From Theory to Evidence: Long-Term Evaluation of the Mechanism of Action and Flap Integration of Distal Vascularized Lymph Node Transfers

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Abstract

Background Nonanatomic (distal) placement of vascularized lymph node (VLN) transfers have shown efficacy in the treatment of extremity lymphedema, but the mechanism by which these flaps provide relief of lymphedema remains unclear. Intrinsic lymphovenous connections have been previously shown to exist in the transferred flap. But, the long-term interaction of the VLN flap and surrounding lymphedematous extremity has not been previously investigated.

Patients and Methods A retrospective review of a prospective maintained database of patients who underwent VLN transfer was evaluated. Patients who underwent distal VLN transfer and had more than 1-year follow-up were identified. Lymphodynamic evaluation was performed using 0.3 to 0.6 mL indocyanine green (ICG) injection at 5 cm proximal to the flap edge on identified patients. Migration direction of dye and latency period was evaluated.

Results In total, 20 patients were identified who met inclusion criteria. Average long-term follow-up was 27.3 months. The average circumference reduction of the affected extremity was 40.5%. ICG appearance within the VLN flap was found in all patients occurring on average in 178.3 seconds. In all cases, flow occurred in the distal direction (toward the flap) with proximal placement of dye. Latency period was found to inversely correlate with circumference reduction ($p < 0.01$).

Conclusions Distal, nonanatomic placement of VLN flaps provide sustained limb circumference reduction in extremity lymphedema patients following a minimum of 1-year postoperatively. Flap integration with the recipient site reliably occurs as witnessed with consistent ICG drainage, and occurs in the gravity-dependent direction. Faster clearance of ICG will result in improved clinical limb circumference reduction.

Keywords
- vascularized lymph node transfer
- lymphedema
- lymphatic microsurgery
- lymphedema surgery
- indocyanine green

Surgical treatment of lymphedema utilizing vascularized lymph node (VLN) transfer has becoming increasingly popular in recent years. Despite its popularity, the mechanism by which VLNs provide relief for symptomatic obstructive lymphedema is poorly understood. The most commonly regarded theory is based on the induction of lymphangiogenesis and reconstitution of lymphatic channels. Animal studies have described the basis for this theory,[1–4] which has prompted clinicians to use VLN flaps to treat obstructive lymphedema.[5–8]

Anatomic (proximal) placement of VLNs is a popular recipient site and is likely based on the theory of local lymphangiogenesis and reconstitution of normal lymphatic

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flow. In addition to anatomic placement of VLNs, our center and others have previously published on nonanatomic (distal) placement of VLN flaps for obstructive lymphedema.[7,9–13] Despite studies reporting clinical success, the mechanism by which nonanatomic placement of VLNs improve lymphedema is far less understood. We have previously proposed the concept that the main mechanism of action is based on intrinsic lymphovenous connections within the VLN, which provides lymphovenous shunting at the level of the flap.[13] Indocyanine green (ICG) venous clearance can be witnessed at the time of flap inset with injection at the flap periphery, thus validating the presence of these intrinsic lymphovenous connections.[7,13] Despite the proven presence of this shunting mechanism, long-term evaluation of these intrinsic connections and the interaction of the flap and surrounding lymphedematous tissue have not been evaluated. To better understand the process of lymphatic drainage following these procedures, we investigated lymphatic flow patterns in patients who have previously undergone distal, nonanatomic VLN transfers.

Patients and Methods

Study Design

An institutional review board–approved review of a prospectively maintained database was performed at Chang Gung Memorial Hospital in Linkou, Taiwan. All patients who underwent VLN flap transfers for symptomatic obstructive upper and lower extremity lymphedema between 2008 and 2012 were identified. Patients were selected for inclusion in the study if the patient (1) had follow-up more than 12 months, and (2) had distal, nonanatomic placement of a VLN flap. Patients' demographic, surgical treatment, and outcomes were evaluated. Patients were excluded if additional surgery related to the affected extremity was performed before ICG evaluation.

Circumference reduction was evaluated at standardized office visits. In the postoperative period, patients were instructed to eliminate compression therapy if they were previously using compression. In addition, measurements before revision surgery were used for the evaluation of changes related to VLN transfer and calculation of correlations.

Lymphodynamic Evaluation

In patients selected for evaluation, subdermal ICG injections (0.3–0.6 mL) were performed proximal to the VLN flap with the patient lying in the supine position. A custom-made device activated infrared signal 760 nm and integrated with a camcorder (Sony HD Handycam CM05; Sony Corp., Tokyo, Japan) filtering out wavelengths below 820 nm was used for real-time evaluation of lymphatic flow. An injection site 5 cm proximal to the flap edge was performed. Flow directionality and the time to appearance of the ICG dye within the flap (latency period) were specifically evaluated. Time zero was calculated following the first injection of ICG dye proximal to the flap. The appearance of dye within the subdermal lymphatic system of the flap marked the second time point used to calculate the latency period. Reported latest follow-up time and latest circumference reduction rates are represented to demonstrate long-term follow-up results. Statistical analysis using Pearson correlation was performed to investigate the relationship of flow characteristics to clinical outcomes.

Results

A total of 20 patients were identified for study inclusion (►**Table 1**). The average patient age and body mass index were 54.9 years and 27.1 kg/m^2, respectively. The average follow-up time to lymphodynamic evaluation was 27.3 months (range, 12–128 months). Of the 20 patients, 13 (65%) had received VLN flaps for breast cancer–related lymphedema, whereas 7 patients (35%) had treatment for postsurgical lower extremity lymphedema. The average duration of symptoms before VLN transfer was 51.2 months. Distal, nonanatomic recipient sites included the wrist (55%) and elbow (10%) in upper extremity lymphedema, and the ankle (35%) in lower extremity cases. Groin (9 patients) and submental (11 patients) VLN flaps were used for all procedures. At long-term evaluation, the average circumference reduction of the affected limb was 40.5%.

All evaluated patients (100%) had distal ICG migration to flap periphery and into the VLN flap (►**Video 1**). The average latency period of ICG was 178.3 seconds (range, 38–420 seconds). When assessing the impact of the latency period in relation to the clinical improvement, an inverse relationship was found between this time and degree of circumference reduction in the affected extremity ($p < 0.01$).

Video 1

A patient with symptomatic left lower extremity lymphedema previously underwent vascularized submental lymph node flap to the distal ankle. Before revision surgery, the patient had lymphodynamic evaluation with indocyanine green (ICG). The patient was lying supine during examination. Two ICG injections were placed proximal to the flap edge. The clear migration of ICG can be seen to the flap with fluorescence enveloping the flap. These findings highlight flap integration in the surrounding lymphedematous tissue.

Online content including video sequences viewable at: www.thieme-connect.com/products/ejournals/html/10.1055/s-0034-1381957.

Case Example

A 53-year-old female patient had a history of a modified radical mastectomy, axillary lymph node dissection, and postoperative radiotherapy 6 years before evaluation (►**Fig. 1**). She developed symptomatic left upper extremity lymphedema (Stage IV) and underwent submental VLN transfer to the volar distal forearm (►**Fig. 2**). Postoperatively,

Table 1 Patient demographics and outcomes

Patient no.	Age, y	BMI, kg/m^2	Symptom duration, mo	Pre-op lymphedema stage	Flap type	Circumference differentiation		Circumference reduction rate, %	ICG dose, c.c.	ICG latency, s	ICG flow direction	Follow–up, mo
						Pre-op	Post-op					
1	63	31.5	72	4	VGLN	103.0	14.8	84.5	0.3	148	Distal	128
2	55	30.0	96	3	VGLN	23.0	13.5	43.5	0.5	60	Distal	60
3	62	30.2	36	3	VGLN	20.0	17.7	35.9	0.4	100	Distal	49
4	46	23.5	120	3	VGLN	20.6	9.0	55.1	0.3	45	Distal	24
5	64	33.6	24	4	VGLN	33.9	23.5	29.6	0.3	160	Distal	21
6	47	24.9	36	4	VGLN	26.6	18.5	28.2	0.3	168	Distal	19
7	46	22.6	24	4	VGLN	29.6	28.0	29.4	0.3	233	Distal	13
8	54	23.0	48	4	VGLN	28.4	21.9	35.0	0.3	180	Distal	14
9	44	22.0	28	4	VGLN	28.0	25.8	13.6	0.3	250	Distal	16
10	53	26.8	48	4	VSLN	30.8	14.7	47.3	0.4	83	Distal	14
11	58	27.0	12	4	VSLN	30.5	13.6	50.0	0.5	120	Distal	16
12	55	24.0	60	4	VSLN	44.0	40.5	5.0	0.3	350	Distal	14
13	56	25.2	36	4	VSLN	29.9	23.1	14.4	0.3	420	Distal	14
14	47	22.0	84	4	VSLN	28.2	13.0	73.9	0.6	156	Distal	34
15	72	30.0	120	1	VSLN	7.7	3.4	70.0	0.3	38	Distal	19
16	50	27.0	48	4	VSLN	55.7	33.5	37.9	0.5	221	Distal	19
17	60	35.0	60	1	VSLN	9.5	7.3	29.0	0.5	240	Distal	22
18	61	26.0	24	3	VSLN	22.3	7.5	60.7	0.5	78	Distal	22
19	61	26.0	36	4	VSLN	25.2	24.9	8.2	0.5	420	Distal	15
20	43	31.1	12	4	VSLN	40.3	11.4	59.3	0.5	96	Distal	12
Average	54.9 ± 7.9	27.1 ± 3.9	51.2 ± 32.8			31.9 ± 19.9	18.3 ± 9.4	40.5 ± 22.2	0.4 ± 0.1	178.3 ± 114.4		27.3 ± 26.7

Abbreviations: BMI, body mass index; ICG, indocyanine green; VGLN, vascularized groin lymph node; VSLN, vascularized submental lymph node.

Fig. 1 A patient with symptomatic left upper extremity lymphedema is shown.

Fig. 2 The recipient site of the vascularized lymph node transfer is shown 1-year postoperatively.

she had limb circumference reduction of 47.3% over the course of 14 months (►**Fig. 3**). She underwent ICG lymphodynamic evaluation at 13 months, which exhibited a latency period of 83 seconds. Distal flow of proximally placed ICG was found when the patient was lying in the supine position.

Discussion

In an early animal study by Shesol et al, VLN transfer to a lymph node–depleted area resulted in restoration of lymphatic flow, whereas transferred nodes to a normal, unoperated area did not induce additional lymphangiogenesis.[4] Conclusions from this landmark animal study and others[1–3,14,15] have supported the use of VLNs in anatomic (proximal) locations to replace lymph nodes and induce

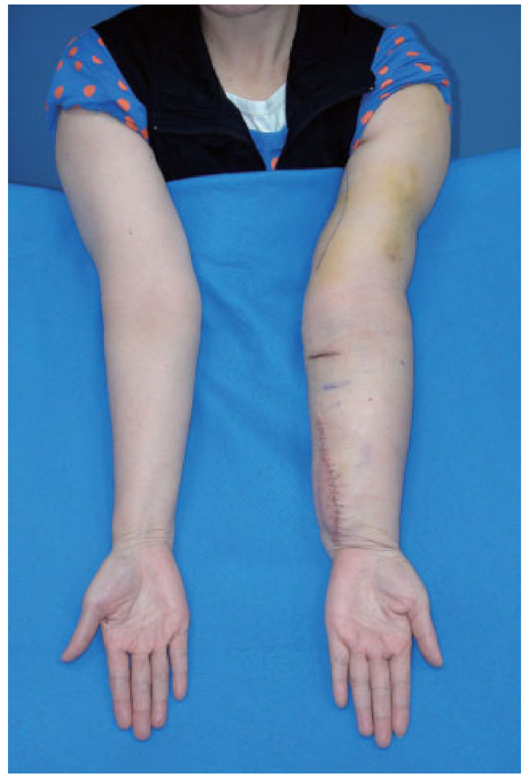

Fig. 3 The patient underwent submental vascularized lymph node transfer to the ulnar aspect of the distal forearm. She achieved approximately 47% circumference reduction to the lymphedematous extremity. The image shown is following revision surgery to the flap skin paddle and liposuction to the upper arm.

lymphangiogenesis for obstructive lymphedema with restoration of normal lymphatic flow.[5,6]

Unfortunately, the "stop-cock" theory may oversimplify this complex disease process and may not account for the progressive changes seen in a lymphedematous extremity.[16] In the same landmark study by Shesol et al, the results suggest a significant decrease in efficacy of anatomic lymphatic restoration when VLN flap techniques are delayed from surgical lymphadenectomy. These findings highlight the temporal changes occurring to the severed ends of the lymphatic ducts, which likely result in significant scarring.[4]

A recent histologic evaluation found progressive and characteristic changes to the distal lymphatic collecting ducts, which correlated with decreased lymphatic function and worsening clinical lymphedema following proximal injury.[17,18] Intrinsic changes to the lymphatic vasculature occur with loss of contractility[19] and alterations to the secondary valve system.[20] Altogether, the progressive changes that occur following proximal injury result in distal lymphatic pump failure.

Lymphatic pump failure results in backflow into lymphatic capillaries, lymphatic precollectors, and the interstitium. In addition, intrinsic changes to lymphatic collectors result in secondary valve regurgitation and bidirectional lymphatic flow.[20,21] Clinically, these changes manifest as pitting edema and are consistently more pronounced in the gravity-dependent (distal) portion of the extremity. With these concepts in mind, distal nonanatomic placement of VLN flaps may represent the ideal recipient location when contemplating treatment for advanced lymphedema. With the results of this study, flap integration into the surrounding tissue results in ICG appearance within the flap, which confirms neo-lymphatic development. Distal flow of lymph fluid is clearly seen despite patients being in a gravity-neutral position (supine). Flow in the gravity-dependent position is amplified when patients are in the upright or standing position. Also, the latency period appears to have an inverse relationship to the degree of limb circumference reduction, which may provide clinical validation of the importance of ICG clearance via the VLN transfer. Future studies are needed to investigate why decreased latency periods are witnessed in certain patients, and why some patient cohorts have greater clinical responses as compared with matched cohorts. In addition, our findings demonstrate the continued patency of intrinsic lymphovenous connections within the VLN flap and continued venous clearance of interstitial fluid in a long-term follow-up evaluation.

There are limitations to this study that must be considered when evaluating the demonstrated outcomes. Correlations made related to the latency period may likely be influenced by factors related to the area and location of injection. Although each patient presented with similar conditions, the differences in etiology and previous treatments likely impact the results of VLN transfer techniques. Also, postoperative exercise and activity levels greatly differ between patients and likely influence perceived outcomes during long-term evaluation. Altogether, patient variables represent confounding factors during long-term evaluation of circumferential changes in lymphedema patients.

Conclusions

Distal VLN transfers provide continued venous shunting of lymphatic fluid following long-term evaluation. Recipient site integration occurs with development of new lymphatic connections. Lymphodynamic assessment with ICG demonstrates distal migration of dye toward the flap and drainage via intrinsic lymphovenous connections occurring in all patients. Decreases in the latency period may result in improvements in clinical limb circumference.

Disclosures
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