FLUID EXCHANGE IN THE MICROCIRCULATION

Definition of the Microcirculation

To understand the functional aspects of the microcirculation, the student must understand that the circulation in our bodies is a pressurized system (see Fig. 1A). When the blood leaves the heart to enter the aorta, it produces an average vascular pressure in the large arteries of ~100 mmHg. However, as the blood flows through the smallest arteries (arterioles), its pressure decreases to 30–40 mmHg at the beginning of the microcirculation, which is the portion of the circulation that exchanges plasma fluid, oxygen, carbon dioxide, nutrients, and end products of metabolism with the tissues.

The blood pressure continues to decrease in the microcirculation and becomes ~10–15 mmHg in the smallest veins. As the small veins course through the tissues, they coalesce to form larger venules, which finally form the larger conducting veins that carry blood back to the heart. The small central portion of the microcirculation has been classically defined as "capillaries," which have diameters of 8–12 µm and a pressure of ~15–20 mmHg. The student should realize that a micrometer is a very small unit of measure, e.g., a micrometer is $4 \times 10^{-5}$ in. In fact, red blood cells have diameters of 7–10 µm, which means that their diameters are about the same size as the microvessels.

The walls of blood vessels are lined with very flattened cells that are called endothelial cells. The surface area of the microcirculation is huge, comprising >95% of the total surface area of all blood vessels in the circulation. The endothelial barrier lining the microcirculation in organs has been defined as 1) continuous, when the endothelial barrier is uninterrupted and each endothelial cell is physically connected to the next endothelial cell, or 2) fenestrated, when the endothelial barrier contains thin regions within the cells resembling windows. The German name for windows has been used to describe this type of barrier (fenestrae). However, the junctions of these endothelial cells with adjacent cells are also physically connected, so this barrier can also be defined as continuous or 3) discontinuous, when the microvascular barrier has large gaps between endothelial cells. An important point to remember about the microcirculation is that it must exchange oxygen, carbon dioxide, nutrients, and waste products with the tissues. This important function of the microcirculation requires an enormous surface area to efficiently exchange these substances with the tissues. In addition, a considerable hydrostatic pressure is always present in the blood vessels of the microcirculation, which is required to maintain blood flow into the larger veins. This hydrostatic pressure, combined with the enormous surface area of the microcirculation produces a tendency for fluid to filter out of the microvessels into the surrounding tissues.

Filtration Across the Microvascular Barrier

The microvascular pressure is highest within the small arteries (40 mmHg) and lowest in the small venules (10–15 mmHg). This indicates that a greater tendency for fluid to filter into the tissues is present in small arteries compared with small veins. In some organs, such as the kidney and small intestine, the microcire-
Filtering and reabsorption of fluid occur in microvessels across different organs. The glomerulus of each nephron in the kidney always filters fluid into the tubules to form the glomerular filtrate. Another extensive microcirculation surrounds the nephrons in the kidneys and must reabsorb 99% of this filtrate as it enters the tissues after having been processed by the renal tubular cells. The microcirculation in the small intestine must reabsorb 4–5 liters of fluid a day when food is present in the small intestine. However, the microcirculation of the small intestine actually filters fluids into the tissues when the small intestine is nonabsorbing. Obviously, the microcirculation of each organ is specifically designed to maintain a proper organ function. Either filtration or absorption can be present across the microvascular walls in different organs, depending on their specific functional requirements.

Physics of an Ideal Microvessel

To evaluate the filtering or absorptive nature of a microvessel, all forces within the microcirculation and tissues must be determined. Although an organ has different pressures present within segments of its microcirculation, a general equation can be developed, using average capillary and tissue forces, that accurately predicts the movement of fluid either into or out of the microcirculation of an organ for any given condition. As shown in Fig. 1A, arteriolar dilation increases microvessel pressures whereas arteriolar constriction decreases microvessel pressures. Decreasing arterial pressure has little effect on microvascular pressure, whereas increasing right atrial pressure greatly increases microvessel pressure (Fig. 1B). Thus the microvascular pressure may fluctuate from moment to moment as organs regulate the proper amount of blood flow to meet their metabolic demands.

**Microvascular Pressure**

If the vascular pressure within the microcirculation ($P_{MV}$) is the only force acting to move fluid out of the microcirculation into the tissues, then filtration is defined as

$$\text{Filtration} = K_F(P_{MV}).$$  \hspace{1cm} (1)

where $K_F$ is a constant that defines the rapidity at which filtration will occur for a given pressure (with physical units of ml-min$^{-1}$-100 g tissue$^{-1}$-mmHg$^{-1}$). We do not use the term capillary exclusively to define the filtering vessels of an organ, because fluid can also filter across other portions of the microvascular barriers, including both small arteries and small veins. Therefore, microcirculation is a more appropriate term to describe this portion of the circulation because it encompasses all portions that exchange substances with the tissues. $P_{MV}$ is defined as the average hydrostatic pressure in the microvessels (with units of mmHg). Although alterations in arteriolar and...
venous resistances can instantly effect $P_{MV}$, they can also be rapidly counterbalanced by changes in cardiac output and tissue regulation of blood flow. However, when the outflow of a single organ is blocked to some extent, $P_{MV}$ will remain increased and cannot be properly regulated until the blockage is removed (see Fig. 1B).

**Tissue Pressure**

A small hydrostatic pressure is also present in all tissues ($P_{TISS}$) that acts in a direction to oppose the microvascular hydrostatic pressure. Therefore, transvascular filtration is a function of the hydrostatic pressure gradient acting across the barrier (the filtration pressure) in the following fashion

$$\text{Filtration} = K_F(P_{MV} - P_{TISS})$$  \hspace{2cm} (2)

Because $P_{MV}$ is always much larger than $P_{TISS}$, Eq. 2 predicts that the microcirculation will always filter fluid into the tissues, unless $P_{TISS}$ is equal to $P_{MV}$. Interestingly, tissue pressure is subatmospheric in many tissues and actually increases the filtration pressure. However, the hydrostatic pressure gradient acting across the microcirculation is not the only force that affects filtration.

**Plasma Protein Osmotic Pressure (Oncotic Pressure)**

In the 1890s Dr. Ernest Starling discovered that plasma fluid contains proteins with a concentration of $\sim 7.3$ g/100 ml (or g%). Importantly, Starling determined that these plasma proteins exerted a sufficient absorbing pressure (osmotic pressure) to counterbalance the filtration pressure gradient acting across the microvascular walls. The major protein in human plasma is albumin, which has a concentration of $\sim 4.5$ g%. Globulins and fibrinogen comprise the remaining proteins in plasma and have a combined plasma protein concentration of 2.8 g%. When all proteins in the plasma are combined, they produce a measured protein osmotic pressure, or plasma oncotic pressure ($\pi_{PL}$) of 25-30 mmHg, i.e., the plasma oncotic pressure is of sufficient magnitude to oppose a hydrostatic filtration pressure of 25-30 mmHg. When $\pi_{PL}$ is included in the microvascular filtration equation, the following relation results

$$\text{Filtration} = K_F[(P_{MV} - P_{TISS}) - (\pi_{PL})]$$  \hspace{2cm} (3)

**Tissue Fluid Oncotic Pressure**

Because plasma proteins leak into tissues of most organs, they produce a protein osmotic pressure within the tissue fluids ($\pi_{TISS}$). This osmotic pressure acts in a direction to promote filtration into the tissues, because it subtracts from the plasma’s oncotic pressure. When $\pi_{TISS}$ is included in the filtration equation, the following results

$$\text{Filtration} = K_F[(P_{MV} - P_{TISS}) - (\pi_{PL} - \pi_{TISS})]$$  \hspace{2cm} (4)

Equation 4 states that the average filtration occurring across the microvascular barrier is governed by the differences between the absorption and filtration forces in the plasma and tissues. Although plasma proteins can leak into their tissues in most organs, it is important to know that the microcirculations of brain, eye, and some specialized capillary-membrane systems, such as the glomerular membrane in the kidney, are impermeable to plasma proteins.

**Permeability of the Microvascular Wall**

$P_{MV}$, $P_{TISS}$, $\pi_{PL}$, and $\pi_{TISS}$ are often referred to as Starling capillary forces, to honor this great physiologist for his many contributions, and especially for discovering $\pi_{PL}$ and understanding its effects on microvascular filtration. An additional factor also affects transmicrovascular filtration. A membrane coefficient, defined as the protein osmotic reflection coefficient ($\alpha_p$), relates the measured oncotic pressure of plasma to the actual oncotic pressure exerted across the microvascular barrier, i.e., this membrane-solute constant determines the effectiveness of the plasma protein oncotic gradient in opposing the hydrostatic pressure gradients acting across microvascular walls.

$$\text{Filtration} = K_F[(P_{MV} - P_{TISS}) - \alpha_p(\pi_{PL} - \pi_{TISS})]$$  \hspace{2cm} (5)

The reflection coefficient of plasma proteins is equal to one when the microvascular wall is not permeable to plasma proteins. However, this coefficient is equal
to zero when the microvascular wall is freely permeable to plasma proteins. When the microvascular barrier is impermeable to plasma proteins, the full oncotic pressure will be exerted across the microvascular wall, but if the microvascular wall is permeable to proteins, they will exert less absorption pressure. Figure 2 shows these forces in an idealized microvessel-interstitium-lymphatic system that also includes a small lymphatic capillary. The lymphatics normally remove the microvascular filtrate, and the tissues neither shrink nor swell under physiological conditions.

Different permeability characteristics are found within the microcirculations of different organs in the body; e.g., the microcirculation of the liver is freely permeable to all proteins in plasma, and proteins cannot exert any counterbalancing force on filtration, i.e., \( \sigma_p = 0 \), and \( 0(\pi_{PL} - \pi_{TISS}) = 0 \). In fact, \( \pi_{TISS} \approx \pi_{PL} \). However, the glomerular barrier in the kidney is almost impermeable to all plasma proteins, and they exert their maximal effect to oppose filtration in this capillary-membrane system. In most organs and in the remainder of this discussion, the reflection coefficient will be assumed to be one, except when otherwise designated.

### Values for Starling Forces in Different Tissues

Table 1 shows values for \( P_{MV}, P_{TISS}, \pi_{PL}, \pi_{TISS} \) as measured in several organs. Obviously, if organs are permeable, a small amount of fluid and plasma protein will always leak into the tissues. If proteins and fluid are not removed from the tissues, then the interstitial fluid volume will increase and a condition known as edema results. However, the lymphatics easily remove the filtrate under normal conditions even over a wide range of filtration.

The student should be able to calculate the net filtration pressure \( \Delta P = (P_{MV} - P_{TISS}) - \sigma_p(\pi_{PL} - \pi_{TISS}) \) for any organ when given \( P_{MV}, P_{TISS}, \sigma_p, \pi_{PL}, \pi_{TISS} \) as shown in Table 1.

### Problem 1

Table 1 shows some very interesting measurements, so let us calculate \( \Delta P \) in some of the
organisms in this table. We can calculate the filtration pressure, \( \Delta P \), as equal to \( (P_{MV} - P_{PTISS}) \) minus \( (\pi_{PL} - \pi_{PTISS}) \). For a skeletal muscle, the glomerular membrane, and renal peritubular capillaries as follows.

\[ \text{a)} \quad \Delta P \text{ for skeletal muscles is } \Delta P = (10.1 + 3) - 12, \text{ or } 13.1 - 12 = 1.1 \text{ mmHg. For skeletal muscle, the imbalance in forces is quite small and only a small filtration occurs.} \]

\[ \text{b)} \quad \Delta P \text{ for the glomerular membrane, which is composed of the glomerular capillaries and a complex glomerular membrane, is } \Delta P = (50 - 15) - (28 - 0) = 35 - 28, \text{ or (35 - 28) = 7 mmHg. This pressure gradient produces a very large filtration; in fact, it causes 120 ml to be filtered in both kidneys each minute because the } K_f \text{ is very large for the total glomerular membrane.} \]

\[ \text{c)} \quad \Delta P \text{ for the renal peritubular capillaries is } \Delta P = (25 - 7) - (32 - 7), \text{ or (18 - 25) = -7. Because } \Delta P \text{ is negative, the peritubular microvessels are absorbing fluid continuously; in fact, 119 ml are absorbed each minute in both kidneys.} \]

In summary, the \( \Delta P \)s acting across the microvascular walls indicate that resting skeletal muscle has only a small imbalance in forces present and microvascular filtration will be very small, but the \( \Delta P \) for the glomerulus is very large and positive, indicating that this microcirculation is always filtering. However, the \( \Delta P \) is negative in the peritubular capillaries of the kidney, indicating that these microvessels are always reabsorbing, and the renal tissue volume neither shrinks nor swells although tremendous amounts of fluid flow through the renal tissues every minute of our life.

**Problem 2.** The student should calculate \( \Delta P \) in a normal and absorbing small intestine and understand what causes the imbalance of force to be present in these conditions.

\[ \text{a)} \quad \text{For normal, nonabsorbing intestines where digestion is not occurring, } \Delta P = (16 - 2) - (23 - 10), \text{ or (14 - 13) = 1 mmHg. The microcirculation is} \]

**b)** For an absorbing intestine during digestion, \( \Delta P = (16 - 2) - (23 - 5), \text{ or (13 - 18) = -5. Therefore, the microcirculation is absorbing in an actively digesting small intestine.} \]

**Question:** Why do peritubular microvessels reabsorb in the kidney?

**Answer:** These microvessels reabsorb because 1) their hydrostatic pressure \( (P_{MV}) \) is greatly reduced relative to that present in the filtering glomerular microvessels and 2) the plasma oncotic pressure is increased because large amounts of filtration occurred across the glomerular membrane that increased the plasma oncotic pressure of the plasma flowing into the peritubular microcirculation. The sum of these forces is -7 mmHg, indicating that the absorptive force is much greater than the filtration force in this microcirculation.

**Question:** Why is \( \Delta P \) negative when the intestine is active?

**Answer:** In the absorbing small intestine, the tissue pressure is slightly increased above normal as fluid enters the tissues from the intestinal lumen. This decreases \( (P_{MV} - P_{PTISS}) \). Also, the tissue oncotic pressure decreases from a normal value of 10 mmHg to 5 mmHg, because the transported fluid entering the tissues of the small intestine during absorption contains no proteins and dilutes the tissue protein concentration \( (\pi_{PTISS}) \). This increases the absorption pressure of the microcirculation \( (\pi_{PL} - \pi_{PTISS}) \), causing the absorptive microvascular force to be 5 mmHg greater than its filtration force.

**Changes in Starling Forces When \( P_{MV} \) is Increased**

Figure 2 shows a microvessel, tissue, and a small lymphatic. In normal tissues the amount of fluid and protein filtered out of the microvessels in the tissues is removed by a very active lymphatic system. If the lymphatics are blocked, there is no other means for proteins and fluid to be removed from the tissues and gradually \( \pi_{PTISS} \) rises to equal \( \pi_{PL} \), causing excessive fluid accumulation to occur within the tissues. When the \( P_{MV} \) is increased because of venous pressure elevation, which is present in heart failure, fluid enters
the tissues and enlarges the tissue spaces surrounding the parenchymal cells. Also, if $\pi_{PL}$ is decreased because of a low-protein diet, liver damage, or blood loss, an increased filtration tendency is also present because $(\pi_{PL} - \pi_{TISS})$ is decreased. Importantly, when microvascular walls are damaged, protein leaks more readily into the tissues. This increases $\pi_{TISS}$, which also decreases the oncotic pressure gradient $(\pi_{PL} - \pi_{TISS})$. Also, when the microvascular wall is damaged, $\sigma_p$ decreases, which amplifies the tendency for fluid to filter into the tissues by further reducing the effectiveness of the net absorption force because $\sigma_p(\pi_{PL} - \pi_{TISS})$ is the actual absorption force. It is important to understand that proteins and fluid entering the tissues will remain there forever unless they are removed by the lymphatic system.

In a normally functioning microcirculation, filtration is self-regulating. When $P_{MV}$ is increased, as shown in Fig. 3, the resulting filtration will 1) decrease $\pi_{TISS}$, which increases $(\pi_{PL} - \pi_{TISS})$; 2) increase $P_{TISS}$, which decreases $(P_{MV} - P_{TISS})$; and 3) increase lymphatic flow, which removes most of the filtrate until $P_{MV} > 25-30$ mmHg. Microvascular pressures can be increased by $\sim 20-25$ mmHg before a significant amount of fluid accumulates within the tissues because of these self-regulating mechanisms. Note that when the membrane is damaged (Fig. 3), the absorption force does not increase significantly because $\sigma_p$ decreases and $\pi_{TISS}$ also increases.

Figure 4 shows the results of increasing microvascular pressure on edema formation in lungs. The lungs are shown as an example of edema because pulmonary edema is life-threatening given that it reduces the ability of the lung to oxygenate blood. Note that as pressure is increased in normal lungs (shown as solid line), edema does not develop until microvascular pressures exceed 20–25 mmHg, a condition that often occurs in left-sided heart failure. The changes that occur in Starling forces, i.e., the increased $P_{TISS}$,
increased $\sigma_p(p_{PL} - p_{TISS})$, and the increased lymph flow, prevent alveolar edema formation (shaded area) at microvascular pressures $<25-27$ mmHg. However, when plasma proteins are decreased by 50% (shown as decreased $p_{PL}$), alveolar edema develops at much lower microvascular pressures (15-17 mmHg). This occurs because $(p_{PL} - p_{TISS})$ cannot increase to any significant extent when $p_{PL}$ is low in plasma. When the microvascular wall has been damaged, the plasma protein permeability increases (shown as increased permeability), and alveolar edema develops at low microvascular pressures (20-21 mmHg) because $\sigma_p$ decreases and $p_{TISS}$ cannot significantly decrease, i.e., $\sigma_p(p_{PL} - p_{TISS})$ is very small.

**Question:** Why does a reduction in plasma oncotic pressure cause alveolar edema to occur at low microvascular pressures?

**Answer:** When $p_{PL}$ is decreased, there is less buffering of the microvascular pressure gradient by the oncotic gradient, as represented by $\Delta P = |(p_{MV} - p_{TISS}) - \sigma_p(p_{PL} - p_{TISS})|$. Because $\sigma_p$ decreases when the microvascular wall is damaged and $p_{TISS}$ also increases, then $\Delta P = |(p_{MV} - p_{TISS}) - \sigma_p(p_{PL} - p_{TISS})|$. Because $\sigma_p$ decreases and $p_{TISS}$ increases (rather than decreasing, which occurs in the normal microcirculation), the absorbing tendency of the oncotic gradient is decreased and alveolar edema occurs at lower microvessel pressures.

**EDEMA SAFETY FACTORS**

The factors that change to oppose edema formation when microvascular pressure is increased are shown in Fig. 3: 1) increased $p_{TISS}$, 2) decreased $p_{TISS}$, and 3) increased lymph flow. These forces are defined as edema safety factors, because they change in a direction to reduce fluid accumulation in normal tissues as filtration pressures increase. In all tissues, fluid can easily enter the very small lymphatics, and the lymphatic system can remove most of the additional filtration entering the tissues without edema formation until microvascular pressures exceed $\sim 20-25$ mmHg. However, once these “safety factors” have attained their maximal changes, then fluid accumulates in the tissues without any opposition, resulting in a rapid and extensive lung edema formation as shown in Fig. 4. Remember that when edema forms in lungs, the oxygenation of the tissues will be greatly reduced, and when edema forms in the gastrointestinal (GI) tract, fluid actually enters the GI lumen and no reabsorption of nutrients and fluids can occur. In other tissues, edema limits the exchange of oxygen, carbon dioxide, nutrients, and end products of metabolism because of the increased diffusion distances that substances must cross to either be removed from the tissues or reach the parenchymal cells.

**Question:** Why did edema occur at low microvascular pressures when the microvascular barrier was damaged?

**Answer:** Because $\sigma_p$ decreases when the microvascular wall is damaged and $p_{TISS}$ also increases, then $\Delta P = |(p_{MV} - p_{TISS}) - \sigma_p(p_{PL} - p_{TISS})|$. Because $\sigma_p$ decreases and $p_{TISS}$ increases (rather than decreasing, which occurs in the normal microcirculation), the absorbing tendency of the oncotic gradient is decreased and alveolar edema occurs at lower microvessel pressures.

**Table 2**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Increased $\sigma_p(p_{PL} - p_{TISS})$</th>
<th>Increased LF</th>
<th>Increased $p_{TISS}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung ($\sigma_p=1$)</td>
<td>50</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Hind paw (dog) ($\sigma_p=1$)</td>
<td>14</td>
<td>24</td>
<td>62</td>
</tr>
<tr>
<td>Small intestine ($\sigma_p=1$)</td>
<td>45</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>Colon ($\sigma_p=1$)</td>
<td>52</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>Liver ($\sigma_p=0$)</td>
<td>0</td>
<td>42</td>
<td>58</td>
</tr>
<tr>
<td>Heart ($\sigma_p=0.7$)</td>
<td>7</td>
<td>12</td>
<td>81</td>
</tr>
</tbody>
</table>

Values represent percent contribution of individual safety factors to the total protection provided to prevent excess tissue fluid and protein accumulation in response to a 20-mmHg elevation in $p_{MV}$.

Note that in liver and heart, $\sigma_p = 0$ and 0.7, respectively, thereby decreasing the relative importance of increased $\sigma_p(p_{PL} - p_{TISS})$ as a safety factor in these organs. However, these tissues still do not normally develop edema because LF and $p_{TISS}$ increase more substantially to oppose edema formation.
Answer: There are two different effects that could explain why $\sigma_p(\pi_{PL} - \pi_{TISS})$ does not increase as microvascular pressure is elevated: 1) $\pi_{TISS}$ may be small under normal conditions and cannot decrease significantly even when fluid filters into the tissues, or 2) the microvascular wall could be highly permeable to proteins and $\sigma_p(\pi_{PL} - \pi_{TISS})$ will not change significantly even with increased microvascular filtration. When filtration increases, $\pi_{TISS}$ cannot decrease significantly in the hindlimb (see Table 1) because its protein concentration is very low and can only change by $\sim 3-4$ mmHg, even though $\sigma_p$ is approximately equal to one in this tissue. Because the liver microvascular barrier is highly permeable to plasma proteins, $\sigma_p \approx 0$ and $\sigma_p(\pi_{PL} - \pi_{TISS})$ cannot change with increased filtration because $\sigma_p = 0$ and $\pi_{TISS} = \pi_{PL}$. Relatively, the heart microvascular barrier is also very permeable to plasma proteins ($\sigma_p$ is $\sim 0.7$) and $\pi_{TISS}$ can only decrease to $0.3 \pi_{PL}$, which limits the changes that can occur in the absorption force, $(0.7)(\pi_{PL} - \pi_{TISS})$.

In summary, the edema safety factors provide a cushion of $\sim 20$ mmHg for microvascular pressure changes in all tissues that oppose edema formation, unless the barrier is damaged. For example, the change in $\pi_{TISS}$ and the lymph flow factors are the most important edema safety factors in the hindlimb, liver, and heart because $\sigma_p(\pi_{PL} - \pi_{TISS})$ does not change significantly in these tissues, whereas increases in $\sigma_p(\pi_{PL} - \pi_{TISS})$ are more important in other tissues. A major concept to remember concerning the formation of edema in all tissues is that microvascular filtration is a self-limiting process that can oppose increases in the microvascular hydrostatic pressure gradients ($P_{MV} - P_{TISS}$) of $\sim 20-25$ mmHg before edema develops. However, the percentage of change in $\pi_{TISS}$, $\sigma_p(\pi_{PL} - \pi_{TISS})$ and lymph flows are often quite different in each microvascular bed because these factors are determined by their protein permeabilities and maximal lymph flows. It must be emphasized that this self-regulating filtration system allows microvascular pressures in the body to change over short periods of time without any significant accumulation of tissue fluids. Organs, therefore, can maintain their needed blood flows and carry out their day-to-day functions without excessive accumulation of plasma in their tissues that would alter their normal functional status.

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Suggested Readings