JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 6, NO. 11, 2021

EDITORIAL COMMENT

Targeting the Lymphatic System for Interstitial Decongestion*

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Congestion is the prevailing symptom in the majority of patients with acute heart failure (AHF). Additionally, most patients with congestion are also volume overloaded, indicating excessive sodium and fluid retention. Most of the sodium and fluid retention in heart failure occurs in the extracellular compartment, yet only 25% is retained in the intravascular space, while 75% is retained in the extravascular space (interstitium and third space). As a result, the ideal decongestive therapy in AHF patients with volume overload would need to be aimed at both removing excess water and sodium from the interstitial space and targeting the excessive plasma volume. Diuretic drugs stimulate renal natriuresis and diuresis, resulting in a reduction in plasma volume. If this is sustained, hemoconcentration of the intravascular space and a reduction in central filling pressures will result in a change of Starling forces in the microcirculation (where the intravascular space and the interstitium intersect with one another), leading to a process called plasma refill, which favors net reabsorption from the interstitium into the intravascular space. Then, once in the intravascular space, this fluid and sodium can be removed by the kidneys. Such a sequential decongestion approach (first targeting intravascular fluid, with subsequent interstitial decongestion) in clinical practice is often hampered because plasma refill rate kinetics drop during decongestion. This is related to a decrease in vasodilatory peptides, leading to a reduction in the capillary surface area (a component of the filtration coefficient K_f in the Starling equation) (1). Additionally, heart failure itself has been shown to be associated with a lower K_f, therefore hampering plasma refill before decongestive therapies are even begun (2). When the rate of diuresis outweighs refill rate kinetics, the ultimate result is intravascular contraction, hypotension, and worsening renal function, while the interstitium can remain volume overloaded. Therefore, having therapeutic interventions that can directly target interstitial volume overload would be valuable.

The interstitium is a complex gel-like structure consisting of glycosaminoglycan (GAG) networks with a negative electrostatic and negative hydrostatic pressure with 2 important characteristics: 1) a low compliance, which pushes any additional water out of the interstitium toward the lymph vessels; and 2) the ability to shield sodium from water because the negative GAG structure of the interstitium attracts the positively charged Na^+ and repels the bipolar molecule H_2O (see **Figure 1A** for normal interstitium) (3). Direct measurement of the hydrostatic interstitial pressure indicates that the normal interstitial hydrostatic pressure is around -2 mm Hg (4). In normal circumstances, the higher hydrostatic pressure in the capillaries favors filtration into the interstitium, supplying it and the cells embedded in it with nutrients (**Figure 1A**). Additionally, in normal circumstances, filtration into the interstitium is present in almost all microcirculations without reabsorption, even at the venule site of the microcirculation (with interstitial transudate totaling up to 8 L per day). This indicates that lymph flow is the predominant way to remove excessive interstitial fluid. In the case of congestion with increased capillary hydrostatic pressure, filtration into the interstitium is much higher.

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views *of JACC: Basic to Translational Science* or the American College of Cardiology.

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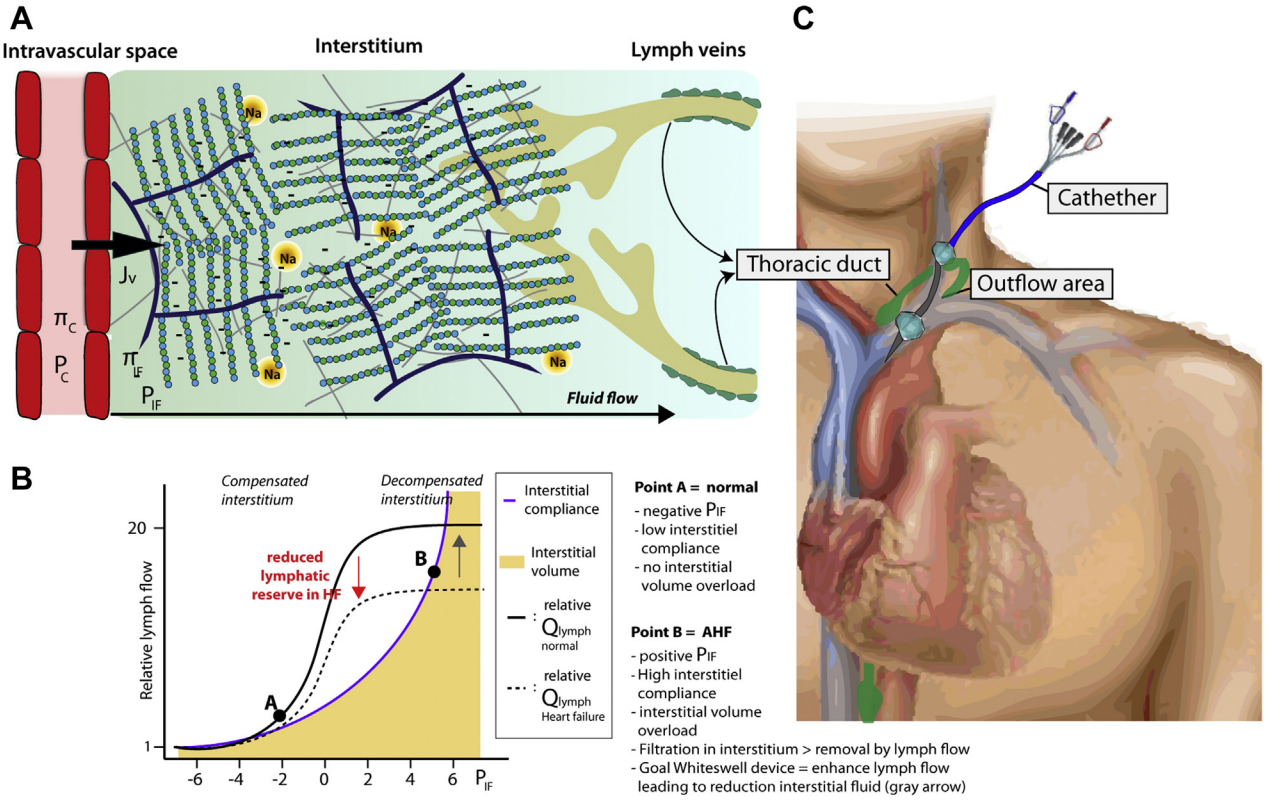
ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2021.10.003

FIGURE 1 Interaction of Interstitium and Lymphatics



(A) Interaction of microcirculation with net filtration (Jv) driven by Starling forces, the interstitium, and the lymph veins. The interstitium consists of negatively charged glycosaminoglycan, which shields Na^+ and pushes fluids toward the lymphatic system. **(B)** Physiology of interstitium in the **(left)** compensated and **(right)** decompensated states. Heart failure is associated with reduced lymphatic reserve leading to easier interstitial fluid accumulation. **(C)** The lymphatic drainage system in situ generating negative pressures and theoretically stimulating lymph flow, leading to interstitial decongestion (reflected in **B** as the **gray arrow**). AHF = acute heart failure.

Therefore, the lymph flow needs to increase proportionally to drain fluid and solutes from the interstitium. Theoretically, the lymph flow can increase up to 20-fold; however, the state of heart failure has been associated with a reduced lymphatic reserve because of structural alterations including not only fewer lymphatic vessels but more dilated ones with incompetent valves. As a result, capillary filtration exceeds lymphatic reserve, leading to a volume-overloaded interstitium. Additionally, interstitial fluid overload disrupts interstitial functioning of the GAGs, which results in a high compliance state (**Figure 1B**) that favors sodium and fluid retention (volume overload) because less fluid is being pushed toward the lymphatic system. Furthermore, increased central venous pressure (CVP), which occurs in the setting of AHF, impedes the outflow of lymph into the venous circulation, thereby further maintaining interstitial volume overload and potentially aggravating intravascular volume depletion during decongestion.

Based on this complex background of volume accumulation in patients with AHF, Abraham et al (5) report on an animal and first-in-human prospective observational study with an interesting lymph flow-stimulating decongestive device. This novel device is a multilumen catheter with 2 compliant balloons capable of generating a reduction in local hydrostatic pressures (**Figure 1C**). By positioning the device in the vicinity of the thoracic duct outflow, which handles approximately 15% to 20% of interstitial fluid drainage, the reduced hydrostatic pressure aims to enhance thoracic duct flow. In this paper, the authors first induced a sheep model of ischemic heart failure via coronary embolization. AHF was then provoked through intravenous fluids and the administration of

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 6, NO. 11, 2021
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phenylephrine. The 7 animals studied exhibited clear features of AHF after coronary embolization and fluid and pressor administration documented by increased biventricular filling pressures and extravascular lung water. Four animals were then treated with the lymphatic drainage catheter. The device resulted in a local reduction of the hydrostatic pressure around the thoracic duct outflow area that can generate a pressure gradient with the CVP. Over a 3-hour period, the device resulted in a drop in extravascular lung water, left ventricular end-diastolic pressure, and the transpulmonary pressure gradient. In a single human patient, the device was also successfully deployed and resulted in a reduction of CVP and natriuretic peptide levels, with an increase in urine output. These results are an interesting proof of concept that local lowering of pressure in the vicinity of the thoracic duct could lower interstitial volume overload through potentially enhanced lymphatic flow (**Figure 1B**), although lymph flow was not measured in this study.

Clearly, additional studies are necessary to determine the clinical utility of such a device because numerous factors remain unknown. For instance, 1) the device does not tackle alterations happening in the interstitium (eg, disruption of GAG function with disruption of electrostatic function and high P_{IF}) and the microcirculation (eg, low K_f with poor plasma refilling) contributing to ongoing interstitial volume overload; 2) success in clinical practice might be variable because of the variable anatomy of the thoracic duct; 3) in tackling total body volume overload, the effect is unknown because the thoracic duct handles only approximately 15% to 20% of all lymph transudate; and 4) the device as designed only works temporarily, and it is unknown if this will be sufficient for a clinically relevant impact if altered anatomy and functioning of lymph vessels persists after device discontinuation. Nevertheless, the authors should be congratulated for this innovative technology that has rejuvenated interest in a relatively understudied field in heart failure, namely, the intersection between the microcirculation, interstitium, and lymphatic system.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Martens is supported by the Belgian American Educational Foundation and the Frans Van de Werf Fund. Dr Tang is partially supported by grants from the National Institutes of Health (R01HL126827, R01HL146754). Dr Tang is a consultant for Sequana Medical AG, Owkin Inc, Relypsa Inc, PreCARDIA Inc, Cardiol Therapeutics Inc, and Genomics plc and has received honoraria from Springer Nature for authorship/editorship and the American Board of Internal Medicine for exam writing committee participation—all unrelated to the subject and contents of this paper.

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KEY WORDS acute decompensated heart failure, decongestion, interstitial, lymphatic, pulmonary edema, thoracic duct, volume overload