Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 52, No. 10, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.06.005

STATE-OF-THE-ART PAPER

Diagnosis and Management of Lymphatic Vascular Disease

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The lymphatic vasculature is comprised of a network of vessels that is essential both to fluid homeostasis and to the mediation of regional immune responses. In health, the lymphatic vasculature possesses the requisite transport capacity to accommodate the fluid load placed upon it. The most readily recognizable attribute of lymphatic vascular incompetence is the presence of the characteristic swelling of tissues, called *lymphedema*, which arises as a consequence of insufficient lymph transport. The diagnosis of lymphatic vascular disease relies heavily upon the physical examination. If the diagnosis remains in question, the presence of lymphatic vascular insufficiency can be ascertained through imaging, including indirect radionuclide lymphoscintigraphy. Beyond lymphoscintigraphy, clinically-relevant imaging modalities include magnetic resonance imaging and computerized axial tomography. The state-of-the-art therapeutic approach to lymphatic edema relies upon physiotherapeutic techniques. Complex decongestive physiotherapy is an empirically-derived, effective, multicomponent technique designed to reduce limb volume and maintain the health of the skin and supporting structures. The application of pharmacological therapies has been notably absent from the management strategies for lymphatic vascular insufficiency states. In general, drug-based approaches have been controversial at best. Surgical approaches to improve lymphatic flow through vascular reanastomosis have been, in large part, unsuccessful, but controlled liposuction affords lasting benefit in selected patients. In the future, specifically engineered molecular therapeutics may be designed to facilitate the controlled regrowth of damaged, dysfunctional, or obliterated lymphatic vasculature in order to circumvent or mitigate the vascular insufficiency that leads to edema and tissue destruction. (J Am Coll Cardiol 2008;52:799–806) © 2008 by the American College of Cardiology Foundation

The lymphatic vasculature, an integral component of the mammalian circulation, is comprised of a network of vessels that is essential both to fluid homeostasis and to the mediation of regional immune responses (1). This vasculature consists of a series of conduits to interconnect the body's interstitial spaces with the lymphoid organs (thymus, spleen, and lymph nodes), and the central circulation, respectively. The vessels are structurally and functionally specialized to mediate the collection and homeostatic regulation of the protein-enriched fluid that is excluded from the venous end of the blood capillary (2). The distinctive structural attributes of the lymphatic capillary network support this vital physiological task: in contrast to the blood circulation, the endothelial monolayers of the lymphatic capillaries display loose junctions that facilitate the entry of fluid, macromolecules, and cells (3). In parallel to its role in extracellular homeostasis, the lymphatic vasculature promotes the traffic of immune cells and fosters lymphocyte population growth (4).

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Manuscript received May 19, 2008; revised manuscript received May 28, 2008, accepted June 3, 2008.

Unlike the circulation of body fluids through the blood vasculature, lymphatic flow occurs through a low pressure system (5). Interstitial fluid gains entry through the initial lymphatics that abut the interstitial space. These structures coalesce into conduits of increasing caliber that, ultimately, become invested with a smooth muscle coat and possess the capacity for rhythmic contractility; these collecting vessels eventually drain their fluid content (lymph) into the central vasculature, chiefly through the thoracic duct (2).

Lymphedema: The Functional Consequence of Impaired Lymphatic Function

A broad spectrum of inherited and acquired disease is characterized by an impaired ability of the lymphatic vasculature to collect and transport fluid. The ensuing stasis of lymph flow is associated with blunted regional immune trafficking, local inflammatory changes, and a heightened propensity to infection, often with ensuing organ or tissue damage (6). The most readily recognizable attribute of lymphatic vascular incompetence is the presence of the characteristic swelling of tissues, called *lymphedema*, which arises as a consequence of insufficient lymph transport.

In health, the lymphatic vasculature possesses the requisite transport capacity to accommodate the fluid load placed

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Abbreviations and Acronyms

CDPT = complex decongestive physiotherapy
KTS = Klippel-Trenaunay syndrome
LAM = lymphangioleiomyomatosis
MLD = manual lymphatic drainage
VEGF = vascular endothelial growth factor
VEGFR = vascular endothelial growth factor receptor

upon it. It is sustained accumulation of fluid within the interstitium that denotes the presence of lymphedema. Thus, lymphedema is the consequence of an imbalance between the rate of lymph production (lymphatic load) and its removal through the lymphatic vascular channels (lymphatic transport capacity). The production of lymph can be enhanced by increased capillary permeability, venous hypertension, or diminished capillary oncotic pressure. Accordingly, local inflammatory responses, venous thromboembolism, or hypoproteinemia can each, individually, produce the clinical appearance of lymphedema, even in the absence of concomitant damage or dysfunction of the lymphatic vasculature. Conversely, when the lymphatic vasculature is disrupted, malformed, or displays inadequate functional responses, the same clinical picture can ensue, with the propensity toward increasing interstitial fluid volume despite a normal rate of interstitial fluid production. Impairment of lymphatic flow can result from either primary or acquired (secondary) anomalies of lymphatic transport. It is conceivable that the binary classification scheme represents a spectrum in which there are anatomic and genetic features that predispose to vascular malfunction or insufficient repair; when coupled with a sufficient initiating stimulus (infection; trauma, either iatrogenic or spontaneous; extrinsic compression; intraluminal tumor invasion), lymphatic vascular insufficiency of clinical proportions may emerge. In this view, larger magnitudes of acquired lymphatic vascular disruption require proportionately smaller degrees of an intrinsic predisposition to the development of lymphedema, while in situations of profound anatomic lymphatic derangement (i.e., congenital lymphedema), no additional environmental stress is required to elicit the functional consequences of lymphatic vascular insufficiency.

The tissue biology of lymphedema is complex and can be distinguished from the other pathophysiological mechanisms that lead to interstitial edema. In the limbs, persistence of lymphedema predisposes, often inexorably, to cutaneous thickening and hypercellularity (7), progressive fibrosis, and pathological increases in the deposition of subcutaneous and subfascial adipose tissue (6,8). In addition to a variable impairment in function of the affected limbs, chronic discomfort often will accompany the dramatic changes in size and structure. Clinically, the presence of lymphedema markedly affects the quality of life and self-perception of the patient, including depression, anxiety, and problems with social adjustment (9). Depending upon pathogenesis and the regional distribution of the vascular defect within the affected individual, various subjective complaints can accompany lymphatic malfunction (Table 1).

Structural alterations of the lymphatic vascular conduits predicate the functional derangements and disease manifestations that ensue (10). With hypoplasia or aplasia of the lymphatic vessels, especially in the presence of primary lymphatic valvular insufficiency, the consequence is decreased contractility, lymphatic hypertension, and the development or exacerbation of valvular incompetence. Obliteration or disruption of lymphatic vessels promotes stasis of lymph, with the attendant accumulation-retained interstitial proteins, and glycosaminoglycans.

Secondary lymphedema. Acquired ("secondary") lymphedema is the most commonly encountered form of lymphatic dysfunction; among these, in the U.S., iatrogenic causes predominate. This pattern reflects the common lymphatic trauma that is engendered by surgical and radiotherapeutic interventions for cancer (11). Within the category of disease

Table 1 The Clinical Spectrum of Lymphatic Vascular Disease

Symptom	Association
General	
Nausea	Lymphangioleiomyomatosis
	Pulmonary lymphangiectasia
Changes in appetite	Noonan syndrome
	Prader-Willi syndrome
Weight loss	Protein-losing enteropathy
Amenorrhea and infertility	Turner syndrome
Delayed puberty	Hennekam's syndrome
Fever	Filariasis
Xerophthalmia	Turner's syndrome
Pruritus	Aagenaes syndrome
Chest pain	Lymphangioleiomyomatosis
Gynecomastia	Klinefelter's syndrome
Respiratory	
Hemoptysis	Lymphangioleiomyomatosis
Sputum production	Lymphangioleiomyomatosis
Dyspnea and wheezing	Intestinal lymphangiectasia
	Lymphangioleiomyomatosis
	Lymphangiomatosis
Gastrointestinal	
Dysphagia	Noonan syndrome
Emesis	Intestinal lymphangiectasia
	Noonan syndrome
Hematemesis	Blue rubber bleb nevus syndrome
Jaundice	Aagenaes syndrome
Bloating	Lymphangioleiomyomatosis
Musculoskeletal	
Joint or muscle pain	Blue rubber bleb nevus syndrome
	Noonan syndrome
Back pain	Neurofibromatosis
Bony fractures	Cystic angiomatosis
Dermatological	
Skin lesions	Blue rubber bleb nevus syndrome
	Maffucci syndrome
	Neurofibromatosis

related to cancer therapeutics, breast cancer-associated lymphedema of the upper extremity is the most commonly encountered problem. Lymph node dissection and adjuvant radiation therapy independently and synergistically predispose to lymphatic vascular insufficiency (12). The most recent estimates suggest that, after axillary intervention, 20% to 30% of breast cancer survivors will experience clinically relevant lymphedema (13,14). Despite recent surgical and radiotherapeutic technical enhancements, lymphedema remains problematic (15). Comparable lymphatic sequelae are encountered after interventions for malignant melanoma and gynecological or urological malignancies (16). Lymphedema can also be acquired from other forms of lymphatic vascular trauma, including burns and large or circumferential wounds to the extremity. Additional causes of acquired lymphedema include pregnancy, contact dermatitis, and rheumatoid arthritis. Autoimmune destruction of the lymphatics has been hypothesized but not directly demonstrated.

Primary lymphedema. Primary lymphedema is not common, but not rare (17), with prevalence estimates for congenital lymphedema that approximate 1:6,000 to 10,000 live births. Many of the associated syndromes have been characterized to possess an autosomal pattern of genetic transmission, yet, somewhat inexplicably, there is often a female predominance, with female:male ratios estimated to be between 2.5 and 10:1.

Primary lymphedema comprises a heterogeneous group of disorders. Among this group of diseases is a broad array of complex syndromes whose pathogenesis has not, in most cases, been delineated (Table 1). Among the entities that are transmitted in a Mendelian fashion, both recessive and dominant genetic transmission has been described for the familial causes of lymphedema. Among the former, one encounters *Hennekam's syndrome* (18), *Prader-Willi syndrome* (19), and *Aagenaes syndrome* (20). In general, the recessive and gender-linked disorders are encountered far less commonly. Dominant transmission characterizes *Noonan's syndrome* (21), *neurofibromatosis*, and *Adams-Oliver syndrome* (22), a profound disorder of vascular development.

It has long been recognized that, for cases of primary lymphedema that lack accompanying phenotypic alterations, there is often, nevertheless, a familial pattern of occurrence. The autosomal dominant form of congenital familial lymphedema, often called *Milroy disease*, was originally described in 1892 (23). Within the last decade, the defect has been linked, in many of the families examined, to a missense inactivating mutation in the flt4 locus that encodes the vascular endothelial growth factor receptor (VEGFR)-3 (24), suggesting that a heritable disorder of lymphatic vasculogenesis is responsible for the hypoplastic lymphatic vasculature and lymphedema that are present at birth.

Lymphedema-distichiasis represents an additional autosomal dominant cause of familial lymphedema. The syndrome is characterized by the pubertal or post-pubertal onset of a more distally distributed form of lymphedema in association with the presence of a supplementary row of eyelashes (distichiasis) that arise from the Meibomian glands. This disorder, among an array of primary lymphedema phenotypes, has been linked to truncating mutations in the forkhead-related transcription factor, FOXC2 (25).

A third, more unusual, form of congenital lymphedema, *hypotrichosis-lymphedema-telangiectasia*, has been linked to mutations in the transcription factor gene SOX18 (26). Autosomal dominant and recessive patterns of transmission have both been described. It is likely that the SOX18 transcription factor plays a role in the development and/or maintenance of lymphatic vessels, but the exact nature of this role remains to be elucidated.

The Clinical Spectrum of Lymphatic Vascular Disease

Beyond lymphedema, there is a broad spectrum of human pathology that has the capacity to impair the functional integrity of the lymphatic vasculature (Table 1) (27).

Lymphangioma is a lesion of embryological development that is usually present at birth and is normally detected clinically within the first 2 years of life (28). When lesions are multiple or widespread, the term *lymphangiomatosis* is applied. The lesions likely arise from the failure of proper anastomosis during vascular development (28). Lymphangiomatous lesions are classified by size and depth of formation.

Complex vascular malformations arise as a consequence of abnormal development or through insult to the blood vascular and lymphatic vascular systems during embryogenesis. Representative diagnostic entities include *cystic angiomatosis* (29), *Maffucci syndrome* (30), *Proteus syndrome* (31), and *blue rubber bleb nevus syndrome. Gorham's disease* results from the uncontrolled growth of nonmalignant vascular channels that lead to lysis of the affected bone. The condition is associated with angiomatosis of blood and lymphatic vessels; chylous pericardial and pleural effusions are associated with this condition, thought to represent a disorder of lymphangiogenesis (32).

Klippel-Trenaunay syndrome (KTS) reflects a constellation of vascular malformations, including capillary, venous, and lymphatic components, accompanied by the hypertrophy of bone and soft tissue (33). Most commonly, KTS manifests in a single extremity, but it can affect multiple limbs or the entire body. Some KTS patients display mutations in the VGFQ gene, an angiogenic growth factor. These mutations are either chromosomal translocations or point mutations, and both tend to enhance the effect of the protein (34).

Patients with *protein-losing enteropathy* develop hypoproteinemia as a consequence of excessive protein loss into the gastrointestinal lumen. In this condition, obstruction of lymphatic vasculature yields increased hydrostatic pressure throughout the gastrointestinal lymphatics, resulting in lymph stasis. Protein loss is nonselective, in contradistinc-

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tion to glomerular diseases, where loss is size dependent. If loss of albumin exceeds its rate of synthesis, edema develops. Other clinical manifestations include ascites and pleural and pericardial effusions.

Intestinal lymphangiectasia is a rare condition characterized by severe edema, thickening of the small-bowel wall, protein-losing enteropathy, ascites, and pleural effusion. If lymphatic fluid and proteins are lost into the gastrointestinal tract, patients present with generalized edema due to hypoproteinemia. The condition may be primary, resulting from a congenital lymphatic vascular disorder, or secondary, as a consequence of inflammatory or neoplastic involvement of the lymphatic system.

Lymphangioleiomyomatosis (LAM) is characterized by the spread of abnormal smooth muscle cells (LAM cells) through the axial lymphatics and the pulmonary interstitium, thereby creating cystic destruction of the lung along with lymphatic wall thickening (35). LAM is also characterized by the presence of pulmonary cysts and angiomyolipomas. LAM is an extremely rare disease, found in less than 1 in a million individuals. It affects mainly women of childbearing age. The clinical presentation is typically pulmonary, featuring primarily cough, hemoptysis, pneumothorax, progressive dyspnea, chylous pleural effusions, and chyloptysis (35).

Diagnosis

The diagnosis of lymphatic vascular disease relies heavily on the physical examination. Lymphedema, even when superimposed upon a more complex vascular presentation, is most often readily identified by its physical characteristics, including edema, *peau d'orange*, cutaneous fibrosis, and positive "Stemmer sign" (the inability of the examiner to "tent" the skin at the base of the digits in the involved extremity) (36). While pitting edema may be absent, it is a common misconception that the presence of pitting precludes a lymphatic origin of limb swelling. However, in all cases, the hallmark of lymphedema is the presence of cutaneous and subcutaneous thickening (Fig. 1), which uniquely identifies the lymphatic pathogenesis of edema formation.

If the diagnosis remains in question, the presence of lymphatic vascular insufficiency can be ascertained through imaging. Direct contrast lymphography has largely been abandoned, in favor of the use of indirect radionuclide lymphoscintigraphy (10,37). The procedure requires intradermal or subcutaneous injection of an appropriate radiolabeled tracer (^{99m}Tc-antimony sulfide colloid, ^{99m}Tc-sulfur colloid, ^{99m}Tc-albumin colloid, or ^{99m}Tc-labeled human serum albumin). Criteria for the diagnosis of lymphatic dysfunction include delayed, asymmetric or absent visualization of regional lymph nodes, asymmetric visualization of lymphatic channels, collateral lymphatic channels, interrupted vascular structures, and visualization of the lymph nodes of the deep lymphatic system. The presence of "dermal back-flow" is abnormal, and is generally interpreted to represent the extravasation of lymph from the vasculature into the interstitium as a consequence of lymphatic venous hypertension.



Figure 1 **A Patient With Severe, Chronic Lymphedema of Both Lower Extremities**

The accentuation of the normal skin folds should be noted. In addition to edema, there is profound thickening of the cutaneous structures.

Beyond lymphoscintigraphy, clinically relevant imaging modalities include magnetic resonance imaging and computerized axial tomography. These imaging techniques permit objective documentation of the structural changes occasioned by the presence of lymphedema (38), inasmuch as the presence of edema within the epifascial plane, along with cutaneous thickening, is characteristic of a lymphatic cause for edema. Magnetic resonance imaging has complementary utility (39). Recent advances in the magnetic resonance approach have vastly facilitated the anatomic and functional visualization of lymphatic vascular anomalies, in both nonenhanced (40) and contrast-enhanced (41) applications. The latter approach has been investigated directly for the evaluation of lymphedema of the limb.

Bioelectric impedance analysis is an emerging diagnostic technique for the clinical evaluation of lymphatic edema. The technique facilitates the noninvasive quantification of extracellular fluid in the extremities; given its sensitivity and reproducibility, it is likely to find increasing application in the early detection and management of lymphatic edema (42).

Treatment of Lymphatic Vascular Diseases

The state-of-the-art therapeutic approach to lymphatic edema relies upon physiotherapeutic techniques. Complex decongestive physiotherapy (CDPT) is an empirically derived, effective, multicomponent technique designed to reduce limb volume and maintain the health of the skin and supporting structures. There is some evidence that this approach stimulates lymphatic transport and facilitates the dispersal of retained interstitial proteins (36).

CDPT relies heavily upon an empirically derived, lymphatic-specific massage technique termed manual lymphatic drainage (MLD) (43). A mild degree of manually delivered tissue compression serves to enhance filling of the cutaneous initial lymphatics and augments dilation and contractility of the lymphatic conduits. MLD is believed to facilitate the recruitment of watershed pathways for lymph flow through its attempts to stimulate the edema-free zones of the trunk and uninvolved extremities. It is also postulated that the technique enhances the development of accessory lymph collectors.

In addition to MLD, the CDPT approach integrates skin care, exercise, and the use of externally applied compression. In the initial management of a previously untreated patient, this compression takes the form of repetitively applied short stretch bandaging, in order to create a multilayer compartment that, during muscular activity, augments the physiological mechanisms that regulate lymphatic contractility and flow (44). In addition, during active tissue compression, there is a reduction in the abnormally increased ultrafiltration which, in turn, leads to improved fluid reabsorption. Eventually, with repetitive physical interventions and bandage applications, edema volume will achieve its nadir; at this point, maintenance of the therapeutic benefits will require the use of fitted elastic garments for use during nonrecumbency. In smaller numbers of patients, nocturnal compression may also be required. Relatively inelastic sleeves and underwear that transmit high-grade compression (40 to 80 mm Hg) will prevent reaccumulation of fluid after successful CDPT. Garments must be fitted properly and replaced every 3 to 6 months.

The therapeutic efficacy of CDPT has been validated. When examined in a series of patients with either upper or lower extremity lymphedema, with an average follow-up of 9 months, average volume reductions of 59% and 68% were observed in the upper and lower limbs, respectively (45); maintenance self-management techniques are effective in sustaining the majority of this benefit in compliant patients (45–47).

While CDPT affords benefit to the majority of patients with lymphedema, the fact that the interventions are labor-intensive, time-consuming, and expensive cannot be refuted. Furthermore, the potentially uncomfortable and very visible impact of the requisite garments may erode the patients' quality of life. Furthermore, the interventions are not uniformly successful. Most patients achieve adequate edema control, but some will require the input of adjunctive devices (43). Notably, intermittent pneumatic compression has been shown to augment the decompressive effects of standard therapies, especially in the context of cancer-associated lymphedema (48). More recently, an adaption of intermittent pneumatic compression has been introduced that, while delivering minimal, phasic external compression, endeavors to simulate the effects of MLD; this device, when used adjunctively in the maintenance phase of therapy, appears to augment the beneficial impact of the standard modalities of CDPT. Other adjunctive approaches, including the external application of hyperthermia (49,50) and low-level laser (51,52), continue to be investigated. Surgical approaches to improve lymphatic flow through vascular reanastomosis have been, in large part, unsuccessful (53), but over the last 15 years there has been consistent evidence for the beneficial effect, in the appropriately selected patient, of controlled liposuction when coupled with the requisite, sustained aggressive post-operative compression (54,55); this approach will restore and maintain normal limb volume and contour after the markedly enlarged subcutaneous adipose layer and hyperplastic soft tissues, both inexorable consequences of long-standing lymphedema (8), have been removed in a controlled surgical intervention. Surgical intervention may be warranted in lymphangiomatosis, and debulking surgery is required for KTS.

The application of pharmacological therapies has been notably absent from the management strategies for lymphatic vascular insufficiency states. In general, drug-based approaches have been controversial, at best. Coumarin has been reported to provide benefit in lymphedema (56), but the salutary effects of the drug are not universally acknowledged, and the poor study design of most of the trials limits interpretability (57). The therapeutic benefit, if present, has been theoretically ascribed to its effect on cutaneous macrophages and, thereby, on local proteolysis. This drug also stimulates other cellular elements of the immune system and may promote protein reabsorption. Despite some encouraging early trials, this agent must still be considered to have an experimental role, which may be further hampered by its capacity to confer hepatotoxicity when given systemically (57). A therapeutic role for selenium, flavonoids, and other antioxidants has been proposed (58), but little supporting evidence exists.

Diuretic therapy has little, if any, role in the management of isolated lymphatic vascular insufficiency, since the pathogenesis of the edema relies upon the elevated interstitial oncotic pressures conferred by macromolecules, rather than upon inappropriate retention of water and electrolytes. However, in cases where hydrostatic pressure is also elevated, such as the post-phlebitic syndrome with secondary hypertension, low-dose thiazide-induced diuresis may play a beneficial complementary role to the primary therapeutic intervention, which is compression.

Dietary therapy plays little role in lymphedema. Of note, however, is the fact that, in selected settings, restriction of dietary fat, when coupled with supplementation of medium chain triglycerides, can markedly reduce the requirement for visceral lymph production; this approach is particularly useful in protein-losing enteropathy and in cases where chylous effusions exist.

Within the spectrum of the lymphatic vascular disease, there are circumstances that mandate specific therapeutic intervention. For patients with lymphorrhea (59) or large, recurrent chylous effusions, the systemic administration of somatostatin or its synthetic analog, octreotide, has been shown to be therapeutically advantageous (60). This approach may be particularly useful when there is evidence of thoracic duct or superior vena caval obstruction. The mechanisms by which somatostatin and octreotide inhibit thoracic duct flow are not well known. Octreotide may act directly on somatostatin receptors in the splanchnic circulation to reduce lymph fluid production. In addition, thoracic duct lymphatic flow depends on splanchnic vascular tone and gastric motility. Because octreotide can decrease the volume of gastric, pancreatic, and biliary secretions, the volume and protein content of fluid within the thoracic duct may reduce concomitantly.

For patients with protein-losing enteropathy, intravenous albumin replacement (61), high-dose corticosteroid therapy (62), or small bowel resection may be beneficial. In patients with enteropathy as a consequence of congenital heart disease, recent heparin administration may reduce leakage of protein into intestinal lumen (61).

Patients with LAM have unique therapeutic strategies. Treatment is often focused on the reduction or prevention of pneumothorax through pleurodesis and pleurectomy (63). Embolization of angiomyolipomas is performed when necessary. Progesterone may slow the progression of LAM, but has a large potential for side effects (64,65). Current research efforts are focused on rapamycin as a useful agent direct against the disease-associated angiomyolipomas (35).

The Future Promise of Molecular Treatment Strategies

The recently acquired insights into the molecular regulation of lymphatic vascular development have fostered sustained interest in the therapeutic potential to modulate post-natal lymphatic vessel growth and remodeling (1,66). A suitable projected target for such therapeutic interventions might be the activation of VEGFR-3 by the secreted growth factor vascular endothelial growth factor (VEGF)-C (67). One of the defined roles of VEGF-C is to trigger a signaling cascade through VEGFR-3 binding that, in turn, allows for stimulation of lymphangiogenesis (68). A similar phenomenon has been demonstrated with VEGF-D (67). Binding of VEGF-C to VEGFR-3 has also been thought to mediate the growth and viability of lymphatic endothelial cells (69).

A murine model of Milroy's disease has been utilized to illustrate the potential for gene therapy in lymphedema. Induction of functional lymphatic vessels in these mice has been observed after overexpression of VEGFR-3 ligands, supporting the sufficiency of VEGF-C/D signaling to promote therapeutic lymphangiogenesis (70). Acquired lymphedema has also been investigated in animal model systems: ablation of the lymphatic vasculature results in lymphedema that is amenable to therapeutic lymphangiogenesis. Both direct administration of recombinant VEGF-C and plasma-mediated gene therapy produce a demonstrable reversal of the pathology of lymphedema (71–73). In addition to the ligands for the VEGFR-3 receptor, VEGF-A (74), fibroblast growth factor-2 (74), and hepatocyte growth factor (75) may each play a significant role in the future molecular therapeutics of lymphedema. In the future, specifically engineered molecular therapeutics may be designed to facilitate the controlled regrowth of damaged, dysfunctional, or obliterated lymphatic vasculature in order to circumvent or mitigate the vascular insufficiency that leads to edema and tissue destruction (76).

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Key Words: lymphatic ■ lymphedema ■ vascular insufficiency ■ edema ■ lymphangiogenesis ■ lymphatic vascular disease.