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LYMPHATIC CIRCULATION AND HEART FAILURE

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Objective: to summarize current knowledge about the interactions between the lymphatic/cardiovascular systems and interstitial tissue, which are associated with heart failure (HF). The authors attempt to answer the fundamental question of whether lymphatic insufficiency is a cause or consequence of HF. Understanding lymph formation processes in HF will allow finding new ways of treating HF.

Keywords: lymphatic system, heart failure, Starling equation, interstitial fluid, lymph, lymphatic drainage.

INTRODUCTION

One of the main physiological functions of the body is water metabolism to maintain fluid homeostasis. Three types of fluids are involved in this process: blood (plasma), interstitial fluid and lymph. The complex mechanisms of movement of water molecules between these compartments have the ultimate goals of delivering nutrients and oxygen to all cells of the body and expelling toxic products of metabolism back through the kidneys, lungs and liver.

The cardiovascular system supplies blood to all organs and tissues, where, by convection, ultrafiltration or diffusion, water, nutrients and oxygen reach the cells through the endothelial capillary wall into the interstitial space (IS). From the IS, the fluid returns back through the lymphatic system (LS) to the circulatory system. These systems, which regulate water exchange between blood, interstitium and lymph, work together to maintain the body's homeostasis. Moreover, each system has a certain buffer capacity, and the failure of one of them affects the relative fluid balance between the sectors.

Of the three fluid types, most is known about blood and the circulatory system, as the heart and large vessels are relatively easy to visualize, and have been studied in detail. In contrast, LS and formation processes of interstitial fluid (IF) have been much less studied and so is their role in development of signs, symptoms and organ dysfunction in heart failure (HF), which can be seen as the inability of LS to adequately compensate for increased fluid flow from the circulatory system to IS. This paper presents current evidence on lymphatic formation and the mechanisms by which lymph returns to the circulatory system, and considers the consequences of inadequate lymphatic flow (LF). Lymph drainage techniques will be explored as an effective therapeutic measure in refractory HF to reduce edema.

The development of new LS imaging technology would expand our understanding of the interaction between the circulatory system and LS in HF and begin to develop new methods for normalizing LF into the venous system.

INTERSTITIAL FLUID FORMATION

In 1894–96, Starling [1, 2] found, based on his experiments on an isolated canine hind limb, that saline solution introduced into the interstitial tissue is absorbed into the bloodstream. He thus concluded that hydrostatic pressure is responsible for fluid ***filtration,*** oncotic pressure is responsible for fluid ***reabsorption***, and that there is a balance between hydrostatic and osmotic pressures in the capillaries and the surrounding tissue, which determine the filtration and reabsorption processes between the capillaries and the tissue.

On this basis, he proposed a classical model that describes the process of fluid filtration and reabsorption in the capillaries as a process of interaction between hydrostatic and osmotic pressure on both sides of the capillaries, which he expressed through the equation, which later became known as Starling's equation (1).

$$Jv = LpS([Pc - Pi] - \sigma[\pi p - \pi i]), \quad (1)$$

where Jv is transcapillary fluid transport; Lp is hydraulic conductivity of the capillary wall; S is surface area of the capillary where fluids are exchanged; Pc is hydrostatic pressure of blood in the capillary; Pi is hydrostatic pressure in the interstitium; σ is reflection coefficient, which reflects protein permeability in the capillaries; πp is capillary colloid osmotic pressure; πi is interstitial colloid osmotic pressure.

When Jv is positive (i.e., when the difference in hydrostatic pressure exceeds the difference in osmotic pressure), the process of fluid ***filtration*** from capillaries into the IS occurs. When Jv is negative, the liquid passes

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from the IS back to the capillaries When Jv is positive (i.e., when the difference in hydrostatic pressure exceeds the difference in osmotic pressure), the process of liquid filtration from capillaries into the IS occurs. When Jv is negative, the liquid passes from the IS back to the capillaries – a ***reabsorption*** process.

In accordance with this, E. Starling argued that the difference between hydraulic pressure in the arterial side of the capillaries and osmotic pressure in the tissues determines fluid filtration from the capillaries in the IS, and that reverse reabsorption of fluid from the IS occurs in the venous side of the capillaries.

A diagram illustrating Starling's hypothesis is shown in Fig. 1.

At the arterial end of the capillary, hydrostatic pressure in the capillary exceeds oncotic pressure in the plasma, resulting in fluid filtration from the vessel into the tissue.

At the venous end of the capillary, hydrostatic pressure drops, oncotic pressure in the plasma turns out to be higher than hydrostatic pressure, and as a result there is a backflow of fluid (*reabsorption*).

Elsewhere, Starling postulated that increased venous pressure (VP) in HF patients is the result of increased blood volume, most likely due to renal fluid retention, and not just due to a mechanical increase in VP with poor cardiac function [3]. In the same work, he proposed the following mechanism of edema in patients with HF: "It seems likely that obstruction of lymph flow from the thoracic duct (TD) into the blood, as well as stretching of the TD, due to a significant increase in lymph formation in the liver, may contribute to the occurrence of edema in the rest of the body".

Starling's work subsequently triggered so many preclinical studies aimed at understanding the mechanisms of lymph formation and interaction between blood, interstitium and lymph.

About 60 years later, A. Guyton, measured the internal hydrostatic pressure, in a perforated capsule implanted into the tissue, corresponding to the pressure in the IS close to the atmospheric pressure [4]. This was later confirmed by other researchers and naturally is equal to 2 mmHg [5, 6].

Interstitial oncotic pressure was also measured in the fluid accumulating in the capsule and was found to be 9–15 mmHg, much higher than previously thought [7].

Since in normal conditions, hydrostatic pressure on the arterial side of the capillaries is ~35 mmHg, whereas on the venous side of the capillary, it is ~15 mmHg, which indicates a positive gradient of filtration from capillary to IS along the entire length of the capillary. Therefore, an important conclusion was made that in norm there is no venous reabsorption along the entire capillary length, although in certain types of pathology, associated, for example, with a drop in blood pressure (BP) in hypovolumic shock, fluid reabsorption from the venous side of the capillary is possible [8–10].

Thus, Starling's concept, which had existed for more than 100 years, was found to be erroneous. Recent discoveries have completely changed the idea of the mechanism of interstitial capillary fluid evacuation. This is based on the fact that in normal conditions, even in venous stasis, all interstitial ultrafiltrate is completely removed through capillaries in the IS and further removed exclusively by the LS, i.e. there is no venous reabsorption (Fig. 2).

It is important to understand that Starling forces leading to IF formation differ in different parts of the body due to differences in hydrostatic pressures at capillary level. For example, sinusoidal pressure in the liver is ~5 mmHg and capillary pressure in soft tissues is ~35 mmHg. The only variable in Starling's equation for all organs and tissues is the oncotic pressure of plasma in the capillary (πp), which is ~24 mmHg.

Therefore, for a positive balance of filtration from the capillaries into the IS, the oncotic pressure in the interstitium (πi) must also be different for different organs. In

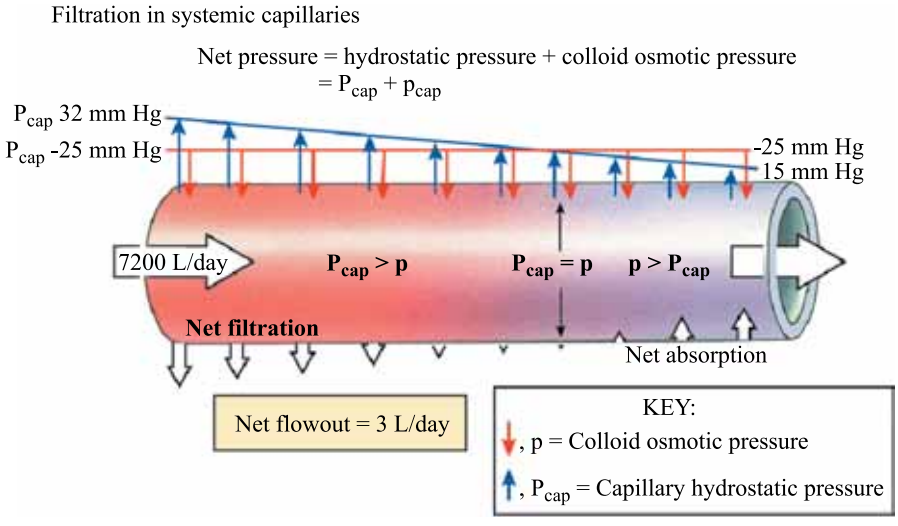

Fig. 1. Fluid movement according to Starling's law

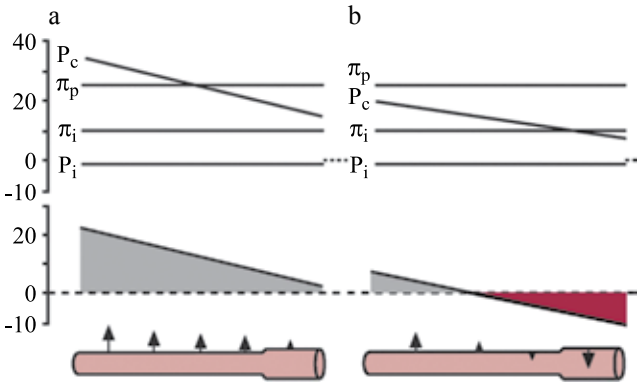

Fig. 2. a) New concept of liquid filtration in the capillary; b) Filtration/adsorption concentration of fluid in the capillary according to Starling's law

addition, the permeability of capillary endothelium for proteins (σ) must differ to allow regulation of flow of proteins from the capillaries into the IS. Consequently, lymph composition and flow, which reflect the composition of the interstitial ultrafiltrate, may differ significantly in different organs.

THE PROCESS OF FLUID REMOVAL FROM THE INTERSTITIAL SPACE TO THE LYMPHATIC SYSTEM

Tissue edema, one of the main clinical manifestations of HF, involves accumulation of fluid in interstitial tissues. The volume of this fluid depends on the balance between capillary filtration and lymph outflow into the venous system (Fig. 3).

In this case, LS is practically the only mechanism for IF removal and transport into systemic bloodstream. As stated above, capillary filtration is determined by the balance of hydrostatic and oncotic pressure (modified Starling equation) and capillary permeability.

Hydrostatic interstitial pressure in most tissues is lower than atmospheric pressure [11], while central venous pressure (CVP) is approximately 5 mmHg and energetically active mechanisms are required for lymphatic transport.

It has been established that lymph movement in vessels is provided both by external factors (compression from surrounding tissues, intestinal peristalsis, external respiratory pressure fluctuations, massage, pulsation of blood vessels, etc.) and internal factors (contractions of lymphatic vessels, the walls of most of which contain a muscular layer that has general biochemical and functional characteristics comparable to those of vascular and cardiac muscles). A segment of the lymph vessels are between the two valves, called the lymphangiome (Fig. 4), which contracts similarly to cardiac muscle [12].

Besides, lymphatic valves are an important mechanism for ensuring unidirectional lymph flow. The pressure differential required to close the lymphatic valve depends largely on the vessel diameter: less than 1 cm H_2O at a small diameter to several cmH_2O when the vessel diameter is close to maximum [13]. Thus, the valves become less effective in dilated vessels, potentially contributing to reverse lymphatic flow when the vessels are chronically dilated, such as in HF [14, 15].

It has been shown that at rest, $^1/_3$ of lymph flow (LF) in human lower extremities depends on compression of skeletal muscle contractions (external pump) and $^2/_3$ of active pumping of collecting vessel network (internal pump), and that active contraction of lymphatic vessels can create from 20 to 120 mmHg pressure [16, 17].

At the same time, the main pathway of LF is the thoracic duct (TD) through which $^3/_4$ of all lymph (from the lower extremities, pelvic walls and organs, abdominal cavity, left half of the chest cavity, left upper extremity, left half of the head and neck) moves to the venous system (Fig. 5). $^1/_4$ of LF is formed by the fusion of the right bronchomediastinal, subclavian and jugular trunks and flows into the right venous system [18].

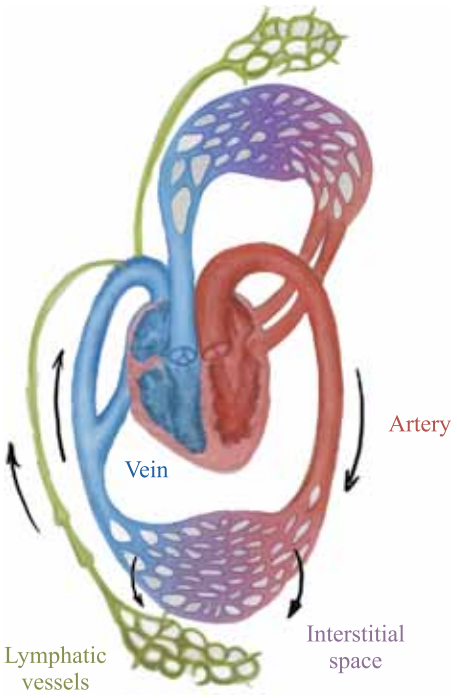

Fig. 3. Interaction between the circulatory system and the lymphatic system

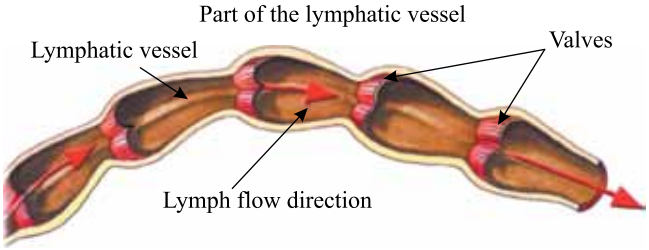

Fig. 4. Structure of the lymphatic vessel

RELATIONSHIP BETWEEN HF AND LF

Loop diuretics are the primary antiedema therapy in patients with HF to maintain euvolemic status. This is despite the lack of high-quality data demonstrating clinical benefit with respect to cardiovascular outcomes. However, in acute HF, patients may exhibit decreased sensitivity to diuretics, which is often referred to as diuretic resistance and is associated with a higher risk of rehospitalization and death [19, 20]. Features of LF in HF, which have linked the pathophysiology of pulmonary edema, have been the subject of many studies, who have shown significant increases in LF and TD pressure despite increased CVP in the lymph outlet area [21]. These studies have prompted several researchers to hypothesize that TD decompression may be one of the treatments for HF. Allen et. al [22] showed that external TD drainage in sheep with increased left atrial pressure reduces pulmonary edema and pleural effusion. Dumont et al. drained TD in 5 patients with HF [23].

Initial lymph drainage from TD ranged from 4–17 liters per day. There was immediate significant improvement in HF symptoms in all patients, a significant decrease in CVP and weight loss.

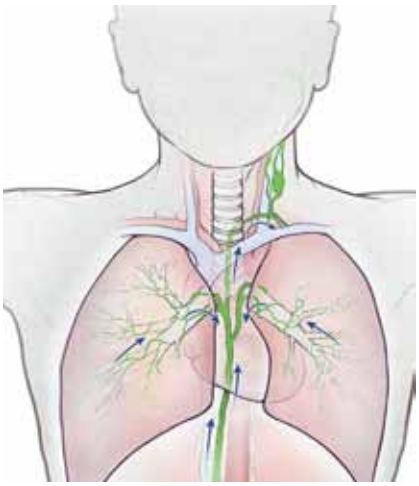

Fig. 5. Lymph flow from the thoracic duct to the vein

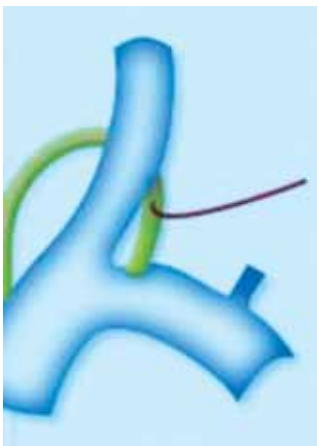

Fig. 6. Lymph drainage from the thoracic duct

In a subsequent study, Witte et al. [24] reported external TD drainage in 12 patients with CHF (four patients with compensated HF and 42 healthy patients; diuretics were discontinued during the whole lymphatic drainage period.

In doing so, they showed that LF from TD was significantly increased from ~1 mL/min to ~8 mL/min. TD pressures were elevated and correlated with elevated CVP. They also noted that HF symptoms improved within hours of initiating TD drainage. In contrast to diuretic treatment, which often leads to a worsening of renal function, they demonstrated a significant improvement in renal function in four oliguric patients. This effect could potentially be explained by decompression of the renal LS, resulting in decreased renal insufficiency and improved diuresis.

After these observations, Clauss and Breed [25] concluded that thoracic duct drainage can be used as therapy in CHF and the significant therapeutic effects of external drainage observed in these works can be explained simply by fluid removal, similar to the effects of diuresis.

Based on previous studies, Hraška V. [26] surgically anastomosed TD to the left atrium, the lowest pressure point in children with Fontan physiology, who had protein loss enteropathy and plastic bronchitis and which is known to result from lymphoedema. He reported significant improvement in symptoms in most of these patients, thus proving that such "internal decompression" of an overloaded LS can potentially eliminate the symptoms of LS edema.

CONCLUSION

There has been tremendous progress in the study of HF mechanisms over the past few decades. However, there are still many questions in understanding the pathophysiological mechanisms of patients' symptoms, which cannot be explained by cardiac muscle dysfunction and vascular system response alone. For many years and up to the present time, even with new basic scientific knowledge about ultrafiltrate formation and the important contribution of LS to fluid removal from tissue, this area remains relatively understudied in modern clinical medicine. The role of LS in chronic HF is still poorly defined.

The general consensus is that edema in heart failure should be seen as the inability of the lymphatic system to remove excess amounts of interstitial fluid. The process of significant increase of lymphatic flow in heart failure remains poorly investigated. Assuming that the only mechanism of fluid movement from the circulatory system to the interstitial space is filtration in the capillaries, the question arises about a significant increase in lymph flow in heart failure, which, in our view, may be associated with increased number of functioning capillaries. We put forward the idea that heart failure leads to decreased

capillary blood flow, which results in oxygen deficiency in the distal ends of capillaries and therefore in the tissue surrounding these ends of capillaries. The natural reaction to this is the opening of the sphincters in this area and the inclusion of additional functioning capillaries into the blood flow and, accordingly, this should lead to increased filtration flow in the interstitial space.

As many studies have shown, in heart failure conditions, increase in lymph production is not compensated by lymph outflow into the venous system, which leads to edema in the organs and tissues. Therefore, one of the promising methods of mechanical support for lymph outflow into the venous system in heart failure involves a local reduction of elevated venous pressure in the area of lymph outlet into the venous system.

The relatively recent clinical introduction of lymphatic system imaging technique based on magnetic resonance lymphangiography provides the basis for a more in-depth analysis of interaction between the lymphatic system and the system in heart failure [27–29].

The authors declare no conflict of interest.

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