Research Priorities in Lymphatic Interventions: Recommendations from a Multidisciplinary Research Consensus Panel

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ABSTRACT
Recognizing the increasing importance of lymphatic interventions, the Society of Interventional Radiology Foundation brought together a multidisciplinary group of key opinion leaders in lymphatic medicine to define the priorities in lymphatic research. On February 21, 2020, SIRF convened a multidisciplinary Research Consensus Panel (RCP) of experts in the lymphatic field. During the meeting, the panel and audience discussed potential future research priorities. The panelists ranked the discussed research priorities based on clinical relevance, overall impact, and technical feasibility. The following research topics were prioritized by RCP: lymphatic decompression in patients with congestive heart failure, detoxification of thoracic duct lymph in acute illness, development of newer agents for lymphatic imaging, characterization of organ-based lymph composition, and development of lymphatic interventions to treat ascites in liver cirrhosis. The RCP priorities underscored that the lymphatic system plays an important role not only in the intrinsic lymphatic diseases but in conditions that traditionally are not considered to be lymphatic such as congestive heart failure, liver cirrhosis, and critical illness. The advancement of the research in these areas will lead the field of lymphatic interventions to the next level.

ABBREVIATIONS
CVP = central venous pressures, CHF = congestive heart failure, RCP = Research Consensus Panel, SIRF = Society of Interventional Radiology Foundation, TD = thoracic duct, TDE = thoracic duct embolization

The lymphatic system is ubiquitous in the body. Its major functions are fluid removal from the interstitial tissue and immune trafficking. The system is complex and consists of multiple organ-based subsystems, including the soft tissue, intestine, lungs, liver, and kidneys, with each having differences in the mechanism of lymph production and composition (Fig 1) (1).

Lymph circulation was discovered by Gaspar Asellius in 1627, approximately the same time as William Harvey described the circulation of blood (2). The history of modern...
lymphatic research starts at the end of the 19th century, with the description of the mechanisms of interstitial fluid production by Ernst Starling (3). His discoveries inspired research aimed at understanding the complexity of lymphatic physiology. However, much of the knowledge has been forgotten owing to the lack of diagnostic or therapeutic applications. Twenty years ago, Dr. Constantine Cope started a new era with the development of thoracic duct embolization (TDE) as a minimally invasive alternative to surgical thoracic duct (TD) ligation (4). In parallel, there have also been significant advances in basic science of lymphatic research (5).

This manuscript aims to summarize the outcomes of the Research Consensus Panel (RCP) meeting of the Society of Interventional Radiology Foundation (SIRF), which focused on lymphatic imaging and interventions. This multidisciplinary group of key opinion leaders and scientists in the lymphatic field was brought together to define priorities in lymphatic clinical research and the ways in which interventional radiology might contribute to advances in the diagnosis and treatment of lymphatic diseases.

MATERIALS AND METHODS

On February 21, 2020, SIRF convened an RCP for the development of research priorities for lymphatic interventions. This panel consisted of 5 adult interventional radiologists, 1 pediatric interventional radiologist, 2 cardiologists, 1 lymphologist, and 3 other investigators with extensive expertise in preclinical and clinical lymphatic research. In addition, industry stakeholders, regulators, and representatives from funding agencies, patient organizations, and SIRF leadership were invited to serve as active audience members.

Meeting Structure and Agenda

Prior to the meeting, SIRF assigned each panelist a presentation topic in his/her area of expertise. The meeting agenda consisted of 3 parts. During the first part of the meeting, each panelist was allotted 15 minutes to present his/her topic. The second part of the meeting was dedicated to a focused panel and audience discussion of potential research projects. Finally, the panelists ranked the discussed research priorities.

Summary of Panelist Presentations

The Changing Times: New Era for the Lymphatic System (Maxim Itkin). The mechanism of interstitial fluid and subsequent lymph production slightly differs in various organs, reflecting the differences of the starling forces. Consequently, capillaries have different permeability in different organs (eg, the sinusoid capillary in the liver and spleen are much more permeable than the continuous capillary in skeletal muscles). Intestinal lymphatics actively participate in fat absorption (6), and kidney lymphatics participate in kidney fluid metabolism (7).

Dr. Kinmonth started the modern history of lymphatic imaging with the development of pedal lymphangiography (8). This development coincided with the description of the Seldinger technique for arterial access. Although the Seldinger technique became the backbone for the development of angiography and vascular interventions, pedal lymphangiography was utilized primarily for lymph node imaging in patients with cancer and less for lymphatic flow.

The development of TDE first drove the development of newer imaging techniques, such as intranodal lymphangiography (9), MR lymphangiography (10), liver lymphangiography (11), and mesenteric lymphangiography (12), which allowed for the discovery of new diseases (Fig 2).

Historical Perspectives on Lymphatic Research (Marlys Witte). In 1960s, the International Society of Lymphology was created to promote international collaboration among leaders in the emerging field of lymphology. The main focuses of clinical research was cancer staging, lymphedema, and lymphatic malformations. Lymphatic imaging techniques, including pedal lymphography and lymphscintigraphy, propelled the field forward.

Lymphedema has 2 pathophysiologic mechanisms: 1) high output, where the overproduction of lymph exceeds the lymphatic transport capacity and 2) low output, where the normal lymphatic load cannot be transported by the defective or obstructed lymphatic system. TD cannulation allowed the investigation of lymph flow in patients with liver cirrhosis and congestive heart failure (CHF), altered composition of lymph constituents, and treatment by TD diversion and decompression (13–15).

Molecular lymphology dawned in the late 1990s with the discovery of lymphatic growth factors, genes underlying familial lymphedema syndromes and lymphatic malformations, animal models of these conditions, and elucidation of molecular signaling pathways in lymphangiogenesis and lymphvasculogenesis. These advances, when taken together, present an unusual opportunity for further translation of basic lymphology into the clinical arena with theranostic implications for improved care.

Overview of the Lymphatic Physiology and Function (Stanley Rockson). The lymphatic system have 3 main functions in the body: 1) fluid transit from the extracellular space into the venous circulation, 2) gastrointestinal lipid absorption, and 3) trafficking of antigen-presenting cells and lymphocytes to the lymphoid tissue (16).

Significant progress has been made in the understanding of lymphangiogenesis. Several factors participate in this process, including VEGFR-3, Prox-1, and podoplanin. These discoveries have energized the attempt to develop medications that treat lymphatic conditions (17). With every passage of blood through the arteriovenous circulation, approximately 1% of the intravascular fluid moves into the
interstitial space. It has been shown that the interstitial fluid is removed from the tissues exclusively by the lymphatic system, without venous reabsorption (18).

The total lymphatic flow in the body under resting condition is approximately 23.1 mL/s. Lymphatic anatomy and lymph flow propulsion are 2 significant lymph transport components.

The lymphatic system starts with initial lymphatics, which are blind-ending sacs. The interstitial fluid enters through endothelial cell-cell junctions that function as primary valves and are characterized by anchoring filaments (100 nm) that connect the initial lymphatics to the collagen in the surrounding extracellular matrix of the interstitium (19).

In a person standing upright, the lymphatic vessels must overcome a significant hydrostatic pressure gradient, approximately 150 cm H₂O, from the lymphatics of the feet to the great veins of the neck. Lymph propulsion through the lymphatic vessels is assisted by the lymphatic valves, which prevent retrograde flow (20). The lymph propulsion has 2 mechanisms: (1) intrinsic contraction by the muscular layer in the lymph vessel wall and (2) extrinsic compression by the surrounding tissue structures, including the arteries (21). Lymphatic vessel contraction is regulated by intrinsic and extrinsic factors. The intrinsic factors include mechanical (lymphatic pressure, stretch, shear force, and flow) and molecular factors to which the contractile elements can respond (autocrine/growth factors and paracrine factors, such as prostanoids, nitric oxide, substance P, and cytokines). The extrinsic factors include neural (epinephrine, norepinephrine, acetylcholine, substance P, and calcitonin-related peptide) and chemical (catecholamines, natriuretic peptides, oxygen radicals, etc) factors.
Anatomy and Function of the TD Lymphovenous Junction (Anthony Phillips). There are at least 9 anatomical variants of TD that are products of complex embryological development (22). This variability means that TD can branch, coalesce, and even have multiple terminations. Anatomical studies have shown that TD terminates in the left greater veins in 92%–95%, bilaterally in 4%, and in the right greater veins in 1%–3% of cases (23). Embryologically, the terminal part of TD is created by the fusion of primordial sacs at the venous angle with the primordial TD (24).

The geometry of entry of TD through the wall of the vein can be perpendicular or oblique to the vein (25,26). The valves can be ultrasonically visualized in approximately 40% of patients (25). The 2 typical morphological forms of the valves are semilunar and ostial. Moreover, there is typically a valve in the draining vein that is positioned next to the lymphovenous junction that often covers it (26,27).

The lymphovenous junction functions as a valve and prevents the reflux of blood into the lymphatic system; however, several studies have reported the absence of valves in up to 50% of cases (26,28,29). The functional significance of the absence of valves is not well understood, especially in clinical settings with high central venous pressure (CVP) and increased TD lymph volumes.

Current Status of Lymphatic Imaging (Gregory Nadolski). Lymphatic imaging is complicated because the lymphatic system consists of multiple subsystems (soft tissue, lung, liver, intestines, etc), each of which has a different need for lymphatic imaging. Lymphatic imaging techniques include: intranodal lymphangiography, dynamic contrast-enhanced magnetic resonance lymphangiography (DCMRL), liver lymphangiography, and mesenteric lymphangiography (30).

Inranodal lymphangiography is performed by injecting the inguinal lymph nodes with oil-based iodinated contrast under fluoroscopy guidance (9,31).

In DCMRL, a gadolinium-based contrast is injected into the inguinal lymph nodes (10,32). The imaging is then performed using MR T1-weighted dynamic angiographic imaging. DCMRL facilitated the discovery of the pathophysiological mechanisms of nontraumatic chylothorax, chylous ascites, plastic bronchitis, and others (33,34).

Liver lymphangiography is performed by inserting a 25-gauge needle in the periportal space and injecting an iodinated contrast thereafter (11). This technique facilitates the diagnosis of protein-losing enteropathy and chylous ascites.

Chylous Ascites and Mesenteric Lymphangiography (Saebom Hur). Chylous ascites is the leakage of chyle from the mesenteric vessels. It is the most challenging lymphatic condition to treat owing to the difficulty in imaging the mesenteric lymphatic system (35). The retrograde access to the TD with balloon occlusion allows the reflux of contrast into the mesenteric lymphatic system to assist in the identification of the leak (36).

Cross-sectional imaging of the mesenteric lymph nodes is challenging due to the intestine. Despite the assistance of retrograde access and balloon occlusion, the visualization of the leakage point of chylous ascites is frequently limited because the contrast agent cannot move against the intestinal lymphatic flow. Mesenteric lymphangiography was recently described (12), in which an X-ray contrast agent was introduced through the mesenteric lymph nodes after
exposure of the mesentery by open laparotomy. This technique is expected to contribute to the diagnosis of some types of protein-losing enteropathy and chylous ascites.

**Retrograde Access of TD (Waleska M. Pabon-Ramos).** The retrograde transvenous approach of TD has been described as an alternative to the more traditional antegrade approach. However, the technical success of the retrograde access is only 50% due to the terminal valves in the TD. Direct fluoroscopy-guided access of the cervical portion of the TD is another alternative. It relies on the opacification of that TD portion by preceding intranodal lymphangiography. Fluoroscopic TD access and embolization is reported to have a 92% (12/13) technical success rate for TD access, 90% (11/12) clinical success rate for TD embolization, and an 8% (1/12) complication rate (TD perforation). Another alternative is the ultrasound-guided access of the TD cervical portion. Ultrasound-guided access and embolization are reported to have a 100% (8/8) technical success rate for TD access, 75% (6/8) clinical success rate for TD embolization, and no complications (37). The clinical application of fluoroscopy- and ultrasound-guided transcervical TD access extends beyond TD embolization, including drainage to treat CHF-related edema and external drainage to reduce systemic inflammation in acute and critical illnesses.

**Gut-Lymph Toxicity and the Rationale for Therapeutic Interventions (John A. Windsor).** Multiorgan failure (MOF) is the leading cause of death in patients in intensive care units. The gut-lymph concept has been suggested to explain MOF. It states that gut-derived endotoxins are transported though the lymphatic system (TD) into the systemic circulation, bypassing the liver, as demonstrated in multiple-animal studies (38). Treatment approaches include 2 main strategies: externally draining the TD lymph to divert the endotoxins outside the body and intralymphatic drug delivery to neutralize toxins. Although a clinical study demonstrated a significant improvement in pulmonary gas exchange, circulatory status, and survival in patients in intensive care units, this approach did not gain popularity, primarily due to the complexity and unpredictability of open surgical drainage (39). Lymph-targeted drug therapy can be delivered via the intestine and peritoneal cavity (40). Percutaneous TD cannulation provides a technically feasible approach for externally draining the TD lymph to prevent the promotion of systemic inflammation and MOF and characterizing the toxic elements of the TD lymph to identify novel biomarkers, disease mechanisms, and potential drug targets.

**Heart Failure and Lymphatic System: a Cardiologist’s Perspective (Daniel Burkhoff).** Heart failure is the primary discharge diagnosis for hospitalized patients in the United States. Lymphatic flow is elevated in CHF (14). Tissue edema, especially pulmonary edema, is the main basis for the symptoms of CHF. It has been shown that all interstitial fluid is drained exclusively by the lymphatic system, and edema occurs when the lymphatic system cannot drain the interstitial fluid at a rate that matches filtration from capillaries, leading to interstitial edema (18). The increased flow results in the dilation of lymphatic vessels, leading to lymphatic valve dysfunction, further contributing to the inefficiency in lymphatic return. Lymphatic congestion of the kidneys can result in decreased kidney perfusion and, in turn, cause resistance to diuretics. External TD drainage was efficacious with a complete resolution of severe edema within a few days (41). Additional studies demonstrated a significant improvement in renal function despite significant fluid losses (14).

**Tricuspid Regurgitation and TD: Novel Observations in Large Animals (Ghassan S. Kassab).** Several studies have established that there is a significant increase in lymph production associated with elevated CVPs. A swine model of tricuspid regurgitation (TR) was used to simulate a chronic increase of CVP (unpublished data). The flow in TD was measured using an implanted flow measuring probe for 28 days. Spectral analysis of the TD flow was then performed. TD was percutaneously accessed, and the pressure in the TD and draining vein were measured. The study demonstrated that the flow in the TD increased 2-fold immediately after the induction of TR and reached a peak of 10-fold 2 days after the procedure. Histological examination demonstrated TD dilation with outward hypertrophic remodeling of the TD walls. The thickened TD restored wall shear stress; however, the analysis revealed that that the increased flow resulted from the increased lymphatic vessel contraction.

**Pediatric Lymphatic Imaging and Interventions: Potential to Reveal the Mystery (Debbie Rabinowitz).** Lymphatic conditions are relatively common in pediatric patients and include isolated chylothorax/ chylopericardium, central lymphatic flow obstruction, lymphatic malformations, and plastic bronchitis. Typical imaging findings in isolated neonatal chylothorax/chylopericardium include an abnormal pulmonary lymphatic perfusion. In central lymphatic flow disorders, DCMR typically demonstrates the failure of contrast agent propagation in TD and cutaneous collaterals. If TD is present and obstructed, as in this condition, a TD-to-vein anastomosis can be performed (42).

Complex lymphatic malformations include Gorham-Stout disease, generalized lymphatic anomaly, and kaposiform lymphangiomatosis. In these conditions, there is a development of abnormal lymphatic tissue in different organs, including the bones, liver, spleen, and lungs, with lung involvement portending a worse prognosis. A recent prospective study demonstrated that abnormal pulmonary perfusion exists in these patients (43). Lymphatic...
embolization of this flow can result in pulmonary function improvement in these patients.

In plastic bronchitis, DCMR is able to demonstrate the abnormal pulmonary lymphatic flow. Lymphatic embolization results in a cure for this condition in the majority of patients (33).

**Panel Discussion**

During the second part of the meeting, the panel discussed the preselected topics to address current gaps in knowledge. Below is a summary of the discussions.

**CHF.** Although the lymphatic system has a significant pathophysiological role in CHF, it has not been included as a therapeutic target. Inadequate diuresis in CHF patients causes high readmission rates. The mechanism of diuretic resistance in patients with CHF is multifactorial and at least partially relates to kidney congestion (44). The obstruction of kidney outflow routes (venous, urinary, and lymphatic) can result in interstitial congestion. The kidneys are more susceptible to interstitial congestion due to the presence of renal capsule that restricts kidney expansion. The liver microcirculation consists of sinusoid capillaries that are highly permeable, and even the smallest increase of the CVP can cause an increase in lymphatic flow. This results in TD congestion that impairs the lymphatic flow.

Surgical external decompression of TD resulted in a significant improvement of CHF symptoms as well as improvement in renal function, presumably due to the reduction of edema. This technique was abandoned in the past; however, with the advent of minimally invasive lymphatic interventional techniques, its utility should be re-evaluated. Azygous venous pressures are lower than subclavian venous pressures, and the creation of a percutaneous connection between TD and azygous vein might be another approach for TD decompression. Clinical outcomes might be predicted using a computational modelling of the lymphatic system, although this needs to be developed.

**TD Externalization for the Treatment of Gut Lung Toxicity.** Although the therapeutic effect of lymphatic drainage in septic shock has been proven in animal studies, it has yet to be clinically implemented. The clinical implementation of TD drainage can achieve 2 overarching goals: drainage of the toxic lymph to influence the course of the acute illness and sampling fluid from TD to provide insight into the toxic components of the lymph to develop targeted antidotes. It appears safe to drain the lymphatic fluid from the TD for a period of 7 days, without an evidence of immunosuppression. The alternative to catheterization of the TD is a sampling of lymph from the vein where the TD is drained, for example, using the double-balloon approach to isolate the segment of the vein into which the TD drains.

**Development of New Lymphatic Imaging Modalities.** Lymphatic imaging is still very rudimentary, and some of the organ lymphatic subsystems (kidneys and lungs) cannot be imaged using current technology. Even though there is a need to develop imaging agents specific to the lymphatic system, the panel believed that the costs of such development may not be economical. For this reason, a wider use of existing and Food and Drug Association-approved imaging agents should be encouraged, and the development should focus on improved delivery techniques.

One of the major challenges of any new type of imaging is to identify normal imaging findings. There is a need to standardize lymphatic imaging among various centers. Currently the standard spinal needle, positioned in lymph-rich tissues, is used for contrast delivery. The main pitfalls of this set up are frequent needle dislodgement and contrast extravasation. The panel suggested that a dedicated lymphatic imaging equipment should be developed.

**Panel Prioritization**

During the last part of the day, each panelist identified 3 research priorities. These were uploaded on a software server called the ForceRank software. The research priorities were ranked according to the following criteria: (1) clinical relevance, (2) overall impact, and (3) technical feasibility. The research priorities were then presented to the panelists and audience. Following further discussion and 2 rounds of ranking, the following list of 7 research priorities were ranked (Table 1).

**CONCLUSION**

During the last 20 years, lymphatic science and clinical lymphatic imaging and interventions have been parallel in terms of development. This summit assembled scientists and bioengineers and clinicians who treat lymphatic disorders to discuss the potential goals for the development of interventional treatments of lymphatic and lymphatic-related disorders. A deep understanding of the anatomy, physiology, and pathophysiology of lymphatic disorders is essential for the development of new and more effective treatments, and this RCP served the purpose of establishing such a foundation.

The key conclusion of this RCP was that the lymphatic system plays a significant role not only in intrinsic lymphatic diseases, but also in conditions that are not customarily considered to be lymphatic, including CHF, cirrhosis, and critical illness. The research priorities defined by the RCP acknowledge the link between these diseases and the lymphatic system and mandate additional research in lymphatic flow physiology, composition, and function for potential translation to clinical lymphatic interventions. Further development of the field will require a continued and an increased collaboration between interventionalists and other clinicians, scientists, and bioengineers.
Table 1. List of the Research Priorities

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<thead>
<tr>
<th>Number</th>
<th>Research Priority</th>
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<tbody>
<tr>
<td>1</td>
<td>CHF and lymphatic decompression (external vs internal)</td>
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<tr>
<td>2</td>
<td>Thoracic duct lymph detoxification in acute illness (drainage vs drugs)</td>
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<tr>
<td>3</td>
<td>Development of newer agents/techniques for lymphatic imaging</td>
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<tr>
<td>4</td>
<td>Determine lymph composition to predict the origin of lymph to allow therapy and predict outcomes</td>
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<td>5</td>
<td>Lymphatic interventions to treat ascites secondary to cirrhosis</td>
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<tr>
<td>6</td>
<td>Molecular analysis of lymph composition to determine toxins</td>
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<tr>
<td>7</td>
<td>Lymphatic drug delivery for the treatment of lymphatic diseases</td>
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</tbody>
</table>

CHF = congestive heart failure

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REFERENCES


Volume ▪ Number ▪ Month ▪ 2021 7