Treatment of Lymphedemas by Microsurgical Lymphatic Grafting: What Is Proved?

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Lymphedemas due to a local blockade of the lymphatic system can be treated by bridging the defect with autologous lymphatic grafts. Under the microscope, grafts are anastomosed to peripheral lymphatics distal to and central lymphatics proximal to the regional blockade. In this way, the diminished transport capacity can be restored.

In the case of unilateral blockade at the groin or pelvis, the grafts connect the lymphatics of the thigh of the affected leg with lymphatics in the contralateral healthy groin.

Between June of 1980 and December of 1986, 55 patients with lymphedemas have been treated by lymphatic grafting. The effect of lymph vessel transplantation has been evaluated by volume measurements and lymphatic scintiscans, showing a persistent patency of grafts, improvement of the transport index, and a persistent reduction in volume of the affected limbs.

The reduction reached a level of 80 percent in patients with a follow-up of at least 3 years. The transport index showed an improvement of 30 percent.

Autologous lymph vessel transplantation has been shown to be a fundamental step toward the microsurgical treatment of lymphedema.

In the search for an operative treatment for lymphedema, many different methods were developed: resectional methods,[1-5] resectional methods combined with drainage,[6] bridging operations using flaps, omentum, and ileum,[7-12] and draining procedures into veins.[13-16] The basis for a new approach lies in a pathophysiologic understanding of the cause of lymphedema. It has its origin in an imbalance between lymphatic load and lymphatic transport capacity.[17] *Lymphatic load* describes the amount of tissue fluid that has to be transported out of one part of the body by the lymphatic system during a given period of time. *Lymphatic transport capacity* depends on the number and function of lymphatic vessels in the same part of the body. A numerical deficit of lymphatic vessels in any defined area causes a decrease in transport capacity and may lead to lymphedema. Reinstatement of the number of lymphatics by transplantation of healthy autologous lymphatics solves the problem in a most natural way.

Extensive experimental studies and progress in the field of microsurgery were necessary to permit the introduction of novel transplantation techniques into clinical surgery. The first experiments were undertaken to evaluate patency of lympholymphatic anastomoses.[18,19] The studies were continued by examining the patency and function of lymphatic grafts in rats and dogs.[19-21] Following this phase of extensive experimental evaluation of lymphatic transplantation, lymphatic grafting was used in patients starting in 1980.[22-24]

Indications

Regional blockage of the lymphatic system is the main indication for lymphatic grafting. In most cases, these blockages result from surgical interventions such as lymphadenectomy (in the axilla, groin, or pelvic area) or dissection of lymphatic trunks in narrow parts of the lymphatic system (e.g., on the medial side of the knee). In addition, infection or radiotherapy often damages the lymphatic pathways additionally and leads to the clinical manifestation of edema.[25]

A further indication can be found in special forms of primary lymphedema, e.g., unilateral pelvic lymphatic atresia.

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Tl following requirements have to be fulfilled prior to surgical treatment of secondary lymphedema:

1. It is necessary to keep an interval of at least 6 months after resectional surgery, which may be followed by transitory swelling. During that period of time, spontaneous normalization might occur and lymphatic grafting may become superfluous.
2. Conservative treatment, which must be performed in every patient prior to surgical therapy, does not improve the situation permanently and a constant surplus of about 50 percent in volume remains.
3. After tumor therapy, an exact evaluation of the patient with respect to possible recurrence of the tumor is necessary.
4. In order to perform autologous lymphatic grafting, one must be able to harvest the lymphatic vessels from the patient's thigh. A preoperative lymphatic scintiscan permits sufficient evaluation of lymphatic transport capacity in the donor region. If lymphatic flow is impaired in the donor region or there is swelling of some region, lymphatic vessels cannot be harvested.
5. General operability must be given.

METHODS

Patients

Between June of 1980 and December of 1986, 55 patients received autogenous lymphatic vessel transplants. Thirty-seven suffered from edema of the upper extremity. All except one had postmastectomy edemas.

Of the 18 patients with lymphedema of the lower extremity, 4 had primary, 13 iatrogenic, and 1 posttraumatic edema. Twelve of the patients were adults; 6 were children or adolescents. The mean age of the adults was 38 years, ranging from 23 to 63 years.

In the group of patients with postmastectomy edemas, the mean age was 56 years, ranging from 40 to 77 years. The mean interval between mastectomy and lymphatic grafting was 10 years, ranging from 17 months to 20 years.

The mean interval between onset of edema and lymphatic grafting was 8 years, ranging from 12 months to 20 years.

Harvesting of Lymphatic Vessels

Lymphatic grafts are harvested from the patient's thigh. According to anatomic studies by Kubik,[26] a ventromedial bundle of the thigh is located medially. It consists of 6 to 17 lymphatic collectors.

Grafts can be prepared between the junctions of the lymphatic system at the groin and the knee with a length of up to 30 cm. Usually two, exceptionally three collectors are harvested. They often have two afferent branches. This means that there are about three to five sites that can be used for peripheral anastomoses.

In order to facilitate preparation, patent blue is injected subcutaneously between the first and second toes. After 15 to 20 minutes, the lymphatics of the thigh are stained blue-green. Thus they are easily visualized and dissected using magnifying glasses (Fig. 1).

Search for Lymphatic Vessels in Edematous Tissues

In order to anastomose the grafts with the lymphatic vessels of the edematous extremity, these must be identified at those locations where they are most likely to be found. Lymphatic vessels superficial to the muscular fascia are identified first. They are usually found at the medial

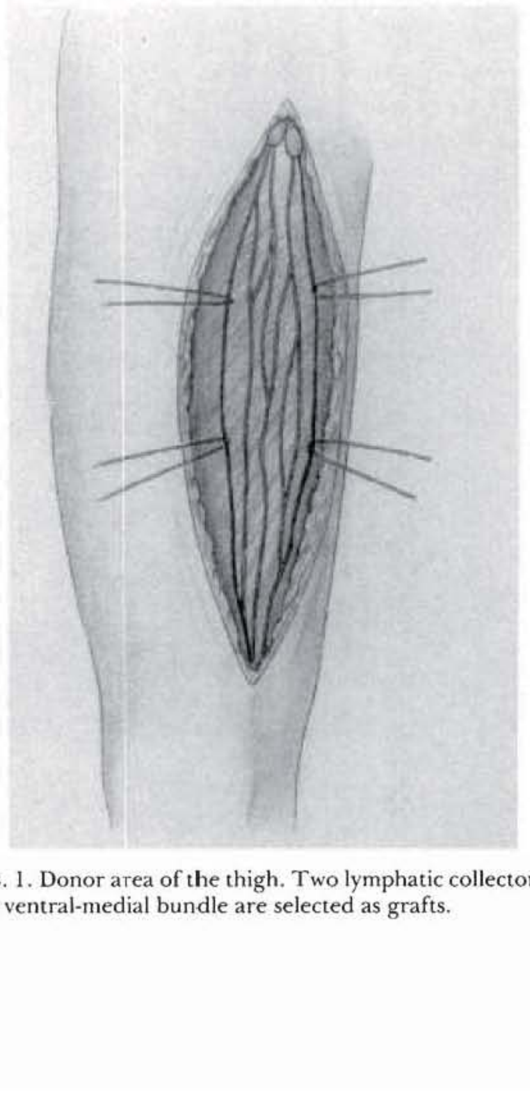

FIG. 1. Donor area of the thigh. Two lymphatic collectors of the ventral-medial bundle are selected as grafts.

aspect of the upper arm or thigh. The deep lymphatics accompany the large vessels and are usually situated between the vein and the artery.

In lymphedematous tissue, the transportation of dye is slow. Therefore, we use no dye in the affected extremities. Instead, we search for lymphatic vessels using the microscope.

Lymphatic vessels in edematous tissues are rarely prominent and distended. They have a thickened wall and look gray. In contrast, nerves have a shiny surface and show transverse stripes. The lumen of a lymphatic vessel in edematous tissues is filled with clear fluid when incised.

Search for Appropriate Lymphatic Vessels for the Central Anastomosis

To treat edema of the arm, lymphatic structures in the neck have to be exposed. Lymphatic vessels run from the head to the subclavian vein lateral to the jugular vein behind the sternocleidomastoid muscle.

To treat unilateral edemas of the lower extremities, the central part of the graft remains attached to the lymph nodes of the groin at the donor site.

Lympholymphatic Anastomoses

Magnification of up to fortyfold is used to construct lympholymphatic anastomoses. These are carried out as end-to-end anastomoses using tension-free technique.[23]

In contrast to the technique of Cobett,[27] in which the vessels are twisted on corner sutures, the lymphatic vessels with their fragile wall are sutured without any tension. First, the corner stitch opposite the surgeon is performed. The back wall is sutured with one to two interrupted single stitches. The vessel wall is elevated as far as necessary for suturing. The anastomosis is completed by the second corner stitch followed by one to two interrupted sutures on the front wall. Absorbable suture material is superior to nonabsorbable.[21] The most appropriate size is 11-0.

The number of peripheral anastomoses that can be constructed in the edematous extremity depends on the number of peripheral branches each graft has. Generally, three to five anastomoses are possible.

Grafting Technique

The grafts are implanted in different ways depending on the site of lymphatic blockade. In edemas due to a blockade in the axilla, e.g., postmastectomy edemas, the grafts are used to connect ascending lymphatic vessels in the upper arm with more centrally located lymphatic vessels in the neck. They are pulled through the tube of a suction drain inserted in the subcutaneous tissue between small incisions. The tube is then removed (Fig. 2).

In unilateral edemas of the lower extremity, the donor grafts from the opposite leg stay connected with the lymph nodes at the groin. They are pulled over the symphysis and anastomosed with ascending lymphatic vessels present within the edematous limb (Fig. 3).

In local lymphedemas of certain regions of the extremities, the grafts are anastomosed distal to and proximal to the blockade. In any case, the grafts may not be placed inverse to the original direction of lymph flow.

Additional Treatment

Following surgery, the limbs are kept elevated and are bound in elastic dressings during the

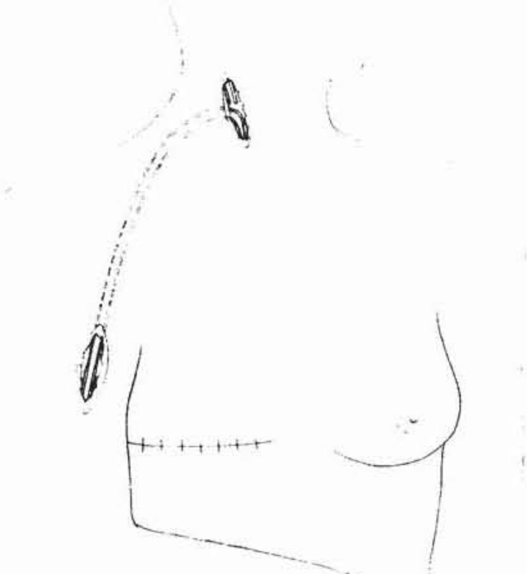

FIG. 2. Postmastectomy edema. Lymphatic grafts are interposed between ascending lymphatics at the upper arm and descending deep lymphatics at the neck.

FIG. 3. Unilateral lymphedema of the lower limb. Lymphatic grafts are transposed by means of the symphysis and are anastomosed with ascending collectors of the affected limb.

patient's in hospital stay. The patients are shown certain exercises to minimize edema. To prevent the formation of erysipelas, the patients receive antibiotics and daily infusions with low-molecular-weight dextrane. Grade II elastic stockings are fitted for each patient and are usually worn for half a year. Then the stockings may be removed depending on the extent of edema remaining.

Evaluation of Results

Results were evaluated using two different methods. The calculation of tissue volume was based on the examination of extremities before and after lymphatic grafting and their comparison to the unaffected contralateral side. Making use of Kuhnke's[28] formula, the extremity is divided into slices of 4 cm. The sum of the volumes of these slices corresponds with the volume of the whole extremity.

Lymph transport capacity and transport behavior were evaluated preoperatively and postoperatively by an independent radiologist. A lymphatic scintiscan is used to determine transport capacity. This method also permits the direct visualization of patent grafts.[29]

About 100 MBq of labeled ^{99m}Tc-pertechnetate stannous sulfur precolloid was injected subcutaneously at the first interdigital space. The precolloid is taken up by the lymphatic vessels, and the outflow is visualized by a gamma camera. The transport index *TI* is calculated by the formula

$$TI = K + D + (0.04 \times T) + N + V$$

where K = lymphatic transport kinetics (0 = no delay; 3 = low-grade delay; 5 = extreme delay; 9 = missing transport)

D = distribution pattern (0 = normal distribution, i.e., nearly no background; 3 = partially diffuse distribution; 5 = diffuse distribution; 9 = transport stop)

T = time until appearance in lymph nodes (time in minutes until the first appearance of regional lymph nodes × 0.04; 9 = no appearance)

N = assessment of lymph nodes (0 = clear visualization; 3 = faint visualization; 5 = hardly recognizable; 9 = no visualization)

V = assessment of lymph vessels (0 = clear visualization; 3 = faint visualization; 5 = hardly recognizable; 9 = no visualization)

A border-line *TI* of 10 was used to differentiate between normal and pathologic lymph drainage. Using this definition, the sensitivity of this technique was 97.4 percent and the specificity was 90.3 percent in 122 investigations.[29]

Figures 4 and 5 show lymphatic scintiscans in postmastectomy edemas preoperatively and postoperatively at different time intervals. Figure 6 shows lymphatic scintiscans in the lower extremity of a patient with a blockade on the left side of the pelvis.

Statistics

Student's *t* test was used for the statistical evaluation of the results.

RESULTS

In the group with postmastectomy edemas, we performed volume measurements of the arm in 36 patients. The mean arm volume of 3268 cm^3 preoperatively decreased to 2509 cm^3 2 weeks after grafting and came down to 2436 cm^3 about 2 years later. Sixteen patients with a follow-up of more than 2 years showed a decrease to 2272 cm^3. Eleven patients with a follow-up of more than 3 years showed a mean decrease to 2195 cm^3. Three years after surgery, the volumes reached an order of magnitude almost similar to those of normal arms. Over the years, the de-

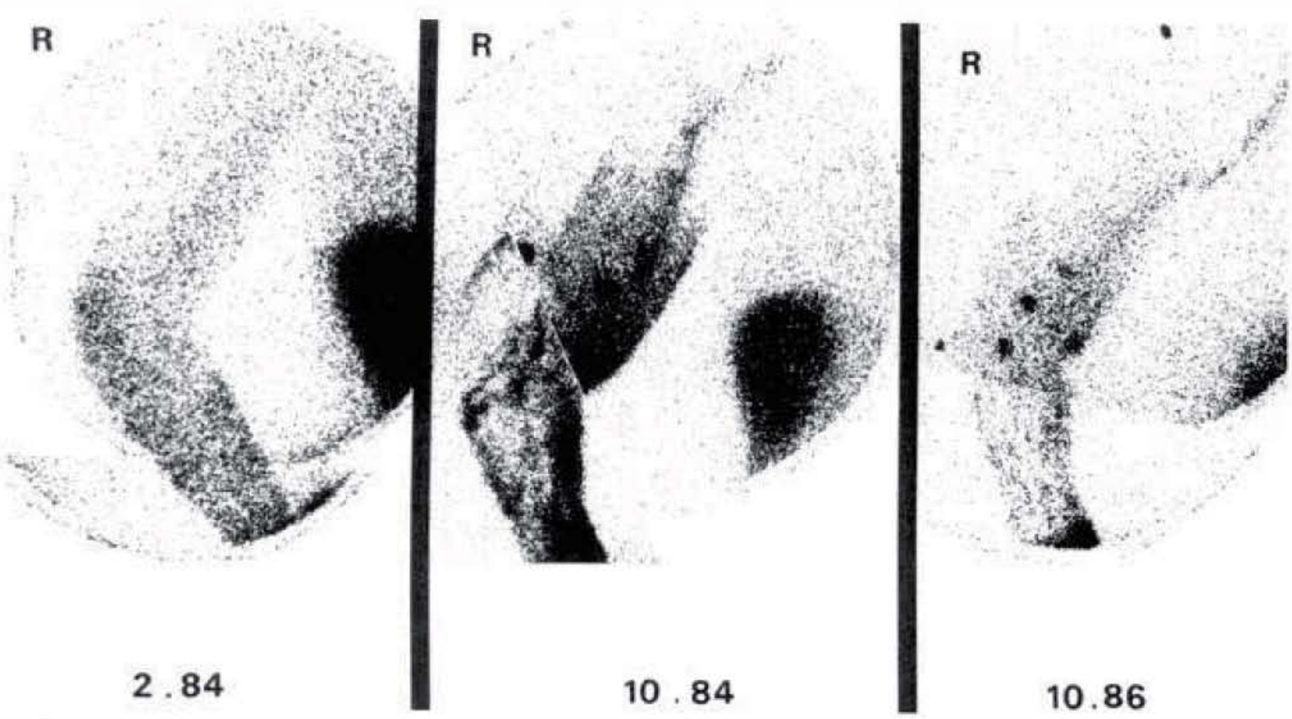

FIG. 4. Lymphatic scintiscan of a 43-year-old patient with postmastectomy edema of the right arm (see also Fig. 9). (*Left*) Before operation (transport index $TI = 38$). (*Center*) Six months after lymphatic grafting. Poorly visible grafts with improved transportation of lymph ($TI = 10$). (*Right*) Two and one-half years after transplantation. Normalized lymphatic transport ($TI = 7$).

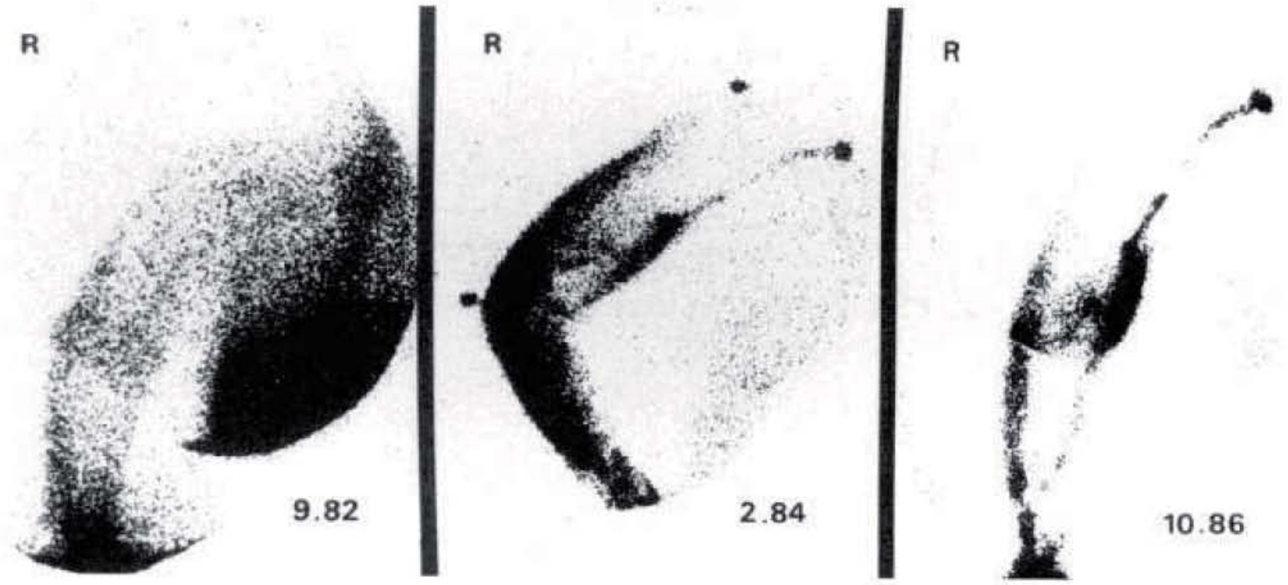

FIG. 5. Lymphatic scintiscan of a 42-year-old patient with postmastectomy edema of the right arm (see also Fig. 10). (*Left*) Before operation ($TI = 20$). (*Center*) One and one-half years after transplantation. Visible grafts provide sufficient transport in the upper, delayed transport in the lower part of the arm ($TI = 7$). (*Right*) Four years after transplantation. Well visible grafts, normalized lymphatic transport ($TI = 3$).

crease in volume was not only maintained but showed further decline. The reduction reached a level of 80 percent in patients with a follow-up of at least 3 years (Fig. 7 and Table I). In all groups, the stated decrease was highly significant ($p < 0.001$).

Graft patency and changes in lymph transport capacity were evaluated by lymphoscintigraphy in 30 patients with postmastectomy edema. Lymphatic outflow improved significantly during a mean follow-up period of 16 months. The transport index decreased from 33 to 23, significantly

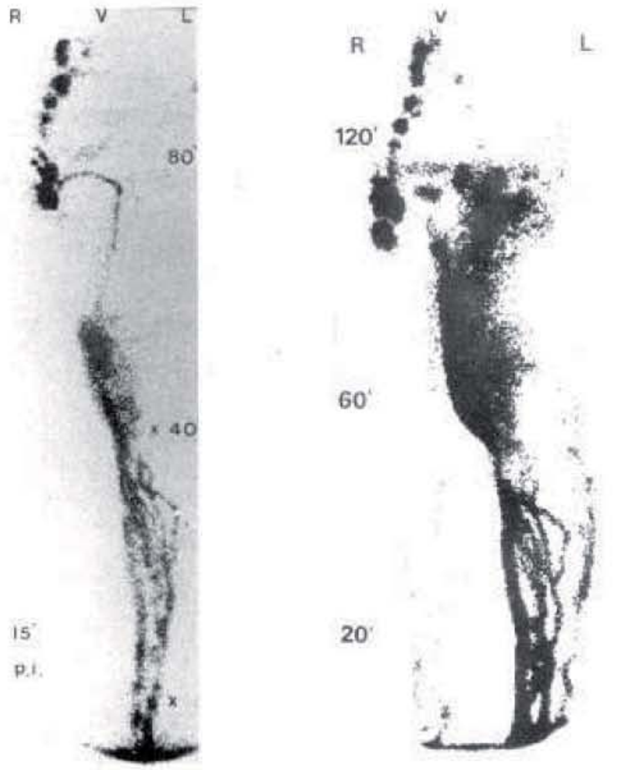

FIG. 6. Lymphatic scintiscan of a 31-year-old patient with lymphedema of the left leg after pelvic lymph node dissection. (*Right*) Injection of the Radiopharmacon preoperatively in both feet. Normal lymph transport in right leg, blockade in the left inguinal region (*TI* = 12). (*Left*) Four years after transposing of lymphatic grafts over the symphysis from the right to the left leg. Injection only in the left foot. Well visible graft, normal lymphatic transport (*TI* = 2).

($p < 0.001$), which is an improvement of about 30 percent.

Fifteen of 37 patients with lymphedema of the arm had one or more episodes of erysipelas in their past history. Five of these patients had no incidence of erysipelas postoperatively. Two of them had one episode of erysipelas before and after the operation. In 8 patients, the number of erysipelas occurring postoperatively was significantly less when compared to the number of preoperative erysipelas.

Lower Extremities

Statistical evaluation of treatment in lower extremities only includes adult patients. The volumes of the unaffected contralateral legs in adults remain constant, making them more comparable as opposed to measurements undertaken in children, in whom normal leg volumes vary considerably during growth.

For each child, an individual follow-up is done, taking into consideration the growth of the normal and operated leg as well.

In 12 adult patients there was a significant reduction in volume after 14 days (preoperatively 11413 cm^3 down to 8920 cm^3) and after 1 year (8 patients, 9432 cm^3). The decrease was significant to values of 0.01 and 0.05, respectively.

Compared to the upper extremity, it is more difficult to maintain or improve reduction in

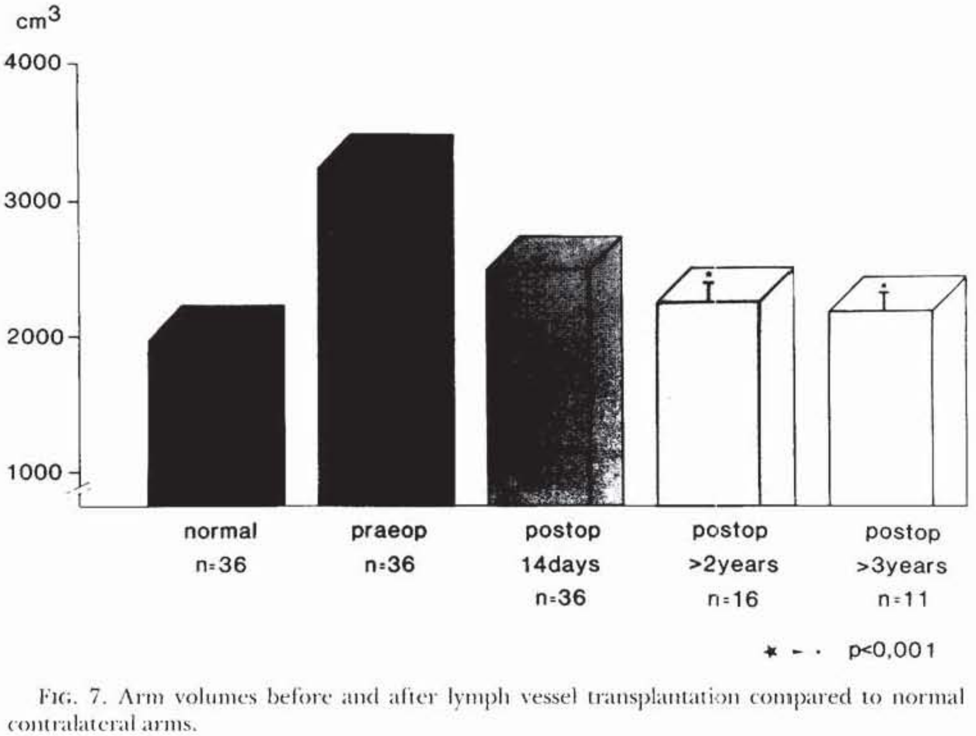

FIG. 7. Arm volumes before and after lymph vessel transplantation compared to normal contralateral arms.

TABLE I

Arm Volumes Before and After Lymph Vessel Transplantation Compared to Contralateral Normal Values (p = Normal vs. Postoperative and Preoperative vs. Postoperative)

	n	cm³	p
Normal	36	1988 ± 53	
Preoperative	36	3268 ± 106	
Postoperative:			
14 days	36	2509 ± 77	<0.001
108 weeks	33	2436 ± 95	<0.001
>2 years	16	2272 ± 149	<0.001
>3 years	11	2195 ± 138	<0.001

lower limb volume after hospital discharge (Table II and Fig. 8).

Postoperative Complications

Swelling of the leg was observed once, presumably due to phlebothrombosis. The patient refused further examination. Furthermore, one lymph cyst in the groin and two immediate postoperative erysipelas were seen. Following these observations, antibiotic treatment was added to our prophylactic postoperative treatment regimen. Since then, no such complications have been observed.

Clinical Case Studies

The largest group of patients treated by lymphatic grafting had irreversible edema of the upper extremity following mastectomy. One of these patients, a 43-year-old woman, is shown in Figure 9 preoperatively and 2 years after grafting. The scintiscan of this patient is shown in Figure 4. The lymphatic scintiscan corresponds well with the clinical findings in this patient.

The second patient, a 42-year-old woman, developed a lymphedema over a 10-year period following mastectomy. Two years after lymph vessel transplantation without additional therapy, a constant reduction in limb volume was achieved (Fig. 10). The scintiscan is shown in Figure 5.

TABLE II

Volumes of Lower Extremities Before and After Lymph Vessel Transplantation Compared to Contralateral Normal Values (p = Normal vs. Postoperative and Preoperative vs. Postoperative)

	n	cm³	p
Normal	12	8316 ± 319	
Preoperative	12	11413 ± 858	
Postoperative:			
14 days	12	8920 ± 428	<0.01
1 year	8	9432 ± 478	<0.05

The third postmastectomy patient (46 years old) suffered from lymphedema of the right arm for 11 years. The arm, which at one time was severely fibrotic with ballooning of the hand, is now soft with remarkable reduction of edematous expansion, although no compressive therapy was applied (Fig. 11).

Figure 12 shows a 45-year-old patient with local lymphatic blockade of the lower limb. He developed a lymphedema of the right lower leg after resection of a benign tumor mass at the right knee. The blockade was bridged by short lymphatic grafts.

Discussion

Direct reconstructive procedures of the lymphatic system have been performed for the first time by using newly developed refined microvascular techniques. Until now, microsurgical treatment of lymphedemas has focused on the direct anastomosis of lymphatic vessels to branches of the peripheral venous system. However, one particular weakness of this method is that in some circumstances venous pressure can be higher than pressure found in the lymphatic vessels, and the clotting activity of the blood can lead to a higher rate of thrombosis at the anastomosis when compared to lympholymphatic anastomoses.[30,31]

A great number of surgical methods for the treatment of lymphedemas have been developed without adequate systematic animal experimentation. In contrast, the development of lymphatic vessel transplantation is based on extensive animal research. The experiments show that the patency rate of lympholymphatic anastomoses is almost 100 percent. The anastomoses were performed using very fine absorbable suture material and by employing a technique that prevents any pull or tension at the anastomoses.[32] The functional efficiency and patency of the lymphatic vessel grafts were demonstrated in experimentally induced lymphedemas in a dog model.[32] The clinical observations coincide very well with these experimental results.

Patency rates that are close to 100 percent must be evaluated very carefully and critically. At this point, it must be remembered that according to an observation by Danese et al.,[33] lymphatic collectors that have been closely approximated will spontaneously connect to one

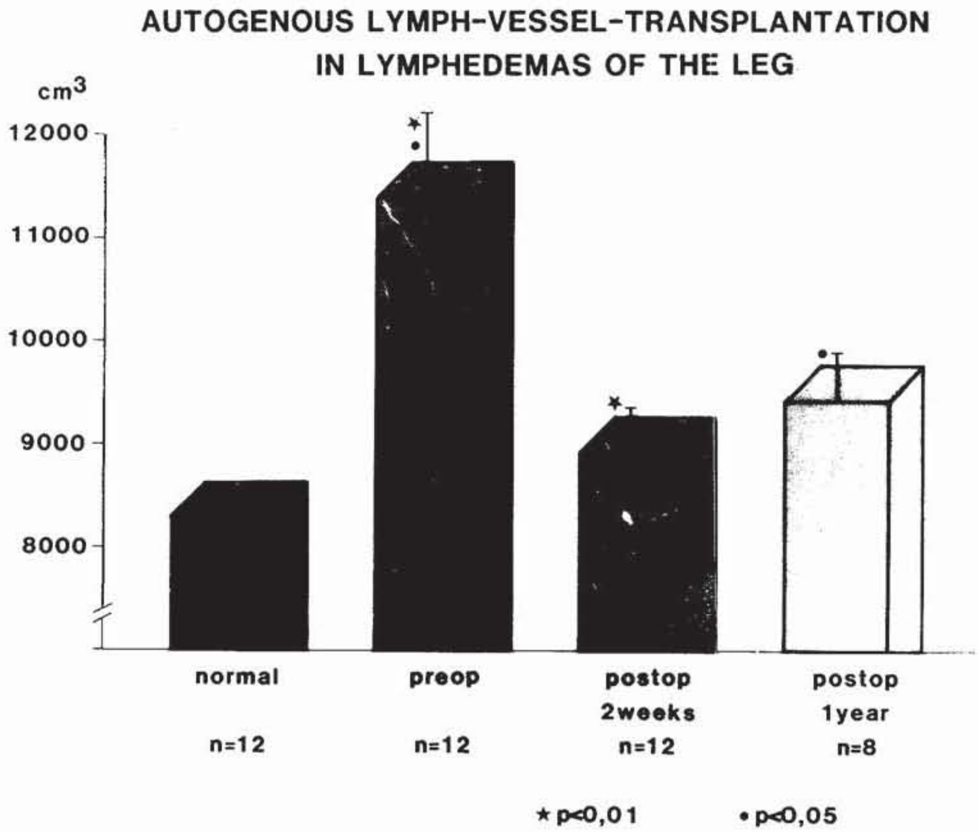

FIG. 8. Volumes of lower extremities before and after lymph vessel transplantation compared to normal contralateral values.

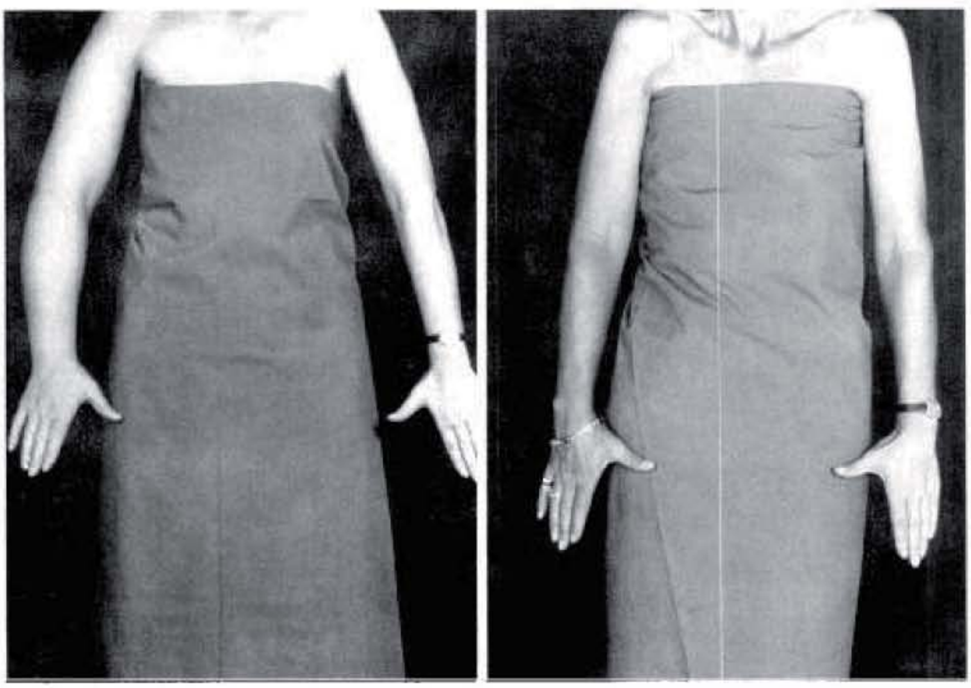

FIG. 9. (*Left*) A 43-year-old patient with lymphedema 2 years after mastectomy on right side. (*Right*) Appearance 1½ years after grafting.

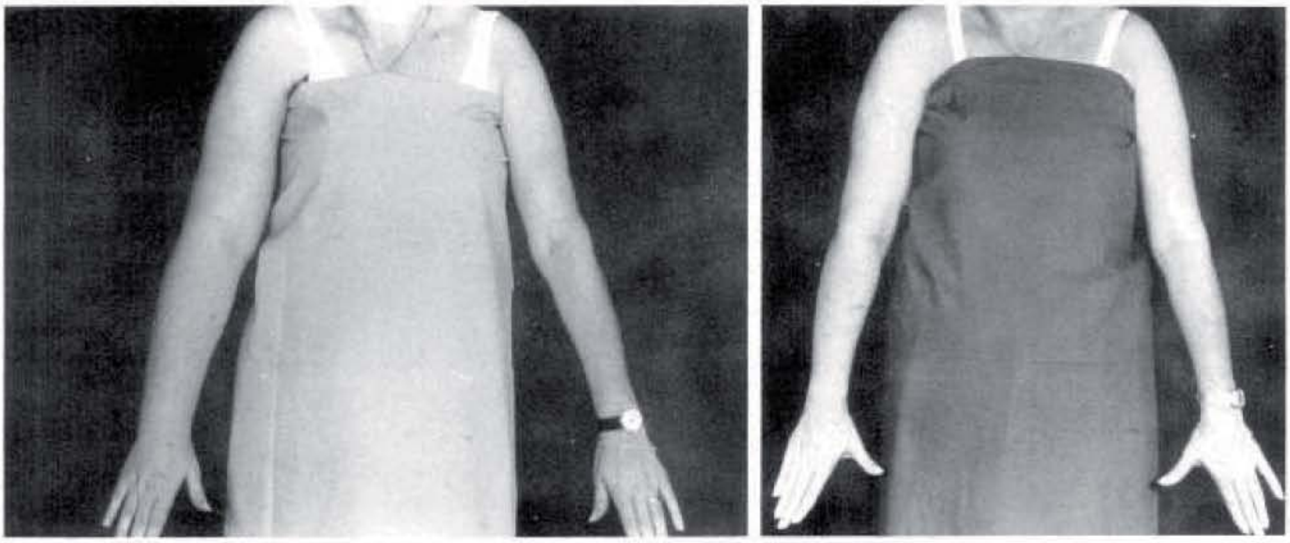

FIG. 10. (*Left*) A 42-year-old patient 10 years after mastectomy with edema of the right arm. (*Right*) Appearance 2 years after lymphatic grafting.

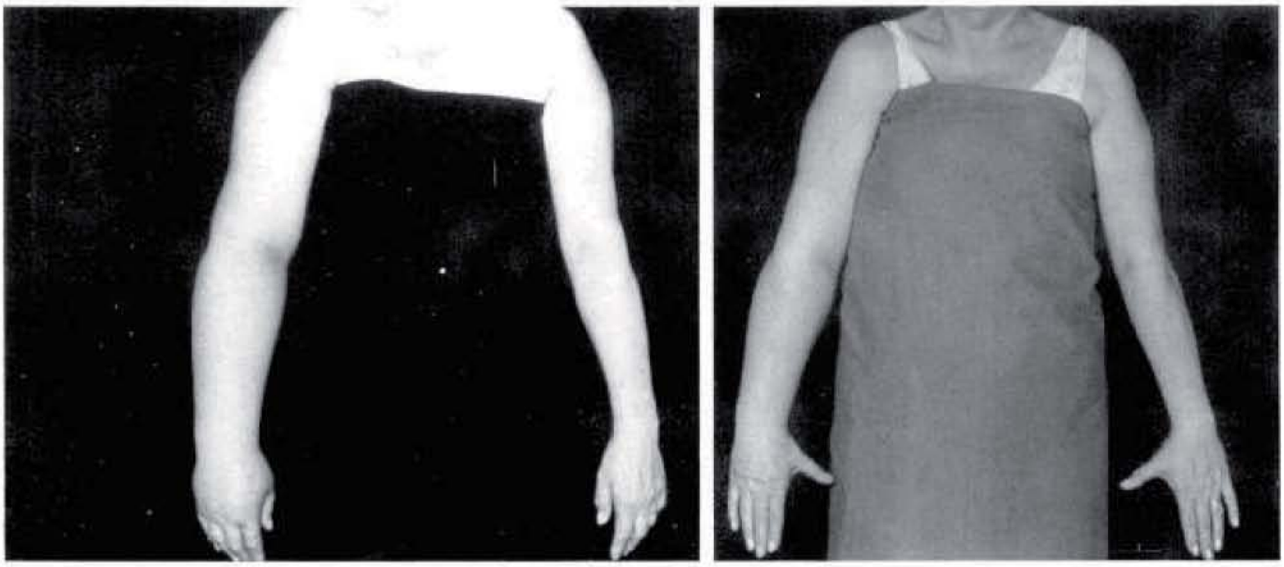

FIG. 11. (*Left*) A 46-year-old patient 14 years after mastectomy on the right side and 11 years after the onset of lymphedema. (*Right*) Appearance 4 years after lymphatic grafting.

another. Approximation of lymphatic collectors alone seems to support and promote reconstructions performed by the microvascular surgeon.

One important question concerning lymphatic grafting is how many lymphatic collectors are necessary to adequately treat lymphedema. On the one hand, it is certainly dependent on the extent to which lymphatic transport capacity has been impaired. An anatomic observation made by Kubik[34] may help in answering this question. He was able to demonstrate that the presence of one or two lympholymphatic anastomoses between the lymphatic territory belonging to the forearm region and the region belonging to the lateral side of the upper arm, which is not drained to the axilla but direct to supraclavicular nodes, may suffice to prevent the development of postmastectomy lymphedema.

The different treatment varieties of clinical lymphedemas have so far been evaluated either subjectively, e.g., by stating whether the edema has gotten worse or better, or objectively, e.g., by listing measurements of circumference or volume. The most accurate evaluation method is probably volume measurement. There are two ways of measuring volume: One method meas-

FIG. 12. (*Left*) A 45-year-old man with lymphedema of the right lower leg after a knee operation. (*Right*) After interposition of lymphatic grafts at the knee region.

ures the degree of water displacement, and another uses a computer that estimates limb volume by measuring the circumferences every 4 cm along the extremity, as Kuhnke[28] described in his slice model. The latter evaluation method is more accurate. The measurement of water displacement highly depends on the way an extremity is dipped into the waterbath. If this is not done correctly, e.g., at a slant, the measurement taken may be inaccurate. Also, this method is more difficult.

Changes in circumference also can be influenced by physical therapeutic procedures and medications. Therefore, it was necessary to employ an additional objective mode of measurement. Sequential lymphatic scintiscan not only estimates changes in lymphatic transport capacity, but also visualizes the grafts directly. Independent radiologists are therefore capable of objectively evaluating the results. Besides just looking at regions of interest in lymphatic scintiscans, e.g., central lymph nodes or sites of injection, many other parameters may be registered, such as the velocity of lymph flow, distribution of the radioactive isotope in collectors, and containment of radioactive material in the lymph nodes. Sequential lymphatic scintigraphy gives a total picture of the lymphatic system in the extremity.

During microsurgical dissection in search for appropriate lymphatic collectors to which lymphatic transplants may be anastomosed, the surgeon often finds sclerosed and obliterated lymph vessels. Such vessels are not visualized in sequential lymphatic scintiscans. However, during the years following surgery, such sclerosed vessels may regain their patency, since they can be found in lymphatic scintiscans in limbs that carry functioning lymphatic transplants. This indicates that sclerosed lymphatic collectors may reconstitute themselves and recanalize as soon as lymphatic flow has improved by means of lymphatic grafting.

Autologous lymphatic vessel transplantation requires grafts to be taken from a certain donor site. Therefore, the consequences of harvesting these grafts must be carefully investigated before these procedures are undertaken. Analyses of variances of the difference in circumferences of donor extremities in postmastectomy patients in comparison to the unoperated side have shown that after a follow-up period of 14 days as well as 2 years there is no change in the circumferences of the donor limbs ($F = 1.23$ and 1.32).

Further perspectives in microsurgery of the lymphatic vasculature are the application of allogenous grafts or the implantation of alloplastic materials that may replace lymphatic vessels. The animal experiments that have looked at these possibilities do not yet justify the application of these materials at the moment.[35] Autologous lymphatic vessel transplantation is the first step toward correcting localized defects of lymphatic flow using microvascular techniques.

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