Proposed pathway and mechanism of vascularized lymph node flaps

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HIGHLIGHTS

• Vascularized submental lymph node flap is effective for limb lymphedema.
• Flaps containing lymph nodes absorbed more fluid than those that did not.
• A mechanism and pathway is proposed based on the results of this study.

ABSTRACT

Objective. To investigate the pump mechanism and pathway of lymph transit in vascularized lymph node flaps.

Background. Microsurgical treatment of lymphedema with vascularized lymph node transfer can improve signs and symptoms of disease, but the pathways and mechanisms of these flaps warrant further exploration.

Methods. (Animal model) 72 flaps were raised in 18 rats: 36 groin flaps contained lymph nodes (LN), 36 deep inferior epigastric artery perforator flaps did not (non-LN). Indocyanine green (ICG) was added into normal saline (NS), 1%, 3%, 5%, 7% and 10% albumin. Three rats were assigned to each group. LN and non-LN flaps were submerged in solution and surveyed for venous fluorescence. In the 7% albumin and NS groups, volumetric change of solution was measured. (Human model) A similar experiment was performed in humans using five submentalLN flaps.

Results. (Animal model) Fluorescence was detected in the venous pedicle of LN flaps submerged in lymph or albumin when the concentration was greater than 3%. Based on these results, a pathway for lymphatic uptake is presented.

Conclusions. ICG fluorescence was detected in the venous pedicle of rat and human LN flaps submerged in lymph or albumin when the concentration was greater than 3%. Based on these results, a pathway for lymphatic uptake is presented.

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1. Introduction

Lymphedema is a complex proliferative process that results from disruptions of the lymphatic circulation, affecting as many as five million Americans, and 200 million worldwide [1–2]. Disease onset may be insidious, with progressive swelling followed by inflammation, fat hypertrophy and fibrosis. Lymphedema may be primary or idiopathic, but more commonly results from lymphadenectomy and radiation.
pump that absorbs interstitial fluids and diverts those fluids to the venous circulation. Fluid is thought to accumulate distally because of gravitational dependency and arm-swinging motion during ambulation (the “catchment effect”). By placing the pump distally where fluid accumulation is greatest, flap efficiency is theoretically maximized [11–12].

VLN flap transfer is feasible for the treatment of mild and severe lymphedema, but the mechanism is not well understood [1]. Interstitial fluid that accumulates in diseased fibrofatty tissue is absorbed by functioning lymphatic tissue and returns to the venous circulation through a network of lymphatic and venous channels that surround the transferred lymph nodes [12–14]. This mechanism is supported by evidence of venous fluorescence detected soon after peripheral intradermal or intra-nodal injection of indocyanine green (ICG) dye [11]. Lymphatic latency time explained why venous uptake was slightly slower after intradermal injection. Contrarians might suggest that the observed phenomenon is better explained by direct uptake by the venous system after injection.

It is thought that the more lymph nodes a flap contains, the better the outcome [15], and that injection of ICG dye into nodes and cutaneous tissue makes its way to the venous circulation [11]. It is premature, however, to assume that lymphatic structures, not veins, mediated venous return of ICG in the aforementioned study. The mechanism for lymphatic or dye uptake is not completely understood. We aim to identify the pathway lymph follows from the extravascular compartment to the intravascular compartment, and enhance the clinical relevance of previous and current data with a simple but carefully-designed set of experiments.

2. Materials and methods

2.1. Animal experiment

Eighteen male Sprague–Dawley rats (Bio LASCO Taiwan, Taipei, Taiwan) weighing 350 g–400 g were obtained and received care that complied with Chang Gung Memorial Hospital Animal Research Guidelines and the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health. The study was approved by the Chang Gung Institutional Review Board (IRB #1013481B). Care was provided in a pathogen-free animal facility and the animals were provided food and water ad libitum. Rats were anesthetized with 2.0–2.5% isoflurane for all procedures (Aesica Ltd., Queenborough, United Kingdom). In every rat, two lymph node-containing groin flaps (LN, n = 36) and two lymph node-devoid deep inferior epigastric perforator (DIEP) flaps (non-LN, n = 36) were raised as described previously by the authors [16].

Bilateral rectangular groin LN flaps were raised in every rat (n = 36 total flaps) and their dimensions were recorded. Flap volume was estimated as the product of length, width, and thickness in centimeters. Composite adipose-and-lymph node flaps were pedicled on the superficial circumflex iliac vessels and dissected to the femoral vessels (Fig. 1A). Special care was taken to identify and palpate lymph nodes, but not to skeletonize them, to preserve surrounding lymphatic channels and lymphovenous connections. All flaps contained several palpable nodes and the quantity was documented for each.

Thirty-six quadrangular non-LN DIEP flaps were raised under the same conditions [16]. The flap boundaries were the xiphoid, costal margin, anterior axillary line to the anterior superior iliac spine, and lower abdomen to the midline. Muscle-sparing perforator flaps were dissected from cranial to caudal by identifying the perforators and source vessel, ligating the superior epigastric artery, and capturing as many perforators as feasible until the flap was isolated on its pedicle (Fig. 1B) [11].

An aliquot of 0.5 mL of 0.5% ICG (Sigma Aldrich, St. Louis, Mo.) was added into 25 mL NS (ICG-NS, 1% 3%, 5% 10% albumin solution (ICG-Ab, CSL Behring, King of Prussia, PA). Three rats (n = 6 LN flaps, n = 6 non-LN flaps) were assigned to each treatment group. LN (Fig. 1C) and non-LN (Fig. 1D) flaps were immersed into each solution for 15 min. The overhead lights were turned off and the flaps were examined with a custom-made device designed to record invisible ICG fluorescence in real-time by emitting and detecting radiation in the near-infrared spectrum. The detector was a charge-coupled camcorder (Sony HD Handycam CMOS, 10.2 megapixels; Sony Corp., New York, N.Y.) that was modified to filter wavelengths less than 820 nm.

The outcome of interest for all groups was detection of ICG fluorescence in the venous pedicle. All rats in the ICG-NS and ICG-Ab (7%) arm were also studied for volume changes in the immersion solution. To achieve this, the weight of fluid before and after immersion for 15 min was recorded. After completion of the experiment, rats were euthanized with intracardiac injection of 1 cm³ of 2% lidocaine hydrochloride, and specimens were evaluated for the number of lymph nodes they contained. Descriptive statistics were generated using Microsoft Excel 2011 (Microsoft Corp., Redmond, CA). Differences in detectable fluorescence were determined using the Mann–Whitney U-test. Volumetric analysis comparisons were made using the two-tailed Student’s t-test (SPSS, Inc., Chicago, Ill. Version 20.0). Statistical significance was established at p < 0.05.

2.2. Human correlate

Patients undergoing vascularized submental lymph node (VSLN) flap transfer for extremity lymphedema were studied. Between July 2014 and January 2015, four patients who underwent unilateral or bilateral VSLN flap transfer for lower extremity lymphedema were included in a parallel study (n = 5 flaps). All procedures were in accordance with the ethical standards of the Chang Gung Memorial Hospital Institutional Review Board (IRB #1013282A3) and national guidelines on human experimentation and with the Helsinki Declaration of 1975 (as revised in 2008). Informed consent was obtained for all patients.

VSLN flaps were harvested as described previously by the authors (Fig. 2A) [13]. A composite flap was elevated en bloc that included skin, subcutaneous fat, lymph nodes, and the vascular pedicle. During recipient site preparation, interstitial fluid that was presumed to be lymph was collected in a sterile container. A sample of the fluid was studied to determine albumin concentration. In those patients, blood was analyzed for albumin and total protein concentration. An aliquot of 0.5 mL of 0.5% ICG was added to 5 mL of normal saline (ICG-NS) or 5 mL lymph (ICG-Lymph). With the arteriovenous pedicle intact, VSLN flaps were immersed in ICG-NS for 20 min, and followed by ICG-Lymph for 20 min (Fig. 2B).

The overhead lights were turned off and the flaps were examined using an identical ICG fluorescence detector as mentioned. Parameters measured were the number of lymph nodes harvested and the presence of detectable ICG fluorescence in the venous pedicle (as represented in Fig. 2C). Clinical outcomes for these patients were evaluated for circumferential differentiation compared to the unaffected contralateral extremity, and subjective parameters.

3. Results

3.1. Animal experiment

All LN flaps had 2 (n = 25, 69.4%) or 3 (n = 11, 30.6%) visible lymph nodes. Results of this the fluorescence experiment are summarized in Table 1. Fluorescence drained around the pedicle vein in 21 of 36 (58.3%) LN flaps. The venous pedicle fluoresced in 3 of 6 flaps submerged in 3% ICG-Ab and in all LN flaps submerged in 5%, 7% and 10% ICG-Ab. Venous fluorescence was not detected in LN flaps immersed in ICG-NS and 1% ICG-Ab. Three of 6 pedicles of LN flaps immersed in 3% ICG-Ab did not fluoresce. There was no detectable fluorescence in the venous pedicle of any non-LN flap placed in any solution at 15 min (0%, p < 0.001).

Table 1 summarizes the results of fluid volume change after flap immersion in 7% ICG-Ab and ICG-NS. The reduction of volume,
determined by weight change of the immersion fluid, was significantly greater in when LN flaps were bathed (0.72 g reduction) than non-LN flaps (0.34 g reduction, \( p < 0.001 \)). LN flaps were larger (flap volume = 3.4 cm\(^3\)) than non-LN flaps (flap volume = 2.9 cm\(^3\); \( p = 0.04 \)). Accounting for this difference, LN flaps still resulted in a greater volume change (0.21 g/cm\(^3\) reduction) than non-LN flaps (0.11 g/cm\(^3\) reduction, \( p < 0.001 \)); this difference occurred in both 7% ICG-Alb and ICG-NS media.

3.2. Human correlate

Results of the human correlate study are listed in Table 2. An 18-year-old woman had unilateral flap transposition for primary lymphedema of her right leg. Two women, 47 and 64-years-old, were treated for right arm lymphedema secondary to axillary node dissection for treatment of breast cancer. The 64-year-old underwent prior radiation therapy. A 60-year old woman underwent bilateral flap harvest for treatment of lymphedema of her left leg secondary to cervical cancer extirpation after radiation; one flap was transposed to her thigh and the other to her ankle. None of the patients had diabetes, a history of current or previous smoking. The average BMI for all patients was 29.7 kg/m\(^2\) (range, 25.5–33.3 kg/m\(^2\)). All patients expressed sufficient lymph to allow for flap submersion in ICG-Lymph solution (\( n = 5 \) flaps). The mean albumin concentration was 3.3 ± 0.3 g/dL in lymph and 3.7 ± 0.6 g/dL in blood. No ICG fluorescence was detected in the pedicle of 5 flaps immersed in ICG-NS after 20 min, but fluorescence was detected in the venous pedicle of all 5 flaps after immersion in ICG-Lymph (see eVideo 1 in the Supplement). The latency time from immersion to detectable venous fluorescence was 13.5 min (range, 10.2–18.3 min). All flaps survived and every patient demonstrated symptomatic improvement at 12 months (see eTable 1 in the Supplement).

4. Discussion

Prior to this study, VLN flaps demonstrated the capacity to divert dye from lymph node parenchyma and cutaneous tissue to the venous circulation [11]. (Table 3) Still, the mechanism of uptake, conduit through which the dye traveled, and clinical significance of the findings remained unclear. A pump mechanism was supported by centripetal transit of peripherally injected dye in a flap [11]. However, in that study the dye was injected into tissues. Transit through circulatory channels might have been driven more by the pressure of injection than other physiologic processes.

We therefore sought a model that more closely represents the conditions that exist during VLN flap transfer by immersing tissues into fluorophore-containing media. Using the model we described, the
mean latency period until fluorescence of immersed VLN flaps was $13.5 \pm 3.8$ min. This was longer than when ICG was injected directly to the subcutaneous tissue in our previous study ($5.7 \pm 2.2$ min) [11]. The results of this study demonstrated: 1) venous fluorescence occurs in both animal and human subjects when LN flaps are soaked in an ICG-Alb medium of a certain concentration. 2) Lymph or albumin-containing media ($>3$ g/dL concentration) are required for venous fluorescence. 3) Lymph nodes effect increased uptake of the immersion medium.

ICG is only weakly fluorescent in its unbound state [17]. Although unbound-ICG (as with ICG-NS) may make its way to the venous circulation and bind to plasma proteins, it may not be adequately concentrated to be visualized within the venous pedicle. However, when ICG is added to lymph or albumin solution of sufficient concentration, ICG rapidly binds to proteins that are taken up by lymphatic capillaries before reaching the venous circulation. The concentration of ICG by albumin and other proteins then generates visible fluorescence in the venous circulation. This may explain why a concentration threshold appears to exist for fluorescence to occur.

An alternative explanation for the concentration threshold warrants a review of physiology. Briefly, Starling's forces dictate capillary and lymphatic capillary permeability, which determines whether lymph or albumin solution can pass through the capillary membrane into the interstitial space. When the capillary permeability is high, fluid and solutes move from the capillary to the interstitial space, while when the capillary permeability is low, fluid and solutes move from the interstitial space to the capillary. This in turn affects the concentration of ICG in the interstitial space and whether it can become fluorescent within the venous pedicle.

Table 1

<table>
<thead>
<tr>
<th>Immersion medium</th>
<th>DIEP (non-LN) flap</th>
<th>Groin (LN) flap</th>
<th>P-value$^a$</th>
<th>Fluorescence in venous pedicle?</th>
<th>Yes, n</th>
<th>No, n</th>
<th>%</th>
<th>Yes, n</th>
<th>No, n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICG-NS</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICG-Alb 1%</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICG-Alb 3%</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>50</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICG-Alb 5%</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>100</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICG-Alb 7%</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>100</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICG-Alb 10%</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>100</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>36</td>
<td>0</td>
<td>21</td>
<td>15</td>
<td>58.3</td>
<td>&lt;0.001</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Volume absorption study

<table>
<thead>
<tr>
<th></th>
<th>DIEP (non-LN) flap</th>
<th>Groin (LN) flap</th>
<th>P-value$^a$</th>
<th>Fluid weight reduction, g</th>
<th>0.34 ± 0.11</th>
<th>0.72 ± 0.30</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduc/volume, g/cm$^3$</td>
<td>2.9 ± 0.6</td>
<td>3.4 ± 0.7</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICG-Alb, 7% ($n = 6$ experiments)</td>
<td>0.11 ± 0.03</td>
<td>0.18 ± 0.10</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICG-Alb, 10% ($n = 6$ experiments)</td>
<td>0.13 ± 0.01</td>
<td>0.25 ± 0.01</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any solution</td>
<td>0.11 ± 0.02</td>
<td>0.21 ± 0.07</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DIEP = deep inferior epigastric artery flap; Non-LN = no lymph nodes in flap; LN = lymph nodes in flap; ICG = indocyanine green; NS = normal saline; Alb = albumin.

Table 2

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, years</th>
<th>LN, n</th>
<th>Albumin concentration</th>
<th>Latency in minutes$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Albumin, g/dL</td>
<td>Blood Albumin, g/dL</td>
</tr>
<tr>
<td>1</td>
<td>18/F</td>
<td>2</td>
<td>3.16</td>
<td>3.64</td>
</tr>
<tr>
<td>2</td>
<td>60/F</td>
<td>4</td>
<td>3.5</td>
<td>3.15</td>
</tr>
<tr>
<td>3</td>
<td>47/F</td>
<td>3</td>
<td>2.9</td>
<td>4.19</td>
</tr>
<tr>
<td>4</td>
<td>64/F</td>
<td>4</td>
<td>3.2</td>
<td>4.54</td>
</tr>
</tbody>
</table>

Case 2 (right side)$^b$ 2 (left side)$^b$

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, years</th>
<th>LN, n</th>
<th>Albumin concentration</th>
<th>Latency in minutes$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>47/F</td>
<td>3</td>
<td>2.9</td>
<td>4.19</td>
</tr>
<tr>
<td>4</td>
<td>64/F</td>
<td>4</td>
<td>3.2</td>
<td>4.54</td>
</tr>
</tbody>
</table>

Fluorescence was not detected in any flap immersed in normal saline.

LN = lymph nodes in flap; TP = total protein; ICG-NS = normal saline immersion medium; ICG-Lymph = lymph immersion medium.

$^a$ Time interval between flap immersion and detection of venous fluorescence.

$^b$ Collected from affected extremity.

$^c$ Same patient with left and right vascularized submental lymph node flap harvest. One was transferred to the left thigh, the other to the left ankle.

$^d$ Fluorescence was not detected in any flap immersed in normal saline.
lymphatic fluid and protein exchange. A strong arteriovenous pressure gradient, and an even stronger intravascular-extravascular pressure gradient, accounts for fluid leakage that accumulates and gives rise to lymph. Lymphatic capillaries absorb accumulating proteins and fluid; they are the predominant site of interstitial protein uptake [18]. Fluid and protein exchange occur until Starling's forces equilibrate and a physiologic lymph-serum albumin ratio is restored. This would favor increased protein uptake with higher concentrations of albumin solution, and hence a threshold exists.

The volume study of the animal experiment demonstrated that a flap's failure to fluoresce was neither an indicator nor a predictor of fluid uptake. In contrast, there was a trend toward increased per-cm² volume change when flaps were immersed in normal saline medium than hypertonic albumin, even though none of those flaps fluoresced. In every experiment, we manipulated the oncotic pressure of immersion medium and the balance of free-versus-bound ICG. Previous studies have shown lymphatic flow increases when the interstitial oncotic pressure approaches plasma concentrations, and our findings are consistent [19].

Venous fluorescence implies avenues exist that allow for protein to enter the venous circulation. Lymphatic channels exist in both lymph node-containing and deficient flaps, but fluorescence cannot occur without lymph nodes. Therefore, the exchange is thought to occur at the level of the lymph node. The two structures that exist in a LN flap that are most likely to permit protein transit are low-resistance blind-ended termini of lymphatic capillaries [20–21] (ingress) and the high endothelial venules (HEV, egress) within the lymph node itself [22–24]. An updated schematic of the proposed mechanism of, and pathway for, lymph uptake in VLN flaps is presented in Fig. 3.

Results of the animal fluorescence study were reproduced in humans, who at one year demonstrated improvement in symptoms and limb circumference. We designed the experimental model to closely represent conditions that occur with VLN flap transfer, however, we did not control for hydrostatic pressure. We expect that the turgor of a congested, lymphedematous extremity will favor early fluid uptake by the flap because hydrostatic pressure of the interstitium is increased. As the interstitial pressure normalizes, interstitial hydrostatic pressure, and therefore lymphatic uptake may decrease. This may explain a pattern of rapid initial decongestion, followed by a plateau, after procedures like LVA [25] and VLN flap transfer [26].

The results of this study support our previous conclusion that vascularized tissue containing lymph nodes is capable of delivering ICG from the extracellular milieu to the venous circulation [27]. We demonstrated that lymph nodes are necessary for venous fluorescence to be detected, ruling out the possibility that venular uptake was contributory to venous fluorescence. Although lymphovenous connections (LVCs) were proposed half a decade ago and studied in human and animals since [22–24,28–32], Shao et al. [33] only recently demonstrated in a mouse model that LVCs exist at the level of the lymph node. We imagine intra-nodal LVCs explain VLN effectiveness, and why quantity of lymph nodes correlates with improved lymphatic drainage [15].

This study identified three requirements for VLN flap function: the presence of vascularized lymph nodes (including afferent lymphatic channels), favorable Starling forces, and intact arteriovenous anastomoses. We recognize the importance of [34–36], but have yet to identify clinical relevance of maintaining as many afferent lymphatic channels in the flap as possible. Since lymphatic capillaries are the predominant sites of lymph ingress, maximizing contiguous lymphatics within that lymphosome [37] might optimize flap efficiency. It is also possible that lymphovenous shunting is the rate-limiting step, not lymphatic uptake, so including more lymphatic capillaries might be futile, perhaps “floodling” the pump. In our experience, preserving a rim of peri-nodal tissue alone is sufficient to achieve clinical improvement. Further study will demonstrate whether inclusion of a more expansive lymphosomal network or “dragnet” would enhance flap efficiency and outcomes. The authors emphasize that pedicle fluorescence provides insight to the mechanism of function, but it does not predict fluid uptake. For example, we demonstrated that in all immersion media, groin flaps absorbed more volume per cm² than DIEP flaps. This was true for groin flaps immersed in NS that did not fluoresce, yet demonstrated a greater rate of fluid uptake (0.25 g/cm²) than DIEP flaps (0.13 g/cm²).

There are important limitations to this study. Most importantly, we relied on macroscopic and grossly measurable parameters like volume change and visible venous pedicle fluorescence to investigate a process that occurs at the molecular and cellular level. The pathway described herein is therefore theoretical. The collective global experience

<table>
<thead>
<tr>
<th>Year/author</th>
<th>Number of patients</th>
<th>Etiology</th>
<th>Donor site</th>
<th>Recipient site</th>
<th>Method of measurement</th>
<th>Mean follow-up (months)</th>
<th>Outcome</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006/Becker et al.</td>
<td>24</td>
<td>Secondary lymphedema</td>
<td>Femoral region</td>
<td>Axillary or elbow</td>
<td>Circumference</td>
<td>96</td>
<td>Reduction: 10 patients: normal 10 patients: some reduction 2 patients: no change</td>
<td>Lymphorrhrea in 8 patients Infectious in 17 patients</td>
</tr>
<tr>
<td>2009/Lin et al.</td>
<td>13</td>
<td>Secondary lymphedema</td>
<td>Groin</td>
<td>Wrist</td>
<td>Circumference</td>
<td>56</td>
<td>Reduction rate: 50.6%</td>
<td>NA</td>
</tr>
<tr>
<td>2011/Gharb et al.</td>
<td>21</td>
<td>Secondary lymphedema</td>
<td>Groin</td>
<td>Wrist</td>
<td>Circumference</td>
<td>40</td>
<td>Visual analog scale scores improved after the operation Reduction rate: Above knee: 64% Below knee: 64% Above ankle: 67%</td>
<td>2 cases of partial flap loss and donor site lymphorrhrea One flap required re-expansion for venous congestion but was successfully salvaged</td>
</tr>
<tr>
<td>2012/Cheng et al.</td>
<td>6</td>
<td>Secondary lymphedema</td>
<td>Submental</td>
<td>Ankle</td>
<td>Circumference</td>
<td>8.7</td>
<td></td>
<td>One episode of skin infectious disease was recorded in 7 patients</td>
</tr>
<tr>
<td>2013/Cheng et al.</td>
<td>10</td>
<td>Secondary lymphedema</td>
<td>Groin</td>
<td>Wrist or elbow</td>
<td>Circumference</td>
<td>39</td>
<td>Reduction rate: 40.4%</td>
<td>NA</td>
</tr>
<tr>
<td>2014/Cheng et al.</td>
<td>20</td>
<td>Secondary lymphedema</td>
<td>Groin or submental</td>
<td>Distal recipient site</td>
<td>Circumference</td>
<td>27.3</td>
<td>Reduction rate: 40.5%</td>
<td>NA</td>
</tr>
<tr>
<td>2015/Akita et al.</td>
<td>13</td>
<td>Secondary lymphedema</td>
<td>Supraclavicular</td>
<td>Distal region of the thigh or the ankle</td>
<td>Circumference</td>
<td>12</td>
<td>Lower extremity lymphedema index: 26.5%</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Table 3

Summary of published literature related to lymph node transfer for lymphedema treatment.
Evaluating outcomes of VLN flap transfer is an emerging science. Although it has been shown that VLN flaps have the capacity to uptake fluid, we can only assume this process is responsible for limb circumference reduction observed in clinical practice. Long-term change and flap efficacy has not been thoroughly studied, nor has the clinical significance of limb circumference reduction. In addition, we do not know whether a history of radiation has an influence on outcomes or the influence of preoperative lymphedema stage on outcomes after flap transfer.

This study provides a better understanding of the pump mechanism of the VLN flap. The conclusions drawn have clinical relevance by allowing us to exploit various aspects of the mechanism to enhance pump efficiency and outcomes. For example, future study may examine the role of the surrounding soft tissue network to identify whether a lymphatic drag net phenomenon exists or whether de-epithelializing and burying flaps improves outcomes by exposing lymphatic channels. Other possibilities to improve pump efficiency might include venous afterload reduction (i.e., with sildenafil), ligation of lymph node efferent vessels in lymphedema in human extremities, Plast. Reconstr. Surg. 97 (3) (1996 Mar) 397–405 discussion 6–7.


Acknowledgments

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