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Review

Hydrodynamic regulation of lymphatic transport and the impact of aging

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Abstract

To accomplish its normal roles in body fluid regulation/macromolecular homeostasis, immune function, and lipid absorption; the lymphatic system must transport lymph from the interstitial spaces, into and through the lymphatics, through the lymphatic compartment of the nodes, back into the nodal efferent lymphatics and eventually empty into the great veins. The usual net pressure gradients along this path do not normally favor the passive movement of lymph. Thus, lymph transport requires the input of energy to the lymph to propel it along this path. To do this, the lymphatic system uses a series of pumps to generate lymph flow. Thus to regulate lymph transport, both lymphatic pumping and resistance must be controlled. This review focuses on the regulation of the intrinsic lymph pump by hydrodynamic factors and how these regulatory processes are altered with age. Intrinsic lymph pumping is generated via the rapid/phasic contractions of lymphatic muscle, which are modulated by local physical factors (pressure/stretch and flow/shear). Increased lymph pressure/stretch will generally activate the intrinsic lymph pump up to a point, beyond which the lymph pump will begin to fail. The effect of increased lymph flow/shear is somewhat more complex, in that it can either activate or inhibit the intrinsic lymph pump, depending on the pattern and magnitude of the flow. The pattern and strength of the hydrodynamic regulation of the lymph transport is different in various parts of the lymphatic tree under normal conditions, depending upon the local hydrodynamic conditions. In addition, various pathophysiological processes can affect lymph transport. We have begun to evaluate the influence of the aging process on lymphatic transport characteristics in the rat thoracic duct. The pressure/stretch-dependent activation of intrinsic pumping is significantly impaired in aged rat thoracic duct (TD) and the flow/shear-dependent regulatory mechanisms are essentially completely lacking. The loss of shear-dependent modulation of lymphatic transport appears to be related to a loss of normal eNOS expression and a large rise in iNOS expression in these vessels. Therefore, aging of the lymph transport system significantly impairs its ability to transport lymph. We believe this will alter normal fluid balance as well as negatively impact immune function in the aged animals. Further studies are needed to detail the mechanisms that control and alter lymphatic transport during normal and aged conditions.

Keywords: Lymphatics; Lymphangion; Lymph pressure; Lymph flow; Lymph pump; Aging

Contents

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1. Introduction – lymphatic transport

To maintain overall body homeostasis and health, the lymphatic system has a number of important tasks it must achieve. Lymph transport is a critical part of processes involved with body fluid regulation, macromolecular homeostasis, lipid absorption, and immune function. Lymphatic transportation of the constituents of lymph begins when fluid and other lymph elements from the parenchymal interstitial spaces, crosses the lymphatic endothelium and moves into the network of lymphatic capillaries. These lymphatics are called by various names, including lymphatic capillaries, initial lymphatics or terminal lymphatics and are the site of the exchange of fluids and constituents between the interstitium and the lymph (i.e. lymph formation) [1]. These lymphatics are typically noted by a lack of muscle cells, a discontinuous basement membrane, endothelial cells with gaps between adjacent cells and special connections to the surrounding matrix called anchoring filaments [2–4]. The exact mechanisms by which these processes occur and are regulated are still unclear, although the preponderance of data shows that convective mechanisms governed by transient gradients in fluid pressures drives the entry of lymph through the inter-endothelial cell gaps and into the initial lymphatic lumen [5–8]. Once within the lymphatic lumen, this fluid and whatever constituents it may contain are properly called lymph. Clearly a better mechanistic and molecular understanding of this process and how it is regulated is needed [9,10]. The lymph must then be moved within the network of lymphatic vessels from the initial lymphatics, into and through the first lymph node where much of the learned immune response develops [11–13]. Lymph will exit the lymph node (after its cell and molecular constituents may have been altered) through the efferent lymphatics. These efferent lymphatics join with other large and small lymphatics to continue through a series of lymph nodes and more post nodal lymph ducts. The larger transport lymphatics will eventually converge into the thoracic duct (for the lower half and upper left quadrant of the body) and right lymphatic duct (for the upper right quadrant of the body) before eventually emptying their lymph into the great veins. This movement of lymph within the lymphatic network, from where it is formed in the initial lymphatics to its final exit into the venous compartment will be dictated by the inherent pressure gradients within that network. Normally the net pressure gradient from the lymphatic capillaries to the venous compartment does not favor the passive flow of lymph centrally. Thus the movement of lymph along the lymphatic network relies on forces that are generated both extrinsically and intrinsically to the lymphatic system (i.e. the extrinsic and intrinsic lymph pumps) and upon the presence of lymphatic valves to minimize backflow. Of critical importance is that both the generation of lymph flow by intrinsic forces and the regulation of flow by both intrinsic and extrinsic forces, rely on the phasic and tonic contraction of lymphatic muscle to produce a controlled net unidirectional transport of lymph. The regulated movement of lymph through this network is absolutely necessary for its transport of fluid, macromolecules, lipids, antigens, immune cells and particulate matter. Thus it is crucial to remember that principal purpose of the lymphatic system is the transport of lymph and that by this regulated lymph transport all the functions that the lymphatic system participates in are served [12].

Table 1
Depiction of the pressures found in different sections of the lymphatic network. Lymph flow begins in the most peripheral portions of the network architecture and continues through the network of lymphatics and nodes towards the final junction of the main lymphatic trunks with the venous circulation (noted by arrows).

Lymphatic network position/flow direction	Lymph/blood vessel	Pressure (mmHg)
Outflow compartment	Left jugular vein	5.8
Most central lower left 3/4	Thoracic duct	5.1
Most central upper right 1/4	Right lymphatic duct	2.1
↑	Left jugular trunk	0.8
↑	Heart efferent trunk	2.9
↑	Hepatic trunk	3.4
↑	Intestinal trunk	3.6
↑	Left lumbar trunk	2.7
Most peripheral	Femoral trunk	0.5

2. Intrinsic and extrinsic lymph pumps

As briefly described above, both extrinsic and intrinsic driving forces can support lymph flow. The intrinsic pump relies on the spontaneous contractions of the muscle cells within the wall of the lymphangion (a section of lymphatic between adjacent valves [14–16]) to generate the pressure to drive lymph flow centrally. The extrinsic lymph pump depends on sources outside the lymphatic (blood vessel pulsations, gastrointestinal muscle contractions, heart contractions, skeletal muscle contractions, breathing movements, etc.) to generate the pressure to drive lymph centrally. Thus, lymph pressure within the lymphatic network is dependent on both the intrinsic and extrinsic forces. The pressures within the various parts of the lymphatic network will dictate the pressure gradient that open and close lymphatic valves and drive flow. There are few studies that have measured lymph pressures along significantly large sections of the lymphatic network to give a comparatively complete understanding of the pressure gradients along it. The most extensive representation of lymph pressures in the lymphatic system was reported by Szabo and Magyar [17]. These measurements of lymph pressure were made via the cannulation of some of the major lymphatic vessels in dogs. While the pressures in each vessel varied over time with various actions, the average pressures can be seen in Table 1. This study demonstrated that there was not a net pressure gradient along lymphatic system that would favor passive lymph flow. Thus the phrase "lymph drainage" is somewhat of a misnomer, since the normal average pressure gradients in the lymphatic network do not favor central lymph flow and "vis a tergo" (the force of