} M) resulted in

a vasodilation of the mesenteric arteries (diameter 250–350 μm). The diameter of the arterioles (15–25 μm) did not change, however, while the blood flow rate (calculated als $V_{RBC} \times \pi D^2/4$ with V_{RBC} indicating the red blood cell velocity and D indicating the luminal diameter) increased, indicating that the arterioles are passively conducting the rise in flow caused by the upstream vasodilation. The vasodilators also caused capillary recruitment, resulting in a rise of the perfused capillary length [24]. In this study, nitroglycerin was found to be the most powerful vasodilator [24].

Many vasoactive drugs and hormones are known to affect peritoneal clearance (Table 4.1). Nitroprusside and isoproterenol are the best studied agents known to augment clearances in peritoneal dialysis [17, 119, 121, 122, 133–135]. Nitroprusside increases the clearance of urea, creatinine, inulin, and protein in a dose-dependent fashion. Small solute clearance appears to be most affected at lower doses, while large solute clearances are significantly increased at higher doses [136]. The maximum effect of intraperitoneally administered nitroprusside appears to occur after three to five consecutive exchanges with the drug, and the effects of nitroprusside are reversed when the drug is removed from the dialysis solution. With nitroprusside, mass transfer coefficients increase proportionately more for inulin than for urea, suggesting that alterations in permeability occur with exposure to the drug [17]. Nitroprusside also enhances the leakage of fluorescein-tagged albumin across the mesenteric microvessels [25, 39].

Studies by Grzegorzewska et al. using gas diffusion techniques in patients receiving intermittent peritoneal dialysis showed that the intraperitoneal administration of nitroprusside produced no significant differences in the peritoneal transfer of CO_2 [137, 138]. Nitroprusside did enhance the removal of certain solutes such as urea and total protein. Thus, the effect of nitroprusside on solute clearance did not appear to be attributable to changes in effective peritoneal blood flow. Studies by Douma et al. in CAPD patients also demonstrated that the mass area transfer coefficient of CO_2 was not significantly different after the intraperitoneal administration of nitroprusside in a glucose dialysate [133]. Since nitroprusside appears to have no significant effects on effective peritoneal blood flow in the setting of peritoneal dialysis (based on gas diffusion of CO_2), the effects of nitroprusside on other parameters such as capillary permeability and perfused capillary density need to be defined in order to explain the increase in solute clearance.

In the same study of CAPD patients, Douma et al. demonstrated that nitroprusside increased the mass transfer area coefficient of low molecular weight solutes and serum proteins. Using kinetic modeling and concepts of the pore theory, they related the effects of nitroprusside to an increase in the radius of both large and small pores and an increase in the effective peritoneal surface area. An increase in the number of perfused capillaries would increase the total number of pores available for exchange but theoretically should not alter the distribution of the sizes of the pores. Nitroprusside had a greater relative increase in the clearance of larger molecular proteins, suggesting a greater relative effect on the large pore radius. In this study the dialysate to plasma concentration of cGMP was greater with the addition of nitroprusside, suggesting a local generation of NO produced by nitroprusside. There was no difference in the dialysate concentrations of PGE_2, 6-keto-$PGF_2\alpha$, or thromboxane B_2 with the addition of nitroprusside. These workers also demonstrated that the ultrafiltration rate was increased with nitroprusside during the initial phase of dwell but the effect on net ultrafiltration was not significantly different for nitroprusside and control after 4 h. This information suggests that the effect of nitroprusside in improving clearance in the setting of peritoneal dialysis is not due to arteriolar vasodilation but to changes in perfused capillary density and alterations in microvascular pore diameter.

Table 4.1 Drugs and hormones that modify peritoneal clearance

Agents that may increase clearance
Albumin, Aminoproprionate, Anthranilic acid, Arachidonic acid
Calcium channel blockers, Cetyl trimethyl NH_4Cl, Cholecystokinin, Cytochalasin D
Desferrioxamine, Dialysate alkalinization, Diazoxide, Dioctyl sodium sulphosuccinate, Dipyridamole, Dopamine
Edetate calcium disodium, Ethacrynic acid
Furosemide
Glucagon
Histamine, Hydralazine, Hypertonic glucose
Indomethacin, Insulin, Isoproterenol
Lipid in dialysate
Nitroprusside, N-myristyl alanine
Procaine hydrochloride, Prostaglandin A1, Prostaglandin E1, Prostaglandin E2, Phentolamine, Protamine, Puromycin
Salicylate, Secretin, Serotonin, Streptokinase
Tris hydroxymethyl aminomethane (THAM)
Agents that may decrease clearance
Calcium, Dopamine, Norepinephrine, Prostaglandin F2, Vasopressin

Isoproterenol administered intraperitoneally increases peritoneal transport. The route of administration is important in determining isoproterenol's effects on clearance. Intravenous isoproterenol increases superior mesenteric blood flow by 88%, but does not alter peritoneal clearances of creatinine and inulin. In contrast, intraperitoneally administered isoproterenol increases superior mesenteric blood flow and increases solute clearance [139]. In animal studies it has been suggested that the vasoactive effects of isoproterenol increase capillary surface area through the recruitment of capillaries. Isoproterenol increases the mass transfer area coefficients of small solutes, especially in the early phases of the dialysis dwell [140].

A possible and major disadvantage for clinical use of nitroprusside is the potential for systemic vasodilation. Some studies indicate the peripheral vasodilatory effects may be limited with appropriate intraperitoneal dosing [122]. In the study of CAPD patients by Douma et al. no marked blood pressure decreases were noted [133]. Intraperitoneal isoproterenol has been used in certain clinical situations [140]. Patients with vascular diseases such as scleroderma may experience decreased clearances during peritoneal dialysis. In a patient with scleroderma, addition of isoproterenol to the dialysis fluid appeared to improve clearance [140]. However, the clinical use of isoproterenol is hindered by its potential cardiac stimulatory actions [139].

The Effects of Peritoneal Dialysis Solutions on the Peritoneal Microcirculation

Peritoneal dialysis markedly affects the mesenteric microcirculation [24, 25, 60, 120, 141–145]. Topical application of a conventional PDF reversibly dilated mesenteric arteries by more than 20%. The extent of the PDF-induced vasodilation was similar to that of nitroglycerin 10^{-4} M, and no additive effects were observed when PDF and nitroglycerin were applied simultaneously [24]. In another study, no further vasodilation was observed after addition of nitroprusside 10^{-4} M, indicating that PDF induces a maximal vasodilation [144]. In contrast, the small arterioles in the peritoneal membrane did not appear to respond directly to the local application of PDF, because their luminal diameters remained unchanged. However, the flow in these arterioles nearly doubled, indicating that they are passively conducting the increased flow caused by the vasodilation of the mesenteric arteries. This PDF-induced increase in peritoneal blood flow resulted in capillary recruitment, increasing the number of perfused capillaries with more than 20% [24]. Conventional PDF have a high osmolality as a result of elevated glucose concentrations and contain lactate as the buffer system. The pH is approximately 5.5 to limit caramelization of glucose during heat-sterilization process with the formation of a variety of toxic glucose degradation products (GDPs). Even at this low pH, considerable formation of GDPs occurs. The vasodilatory effects of low pH, lactate, and hyperosmolarity are well recognized. However, adjustment of the pH of the PDF to 7.4 did not decrease the vasoactive effects [24, 120, 144], indicating that although low pH *per se* may cause vasodilation, it is not essential for the observed dialysate-induced hemodynamic effects. These observations are important because acidity is rapidly corrected after infusion of standard PDF in the abdominal cavity. Conventional PDF may thus maintain its vasodilatory potential during the entire dwell time.

Novel techniques to prepare PDF have been developed in order to decrease GDP content. A substantial reduction in GDP formation can be achieved by sterilizing glucose separately at a pH of approximately 3. The electrolytes and buffer are kept in another bag compartment at a pH of approximately 8. The contents of both chambers are mixed immediately before use, yielding a solution with neutral pH [146]. A similar double-chamber system has been applied to allow use of bicarbonate as the buffer system. Since bicarbonate and the divalent ions are kept in separate chambers and mixed immediately before use, the precipitation of calcium and magnesium carbonate is avoided [147]. Because glucose is also sterilized separately at a low pH, formation of GDPs is in addition markedly reduced [146]. Local application to the mesenteric microcirculation of a PDF with low GDP content and high lactate concentrations induced only a transient vasodilation and capillary recruitment despite ongoing exposure. Exposure of the peritoneal membrane to a PDF with low GDP content and use of bicarbonate as the buffer was found to be entirely neutral with respect to hemodynamic parameters. Resterilization of the PDF with low GDP content and bicarbonate as the buffer increased GDP levels without otherwise altering the composition of the solution. The resterilized solution caused similar increases in blood flow and capillary recruitment in the peritoneal microcirculation as the conventional solution [24]. Taken together, these results indicate that lactate is only in part responsible for the PDF-induced vasoreactivity, whereas GDPs exert major hemodynamic effects [24]. The results do not support a role for hyperosmolarity in PDF-induced vascular reactivity, because the bicarbonate solutions were hemodynamically inert, even though their osmolality is identical to that of conventional PDF. In addition, the neutral effect of the bicarbonate solutions demonstrates that high glucose concentrations *per se* do not have hemodynamic effects [24].

Superfusion of the peritoneal membrane with conventional PDF rapidly reverses the vasoconstrictive effects of NO synthesis inhibitors [60]. When L-NAME and PDF are simultaneously superfused, the arteriole remained significantly

vasodilated throughout a 1-h superfusion period. Thus, PDF remain vasoactive despite arteriolar exposure to NO synthesis inhibitors, suggesting that the vasoactive properties are largely NO-independent. In studies of CAPD patients using amino acid-based peritoneal dialysis solutions, amino acid solutions increased estimated peritoneal blood flow. Based on nitrate and cGMP mass transfer area coefficients, this effect was not attributable to NO [148]. The exact mechanism through which PDF are vasoactive remains imprecisely defined, but it does not appear to be attributable to NO.

Summary

Animal studies and other evidence suggest that peritoneal clearance is not blood flow limited as long as effective peritoneal blood flow is greater than 30% of normal (with the exception of the liver). Ultrafiltration does not appear to be significantly limited by blood flow under usual conditions. Numerous vasoactive agents can affect peritoneal clearance and one of the most studied vasoactive agents is nitroprusside. Conventional PDF are vasoactive and have pronounced vasodilatory effects on mesenteric arteries. They increase microcirculatory blood flow and cause capillary recruitment. PDF with a low GDP content and lactate as buffer induce only a transient vasodilation, while PDF with low GDP content and bicarbonate as the buffer do not cause hemodynamic effects. Lactate may thus be in part responsible for the PDF-induced increase in peritoneal blood flow, whereas GDPs exert major hemodynamic effects.

The Peritoneal Microcirculation in Inflammation

The microcirculation plays a critical role in inflammatory responses associated with peritoneal dialysis. An important aspect of this response is the interaction of leukocytes with the vascular endothelium during inflammation. In pathophysiological states such as peritonitis the intraperitoneal leukocyte cell count may rapidly increase from a few cells to thousands of cells per mm^3. This rapid rise in the number of peritoneal leukocytes is dependent on factors that govern adhesive interactions between leukocytes and the microvascular endothelium. This section will focus on leukocyte-endothelial interactions in the peritoneal microcirculation.

General Principles of Leukocyte–Endothelial Interactions

Leukocyte recruitment from the vascular to the extravascular compartment follows a multistep process, directed by adhesive interactions. Leukocyte adhesion is localized primarily to postcapillary venules [41–44]. In order for a leukocyte to establish an adhesive interaction with the endothelium it must first be displaced from the center stream to the vessel wall. This appears to be related to microvascular network topography and radial dispersive forces. As the blood vessel diameter increases from the capillary to the postcapillary venules, the more flexible erythrocytes begin to pass the leukocytes and deflect them towards the vessel wall [149]. Once displaced to the vessel wall, the leukocyte can begin to adhere. Adhesion begins as a rolling movement along the postcapillary endothelium. As the inflammatory process proceeds, the number of rolling neutrophils increases and the velocity of the rolling decreases. This exposes the leukocyte to chemotactic agents released from parenchymal cells and/or the endothelium. Leukocyte activation allows the establishment of firm (stationary) adhesive interactions. The firmly adherent leukocyte may then migrate across the endothelial barrier and enter the interstitium (Fig. 4.5) [150].

The adhesive interaction between the leukocyte and the endothelium is mediated by a complex, highly coordinated, dynamic interplay between adhesion glycoproteins expressed on the surface of both the leukocyte and the endothelium [151]. The selectin family of adhesion molecules and their carbohydrate-containing ligands mediate the leukocyte rolling. At flow conditions typical of postcapillary venules, selectins are capable of interacting with their ligands within a fraction of a second. The rates of bond formation and dissociation are very high, but the bonds have a high tensile strength [152]. These qualities give rise to the rolling phenomenon, which brings the leukocyte into transient but close contact with the endothelial cells. If the appropriate stimuli are present, the leukocyte undergoes juxtacrine activation and prepares for firm adhesion and transendothelial migration. The firm adherence and transendothelial migration are mediated by the interaction of integrins with Ig-like molecules.

The integrins are heterodimers composed of a common beta subunit (CD18) and a specific alpha subunit (CD11a, CD11b, or CD11c). The superimmunoglobulin family is represented by intercellular adhesion molecules known as ICAM. The selectins are represented by L-selectin, E-selectin, and P-selectin. The integrins and L-selectin are

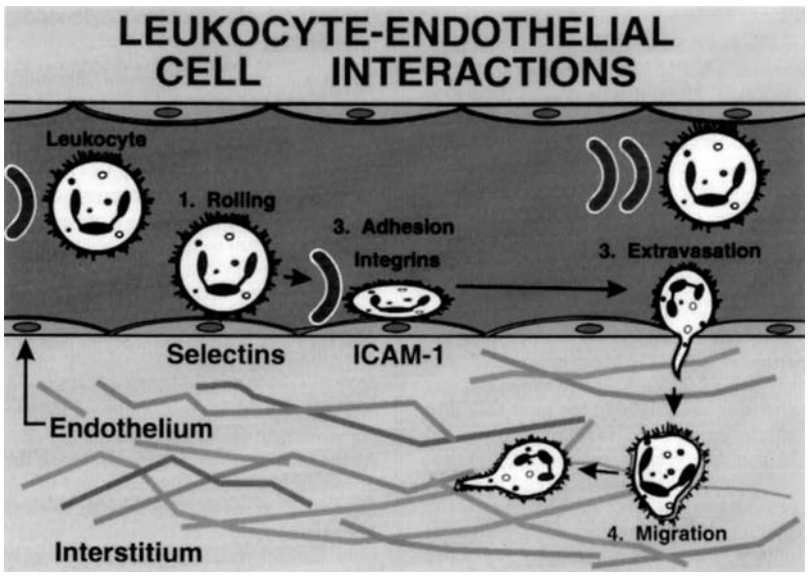

Fig. 4.5 The sequence of events involved in leukocyte adherence and migration to sites of inflammation requires coordination of the adhesive interaction between the leukocyte and vascular endothelium. (1) The initial leukocyte rolling appears to involve interaction between l-selectin on the neutrophil and E-selectin and P-selectin on the vascular endothelium. (2) This interaction allows for the up-regulation of the leukocyte integrin CD11b/CD18, which can bind to ICAM-1 and strengthen neutrophil adhesion. (3) The firmly adherent leukocyte may then extravasate by a process that is dependent on CD11a/CD18, CD11b/CD18, and ICAM-1. (4) The leukocyte may then migrate into the interstial tissue. Figure courtesy of Kristine Bienvenu

expressed on the surface of neutrophils. ICAM-1 is present on endothelial cells and its expression may be increased by endotoxin and cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF). Cytokines can also activate endothelial cells to express E-selectin. P-selectin is present on platelets and vascular endothelial cells [153–158].

The sequence of events involved in neutrophil adherence and migration to sites of inflammation requires coordination of the adhesive interactions between the neutrophil and the vascular endothelium. The initial leukocyte rolling appears to involve interactions between L-selectin on the surface of leukocytes and E-selectin and P-selectin on the vascular endothelium with their carbohydrate-containing ligands. These interactions allow for the up-regulation of CD11b/CD18 which can bind to ICAM-1 and strengthen neutrophil adhesion (Fig. 4.6). L-selectin is then

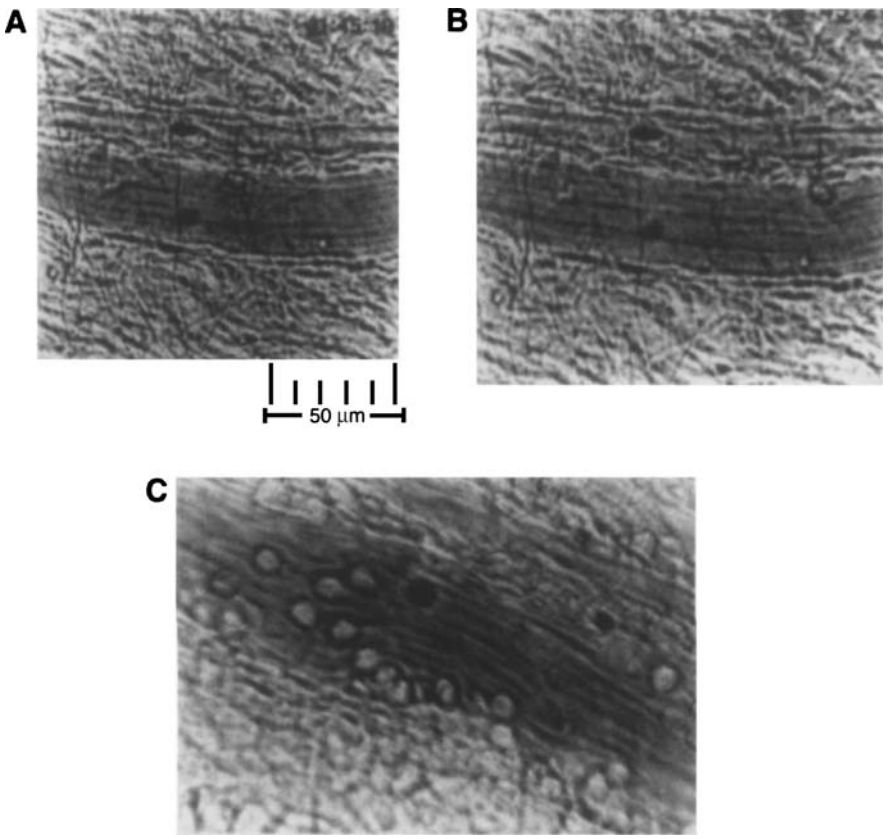

Fig. 4.6 (**a**) A mesenteric venule with a leukocyte (arrow) rolling along the length of the venule. (**b**) This micrograph was taken 2 s after the micrograph depicted in **A** to demonstrate that the leukocyte moved approximately 40 μm downstream in the venule. (**c**) A mesenteric venule during 2 ng/min platelet-activating factor (PAF) infusion. Note the numerous white blood cells adhering to the endothelial wall after PAF infusion [170]

down-regulated (shed) from the cell surface. The firmly adherent neutrophil may then migrate across the vessel wall by a process that is dependent on CD11a/CD18, CD11b/CD18, and ICAM-1.

Inflammatory Mediators and the Microcirculation

The physiological interaction between leukocytes and the endothelium may be influenced by several factors. Intravital videomicroscopic approaches have provided a wealth of information regarding the influence of intravascular hydrodynamic dispersal forces [41, 159, 160], leukocyte capillary plugging [161–163], electrostatic charge [164], and chemical mediators on leukocyte–endothelial cell interactions during inflammation. Table 4.2 lists several agents that affect leukocyte rolling and adherence in postcapillary venules.

As examples, platelet-activating factor (PAF), leukotriene B_4 (LTB_4), and nitric oxide synthesis inhibitors (such as L-NAME and ADMA) and superoxide have been shown to increase microvascular leukocyte adherence. The presence of adherent leukocytes and inflammatory agents may also promote changes in permeability. As an example, adherent leukocytes mediate PAF-induced vascular leakage. Pretreatment with monoclonal antibodies directed against the common beta subunit of the leukocyte integrin CD11/CD18 largely prevents the increased vascular protein leakage caused by infusion of PAF [165]. In the cat mesentery, local intra-arterial infusion of either LTB_4 or PAF promotes leukocyte adherence, but only PAF alters microvascular permeability. This indicates that leukocyte adhesion alone does not always result in increased microvascular permeability. When LTB_4 and PAF are infused simultaneously, LTB_4 causes a further increase in microvascular permeability than is observed with PAF alone. While PAF *per se* may increase microvascular permeability in the presence of adherent leukocytes, it may also serve as a "priming agent" that sensitizes neutrophils and/or the endothelium to other stimuli such as LTB_4 [166]. Reactive oxygen metabolites such as superoxide and hydrogen peroxide may be produced by neutrophils and endothelial cells [167–169]. Hydrogen peroxide appears to promote leukocyte adhesion to vascular endothelium by a PAF-mediated up-regulation or activation of CD11/CD18. Superoxide-induced increases in leukocyte adherence may be related to inactivation of nitric oxide by superoxide [170]. The inhibition of nitric oxide production by the vascular endothelium can produce an increase in microvascular protein efflux that is mediated in part by leukocyte-dependent mechanisms in the mesentery [171].

Thus, several agents promote leukocyte rolling and adherence in mesenteric postcapillary venules. Leukocyte adherence in the presence of an appropriate chemical stimulus may affect microvascular permeability. Since leukocyte adhesion has been associated with changes in permeability, the question arises as to whether leukocyte adhesion could modify endothelial junctional elements. Recent in vitro studies have shown that PMN adhesion to endothelial cells activated by tumor necrosis factor results in VE-cadherin/catenin disorganization [172]. This effect could be blocked by an anti-integrin beta 2 antibody. PMN adhesion also resulted in increased endothelial cell permeability. In vivo animal studies have shown that a monoclonal antibody against VE-cadherin increases vascular permeability and accelerates the entry of neutrophils into inflamed mouse peritoneum [173]. Thus, it appears that some agents which promote leukocyte adhesion may affect microvascular permeability through modulation of some junctional adhesion proteins.

The Effect of Peritoneal Dialysis Fluids (PDF) on Microvascular Leukocyte Adhesion

A large body of evidence indicates that conventional PDF cause a functional impairment of peritoneal host defense mechanisms [174]. The viability and production of inflammatory cytokines and chemoattractants by polymorphonuclear

Table 4.2 Substances or conditions that affect leukoctye adherence to postcapillary venules

A. Stimulants for leukocyte rolling
Superoxide, Histamine, Interleukin-1, Hydrogen peroxide, Indomethacin, Ischemia–reperfusion, Endothelin
Stimulants for adherence
C5a, PAF, Leukotriene B4, N-formylmethionyl-leucyl-phenylalanine, Hydrogen peroxide, Indomethacin, Nitric oxide synthesis inhibitors, Ischemia–reperfusion, Endotoxin, Superoxide
Substances which reduce leukocyte adherence
Adenosine, PGI_2, Iloprost (PGI_2 analogue), NO donors, 8-Bromo-cGMP (cGMP analogue), Superoxide dismutase, Catalase, Quinacrine (phosopholipase A_2 inhibitor), WEB2086 (PAF antagonist), Misoprostol (PGE_2 analogue), Colchicine, Methotrexate, Cromolyn (mast cell stabilizer), Salicylate

leukocytes, monocytes, and peritoneal macrophages is markedly affected by standard PDF. Phagocytosis, respiratory burst, and bacterial killing are lower when polymorphonuclear leukocytes, monocytes, and peritoneal macrophages are exposed to conventional PDF [174].

This section will focus on the effects of PDF on leukocyte recruitment in the peritoneal microcirculation. Intravital microscopy studies allow a direct visualization of the acute effects of PDF on leukocyte recruitment in mesenteric postcapillary venules [175–177]. Exposure of the rat peritoneal membrane to either LPS derived from *Escherichia coli* or a supernatant of a strain of coagulase-negative staphylococci previously isolated from a peritoneal dialysis patient with peritonitis resulted in an impressive increase in the number of rolling, adhering, and extravasated leukocytes in the postcapillary venules and a decrease in leukocyte rolling velocity [176]. The leukocyte response to these inflammatory stimuli was, however, dramatically suppressed by concomitant exposure to conventional PDF [176, 177] (Fig. 4.7). In contrast, superfusion with a pH-neutral, exclusively bicarbonate buffered PDF with low GDP content [176] and a pH-neutral bicarbonate/lactate-buffered PDF with low GDP content [177] had minimal suppressive effects. A lactate-buffered icodextrin solution partially blocked leukocyte-endothelial interactions and a lactate-buffered amino acid–based or amino acid/glycerol–based PDF abolished leukocyte recruitment in a similar manner as conventional PDF [177]. The differences between the responses to the various PDFs could not be attributed to variability of systemic blood pressure, circulating leukocyte numbers, or baseline levels of rolling, adhesion, extravasation, leukocyte rolling velocity, or venular shear rate, as these parameters did not vary between the groups. In addition, no correlation was found between the number of rolling leukocytes and venular wall shear rate at any time point, indicating that potential dialysate-induced variations in blood flow [24] were not responsible for the observed effects. The impairment of leukocyte recruitment by conventional PDF persisted after pH-adjustment to 7.4, indicating that, although low pH has well-documented inhibitory effects on various leukocyte effector functions in vitro [174], it does not appear to be essential for the observed inhibition in vivo. In order to identify the causative PDF-components in greater detail, additional experiments were performed. While superfusion with a pH-neutral solution containing high lactate concentrations and physiologic glucose levels caused a partial inhibition of leukocyte recruitment, a pH-neutral solution with both high lactate and high glucose concentrations abolished the leukocyte response similarly to conventional PDF [176], suggesting additive effects of lactate and hyperosmolarity on leukocyte kinetics.

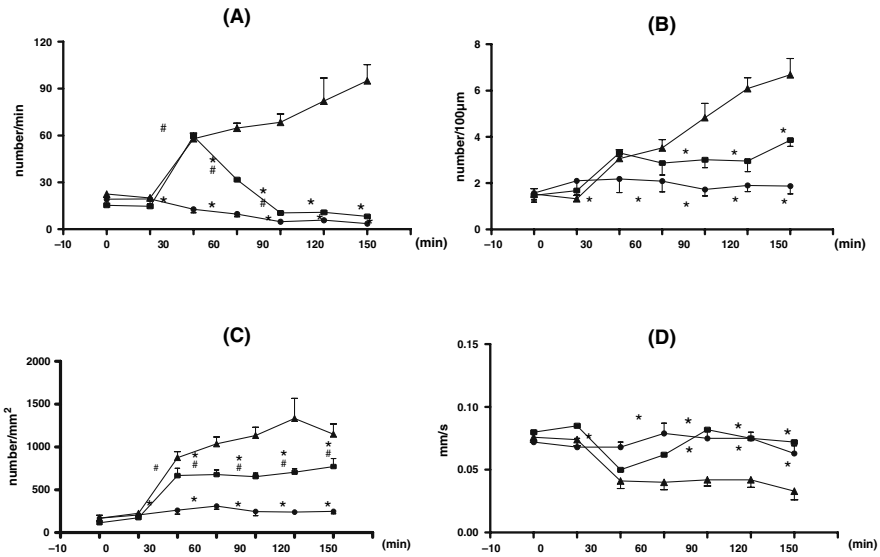

Fig. 4.7 The different aspects of leukocyte recruitment in peritoneal postcapillary venules after stimulation with LPS were evaluated with intravital microscopy, during superfusion with a pH-neutral buffer solution with physiological glucose and bicarbonate concentrations (EBSS) (triangles), a standard peritoneal dialysate fluid (PDF) (circles) and a pH-neutral bicabonate-buffered PDF with low glucose degradation product content (squares). (**a**) The number of rolling leukcytes rises progressively after an inflammatory stimulus, but not when the peritoneal membrane is superfused with a standard PDF. The suppressive effect of the pH-neutral bicarbonate-buffered PDF is less pronounced. *$p < 0.005$ versus EBSS, #$p < 0.01$ versus standard PDF. (**b**) The number of firmly adherent leukocytes in response to LPS increases after superfusion with EBSS, but not with standard PDF. During exposure to pH-neutral bicarbonate-buffered PDF, the response is intermediary. *$p < 0.05$ versus EBSS. (**c**) Extravasation of the leukocyte is the final step in leukocyte recruitment. The number of extravasated leukocytes rises sharply after LPS and reaches a plateau after 60 min. No recruitment occurs during standard PDF exposure, while a somewhat lower plateau is reached after pH-neutral bicarbonate-buffered PDF. *$p < 0.05$ versus EBSS, #$p < 0.005$ versus standard PDF. (**d**) Leukocyte rolling velocity decreases during EBSS, but not during standard PDF and only transiently during pH-neutral bicarbonate-buffered PDF. *$p < 0.05$ versus EBSS [176]

After resterilization, in order to increase GDP levels without otherwise altering the composition of the solution, the pH-neutral bicarbonate-buffered PDF suppressed leukocyte recruitment to a similar extent as the standard solution. These results thus support the inhibitory effects of GDPs on leukocyte recruitment, as suggested by in vitro experiments [174]. However, as the combination of lactate and hyperosmolarity already caused a maximal suppression of leukocyte recruitment, lowering the GDP content of a PDF alone may not be sufficient to improve host defense. The subordinate effect of GDPs on leukocyte recruitment is supported by observations of a lower influx of neutrophils in the peritoneal cavity of rats infected with *Staphylococcus aureus* after previous exposure to both a pH-neutral lactate-buffered PDF with low GDP content and a conventional PDF [178]. The pivotal role of lactate in the inhibition of leukocyte recruitment is further corroborated by the previously mentioned suppressive effects of the nonglucose lactate-buffered PDFs (icodextrin, amino acids, and amino-acid glycerol), that all have a low GDP content [177]. The low lactate concentrations in the combined bicarbonate/lactate-buffered PDF, however, do not appear to exert an adverse effect on leukocyte recruitment. These observations are in line with the finding that the migration distance of polymorphonuclear cells was not adversely affected unless lactate concentrations rose above 15 mmol/L [179].

The nonphysiologic composition of PDF disappears progressively during the dwell time. Osmolarity decreases due to glucose absorption and water ultra-filtration, although it never reaches physiologic values. Lactate concentration also diminishes rapidly during the dwell. Spent dialysate obtained from a patient after a 6-h dwell, however, affected leukocyte kinetics to a similar extent as fresh PDF [176], suggesting that osmolarity and lactate concentration remain sufficiently elevated to profoundly inhibit leukocyte recruitment. Alternatively, uremic toxins and reactive carbonyl compounds that accumulate in the dialysate during the dwell [180, 181] may affect peritoneal leukocyte behavior. Taken together, the results indicate that inhibition of leukocyte recruitment by conventional dialysate will persist throughout the entire PD cycle.

The underlying molecular mechanisms of the inhibition of leukocyte recruitment by PDF is unknown, but it likely involves effects on the adhesion molecules. Superfusion of the peritoneal membrane with L-NAME increased the number of firmly adherent leukocytes in the postcapillary venules. A standard PDF attenuated L-NAME-induced leukocyte adhesion, returning it to baseline conditions [182]. This suggests a possible effect on either the integrins or ICAM. In vitro studies have demonstrated that hyperosmolar solutions affect integrin expression. Kaupke and colleagues have demonstrated that incubation of blood with PDF resulted in depressed basal neutrophil expression of CD11b and CD18 and monocyte expression of CD14 [183]. In addition, the glucose-containing PDF decrease the LPS-induced upregulation of CD11b and CD18. PDF in which sodium chloride was substituted for glucose to obtain similar osmolalities as the glucose-based PDF also show a reduction in basal and LPS-stimulated expression of CD11b.

It is important to note that these in vitro and in vivo studies have been performed with acute exposure to PDF. Chronic exposure to conventional PDF resulted in neoangiogenesis and an increase in the baseline rolling of the leukocytes, while baseline leukocyte adhesion was unchanged [184]. These results possibly indicate changes in adhesion molecule expression in newly formed blood vessels in response to exposure to conventional PDF.

Summary

Several inflammatory mediators promote leukocyte rolling and adhesion in the mesenteric microcirculation. In the presence of some inflammatory agents, leukocyte adherence may affect microvascular permeability, possibly through modulation of junctional adhesion proteins. Animal models have demonstrated that PDF acutely affect leukocyte-endothelial interactions. Conventional PDF decrease leukocyte recruitment, most likely owing to a combination of high lactate concentrations, hyperosmolarity, and presence of GDPs. In contrast, bicarbonate-buffered PDF with low GDP content have only minimal effects on leukocyte kinetics.

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