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Version 10

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Physiology and Pathophysiology of the Lymphatic System

The Functions of the Lymphatic System

1. The lymphatic system prevents edema by returning protein and capillary filtrate (water) to the systemic circulation.

   The lymphatic system transports fluid (lymph) from the interstitium (tissue spaces) back into the systemic circulation, thus preventing fluid accumulation (edema) in the tissues (Fig. 1). Most important is the removal of protein molecules from the tissue spaces because they cannot be removed by absorption directly into the blood capillaries. The return of proteins from the interstitium to the blood is an essential function without which we would die within about 24 hours.

2. The lymphatic system absorbs fat and fat-soluble vitamins from the small intestine.

   Lymph capillaries of the small intestine, called lacteals, absorb fat and fat-soluble vitamins. After the ingestion of fat, the lymph fluid from the small intestine takes on a milky-white appearance and is referred to as “chyle” or “chylous fluid.” The intestinal lymph trunk transports chyle into the cisterna chyli and from there into the thoracic duct before the fluid enters into the left subclavian vein.

3. The lymphatic system provides immune surveillance by recognizing and responding to foreign cells, microbes, viruses and cancer cells.

   The lymphatic system circulates lymphocytes and other white blood cells and makes them available to fight off bacteria and viruses that are potentially harmful to the human body.

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Fig. 1 Diagram of the relationship between the blood circulatory and lymphatic systems.
**Lymphatic Load**

Lymphatic load (LL) is the term used to describe the substances that are removed from the interstitium by the lymphatic system. It consists of:

1. **Protein.** It is estimated that about 75-100 grams of protein are transported in the lymph system each day. This equals approximately one-half the total amount of protein circulating in the systemic circulation.
2. **Water.** Water that has filtered from the capillaries into the interstitium. Also called capillary filtrate.
3. **Cells.** Lymphocytes, cancer cells and cell debris.
4. **Fat.** Long-chain fatty acids and fat-soluble vitamins from the small intestine.
5. **Other.** Similar to plasma, lymph fluid also contains electrolytes, urea, amino acids, creatinine and carbohydrates. In addition, lymph fluid carries coagulation factors which allow lymph to clot, similar to blood. However, the main components are **protein, water, cells and fat.**
Lymph Time Volume and Transport Capacity\textsuperscript{4,5}

The term lymph time volume (LTV) describes the amount of lymph which is transported by the lymphatic system over a period of time. The lymph time volume of the thoracic duct is estimated to be up to 4 l/day in humans.\textsuperscript{5} The normal lymph time volume equals about 10% of the maximum possible transport in a healthy lymphatic system. (Fig. 2)

![Fig. 2 Diagram showing the relationship between the normal lymph load and the transport capacity. Because the lymph time volume is only about 10\% of the maximum transport capacity, the lymphatic system has a large functional reserve.]

Safety Function of the Lymphatic System\textsuperscript{4,5}

If necessary, the lymphatic system is able to activate its safety function/safety-valve function and respond to an increase in lymphatic load by increasing its lymph time volume (Fig. 3). The lymphatic system is limited in how much lymph it can handle by the filling capacity of the lymph angions and the maximum frequency of lymph angion contractions. This maximum amplitude and frequency is called the transport capacity (TC) of the lymphatic system. The transport capacity is equal to the \textit{maximum} lymph time volume.

![Fig. 3 Diagram showing how the lymphatic system responds to an increase of interstitial fluid (water and/or protein load) with an increase in lymph capillary uptake and activation of the motor function of the lymph vessels.]

\textsuperscript{4,5}Klose Training 2018
**Interstitium**

Approximately 1/6 of the human body consists of interstitium which is made up of proteoglycan filaments, collagen fiber bundles, and fluid. This gelatinous substance is the “glue” that keeps our cells together. Proteoglycan filaments are extremely thin, coiled and create a mat of reticular fibers. Interstitial fluid becomes entrapped in that mat which limits the ability of large numbers of its molecules to flow at once. Instead, individual molecules diffuse through the gel. (Fig. 4)

Blood capillaries release water and proteins into the interstitium. Because protein molecules have difficulty passing the basement membrane of the blood capillaries, the protein concentration in interstitial fluid is much lower than in plasma.

The interstitium is also composed of “free fluid” which is <1% of normal tissue. Free fluid lacks proteoglycan filaments so has the ability to flow. In edematous tissue, small streams (rivulets) of free fluid can expand and more fluid becomes free flowing.

![Fig. 4](image)

Fig. 4 Structure of the interstitium. Proteoglycan filaments are everywhere in the spaces between the collagen fiber bundles. Free fluid vesicles and small amounts of free fluid in the form of rivulets occasionally also occur.

To help you and your patients understand the interstitium, imagine the interstitium as a bowl of jello with pineapple pieces in it. The pineapple pieces represent the tissue cells and the jello is the “glue” that holds the tissue cells together. Without the jello, the pineapple pieces (cells) would be loose and unable to form tissue.
The properties of the interstitium can help answer the following common question:

Q: Why does a patient’s affected limb feel heavier than the non-affected limb without there being a noticeable increase in size?

A: The interstitium can be compared to a sponge. In healthy tissue, the “sponge” carries a moderate amount of water. In edematous tissue, the “sponge” takes on more fluid and becomes heavier without changing size. In human tissue, the interstitium can store up to 30% more water before the swelling becomes visible. The weight change will be noticed as a subjective complaint by the patient.

**Blood Capillary Permeability**

Lymph fluid is mainly the result of blood capillary filtration and the release of protein molecules from the blood capillary into the interstitium. The amount of capillary filtration depends on the specific permeability of the blood capillary toward water and varies in capillaries of different organs of the body.

All blood capillaries consist of one layer of endothelial cells and a basement membrane. The permeability of the capillaries varies based on the integrity of these two layers. The permeability is relatively low in continuous capillaries, e.g. in the brain, and highest in the sinusoid capillaries of the liver.

![Blood Capillary by Type](chart)

**Fig. 5** Various types of blood capillary membranes.

<table>
<thead>
<tr>
<th>Continuous</th>
<th>Fenestrated</th>
<th>Sinusoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. With numerous transport vesicles (openings):</td>
<td>Endocrine glands</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Intestines</td>
<td>Lymph nodes</td>
</tr>
<tr>
<td>Skin</td>
<td>Pancreas</td>
<td>Liver</td>
</tr>
<tr>
<td>2. With few vesicles (openings): Central nervous system</td>
<td>Glomeruli of kidneys</td>
<td>Spleen</td>
</tr>
</tbody>
</table>
Fluid Exchange at the Blood Capillary

DIFFUSION

Diffusion is the most important process for the nourishment of the tissues! Diffusion is the tendency of molecules of a substance (gaseous or liquid) to move from a region of higher concentration to one of lower concentration. Diffusion is caused by the tendency of the molecules to establish equilibrium.

This movement of the molecules depends on the size of molecules, the difference in concentration, distance, the total cross-sectional surface and temperature.

![Diffusion Diagram](image)

**Fig. 6** Diffusion occurs continually in the human body, e.g. the wall of the blood capillaries is permeable for plasma and small organic and small inorganic molecules. The entire exchange of oxygen and carbon dioxide happens through diffusion.

FILTRATION AND REABSORPTION

**Note:** Until recently, Starling’s Equilibrium of capillary exchange, a theory published in 1896, was accepted by the scientific community without question. However, newer findings published by Levick et al. and other authors reveal discoveries that necessitate a revision of Starling’s principle.

Because the original theory of Starling’s Equilibrium had been accepted and remained unchanged for over a century, many current textbooks, publications, and video presentations still show Starling’s theory as the basis for their interpretation of microcirculation. For that reason, it is important that health care professionals engaged in the treatment and research of lymphedema have a complete understanding of both the historical interpretation and the updated understanding of microcirculation. Both models are described here.
STARLING’S EQUILIBRIUM FOR CAPILLARY EXCHANGE

In 1896, British physiologist Ernest Starling (Fig. 7) pointed out that under normal conditions, a state of near-equilibrium exists at the capillary membrane. That is, the amount of fluid filtering outward from the arterial side of capillaries almost exactly equals the fluid returned to the circulation by absorption. He postulated that the slight dis-equilibrium that does occur accounted for the small amount of fluid that is eventually returned by way of the lymphatics.

According to Starling:

Filtration is caused by hydrostatic pressure/blood capillary pressure (BCP) inside the blood capillaries. It is this pressure which forces fluid out of the capillaries. This pressure tends to be 30-40 mmHg at the arterial side and 10-15 mmHg at the venous side of the capillary. (Fig. 8)

Reabsorption is caused by plasma colloid osmotic pressure (COPp). It is the ability of proteins within the plasma to hold water. This pressure prevents significant loss of capillary fluid and approximates 28 mmHg.

Lymphatic Drainage

Protein molecules continuously migrate from the blood capillaries into the interstitium but are unable to be reabsorbed directly into the blood capillaries. However, the lymphatic system is able to absorb these proteins along with a fraction of the capillary filtrate and returns them into the systemic circulation.

On the arterial side
BCP>COPp = Filtration

On the venous side
BCP<COPp = Resorption

Fig. 8  Simplified diagram of microcirculation according to Starling’s theory established in 1896. Capillary filtration and reabsorption are in a state of near equilibrium. The effects of interstitial fluid pressure (IFP) and colloid osmotic pressure of the interstitium (COPi) on filtration and reabsorption are omitted.
ADDITIONAL STARLING FORCES OUTSIDE THE CAPILLARY

Filtration is increased or decreased by the amount of interstitial fluid pressure (IFP). IFP helps to force fluid into the capillaries when positive (+) and out of the capillaries when negative (-). This pressure is normally -3mmHg, thus, it helps to draw fluid into the interstitium.

Reabsorption is reduced by interstitial fluid colloid osmotic pressure (COP$_i$). This reflects the ability of proteins in the interstitial fluid to hold water. This pressure approximates 8mmHg.

Starling’s Equilibrium refers to the balance of all 4 forces (pressures) at the capillary membrane (Fig. 9). Under normal conditions, all but capillary pressure tends to remain constant.

Blood capillary pressure changes from approximately 30-40mmHg on the arterial side to 10-15mmHg on the venous side. Capillary pressure on the arterial side exceeds all other pressures combined, resulting in filtration of fluid from capillary to the interstitium. Capillary pressure is lower on the venous side, resulting in reabsorption of fluid back into the capillaries. This process of filtration and reabsorption, along with adequate lymph drainage, maintains normal tissue fluid homeostasis.

![Fig. 9 The four pressures at the capillary membrane.](image_url)
REVISED STARLING’S PRINCIPLE OF FLUID EXCHANGE

New research demonstrates that, even though the hydrostatic pressure in the capillaries falls below the average colloid osmotic pressure in the plasma on the venous side of the capillary, there is dwindling filtration but no reabsorption!

Since we now know that water and protein are not directly reabsorbed into the venous side of the capillaries, the lymphatic drainage system has an even greater role in the removal of these lymphatic loads than previously thought (Fig. 10).

Fig. 10 Comparison of the traditional and revised Starling’s principle of fluid exchange. The illustration on the left shows filtration and reabsorption in a state of equilibrium with very little to no loss of capillary fluid. The diagram on the right illustrates the revised Starling’s principle of fluid filtration throughout the capillary surface with no reabsorption into the capillary. The entire filtrate will become lymphatic water load which needs to be removed from the interstitium by the lymphatic system. (Note: This diagram was modified from Reference #7.)

EXCEPTIONS TO THE REVISED STARLING’S EQUILIBRIUM

As mentioned above, the sum of all Starling forces does not cause absorption in the venous capillaries. However, capillaries and post-capillary venules can absorb fluid for a short period of time if the Starling pressures are disturbed.

For example, in the case of hemorrhaging, pre-capillary vasoconstriction - combined with a drop in both arterial and venous pressures - will reduce capillary pressure sufficiently for transient (temporary) absorption to develop. Very soon, however, the reabsorption of interstitial water raises the protein concentration in the pericapillary space, thus raising the local osmotic pressure in the interstitium. Consequently, reabsorption stops and slight filtration is restored.

Also, sustained absorption of fluid into capillaries is a normal function of intestinal mucosal capillaries, renal peritubular capillaries, and lymph node capillaries, but not peripheral tissue.
**Blood Capillary Pressure**

**Active and Passive Hyperemia**

The average blood pressure in the aorta is 100 mmHg; at the vena cava, it’s only 2-4 mmHg. The blood pressure undergoes a steep drop at the small arteries and arterioles. Together, they account for about 50% of the total peripheral resistance (Fig. 11).

![Fig. 11](image1)  
*Fig. 11* Diagram showing the average blood pressure in different parts of the systemic circulation.

The muscle in the wall of the precapillary arteriole is regulated by the sympathetic nervous system. This accounts for the resting arterial tone. The vasomotor activity of the precapillary arterioles is regulated by the O₂ concentration and the metabolism of the tissues as well as other influences such as thermal and hormonal fluctuations.

![Fig. 12](image2)  
*Fig. 12* Precapillary arterioles are rich in smooth muscle fibers.  
Postcapillary venules have much less muscle tissue in their walls.
ACTIVE HYPEREMIA

If the sympathetic nervous system is activated, the number of impulses reaching the periphery increases, the muscle tone increases, the arteriole contracts, and the blood capillary pressure and the blood flow decreases.

A decrease in muscle tone results in the opposite response. The precapillary arterioles dilate and blood flow increases. This leads to increased blood volume in the capillaries and increased blood capillary pressure, a state called active hyperemia. As a consequence of active hyperemia, BCP increases leading to increased filtration – lymphatic load increases! (Fig. 13) Active hyperemia can be caused by inflammation (Fig. 14), massage, or the application of heat (Fig. 15).

Fig. 13 Comparison of normal capillary perfusion (left) and increased capillary volume in active hyperemia (right).

Fig. 14 Patient with BLE lymphedema and cellulitis of the LLE.

Fig. 15 Use of a heating pad may result in active hyperemia.
PASSIVE HYPEREMIA

In cases of venous obstruction or poor venous return, there is more blood volume in capillaries which increases blood capillary pressure. This state is called passive hyperemia. As a consequence of passive hyperemia, BCP increases leading to increased filtration – lymphatic load increases! (Fig. 16) Passive hyperemia can be caused by congestive heart failure (Fig. 17), deep venous thrombosis (Fig. 18), tumor growth, or chronic venous insufficiency.

Fig. 16  Comparison of normal capillary perfusion (left) and increased capillary volume through passive hyperemia (right).

Fig. 17a  Patient with BLE edema from congestive heart failure.

Fig. 17b  Same patient after diuretic treatment.

Fig. 18  Patient with LUE lymphedema and DVT in the left subclavian vein.
Hypoproteinemia

**Hypoproteinemia** is a condition where there is an abnormally-low level of protein in the blood. The decrease of plasma protein in the systemic circulation causes increased capillary filtration. As a consequence of hypoproteinemia, lymphatic load increases!

Hypoproteinemia can be caused by malnutrition, malabsorption, liver disease, nephrotic syndrome (renal disease) or protein-losing enteropathy.

![Fig. 19](image_url) Patient with BLE edema as a result of malnutrition.

The following conditions can potentially increase lymphatic load:

- **Active Hyperemia** (dilation of the precapillary arterioles)
- **Passive Hyperemia** (venous obstruction or decreased venous return)
- **Hypoproteinemia** (decreased plasma protein concentration)
High and Low Output Failure of the Lymphatic System

**HIGH OUTPUT FAILURE**, a.k.a. high volume insufficiency or dynamic insufficiency.

In high output failure, the lymphatic load exceeds the transport capacity of a healthy lymphatic system. The result of high output failure is edema (Fig. 20).

Edema as a result of high output failure is usually low in protein (<1.0 gm/dl protein) and is NOT lymphedema. High output failure of the lymphatic system can be caused by conditions such as congestive heart failure or chronic venous insufficiency. It may also occur from venous obstruction such as with deep venous thrombosis or a tumor growth obstructing the venous return.

![Fig. 20](image)

**LOW OUTPUT FAILURE**, a.k.a. low volume insufficiency or mechanical insufficiency.

In low output failure, the lymph system is unable to remove the necessary lymphatic load from the interstitium due to organic or functional causes. The result of low output failure is lymphedema! (Fig. 21)

Examples of *organic* lymphatic failure include valvular insufficiency, thrombosis, and sclerosis of the lymph vessels. Examples of *functional* lymphatic failure include obstruction of the lymphatic vessels by tumor growth, or scarring from surgery and/or radiation.

![Fig. 21](image)
COMBINED LYMPHATIC INSUFFICIENCY

Combined lymphatic insufficiency is a mixture of high and low output failure of the lymphatic system. The lymphatic system is impaired so transport capacity is reduced. At the same time, the lymph load is higher than normal. (Fig. 22)

Fig. 22 Combined lymphatic insufficiency. Combination of high and low output failure.

Here are two examples of combined lymphatic insufficiency:

1. In a patient with congestive heart failure, the lymphatic load increases and can cause high output failure. If the condition becomes chronic, the lymphatic system can become fatigued and develop low output failure in addition to the existing high output failure.

2. If a patient with primary lymphedema of the lower extremity develops chronic venous insufficiency or congestive heart failure, the transport capacity is reduced because of the congenital impairment of the lymphatic system. In addition, the lymphatic load can be higher than normal.

Hemodynamic Insufficiency

Hemodynamic insufficiency is similar to high output failure in that the lymphatic load exceeds the transport capacity of a healthy lymphatic system leading to edema. However, the situation is complicated because the lymphatic system is unable to adequately return fluid to the systemic circulation because of high central venous pressure.

Example: Congestive heart failure causes increased venous pressure which leads to passive hyperemia and an increased lymph load. The lymphatic system tries to return the extra fluid into the venous system through activation of the lymphatic safety function. Lymphatic transport increases. Unfortunately, the venous pressure is also elevated in the subclavian vein and the thoracic duct is unable to unload the increased lymphatic load back into the venous system resulting in edema. Edema from congestive heart failure is low in protein and generalized throughout the body. However, the swelling is much more pronounced in the lower extremities because of dependence in either a seated or standing position.
Edema versus Lymphedema

Edema, or excess fluid in the body tissues, occurs primarily in the extracellular compartment (interstitium). Extracellular edema results from either abnormal leakage of fluid across capillaries from the plasma to interstitial spaces (increased filtration), or from failure of the lymphatic system to adequately return fluid from the interstitium to the blood.

Edema can also be classified as generalized edema (concerning the whole body) or local edema (present in only one part of the body). Any combination of extracellular, intracellular, generalized, and local edema is possible.

Lymphedema develops from low output failure due to a damaged or malformed lymphatic system. The lymphatic system can be damaged through surgery, radiation, or some type of dysplasia.
Factors in Edema/Lymphedema Formation

Any one of the following items, alone or in combination, can cause the formation of edema:

1. Increased capillary hydrostatic pressure
2. Decreased plasma proteins (hypoproteinemia)
3. Increased capillary permeability
4. Blockage of lymphatic return (lymphedema)

1. Increased capillary hydrostatic pressure
   May be caused by:
   A. Excessive retention of salt and water
   B. Decreased arteriolar resistance - heat, exercise, inflammation
   C. High venous pressure
      • Heart failure
      • Local venous block
      • Failure of venous pumps, e.g. paralysis, immobilized body part, valvular insufficiency

2. Decreased plasma proteins (hypoproteinemia)
   A. Loss of protein
      • In urine (nephrosis)
      • In the intestinal tract (enteropathy)
   B. Loss of protein from damaged skin
      • Burns
      • Wounds
   C. Failure to produce protein
      • Liver disease
      • Malnutrition

3. Increased capillary permeability
   A. Immune response resulting in histamine or other vasodilator release
   B. Toxins
   C. Bacterial infections

4. Blockage of lymphatic return (lymphedema)
   A. Blockage of lymph nodes by:
      • Cancer
      • Infection
      • Filarial parasites
      • Scar tissue
      • Other
   B. Lymphatic dysplasias
References - Anatomy and Physiology


