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Lymphatic Dysfunction in Critical Illness

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Abstract

Purpose of review—The essential role of the lymphatic system in fluid homeostasis, nutrient transport, and immune trafficking is well-recognized, however there is limited understanding of the mechanisms that regulate lymphatic function, particularly in the setting of critical illness. The lymphatics likely affect disease severity and progression in every condition, from severe systemic inflammatory states to respiratory failure. Here, we review structural and functional disorders of the lymphatic system, both congenital and acquired, as they relate to care of the pediatric patient in the intensive care setting, including novel areas of research into medical and procedural therapeutic interventions.

Recent findings—The mainstay of current therapies for congenital and acquired lymphatic abnormalities has involved non-specific medical management or surgical procedures to obstruct or divert lymphatic flow. With the development of dynamic contrast-enhanced magnetic resonance lymphangiography, image-directed percutaneous intervention may largely replace surgery. Because of new insights into the mechanisms that regulate lymphatic biology, pharmacologic inhibitors of mTOR and leukotriene B4 signaling are each in Phase II clinical trials to treat abnormal lymphatic structure and function, respectively.

Summary—As our understanding of normal lymphatic biology continues to advance, we will be able to develop novel strategies to support and augment lymphatic function during critical illness and through convalescence.

Keywords

image-directed percutaneous embolization; chylothorax; plastic bronchitis; lymphatic dysfunction in critical illness; sirolimus; ubenimex

Introduction

References to the lymphatic system have dotted the medical literature since the 4th century BC, when Aristotle described "fibers which take position between the blood vessels and nerves and which contain a colorless liquid" [1]. Hippocrates' exposition "On glands" similarly reported a system of vessels and nodes which "attract and receive fluid" in health, but in illness, when overwhelmed with humors, become inflamed "in sympathy with the

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Conflicts of Interest

The authors have no conflicts to disclose.

body" [2]. Subsequent writers documented milky vessels coursing through the mesentery, with Gasparo Aselli being credited in 1622 with describing prominent "lacteal arteries" during vivisection of dogs that were well-fed but not those that were starved [1].

By no later than the 17th century, then, investigators had described or foreshadowed the three major functions of the lymphatic system as it is understood today: the homeostasis of fluid and solute balance between the interstitial and intravascular spaces; the absorption and transport from the viscera of fats; and the surveillance of the body for infection and its role as a locus for immune response. Yet, despite its early recognition and its presence in nearly every vascular tissue, the "other" circulatory system has garnered a fraction of the attention and research afforded the vascular system, a state of neglect historically blamed on challenges in visualizing its components *in vivo* [3].

The 21st century, however, has heralded a renaissance in lymphatic investigation, a boom aided primarily by advances in techniques that allow lymphatic imaging and by improved understanding of the molecular and genetic determinants of lymphatic structure and function, areas of progress which together offer both diagnostic and therapeutic advances. Despite this progress, it is still not well understood what role the lymphatics play in critical illness. It is known that the lymphatic vasculature is broadly distributed over the entire body [4], including the central nervous system [5,6] which until very recently was considered a site of immune privilege [7]. The lymphatics likely affect disease severity and progression in every condition that is treated in the intensive care unit (ICU), including in patients with congenital heart disease, acute pancreatitis, respiratory failure, neurologic deterioration, and after solid organ transplantation and burn injury. In this article, we will review structural and functional disorders of the lymphatic system, both congenital and acquired, as they relate to care of the pediatric patient in the intensive care setting, including novel areas of research into medical and procedural therapeutic interventions. This review will not cover in any detail the genetic determinants of lymphangiogenesis or the lymphatic disorders that result from syndromes or altered developmental programs, which have been extensively covered elsewhere [8–12].

Congenital and Acquired Disorders of the Lymphatic System in the Cardiac Patient

The cardiac patient may manifest disorders of the lymphatic system due to chronic exposure to the abnormal physiology of single ventricle palliation; acutely, after cardiothoracic surgery; before surgical repair or palliation due to developmental lymphatic abnormalities associated with abnormal fetal physiology; or possibly from primary lymphatic dysgenesis as part of an underlying genetic disorder affecting both cardiac and lymphatic development.

Noting the strong association of nuchal translucency (a finding caused by edema related to lymphatic insufficiency) with a wide variety of cardiac defects in both aneuploid and euploid patients, Burger et al identified 15 candidate genes that contribute to both congenital heart disease and lymphatic abnormalities in a mouse model [13], and while much remains to be elucidated from a genetic perspective about the related development of these two systems in

humans, it may be that the cardiac patient is abnormal from a lymphatic standpoint from the earliest phases of development.

More is understood about the effects of abnormal fetal physiology on the lymphatic system, with perhaps the best-studied model being hypoplastic left heart syndrome with intact atrial septum. Comparing histopathology specimens in HLHS patients with and without intact atrial septum, Rychik et al reported massively dilated lymphatics in the former group [14], presumably related to the impediment to pulmonary venous drainage, similar to an earlier report from 1986 by Moerman et al who described congenital pulmonary cystic lymphangiectasis due to premature closure of the foramen ovale in patients with severe aortic stenosis [15]. It is not only patients with obstruction to pulmonary venous return in fetal life who may be at risk for congenital lymphatic dysplasia. In a surgical sheep model of increased pulmonary blood flow from our group, late gestation lambs underwent placement of an aorto-pulmonary graft, and after delivery, cannulation of the draining vessel of the pulmonary lymphatics. In this model, chronically increased pulmonary blood flow was associated with impaired pulmonary lymph flow, dilated pulmonary lymphatics, and altered expression of genes known to be important for lymphatic growth and development [16]. Taken together, these studies suggest that many cardiac patients may already have abnormal lymphatic structure and/or function at the time of birth.

A frequently encountered lymphatic issue in the ICU is chylothorax, or accumulation of lymph fluid in the thorax, an entity which may be either congenital or acquired. Congenital chylothorax may be due congenital lymphatic malformations such as lymphangiomatosis, lymphangiectasia or atresia of the thoracic duct, or may be found in association with a wide range of syndromes, such as Down, Noonan, Turner and Gorham-Stout syndromes, with or without gross lymphatic disorganization [17]. As a congenital disease, chylothorax carries a high mortality, with death rates reported to be as high as 33% [18]. Chylothorax is also a fairly common complication after cardiothoracic surgery with a reported incident of 2%-5% [19]; a recent study of the Pediatric Health Information System database noted that the highest incidence was seen after superior and inferior cavopulmonary anastomosis surgeries as part of staged palliation in single ventricle patients, arterial switch operation, and heart transplant [20]. The potential effects of postoperative chylous effusion are myriad, with the same study reporting an increase in in-hospital mortality (OR 2.3), as well as increased length of stay and cost of hospitalization. Accumulation of fluid in the thorax may lead to respiratory failure and has been associated with increased time of postoperative mechanical ventilation [21], while other effects are related to impairment of the various functions of the lymphatic system as elaborated above. Indeed, long term chylothorax may lead to muscle wasting, weight loss and other signs of compromised nutrition [22], as well as immunocompromise due to loss of immunoglobulin and lymphocytes [23].

Chylothorax has been long recognized as a complication after surgery, but advances in imaging have allowed a greater understanding of its varied causes. Using dynamic contrast-enhanced magnetic resonance lymphangiography (DCMRL), a recently described technique based on intranodal injection of a gadolinium-based contrast [24,25], Savla et al evaluated 25 patients with postoperative chylothorax [26] and reported three distinct etiologies. Only two patients were identified as having traumatic leak, in both cases in a tributary to the

thoracic duct, while 14 were deemed to have pulmonary lymphatic perfusion syndrome (PLPS) and 9 to have central lymphatic flow disorder (CLFD), two complex disorders of lymphatic flow that have been described as imaging has allowed their identification. PLPS was first reported in the post-Fontan population and is marked by centrifugal flow from the thoracic duct toward peribronchial vessels and the lung parenchyma, a reversal of the typical centripetal flow from the periphery towards the central duct. CLFD, meanwhile, is a disorder marked by reduced or absent central lymphatic flow, effusions in multiple compartments, and dermal reflux of lymph through collateral vessels in the abdominal wall. The central flow abnormality may be related to congenital absence of the thoracic duct, anatomic thoracic duct outlet obstruction or previous thoracic duct ligation.

Management of chylous effusion includes both medical and interventional approaches and an optimal treatment algorithm will evolve only with time. Successful percutaneous approaches to target implicated lymphatic vessels have been described [27,28], with the goal of directing lymph flow away from the intrathoracic space, but it is clear that patient factors play a crucial role. In the above paper, Savla et al reported that patients in the PLPS and traumatic injury groups responded well to percutaneous intervention in the form of selective or total thoracic duct embolization, but in contrast, patients in the CLFD group had poor outcomes, with most dying [26]. Image-directed percutaneous intervention may have largely replaced surgical thoracic duct ligation and pleurodesis [26], but until there is more cumulative experience with lymphatic imaging and intervention, the initial treatment for most patients will continue to be medical. An exhaustive review of medical treatment is outside of the scope of this review but effective treatment of postoperative chylothorax may include NPO status, reduction in long chain trigylcerides and use of the somatostatin analogue octreotide [29,30]. In the congenital chylothorax population, successful medical management has been reported with propranolol [31], sirolimus [32], an inhibitor of mammalian target of rapamycin (mTOR), and oral sildenafil [33].

Many of the same anatomic and physiologic perturbations of the lymphatic system that lead to chylothorax in the acute period after cardiothoracic surgery may contribute to plastic bronchitis in the post-Fontan cardiac patient. Plastic bronchitis is caused by the exudation of proteinaceous material and cells from the lymph into the airway, leading to formation of tell-tale “casts” in the lower airways with potentially severe respiratory compromise. It is a rare complication of the Fontan circulation, with an estimated prevalence in that group of 4% [34], but one with a high mortality, reported between 12 and 50% [35]. Effective interventional therapies have included procedures aimed at lowering central venous pressure and improving lymphatic egress into the venous system [36] as well as heart transplantation [37], while successful medical management has been described with steroids [38], mucolytic therapy [39], and sildenafil [40]. More recently, the same advances in lymphatic imaging and intervention have opened a promising avenue of treatment. Dori et al described their experience with 17 patients undergoing thoracic duct embolization or placement of covered stents to exclude centrifugal flow and reported symptomatic improvement in 88% of their cohort [35].

Lymphatic Malformations and Airway Compromise

Congenital or acquired vascular malformations of the lymphatics, known as lymphatic malformations (LM), are characteristically cystic, fluid-filled collections surrounded by lymphatic endothelium and connective tissue [41]. LM can be associated with pediatric syndromes, like Klippel-Trenaunay, Noonan, Proteus, and Turners or may occur in isolation. LM may be merely uncomfortable and cosmetically displeasing, but depending on their relation to normal anatomical structures, can also have more severe consequences. Nearly three-quarters of patients with LM that involve the head and neck can compromise the airway [42] and become life-threatening, necessitating endotracheal intubation or tracheostomy. Excision, laser ablation, and sclerotherapy have been the mainstays of surgical interventions [42,43]; however, recent results from a Phase 2 pediatric and adult trial (NCT00975819) on the treatment of complex vascular anomalies [44] as well as from two smaller series [45,46], have all suggested benefit with sirolimus (rapamycin). Additionally, a French pediatric Phase 2 trial (NCT03243019) is set to begin in March 2018 to further assess the efficacy of rapamycin in the treatment of cervicofacial LM.

Lymphatic Dysfunction and Multiorgan Dysfunction Syndrome

As noted above, an essential function of the lymphatic vasculature is to participate in immune trafficking and surveillance. Inflammatory states, such as during critical illness, can lead to structural and functional alterations of the lymphatics [47]. For example, in a rodent model of ileitis, Wu et al demonstrated that mesenteric lymphatic vessels were dilated, with impaired contractility [48].

In recent years, the role of the gastrointestinal tract and its associated lymphatic network in mediating critical illness has become much better appreciated [49]. Deitch and his group hypothesized that toxins released by the mesentery after an ischemic insult could bypass the portal circulation and be directly transported by the gut lymphatics to distant organs, resulting in dissemination of tissue injury [50]. Specifically, severe inflammatory states such as acute pancreatitis, can lead to systemic inflammatory response syndrome (SIRS) and multiorgan dysfunction; this most frequently includes severe lung injury and respiratory failure [51]. Interestingly, in a rat model of trauma/hemorrhagic shock, ligation of the efferent mesenteric lymphatics protected the lungs from injury [50]. This benefit has been demonstrated in dogs and primates as well. The results in humans have been more equivocal [52]; these therapies, as for the treatment of chylothorax, have involved occlusion or diversion of the lymphatics, but only after the onset of lung injury, thus limiting potential benefit. Perhaps not too surprisingly, what's old is new again [53] – Cole et al reported on the benefits of a lympho-venous graft to treat right heart failure in a canine model of tricuspid regurgitation and pulmonic stenosis, in 1967 [54]!

Future Promise and Conclusions

While we very much appreciate that interventions such as ligation or embolization that necessarily obliterate vital lymphatic structures, like the thoracic duct or mesenteric lymphatics, are usually only offered in a desperate attempt to try and save the lives of

critically ill patients, it must not be overlooked that these structures are fundamental to the normal and essential functioning of the lymphatic vasculature. Our hope is that as our understanding of normal lymphatic biology continues to advance, we will be able to develop novel strategies to support and augment lymphatic function during critical illness and through convalescence.

To this end, analysis of altered microRNA [55] and proteomic [56] signatures in the mesenteric lymph under conditions of severe systemic inflammation may identify just such promising therapeutic targets. Similarly, specific inhibition of pro-inflammatory cytokines and other inflammatory mediators may prove beneficial in supporting lymphatic function through critical illness. Indeed, inhibition of inducible nitric oxide synthase (iNOS) blunts the inflammatory response associated with burn injury-induced multi-organ dysfunction, decreases pulmonary vascular permeability, normalizes pulmonary lymph flow, and preserves lung function [57]. Alternatively, inhibition of inflammation-mediated lymphangiogenesis using inhibitory antibodies against vascular endothelial growth factor receptor 3 (VEGFR3), has shown benefit in limiting immune rejection following kidney [58,59], heart [60] and corneal transplant.

An expanding body of literature indicates that lymphatic vessel capacitance and pumping primarily dictate lymphatic function under normal physiologic conditions [61–70], and that endothelial nitric oxide (NO) signaling is an important modulator of lymphatic pump activity and lymph flow [64,67,71–75]. However, this has not translated into effective therapies in the ICU. For example, in the setting of severe lung injury and acute respiratory distress syndrome, where supporting pulmonary lymphatic function with inhaled NO would seem to hold great promise, it has not shown any mortality benefit [76] and may cause harm [77].

Perhaps one of the more exciting publications in the last year demonstrated that in a mouse model of experimental lymphedema, targeted pharmacologic inhibition of leukotriene B4 restored lymphatic vessel architecture, improved lymphatic function, and decreased lymphedema [78]. This drug, ubenimex, is currently in a Phase II clinical trial for safety, tolerability, and efficacy (NCT02700529) in patients with lower extremity lymphedema.

Finally, the accelerating field of glymphatics and the recent discovery of lymphatic networks in the meninges of the central nervous system [5,6] could have fundamental implications for how we evaluate the neurologically compromised patient in the ICU, including those with ICU delirium, neuroinflammatory and neurodegenerative diseases, and traumatic brain injury in the critically ill child [79].

- ➢ The role of the lymphatic system in critical illness is not well understood, but it likely plays a fundamental role in disease severity and progression in everything from severe systemic inflammatory states to respiratory failure.
- ➢ The mainstay of current therapies for congenital and acquired lymphatic abnormalities involves non-specific medical management or surgical intervention to obstruct or divert lymphatic flow.

➢ As our understanding of the signaling pathways that regulate normal lymphatic biology improves, novel avenues of therapy may be directed toward supporting and optimizing lymphatic function during critical illness.

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