Lymphaticovenular Bypass for Lymphedema Management in Breast Cancer Patients: A Prospective Study

Foot

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Background: Lymphedema is a common and debilitating condition. Management options for lymphedema are limited and controversial. The purpose of this prospective study was to provide a preliminary analysis of lymphaticovenular bypass for the treatment of upper limb lymphedema in breast cancer patients.
Methods: Twenty patients with upper extremity lymphedema secondary to treatment of breast cancer underwent lymphaticovenular bypass using a "supermicrosurgical" approach. The mean age of the patients was 54 years, 16 patients had received preoperative radiation therapy, and all patients had received axillary lymph node dissection. The mean duration of lymphedema was 4.8 years, and the mean volume differential of the lymphedematous arm compared with the unaffected arm was 34 percent. Evaluation included qualitative assessment and quantitative volumetric analysis before surgery and at 1 month, 3 months, 6 months, and 1 year after the procedure.
Results: The mean number of bypasses performed per patient was 3.5 (range, two to five), and the size of bypasses ranged from 0.3 to 0.8 mm. The mean operative time was 3.3 hours (range, 2 to 5 hours). Hospital stay was less than 24 hours for all patients. The mean follow-up time was 18 months. Nineteen patients (95 percent) reported symptom improvement following surgery, and 13 patients had quantitative improvement. The mean volume differential reduction was 29 percent at 1 month, 36 percent at 3 months, 39 percent at 6 months, and 35 percent at 1 year. No patients experienced postoperative complications or lymphedema exacerbation.
Conclusions: Lymphaticovenular bypass may effectively reduce the severity of lymphedema in breast cancer patients. Long-term analysis is needed. (*Plast. Reconstr. Surg.* 126: 1, 2010.)

The lymphatic system helps remove excess fluid from tissues, absorbs fatty acids, transports fat to the circulatory system, helps immune cells mature, and is also a pathway for cancer metastasis. The lymphatic system consists of lymph capillaries in the dermis that drain excess interstitial fluid into lymphatic vessels in subcutaneous and deep tissues that ultimately drain into the right and left subclavian veins.

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Received for publication January 7, 2010; accepted February 16, 2010.
Presented at the 88th Annual Meeting of the American Association of Plastic Surgeons, in Rancho Mirage, California, May 21 through 24, 2009.

DOI: 10.1097/PRS.0b013e3181e5f6a9

Lymphedema is caused by lymphatic system failure that results in the stagnation of plasma protein molecules, causing high-protein edema. Lymphedema is common, affecting up to 250 million cases worldwide, with filariasis being the most common cause. In the United States and other developed countries, cancer and its treatments are the most common causes of lymphedema. In breast cancer patients, the incidence of lymphedema ranges from 10 percent in those who have undergone axillary node dissection to 40 percent in those who have received radiotherapy.[1–12]

Lymphedema is a chronic, debilitating condition that causes physical and psychological mor-

Disclosure: *The author has no financial interest in any of the products, devices, or drugs mentioned in this article.*

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bidity. The affected limb, which may become swollen, heavy, and/or deformed, is often painful and prone to repeated infections. Lymphedema can also pose a significant financial burden to patients and society. Unfortunately, there is currently no definitive treatment for lymphedema.

The various surgical procedures that have been used to treat lymphedema can be classified into two categories: ablative operations and physiologic operations. Although surgical debulking is the simplest approach to reducing the size of lymphedematous limbs, it causes extensive scarring and substantial morbidities. Consequently, surgical debulking is no longer used to treat lymphedema, except in extreme cases.

In physiologic operations for lymphedema, surgeons create new channels to increase the lymphatic system's capacity to transport lymph. Various procedures have been used to drain excess fluid trapped in lymphedematous areas into other lymphatic basins or the venous circulation.

Lymphaticovenular bypass is a type of lymphovenous bypass, in which a supermicrosurgical technique is used to anastomose distal subdermal lymphatic vessels and adjacent venules less than 0.8 mm in diameter.[13,14] A rationale for this approach is that because distal subdermal lymphatic vessels are less affected by lymphedema, they are more readily available for bypass. In addition, because the pressure in subdermal venules is lower than that in the deep, larger veins used in lymphovenous bypass, there is less venous backflow, resulting in more permanent improvement of lymphedema. The purpose of this study was to evaluate whether lymphaticovenular bypass is effective in treating lymphedema in breast cancer patients.

PATIENTS AND METHODS

This prospective study was approved by the University of Texas M. D. Anderson Cancer Center Institutional Review Board. Between December of 2005 and September of 2008, 20 women with stage II or III unilateral upper extremity lymphedema after partial or total mastectomy for breast cancer were enrolled in the study and underwent lymphaticovenular bypass at M. D. Anderson.

The mean age of the patients was 54 years. The mean duration of lymphedema was 4.8 years (range, 1 to 17 years). Of 20 women, 10 presented with stage II and 10 presented with stage III lymphedema. The mean preoperative volume differential for patients' lymphedematous arms compared with their unaffected arms was 34 percent (range, 5 to 69 percent). All 20 patients had undergone previous axillary lymph node dissection, and 16 patients had received radiation to the axilla.

Patients' lymphedema was classified according to Campisi's criteria as follows: stage I, irregular edema; stage II, persistent edema; stage III, persistent progressing edema with acute lymphangitis; stage IV, fibrolymphedema; and stage V, elephantiasis. A lymphedema therapist performed qualitative assessment and quantitative volumetric analysis before lymphaticovenular bypass and at 1 month, 3 months, 6 months, and 1 year after bypass. Volumetric analysis of patients' lymphedematous and unaffected arms was performed using an optoelectronic limb volumeter (Perometer model and software; Pero-System, Wuppertal, Germany), which uses infrared light to scan the limb and then performs a circumference measurement every 0.5 cm to calculate the total volume of the limb.

Surgical Approach

All procedures were performed with the patient under general anesthesia. Before making each incision, local anesthetic with epinephrine was injected at the incision site for optimal hemostasis. To help identify lymphatic vessels, a 30-gauge needle was used to inject 0.1 to 0.2 ml of isosulfan blue dye (Lymphazurin; United States Surgical Corp., Norwalk, Conn.) 1 to 2 cm distal to each incision.

Lymphaticovenular bypasses were performed through 2- to 3-cm incisions at the distal wrist, midforearm, and proximal forearm on the ulnar-volar aspect in the affected side (Fig. 1) using a surgical microscope (25× to 50× magnification). F1
The subdermal region was dissected to identify lymphatic vessels. Lymphatic vessels either appeared blue with Lymphazurin dye or clear if no dye was taken up. Once we identified a viable lymphatic vessel, a similarly sized adjacent recipient venule was explored to anastomose the vessels to create the bypass. Superfine microsurgical instruments (S&T Surgical, Switzerland) were used AQ: 1
for dissection and for performing the bypasses. Bypasses were generally performed end to end using 11-0 or 12-0 nylon sutures on a 50-μm needle (Fig. 2). F2

After surgery, the affected arm was wrapped loosely with compression bandages and elevated on a pillow, and the patient was given a prophylactic intravenous antibiotic. All patients were discharged within 24 hours. Patients were encouraged to continue previous compression therapy and wear compression arm sleeves beginning 4 weeks after surgery.

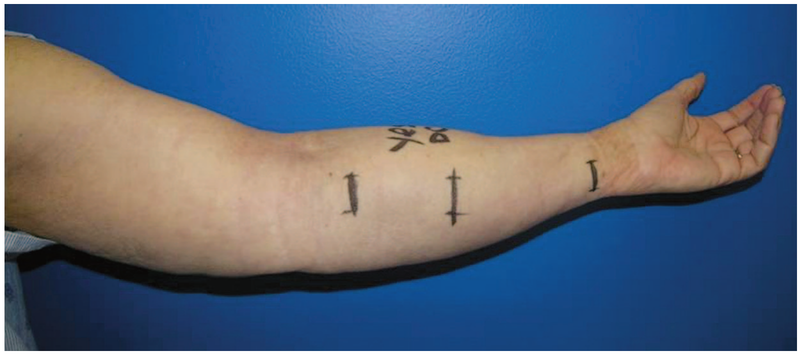

Fig. 1. Incisions (2- to 3-cm) are made at the distal wrist, midforearm, and proximal forearm on the ulnar-volar aspect on the affected side.

RESULTS

The mean number of bypasses performed per patient was 3.5 (range, two to five). The diameter of the lymphatic vessels used for bypass ranged from 0.2 to 0.8 mm. The mean operative time was 3 hours (range, 2 to 5 hours). No patients experienced postoperative complications or worsening of lymphedema during the study period.

Nineteen patients (95 percent) reported symptom improvement immediately after surgery. Symptoms began to improve as early as postoperative day 1. Patients reported that their lymphedematous arms felt lighter, softer, and less painful than they did before surgery. However, in three patients, this improvement was only temporary; lymphedema was exacerbated in one patient after she underwent surgery for carpal tunnel syndrome in the affected arm; in another patient on her return to work as a flight attendant; and in the third patient, also a frequent traveler, after resuming her busy travel schedule.

However, not all patients with symptomatic improvement demonstrated a quantitative measurable difference. Thirteen patients (65 percent) had quantitative improvement of lymphedema after lymphaticovenular bypass. After surgery, the mean volume differential reduction was 29 percent at 1 month, 36 percent at 3 months, 39 percent at 6 months, and 35 percent at 12 months
F3 (Fig. 3). The volume differential is defined as follows: (volume of the lymphedematous arm – volume of the unaffected contralateral arm)/volume of the unaffected contralateral arm. This is the excess volume of the lymphedematous arm compared with the unaffected contralateral arm. The volume differential reduction is defined as follows: (preoperative volume differential – postoperative volume differential)/preoperative volume differential. This is the reduction in the excess volume of the arm following the procedure. The duration of the lymphedema, the stage of the lymphedema at the time of the presentation, and the number of bypasses performed did not have significant impact on the surgical outcome.

DISCUSSION

In this study, lymphaticovenular bypass effectively reduced the severity of lymphedema in most patients. Symptomatic improvement was noted initially by 19 of 20 patients. In most patients, symptomatic relief is immediate. Not all patients with symptomatic improvement, however, demonstrated a quantitatively measurable difference, as only 13 patients demonstrated quantitatively measurable improvement. In six other patients, although they felt that the arm was definitely softer and lighter, soft tissues that have already developed chronic fibrosis apparently were resistant to significant volume and size reduction. Also, in three patients, this improvement was only temporary.

Based on my experience, there are two main factors that determine the effectiveness of this procedure: identification of viable lymphatic vessels and the extent of lymphedema-related tissue fibrosis. To a degree, these two factors are related. It is generally understood that lymphedema initially presents as a soft pitting edema but can progress to nonpitting edema with fibrosis and skin hardening, ultimately causing irreversible structural changes in the lymphatic walls, such as interstitial fibrosis and smooth muscle atrophy. Thus, the severity of lymphedema-related fibrosis appears to correlate with the duration of lymphedema; however, I have found that this is not always the case. Some patients who have had lymphedema for only a short time can have severe fibrosis, whereas some patients with long-term lymphedema may have a lesser degree of fibrosis. It is unclear why this is so; perhaps it has to do with the individual's lymphatic anatomy, which we do not

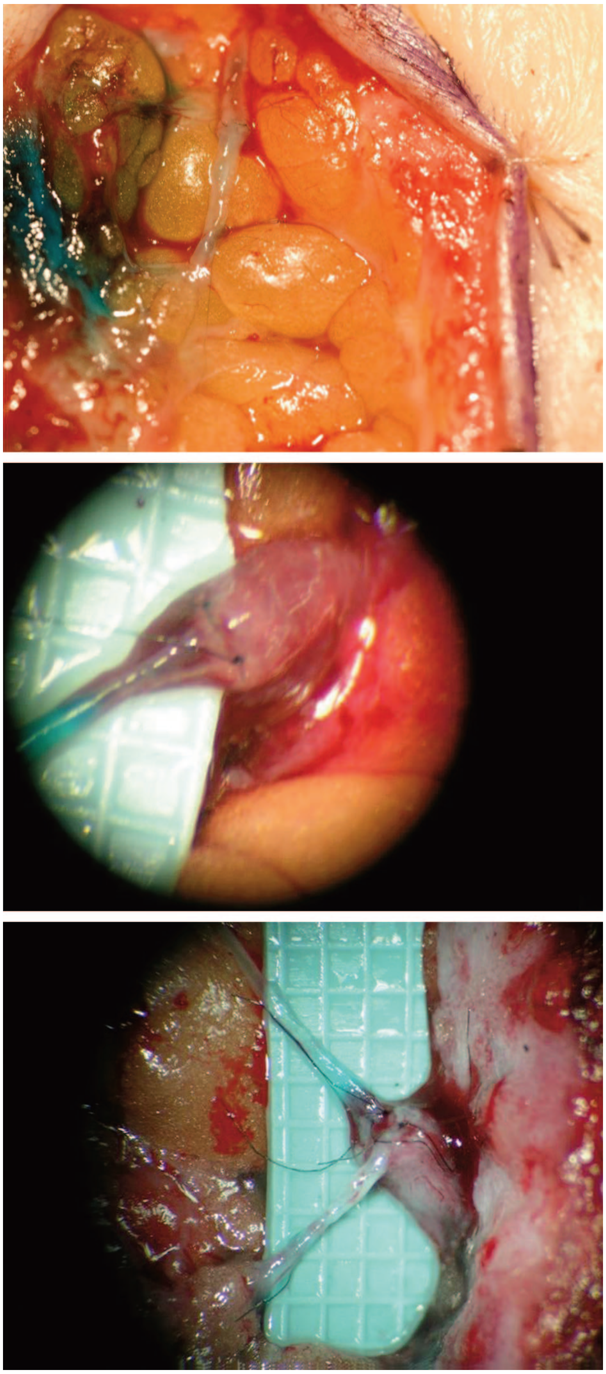

Fig. 2. (*Above*) An example of lymphaticovenular bypass. Note the blue Lymphazurin dye within the lymphatic vessel and the red blood within the venule. (*Center*) Another example of lymphaticovenular bypass. A grid in the background measures 1 mm. (*Below*) Two lymphatic vessels anastomosed to a venule.

yet fully understand. Regardless of the duration of lymphedema, patients with less severe tissue fibrosis generally have more easily identifiable lymphatic vessels suitable for lymphaticovenular bypass. Also, patients with less severe tissue fibrosis respond better to bypass than patients with severe tissue fibrosis. When the arm affected with lymphedema already has developed significant tissue fibrosis, even if the bypasses are successful and the patient notices the symptomatic improvement, usually there is less significant volume change that can be measured quantitatively.

Furthermore, although lymphaticovenular bypass can help reduce the severity of lymphedema in most patients, it does not cure lymphedema. All patients who undergo lymphaticovenular bypass are recommended to continue with ongoing conservative management of their lymphedema, including the continued use of compression arm sleeves. However, in many patients, the compression arm sleeve had to be refitted as the size of the arm was reduced. Thus, critics may ask, "How do you know it is not the compression therapy that is contributing to the improvement in lymphedema?" All of our patients have already tried compression therapy and other conservative treatments with little success before surgery. In all patients, significant improvement was noted before the reinitiation of compression therapy, which usually resumed well after 4 weeks after the operation. Because the lymphaticovenular bypass does not cure lymphedema, ongoing conservative management including the use of compression arm sleeves should remain an important part of lymphedema management to maintain the improvement and to prevent exacerbation of lymphedema.

Surgery for Lymphedema

In 1912, Charles was the first to report a surgical procedure for lymphedema.[15] In this aggressive debulking surgery, all overlying skin and soft tissue above the deep fascia in the lymphedematous area are resected, and the raw surface is covered by a skin graft.

Sistrunk first described a surgical procedure for breast cancer–related upper extremity lymphedema in 1927 and attempted to create a spontaneous connection between the superficial and deep lymphatic vessels by excising the excess skin and soft tissue including the deep fascia by means of a spindle-shaped incision in the medial limb.[16] Decades later, Thompson used a lymphatic transposition approach in which a deepithelialized, rectangular hinge skin flap was raised from the entire length of the arm and the tip of the flap embedded beside the neurovascular bundle in an attempt to bridge the superficial and deep lymphatic systems.[17,18] However, there is no objective evidence that Sistrunk's or Thompson's attempts

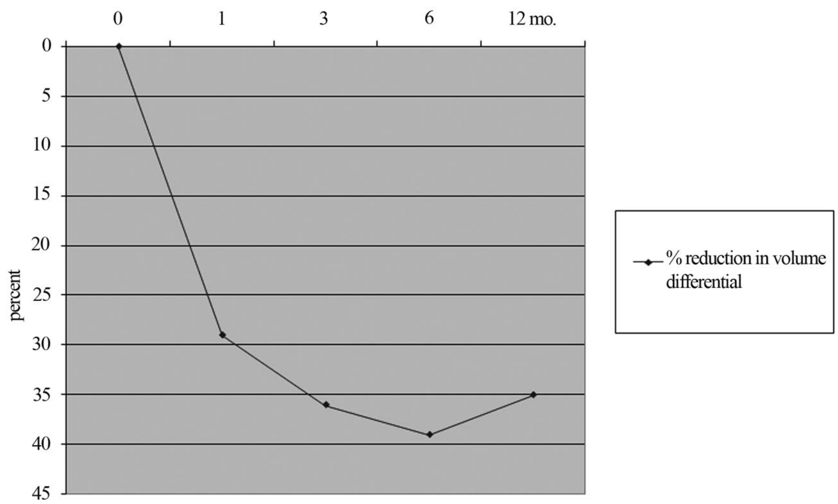

Fig. 3. A quantitative volumetric analysis at 1 month, 3 months, 6 months, and 1 year after bypass.

to create alternative pathways of lymphatic drainage succeeded.

In 1989, O'Brien et al. reported using liposuction to treat lymphedema.[19,20] Although liposuction effectively reduces the volume of hypertrophic adipose tissue, the procedure can also damage the residual lymphatic vessels, thus exacerbating lymphedema.

Baumeister and Siuda and Ho et al. reported using a lymphaticolymphatic bypass approach to treat upper limb lymphedema in which healthy lymphatic vessels from the medial thigh were used as grafts.[21–23] The graft is inset under the skin of the shoulder to create lymphatic bypass routes between the upper arm and supraclavicular region. Lymphatic vessels at each end of the graft are identified and anastomosed with recipient lymphatic vessels in the neck and upper arm in accordance with the direction of lymph flow in the donor vessels. However, harvesting the lymphatic vessels leaves a long scar at the donor site and may lead to lymphedema in the donor leg. Campisi advocated using a vein interposition graft between the lymphatic vessel bundles above and below the site of lymph blockage to bypass the obstruction.[24,25]

Others have reported transplanting composite soft tissue, including inguinal lymph nodes, to the lymphedematous limb.[26,27] Theoretically, microvascular lymph node transfer causes new lymphatic vessels to sprout from the transplanted lymph node to drain the region; however, there is no evidence that lymphatic vessels actually grow from transferred nodes. Also, harvesting lymph nodes may cause lymphedema in the donor extremity.

Laine and Howard first described the use of lymphovenous bypass in a rat model in 1963.[28] Laine and Howard used a microsurgical technique to anastomose peripheral lymphatic vessels to adjacent veins to drain excess fluid from the lymphedematous limb into the venous system. Later that decade, Yamada performed similar operations in dogs and then used lymphovenous bypass to treat lower limb lymphedema in humans; since then, others have refined the technique.[29–36] However, lymphatic vessels are often difficult to identify, and venous pressure often exceeds lymphatic pressure, which can lead to backflow and thrombosis in the bypass, thus resulting in only temporary improvement.

Lymphaticovenular Bypass

Lymphaticovenular bypass is a type of lymphovenous bypass in which a supermicrosurgical technique is used to anastomose distal subdermal lymphatic vessels and adjacent venules less than 0.8 mm in diameter.[13,14] A rationale for this approach is that because distal subdermal lymphatic vessels are less affected by lymphedema, they are more readily available for bypass. In addition, because the pressure in subdermal venules is lower than that in the deep, larger veins used in lymphovenous bypass, there is less venous backflow, resulting in more permanent improvement of lymphedema.

Koshima et al. performed biopsies on lymphatic trunks and demonstrated that the proximal-to-distal destruction of the endothelial and smooth muscle cells within the tunica media is a key step for lymphedema progression.[13] Clinical experiences have been consistent with the findings of Koshima et al. in that subdermal lymphatic vessels are easily identifiable at the distal arm but much more difficult to identify in the proximal arm. Although in many patients lymphedema is most severe proximally, lymphaticovenular bypasses are performed distally because proximal subdermal lymphatic channels have often been damaged or destroyed and cannot be found.

Challenges

One of the challenges of lymphaticovenular bypass is identifying functional lymphatic vessels. Fluorescence lymphography, which has been used to image the lymphatic system during lymphovenous shunt operations, may provide a solution.[37,38] Fluorescence lymphography detects near-infrared light emitted by indocyanine green dye that has been injected into the affected limb to demonstrate the path of the lymphatic vessels; the technique enables surgeons to locate a functional lymphatic vessel for the lymphovenous shunt before making any incisions, thus substantially reducing operating time and potentially improving the success rate of the operation.

Additional data are needed to help develop a definitive treatment for lymphedema. The lack of available research may be attributable to certain features of the lymphatic system that make it difficult to study, such as its transparency, fragility, and numerous valves. However, these challenges may soon be overcome. Several immunohistochemical markers for histologically examining the lymphatic system are now available, and a new anatomical method for radiographically visualizing lymphatic vessels has been developed.[39–45] Several experimental animal models have also been developed for evaluating potentially definitive surgical procedures for lymphedema.[46,47]

Whether lymphaticovenular bypass is the best treatment for lymphedema is unclear; however, our findings suggest that the procedure initially reduces the severity of lymphedema in most patients. One of the advantages of this approach is that the procedure is minimally invasive: patients experienced minimal pain, and all patients were discharged from the hospital within 24 hours after surgery. Another advantage is that there is minimal associated morbidity: there were no complications or exacerbation of the lymphedema. The main morbidity is three small scars at the surgical site. However, lymphaticovenular bypass is a technically challenging procedure that requires surgeons to manipulate extremely small vessels under high magnification. Furthermore, the extent of improvement is unpredictable, and currently we do not have a definitive way of predicting which patients are the best candidates for this procedure. Also, because our follow-up data are preliminary, it remains unclear whether lymphaticovenular bypass provides a benefit beyond 5 to 10 years in breast cancer patients with lymphedema. Long-term data and better preoperative and postoperative evaluation methods are needed. Technical refinements in lymphaticovenular bypass are also warranted.

CONCLUSIONS

The current study's findings indicate that lymphaticovenular bypass effectively reduces the severity of breast cancer–related lymphedema in most patients, thus offering them a quality-of-life benefit.

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