Lymphodynamics

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Summary of Basic Concepts

As a tributary of the arteriovenous blood circulation, the lymphatic vasculature plays an exquisite, finely modulated role in the regulation of body fluid homeostasis and interstitial fluid balance.

- It is estimated that approximately one-sixth of the body's total volume resides in the interstitial space.
- The lymphatic circulation is responsible for unidirectional fluid transport.
- By definition, without any initial change in composition, the interstitial fluid becomes lymph once it enters the initial lymphatics.
- Under resting conditions, it is estimated that there are 2–3 l/day of lymph formed in the human body.
- Entry of interstitial fluid into the lymphatic capillary is primarily governed by the prevailing interstitial fluid pressure.
- Any physical force that increases interstitial fluid pressure will increase lymph flow.
- Lymph flow becomes maximal when interstitial pressure is slightly higher than the atmospheric pressure.
- The lymphatic circulation relies upon the effects of both intrinsic and extrinsic pumps.
- Cyclical changes in prevailing pressure gradients provide the dynamic forces that favor fluid entry.

As a tributary of the arteriovenous blood circulation, the lymphatic vasculature plays an exquisite, finely modulated role in the regulation of body fluid homeostasis and interstitial fluid balance. An estimated one-sixth of the body's total fluid volume resides in the interstitial compartment [6].

In this context, the lymphatic circulation is responsible for unidirectional fluid transport, moving protein-enriched fluid from the interstitium through a complex vascular network that converges upon the thoracic duct(s) and, ultimately, the great veins [1].

Given the near inaccessibility of the lymphatic vasculature to direct visualization or instrumentation, it is not surprising that insights into the dynamics of this vascular system have been slow to accrue. Remarkably, substantial progress has been made, particularly in the last 20 years.

By definition, without any initial change in composition, the interstitial fluid becomes lymph once it enters the initial lymphatics. The protein content of lymph is determined by the cellular identity of its organ of origin. In most of the body's tissues, interstitial fluid protein concentration approximates 2 g/dl, but mesenteric lymph protein content approaches 3–4 g/dl and that of the liver is even higher. Ultimately, lymph derived from the thoracic duct reflects the relative contributions of these various elements and approximates concentrations of 3–5 g/dl.

Under resting conditions, it is estimated that there are 2–3 l/day of lymph formed in the human body. Thus, it is apparent that in the absence of intact lymphatic transport

mechanisms, circulatory collapse would occur promptly: it has been estimated that the total plasma volume of the human body (≈3 L) extravasates from the blood circulation every 9 h and the vast preponderance of this fluid is transported back to systemic circulation through the lymphatic system [7, 8].

Entry of interstitial fluid into the lymphatic capillary is primarily governed by the prevailing interstitial fluid pressure which, under steady-state conditions, is typically subatmospheric [9]. In situations where the pressure drops below the normal value of −6 mmHg, lymph flow becomes negligible. In contrast, any physical force that increases interstitial fluid pressure will increase lymph flow. Such factors chiefly reflect the influence of Starling forces, such that *increased capillary hydrostatic pressure*, *decreased plasma oncotic pressure*, or *increased interstitial oncotic pressure*, along with *increased capillary permeability*, can all result in an increase in tissue lymph production. Lymph flow becomes maximal when interstitial pressure is slightly higher than the atmospheric pressure. It is somewhat paradoxical that the typical prevailing pressure gradients do not seem to favor fluid entry into the terminal lymphatics [1]. Based upon the available evidence, it has been proposed that *cyclical* changes in prevailing pressure gradients provide the dynamic forces that favor fluid entry [10–12]. Furthermore, there is accruing evidence [2, 13, 14] that active regulation of transendothelial transport of solutes, lipids, and even water across lymphatic capillaries can occur [3]. These active mechanisms are hypothesized to potentiate rapid control over lymph formation rates without altering lymphatic vessel integrity [3].

Beyond hydrodynamics, in order to drive fluid transport through the vasculature, the lymphatic circulation relies upon the effects of both intrinsic and extrinsic pumps [4, 15]. The extrinsic pump mechanism is constituted by the cyclical lymphatic compression and expansion that derives from the operation of extrinsic tissue forces [1]. Extrinsic forces can include the physical movements of parts of the body, contraction of the skeletal musculature, arterial pulsation, and tissue compression by extrinsic forces. Ultimately, normal lymphatic pump function is determined by the intrinsic properties of lymphatic muscle and the regulation of pumping by lymphatic preload, afterload, spontaneous contraction rate, contractility, and neural influences [4].

Historically, the effect of physical activity on lymph flow was deduced from direct measurements after direct thoracic duct cannulation, but previously, there have been no studies of thoracic duct flow as a function of exercise intensity. More recently, it has become feasible to surgically instrument the canine thoracic lymph duct with ultrasonic flow transducers and, after surgical recovery, to determine the effect of exercise intensity [16].

Such experimentally derived insights will be necessary if, in future, we desire to harness the forces of lymphatic physiology for enhanced lymphatic imaging, diagnostics, and therapeutics. Lymphatic contractile dysfunction, barrier dysfunction, and valve defects are observed in disorders that directly involve the lymphatic system, such as inherited and acquired forms of lymphedema, and systemic disorders that indirectly involve the lymphatic system [4]. Just one clinically relevant example resides in the fact that there is growing evidence for constitutive alterations in the lymphatic pumping mechanisms that are thought to contribute to the pathogenesis of breast cancer-associated lymphedema [5, 17].

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