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Comprehensive Review

Role of Lymphatics in Heart Failure

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ABSTRACT

The lymphatic system plays a crucial, yet often overlooked, role in maintaining fluid homeostasis, and its dysregulation is a key feature of heart failure (HF). Lymphatic dysregulation in patients with HF typically results from a combination of self-perpetuating congestive mechanisms, such as increased fluid filtration, decreased lymph drainage into the central venous system, impaired lymph vessel integrity, dysfunctional lymphatic valves, and dysfunctional renal lymphatic system. These pathomechanisms collectively overwhelm the lymphatic system and hinder its ability to decongest the interstitial space with subsequent manifestation and progression of clinical congestion. Targeting the lymphatic system to counteract these congestive pathomechanisms and facilitate interstitial fluid removal represents a novel pathway to treat congestion in HF. In this study, we discuss the physiological roles of the lymphatic system in fluid homeostasis and the pathophysiological alteration of these roles in HF. We also discuss innovative technologies that aim to use the lymphatic system pathway to treat congestion in HF and provide future directions related to these approaches.

Introduction

The circulatory system comprises 2 primary components: the cardiovascular system and the lymphatic system.[1] The cardiovascular system operates as a closed, high-pressure circulatory system, with the heart serving as the central pump.[1] By contrast, the lymphatic system functions as an open, low-pressure circulatory system without a central pump.[1] The lymphatic vascular system is present throughout most tissues, excluding bone marrow, cartilage, and the cornea.[1] Beyond its roles in immune cell trafficking, inflammatory modulation, and blood pressure regulation, the lymphatic system also plays a significant part in fluid homeostasis within the body. Dysregulation of the lymphatic system is associated with the development of self-propagating congestive mechanisms and is a key characteristic of congestive disorders, such as heart failure (HF).[2] The role of lymphatic dysregulation in patients with HF has been overlooked in the past decades mainly owing to the inherent complexity in visualizing, assessing, and accessing the lymphatic vascular system. However, advancement in imaging and interventional techniques over the past years along with the persistent need for innovative pathways to address congestion in HF has positioned the lymphatic as a potential target for HF therapy.

Physiological roles of the lymphatic system in fluid homeostasis

The semipermeable membrane within blood capillaries permits the daily filtration of several liters of fluids into the interstitial space.[3] This filtered fluid serves multiple physiological roles, such as tissue nourishment and hydration.[4] The volume of filtered fluid is determined by the Starling equation for fluid filtration, expressed as $J_V = L_pS[(p_c - p_i) - \sigma(\pi_c - \pi_i)]$.[3] In this equation, J_V represents the filtered volume per unit time; L_p, the membrane's hydraulic conductance; S, the capillary surface area available for filtration; p_c, the hydrostatic pressure within the capillaries; p_i, the hydrostatic pressure within the interstitial space; σ, the reflection coefficient; π_c, the oncotic pressure of plasma proteins; and π_I, the oncotic pressure of interstitial proteins (Figure 1).

In the physiological state, the lymphatic vascular system drains the accumulated filtered fluid within the interstitial space and returns it to the central venous system at a rate comparable with its accumulation rate in the interstitial space.[5] This collected fluid, along with immune cells, antigens, lipids, and proteins generated by tissue metabolic processes, collectively forms lymph.[5] Lymph is returned into the cardiovascular system through 2 major lymphatic ducts, namely the right lymphatic duct and the thoracic duct.[5] The right lymphatic duct drains lymph originating from the right side of the head, neck, thorax, and the

Abbreviations: CVP, central venous pressure; HF, heart failure.

Keywords: congestion; direct interstitial decongestion; fluid homeostasis; heart failure; lymphatic system.

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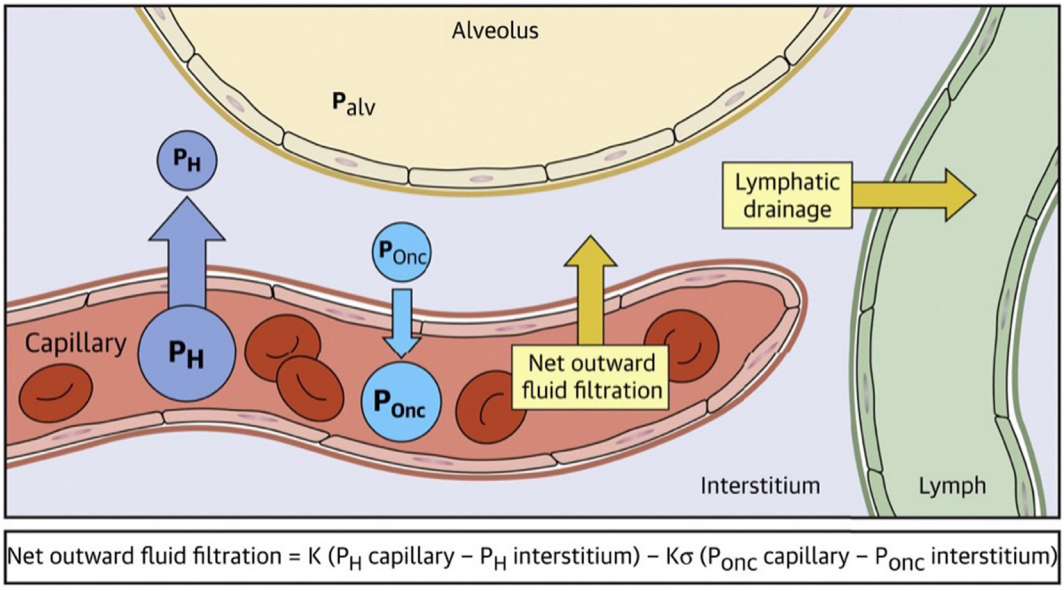


Figure 1.
Fluid filtration is governed by the Starling equation, which depends on the hydrostatic and oncotic pressures in the capillaries and the interstitium. K, constant; Palv, alveolar pressure; Ph, hydrostatic pressure; Ponc, oncotic pressure; σ, reflection coefficient. Figure is reproduced from Fudim et al.[2]

right upper extremity, emptying into the venous system at the junction of the right subclavian vein and the right internal jugular vein.[5] On the contrary, the thoracic duct collects lymph from the rest of the body and empties into the venous system at the junction of the left subclavian vein and the left internal jugular vein (Figure 2).[5]

Dysregulation of the lymphatic system in HF

Dysregulation of the lymphatic system in the context of HF is often overlooked, yet its contributions to the hemodynamic and clinical congestion in patients with HF play a key role in development and progression of HF syndrome and significantly modifies its response to treatments, such as diuretic therapy.[2,6] HF is primarily characterized by venous congestion, and the elevation of central venous pressure (CVP) plays a pivotal role in adverse clinical outcomes, such as impaired renal function, and serves as an independent predictor of mortality among patients with HF.[7] Furthermore, the majority of hospitalizations for HF are associated with signs of venous congestion rather than a decrease in cardiac output.[8] Endothelial cells within the blood vessels can sense biomechanical forces and respond to increased hydrostatic pressure by transitioning from a dormant state to an activated state, marked by inflammation, vasoconstriction, and increased oxidative stress.[9] Consequently, prolonged venous congestion can result in organ damage, which may manifest as pulmonary vascular remodeling, hepatic impairment, and renal damage.[9]

Similar to venous congestion, lymphatic congestion is a key feature of HF and plays a central role in the clinical presentation and adverse outcomes among patients with HF.[2,10] In HF, several interconnected pathophysiological mechanisms contribute to the accumulation of interstitial fluid, leading to clinical manifestations of congestion, such as peripheral edema, pulmonary edema, ascites, and renal dysfunction.[2,10] Although, the individual components of these pathophysiological mechanisms are unlikely to result in interstitial congestion; in the context of congestive disorders, such as HF, these pathophysiological abnormalities concurrently manifest and work in parallel, leading to disruption of the homeostasis of the lymphatic system with subsequent manifestations of clinical congestion. These mechanisms are summarized as follows:

1. Increased fluid filtration: elevated capillary hydrostatic pressure, essentially caused by venous congestion, results in increased fluid filtration.[11] In the absence of a proportional increase in lymph fluid drainage, interstitial congestion ensues.[11]
2. Decreased drainage: elevated CVP hinders the drainage of lymph through the thoracic duct and right lymphatic duct into the central venous system. This drainage process is a passive one that mainly relies on a negative pressure gradient between the lymphatic ducts and central venous system; therefore, an increase in CVP decreases lymph drainage into the central venous system.[2]
3. Impaired lymph vessel integrity and compliance: increased vascular permeability enhances the leakage of plasma and proteins into the interstitial space, which contributes to the accumulation of interstitial fluid.[12] HF is characterized by systemic inflammation, which increases vascular permeability and allows large molecules such as proteins to enter the interstitial space.[13] This, in turn, reduces plasma oncotic pressure while increasing interstitial oncotic pressure, resulting in a net increase in filtration volume. As the interstitial fluid accumulates, lymphatics adapt by altering their contractile activity. Although this adaptation is effective in acute inflammation, it decreases significantly in chronic inflammation, such as in HF, possibly indicating impaired lymph vessel integrity and compliance.[14] In addition, infiltrating neutrophils during inflammation release neutrophil elastase, which degrades elastin microfibril interfacer 1, weakening the intercellular junctions of lymphatic endothelial cells and leading to lymphatic vessel collapse.[15] In a recent study examining the concept of impaired lymph integrity in patients with HF, patients with HF with preserved ejection fraction exhibited decreased density but increased size of the lymphatic vessels on skin biopsies.[16]
4. Dysfunctional lymphatic and lymphovenous valves: lymphatic vessels contain lymphatic valves that regulate unidirectional lymph flow.[17] Dysfunction of these valves can result in lymph reflux and lymphedema.[17] Similarly, lymphovenous valves control the return of lymph to the cardiovascular system.[17] The chronic elevation of CVP seen in HF with the resultant retrograde pressure changes in the lymphatic system could potentially lead to dysfunctional lymphatic and lymphovenous valves.

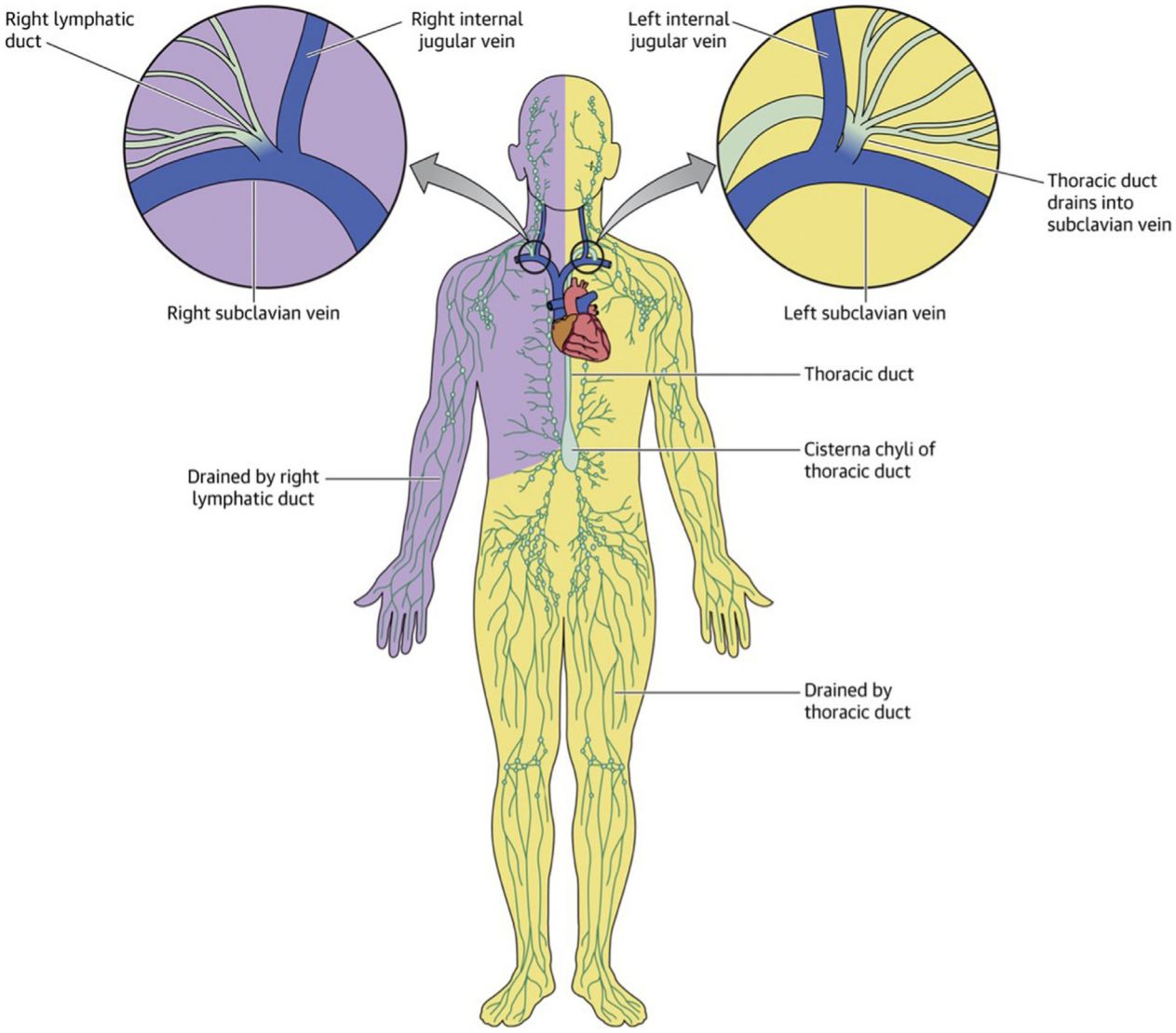


Figure 2.
The two major lymphatic ducts (the thoracic duct and the right lymphatic duct) return lymph to the cardiovascular system by passively emptying into the venous system. Figure is reproduced from Fudim et al.[2]

5. Dysregulation of the renal lymphatic system: elevated post-glomerular capillary hydrostatic pressure results in increased fluid filtration and the accumulation of fluids within the renal interstitial space.[10] The renal lymphatic system attempts to counteract this accumulation by increasing fluid drainage from the interstitial space, resulting in elevated lymph flow and pressure.[10] The rate of renal lymph flow is directly linked to CVP and may equal or even surpass the urinary output from the same kidney.[18] However, after a certain point, the renal lymphatic system becomes overwhelmed and unable to match the increased fluid filtration, ultimately causing interstitial space congestion and a rise in renal interstitial pressure.[19] In contrast to other organs, the kidney is encased in a rigid and nonexpandable capsule.[19] Consequently, increased renal interstitial pressure compresses renal structures, such as glomeruli, tubules, and intrarenal veins, leading to a state akin to "renal tamponade" with subsequent damage to the renal structures.[19] Renal compression can further exacerbate local inflammation, in addition to the systemic inflammation present in HF, resulting in further

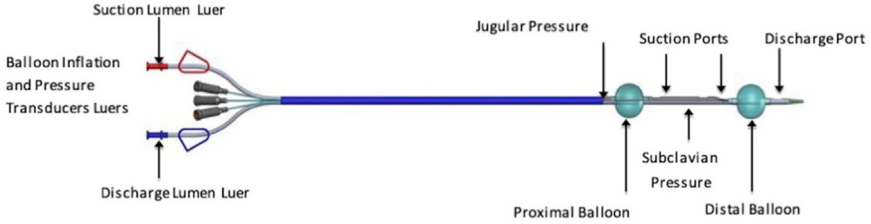


Figure 3.
Direct interstitial decongestion using the first generation of the WhiteSwell system. Figure is reproduced from Abraham et al.[36]

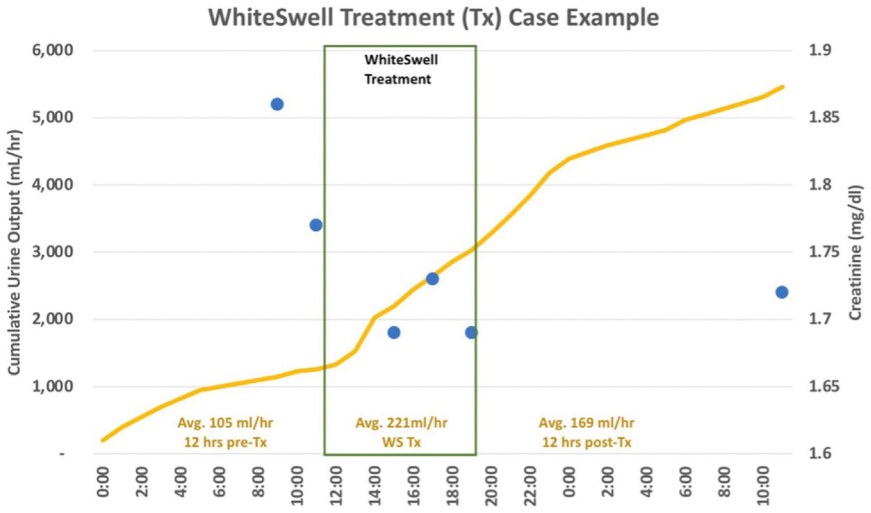


Figure 4.
In the first-in-human use of the direct interstitial decongestion system in a patient with heart failure, decongesting the lymphatic system resulted in a significant increase in urine output. Figure is reproduced from Abraham et al.[36]

compromise of renal blood and lymph vessel integrity and lymphatic stasis.[20,21] Furthermore, increased intrarenal pressure can potentially hinder kidney perfusion, ultimately contributing to renal dysfunction.

6. Alteration of cardiac lymphatics: similar to the role of the lymphatic system in other organs and tissues, cardiac lymphatics play an important role in regulating myocardial extracellular volume, and dysregulation of cardiac lymphatics due to maladaptive remodeling (as seen in various ischemic and nonischemic cardiac diseases) can result in myocardial edema.[22] Myocardial edema can subsequently trigger myocardial interstitial fibrosis and cardiac dysfunction.[22]

However, studies aiming at understanding the effect of lymphatic dysregulation on HF outcomes are sparse. Recent evidence suggests that the degree of lymphatic dysregulation in patients with HF, as assessed by the level of the lymphangiogenesis modulator vascular endothelial growth factor C, is directly associated with adverse HF outcomes (death and HF hospitalizations).[23,24]

Imaging modalities to assess the lymphatic system

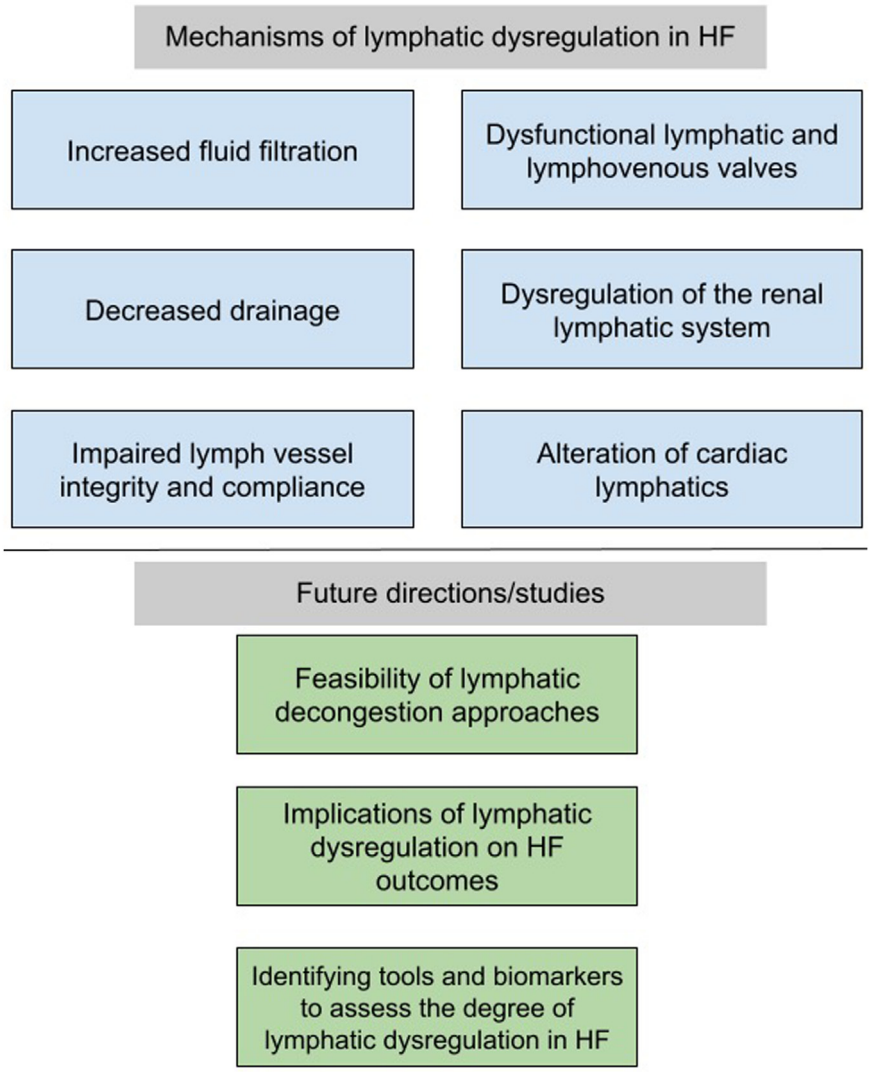
There are several imaging modalities that can be used to assess and visualize the central lymphatic system. Although none of these imaging modalities has been specifically studied in HF, they could potentially be helpful in assessing the degree of lymphatic dysfunction in HF and aid future interventional approaches targeting the lymphatic system as follows:

1. Pedal lymphangiography: this approach entails the insertion of needles into lymphatic ducts through small incisions on the dorsum of the feet.[25] Then, radiopaque ethiodized oil is injected through these needles, followed by normal saline.[25] This process eventually leads to opacification and visualization of the cisterna chyli and thoracic duct.[25]
2. Intranodal lymphangiography: this technique involves accessing the bilateral inguinal lymph nodes using 25-gauge spinal needles under ultrasound guidance.[25] Subsequently, oil-based contrast is injected under fluoroscopic guidance.[25]
3. Dynamic contrast-enhanced magnetic resonance lymphangiography: this imaging modality involves ultrasound-guided injection of gadolinium-based contrast into the inguinal lymph nodes with simultaneous dynamic acquisition of magnetic resonance images of the chest and abdomen.[26]

Targeting the lymphatic system in HF

The initial management of congestion in HF primarily centers on alleviating venous congestion, typically through the use of diuretics.[27,28] This approach aims to modify the Starling forces by reducing fluid filtration, which results from a decrease in capillary hydrostatic pressure, leading to an improvement in interstitial congestion.[27,28] However, in certain patients, this strategy often fails, partly because the self-perpetuating congestive mechanisms (especially renal congestive mechanisms) persist, hindering the kidney's response to diuretics with subsequent manifestation of diuretic resistance. Therefore, alternative decongestive approaches have been developed to overcome these limitations in selected patients. Ultrafiltration was proposed as an attractive strategy to predictably remove sodium and water from patients with congestion[29,30]; however, randomized evidence showed conflicting results and did not generally demonstrate superiority of ultrafiltration (compared with pharmacological strategies) regarding serum creatinine level and body weight changes but showed an increased risk of complications.[29,30] Although these results may be partly related to the use of a fixed rate of ultrafiltration irrespective of the patient's hemodynamic status and renal function, the efficacy and safety of ultrafiltration for decongestion in patients with HF are still not established.[29,30] Given the constant need for alternative decongestive strategies in patients with persistent congestion and the key role that the lymphatic system plays in congestion, targeting the lymphatic system has been proposed a novel pathway for fluid removal in patients with HF.

A number of early animal and human studies explored the feasibility and effectiveness of lymphatic drainage in HF. In a dog model of right HF through the combination of tricuspid insufficiency and pulmonary stenosis,[31] the construction of a thoracic duct-to-pulmonary vein shunt resulted in a rapid reduction in systemic venous pressure and an increase in urinary sodium and water excretion.[31] The initial documented attempt to target the lymphatic system for fluid removal in human dates back to 1963; in a study involving 5 patients with HF and intractable congestion despite diuretic therapy, passive lymph drainage through cervical thoracic duct cannulation resulted in a significant fall in CVP in all patients with improvement in congestive symptoms and signs (ie,



Central Illustration.

Several self-propagating congestive mechanisms are involved in lymphatic dysregulation in heart failure. Although targeting the lymphatic system can potentially provide a novel treatment pathway in heart failure, there remain significant gaps in our understanding of this approach and its feasibility. HF, heart failure.

distended jugular veins, peripheral edema, and ascites).[32] A subsequent study in 1969 examined cervical thoracic duct cannulation in 12 patients with HF and intractable congestion.[33] Thoracic duct cannulation in these patients resulted in a significant reduction in CVP (from a mean of 32.9-14.0 cm H_2O).[33] This reduction was also associated with an increase in urine output and improvement in clinical status.[33]

After these early studies, targeting the lymphatic system in patients with HF remained quiescent for several decades, mainly owing to significant advancement in medical therapy for HF over the following decades. However, given the increased complexity and rising burden of congestion over the past years coupled with major advances in imaging and transcatheter approaches,[34,35] novel approaches targeting the lymphatic system in patients with HF have been developed.

Direct interstitial decongestion

Direct interstitial decongestion using the WhiteSwell system (WhiteSwell) is a transcatheter delivered, device-based approach that comprises a multilumen catheter equipped with 2 compliant balloons, 1 positioned proximally and the other distally.[36] It also includes a blood pump mechanism that enables blood withdrawal between the balloons and its return through the distal end.[36] The system reduces local venous pressures within the region enclosed by the balloons, thereby promoting the drainage of interstitial fluid while ensuring the continued flow of blood through the left internal jugular and left subclavian veins.[36] To achieve this, a catheter with 2 balloons placed at intervals is inserted across the junction of the jugular and innominate veins.[36] When inflated, these balloons isolate the thoracic duct outflow.[36] Both balloons incorporate built-in flow paths to facilitate jugular and subclavian blood flow, and a blood pump is used to lower the pressure within the isolated area (Figure 3).[36]

This approach was initially studied in a sheep model of acute decompensated HF. Deployment and activation of the WhiteSwell device resulted in a reduction in the extravascular lung water with a moderately lower left ventricular filling pressures and increased urine output.[36] Subsequently, the system was examined in a patient with HF with preserved ejection fraction who was admitted for acute HF and received intravenous diuretics for 2 days with persistent congestion.[36] Introduction of the WhiteSwell device in this patient resulted in a significant improvement in urine output, reduction in CVP and N-terminal-pro-B-type natriuretic peptide, and improvement in orthopnea and edema (Figure 4).[36] The Safety and Feasibility of the WhiteSwell System

for the Reduction of Interstitial Fluid Overload in Patients With Acutely Decompensated HF ([SWIFTHF] NCT02863796) is an ongoing U.S. Food and Drug Administration early feasibility study that aims to evaluate this approach in the treatment of congestion in patients with acute HF.

Conclusion and future directions

The lymphatic system plays an integral but underappreciated role in fluid homeostasis and its dysregulation is a key characteristic in patients with HF. Dysregulation of the lymphatic system in patients with HF stems from several self-propagating congestive mechanisms that work concurrently and result in overwhelming of the interstitial drainage process with subsequent manifestations of congestion. Therefore, targeting the lymphatic system to counteract these congestive mechanisms and aid in direct interstitial decongestion represents a novel and attractive decongestive approach in patients with HF. However, as feasibility studies of this approach are underway, there is a pressing need for studies aiming at understanding the full dimensions of the relationship between lymphatic dysregulation and HF, such as different HF phenotypes and acuity (ie, acute vs chronic HF) and the implications of lymphatic dysregulation on HF outcomes. In addition, studies aiming to understand the short-term and long-term outcomes of targeting the lymphatic system are needed. Finally, there is a need for the development of tools and biomarkers to assess the degree of this dysregulation because this would help select patients with HF who may benefit the most from lymphatic interventions (Central Illustration).

Declaration of competing interests

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Ethics statement and patient consent

The research reported has adhered to the relevant ethical guidelines.

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