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Supermicrosurgical lymphaticovenular anastomosis *vs.* vascularized lymph vessel transplant - technical optimization and when to perform which

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Abstract
Early surgical intervention for lymphedema can delay, prevent, and even reverse lymphatic degeneration. Vascularized lymph vessel transplant (VLVT) has emerged as an alternative to vascularized lymph node transplant (VLNT) for the treatment of advanced, fluid-predominant lymphedema, providing highly favorable outcomes with reduced donor-site complications. Lymphaticovenular anastomosis (LVA) has traditionally been reserved for early disease. However, technical refinements have improved its results and expanded its efficacy, creating an overlap between the indications for VLVT/VLNT and LVA. This article describes our technical approach to VLVT and LVA and explores the nuances of treatment selection in the light of their shifting indications.

Keywords: Lymphedema, supermicrosurgery, lymphaticovenular anastomosis, lymphovenous bypass, vascularized lymph vessel transplant, vascularized lymph node transplant

INTRODUCTION

Supermicrosurgical advancements over the past few decades have given rise to a myriad of efficacious options for surgical treatment of lymphedema. In contrast to traditional belief, recent evidence shows that early surgical intervention for lymphedema can delay, prevent, and even reverse lymphatic degeneration[1,2]. Supermicrosurgical lymphaticovenular anastomosis (LVA) and vascularized lymph node transplant (VLNT) are established physiologic techniques for the treatment of fluid-predominant lymphedema[3,4]. While VLNT is efficacious in the treatment of advanced, fluid-predominant lymphedema, its risk of iatrogenic donor-site lymphedema makes the procedure undesirable to many. Vascularized lymph vessel transplant (VLVT) has recently been introduced as a less-invasive alternative to VLNT for these advanced cases[5-7]. LVA is traditionally reserved for early-stage, fluid-predominant lymphedema. However, recent technical refinements have shown that the efficacy of LVA in advanced disease has been underestimated. With this expanded potential, there is now an overlap between the indications for LVA and VLVT/VLNT. This paper aims to share the technical and decision-making pearls for improving outcomes of LVA and VLVT, both of which are safe and powerful procedures to treat fluid-predominant lymphedema.

History of LVA and VLNT

Supermicrosurgical lymphaticovenular anastomosis and its precursor, microsurgical lymphovenous bypass (LVB), re-route native lymphatic vessels into the venous circulation of the affected extremity[8]. LVB was first described by Jacobson and Suarez[9] in a canine model in 1962. Simultaneously, Chang *et al.*[10] adapted this canine model to study lymphovenous bypass, lymph node-to-vein anastomosis, lymphatic vessel interposition grafts, and vein interposition grafts to bridge lymphatic defects. Techniques were refined by various others using canine and rat models[11-14]. In 1977, O'Brien *et al.*[15] published their series of microsurgical LVB in human proximal upper limbs. Because microsurgical techniques were still in development, the anastomoses were created in the proximal limb, which contains larger veins but more functionally impaired lymphatics. The combination of these high-pressure veins with lower-quality lymphatics resulted in inconsistent surgical outcomes[16-18]. Subsequent advances in pre- and intra-operative imaging, operating microscopes, and surgical instruments facilitated the anastomosis of vessels smaller than 0.8 mm in diameter, ushering in the era of supermicrosurgery[2]. First described by Koshima *et al.*[19] in 2000, supermicrosurgical LVA allowed for the anastomosis of smaller lymphatics with venules ranging from 0.1-0.6 mm in diameter. The ability to use smaller vessels allowed surgeons to operate in the distal extremity, where lymph vessel function was more likely to be intact and to select small, low-pressure venules that offered more favorable pressure gradients[19,20].

In 1979, Shesol performed a pedicled flap transfer of groin lymphatic tissues for popliteal fossa defects in rats, showing lymph flow reestablishment at 7 days[21]. It set the groundwork for the development of VLNT[22,23]. The mechanism of action of VLNT is believed to be due to: (1) bridging lymphangiogenesis mediated by lymphatic growth factors, particularly vascular endothelial growth factor C[24] secretion from the transplanted lymphatic tissue; and (2) "pumping" action-driven by perfusion gradients between arterial inflow and venous outflow[22-29]. However, there is no clear evidence that these mechanisms rely on the lymph nodes contained in these flaps. It has not been consistently demonstrated that different VLNT flap donor sites - which often contain different numbers of nodes - produce different outcomes[30-32]. The sole study comparing different VLNT flaps within a single institution did not demonstrate a significant difference[33], and studies attempting to establish a correlation between the number of LNs and the effectiveness of the flap have yielded mixed results[34,35]. Moreover, while it is difficult to compare VLNT flaps with and without skin paddles in a controlled manner, increasing understanding of the dermal and subcutaneous lymphatic system strongly suggests that lymphadiposal tissue is essential for the efficacy of the flap[36,37]. Additionally, lymphatic vessels are likely the main drivers of lymph pumping, as evidenced by their smooth muscle lining and peristaltic action. Now that advancements in lymphography allow precise pre- and intra-operative visualization of superficial lymph vessels, their pumping action can be harnessed with intentional inclusion in flaps and proper orientation in recipient sites[38]. Combined with lymphatic channels' abilities to absorb lymph and stimulate lymphangiogenesis, it supports the hypothesis that vessels

- not nodes - are the therapeutic components of these flaps[39,40].

Vascularized lymph vessel transplant - the third surgical alternative

Vascularized lymph vessel transplant was introduced by Koshima *et al.*[5] in 2016 when they used first dorsal metatarsal artery (FDMA)-based lymphadiposal flaps on treating advanced lymphedema in thirteen patients. It represented a conceptual departure from the accepted belief that nodal tissue transfer is required to restore of lymphatic drainage. Subsequently, the senior author implemented FDMA-based VLVT with favorable recipient-site outcomes. However, the location of the donor site precluded the flap's use in bilateral lower extremity disease. Additionally, FDMA flap harvest frequently caused devascularization of the skin over the first metatarsal space, resulting in donor wound breakdown[7]. Nevertheless, the success of the procedure drove the senior author to establish alternative lymphatic-rich donor sites: the groin [superficial circumflex iliac artery perforator (SCIP) flap] and trunk [thoracodorsal artery perforator (TDAP) flap][6]. The SCIP flap's familiar vascular anatomy and successful use as a thin flap make it an ideal candidate for VLVT. However, the SCIP flap is not a feasible option in patients with bilateral lower extremity lymphedema. The TDAP flap's location makes it suitable for bilateral lower extremity disease and contralateral upper extremity disease. Our early outcomes show similar efficacy and safety profiles to that of the SCIP flap. As shown in Figure 1, satisfactory decompression of the lymphedematous limb with minimal complications is achievable. By selectively harvesting only lymph vessels and completely preserving lymph nodes, VLVT greatly reduces the risk of donor-site complications while still offering results comparable to VLNT. As of the writing of this article, the senior author (Chen WF) has completely replaced VLNT with VLVT in his practice for the treatment of advanced fluid-predominant lymphedema.

Revisiting the indications for LVA

As surgeons' worldwide developed expertise in supermicrosurgery, the practice of LVA grew in sophistication. New technology and techniques further enhanced an already efficacious procedure. Indocyanine green (ICG)-lymphographic[41], infrared[42], and high-frequency duplex ultrasound[43,44] guidance facilitates the precise placement of small incisions with high success rates. Different anastomotic configurations were developed to increase the number of drainage pathways and to successfully complete LVA even under technically challenging conditions[45,46]. These technical innovations allowed supermicrosurgeons to successfully treat even advanced lymphedema cases with LVA when these cases were previously considered only treatable with VLNT. Because VLVT and VLNT have similar indications, with the expanding scope of LVA, indications for LVA and VLVT/VLVT have started to overlap.

Technical tips: LVA

Vessel mapping and dissection

Incisions for LVA are planned where ICG-mapped lymph vessels and infrared-mapped veins lie in close proximity, as shown in Figure 2, maximizing the possible number of LVAs created per incision[47-51]. The anatomy of the superficial lymphatic system closely follows that of the superficial venous system; thus, in advanced cases with difficult-to-identify lymphatics, careful dissection along main superficial veins can still reveal suitable lymph vessels[52], as shown in Figure 3. In these advanced cases, any dermal backflow pattern on delayed images of diagnostic ICG lymphography suggests the presence of lymphostatic choke points. LVAs incisions should ideally be placed anatomically in or just proximal to these dermal backflow patterns. Injection of isosulfan blue 2 cm distal to skin markings just before each incision enhances identification of lymphatic vessels during dissection[52]. We use 20-25x magnification and proceed in a caudo-cephalad direction[48]. All dissected lymphatics are inspected and graded as healthy, ectatic (mild injury), contracted (moderate injury), or sclerotic (severe injury)[16,53]. Although healthy vessels are preferred, ectatic and contracted vessels can also be used when necessary to achieve a sufficient number of LVAs per case[47,54].

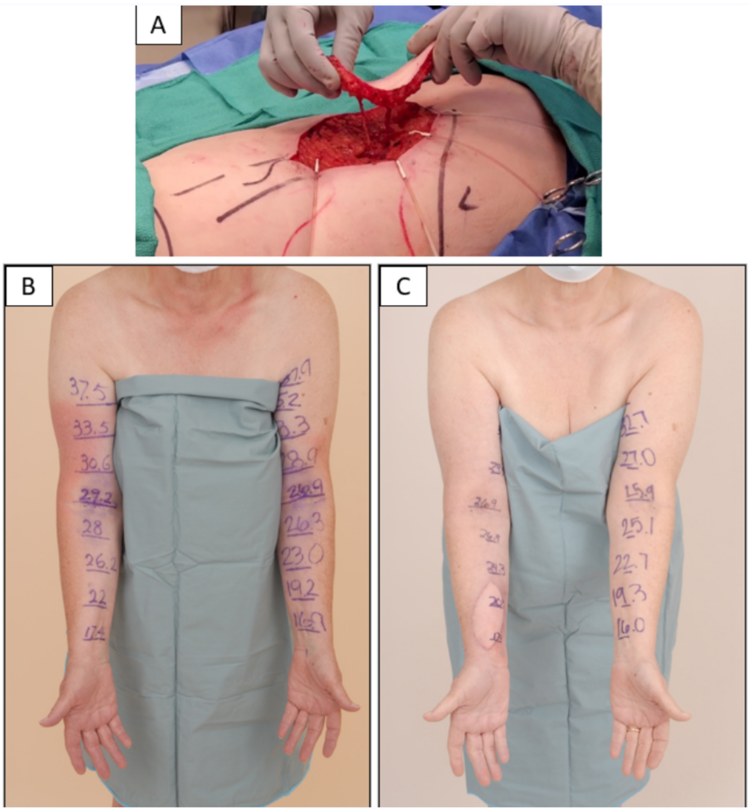

Figure 1. A representative case of TDAP-based VLVT for unilateral upper extremity lymphedema. (A) TDAP flap was harvested superficially to the superficial fascia for inset into the distal volar forearm. (B) Preoperative image showing significant swelling of the right upper extremity. (C) Measurements 3 months postoperatively show a significant reduction in the girth of the right upper extremity. The thin profile of VLVT flaps minimizes flap bulk; thus, contour deformity of the recipient site is avoided. TDAP: Thoracodorsal artery perforator; VLVT: vascularized lymph vessel transplant.

Anastomosis

The overall goal of LVA is to create lymphatic-to-venous anterograde flow in as many drainage pathways as possible[48,55-57]. Scenarios of vessel number mismatch, unfavorable pressure gradients, vessel size mismatch, and awkward vessel positioning can be encountered in different combinations. A variety of anastomotic configurations have been developed to overcome such obstacles, named in a lymph-to-vein convention[57-60], as shown in Figure 4.

When lymphatic pressure exceeds venous pressure, all configurations should work; end-to-end will often be chosen as it is the most technically straightforward. However, when the pressure gradient is unfavorable, side-to-side or end-to-side is chosen to take advantage of Bernoulli's principle[54]. Side-to-side is the more technically challenging and should be performed only if the involved vessels are 0.4 mm or more in diameter. If end-to-end configuration is the only option available due to size limitations, immediate postoperative compression can alter the pressure gradient to facilitate anterograde flow[61].

12-0 nylon on a 50-um needle is generally preferred for anastomosis, but 11-0 nylon can be used for vessels 0.5 mm or larger in diameter. As the vessels are too small for supermicrosurgical forceps tips to insert into the lumen, the needle tip can be used to evert the vessel edge against the side of the forceps[48] with or without the use of a 7-0 monofilament nylon suture acting as an intravascular stent[60,62,63].

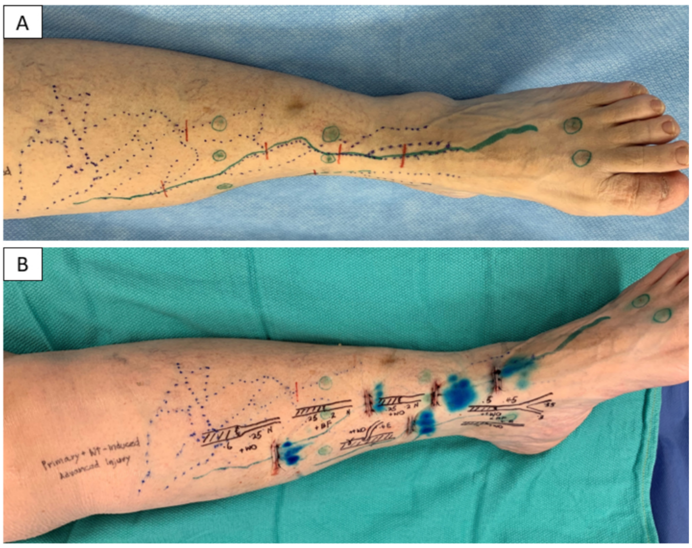

Figure 2. Incision planning for LVA. (A) Lymphatic channels (solid green lines) are mapped with ICG lymphography, and veins are mapped (dotted blue lines) with an infrared vein finder. 2-3 cm incisions are marked in sites where veins and lymphatics lie in proximity (red lines). Green circles mark the sites used for ICG injection in a distal-to-proximal sequence. (B) Immediate postoperative picture depicting the location of selected venules and lymphatics at each incision, with diagrams of the anastomotic configurations chosen. Blue staining of skin seen at sites of isosulphan blue injection is used for enhanced visualization of lymphatic channels during dissection. LVA: Lymphaticovenular anastomosis; ICG: indocyanine green.

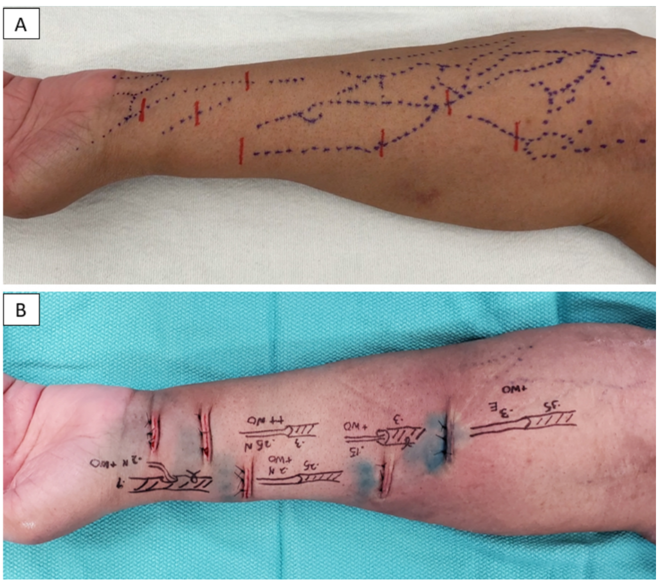

Figure 3. In this representative case of upper extremity lymphedema, ICG lymphography was contraindicated due to iodine allergy, necessitating intraoperative exploration to locate suitable lymphatics for LVA. (A) Because the anatomy of the superficial lymphatic system closely follows that of the superficial venous system, incisions (red lines) were planned near infrared-mapped veins (dotted blue lines). (B) All incisions used were positive for suitable lymphatic vessels; diagrams depict the anastomotic configurations chosen at each incision site. ICG: Indocyanine green; LVA: lymphaticovenular anastomosis.

After anastomosis, patency is confirmed by washout of the venous lumen by lymphatic fluid[48]. It may not occur immediately after LVA completion due to the slow peristaltic action of lymphatic vessels. Diseased lymphatic vessels may display a particularly delayed washout phenomenon owing to their compromised smooth muscle function. Therefore, anastomoses should be re-assessed several minutes after completion

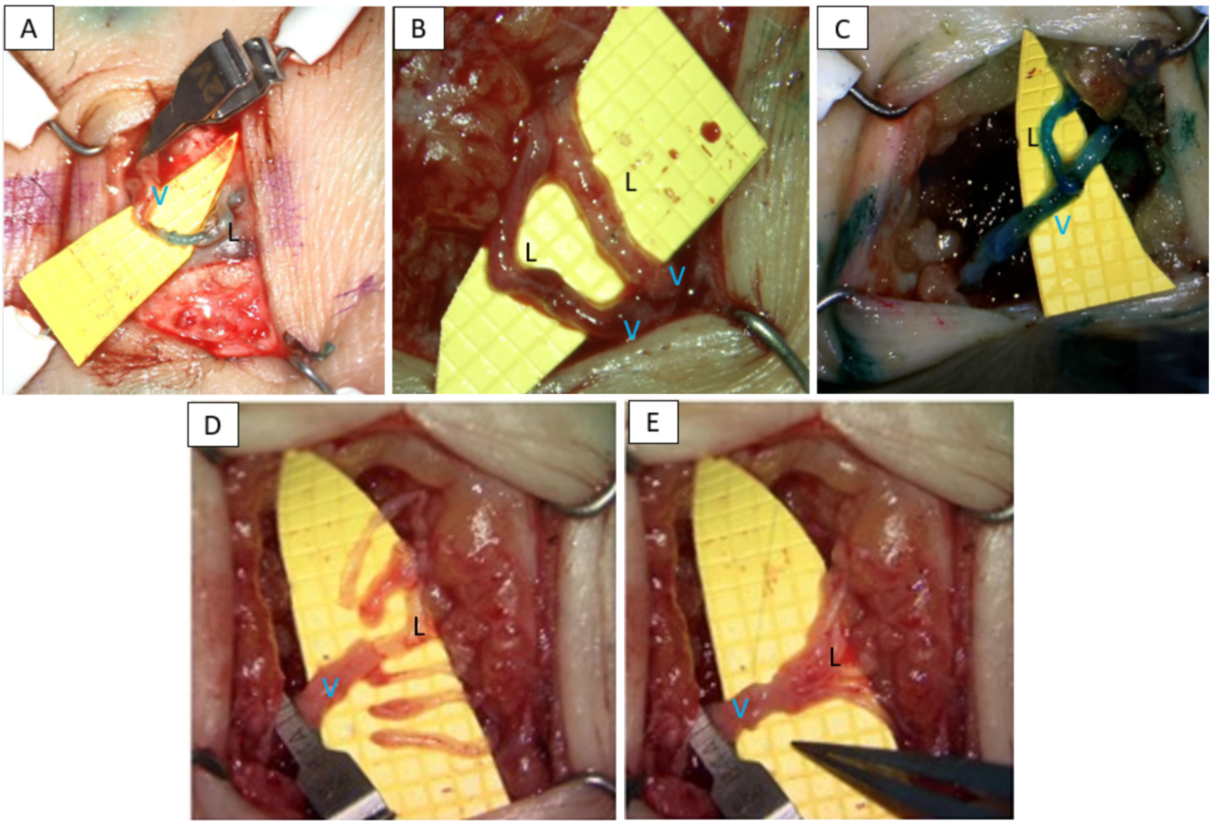

Figure 4. A variety of anastomotic configurations (named in a lymphatic-to-vein convention) are available to maximize anterograde drainage. (A) Single end-to-end anastomosis, (B) end-to-end anastomosis of two lymphatics to two venous branches, (C) end-to-side anastomosis, (D) depicts multiple small-caliber, fibrotic (non-translucent) lymphatic vessels and a single, large-caliber vein, for which (E) an invaginating "octopus" technique is most appropriate. L: Lymphatic; V: venule.

before declaring failure[64]. It can be promoted by massaging distal to incision. Leakproof anastomosis is essential to allow lymphatic pressure to build up and overcome the venous pressure[65]. If the microscope is equipped with an ICG module, patency can be confirmed by observing ICG flow into the veins[65]. If backflow of blood into the lymphatic vessel is observed, venous pressure has exceeded lymphatic pressure, and the anastomosis is at risk of thrombosis.

Controversy exists regarding the optimal number of LVAs[31]. Theoretically, a few high-quality anastomoses (antegrade flow anticipated) should suffice, but reality often necessitates a quantity-over-quality approach. In keeping with this, the senior author (Chen WF) has demonstrated considerable clinical success when using suboptimal vessels by creating 8 to 15 LVAs per case[48,54,64]. The following are used as the procedure endpoints: (1) six hours of operative time; for experienced microsurgeons, continuing beyond this duration typically yields diminishing returns; (2) three consecutive negative incisions (i.e., no suitable lymphatics found when proceeding in a distal-to-proximal fashion); or (3) substantial drainage through LVAs causing visible limb decompression on the table[54].

Frequently refreshing supermicrosurgical skills on practice models can shorten the learning curve for LVA in budding lymphedema surgeons[66].

Technical tips: VLVT

Due to its comparable outcomes and lower invasiveness, SCIP-based VLVT has replaced VLNT as our procedure of choice for those with upper extremity lymphedema who are not LVA candidates. Vascular anatomy is imaged preoperatively with computed tomography angiography or high-resolution duplex ultrasound[67], allowing the more robust-appearing side to be chosen for harvest. Lymphatic vessels are then mapped using ICG imaging after four intradermal injections of 0.05 mL of 0.25% ICG, lateral to the anterior superior iliac spine. Most frequently, the superficial branch of the superficial circumflex iliac artery (SCIA) is selected as the pedicle due to its fast and easy dissection. One should be prepared for occasional anatomic variation necessitating the use of a deep branch. The dissection plane is kept immediately superficial to Scarpa's fascia, ensuring the exclusion of lymph nodes from the flap and is advanced in a lateral-to-medial direction. It is important to adhere to Scarpa's fascia during flap elevation and not dissect more superficially as more superficial dissection risks exclusion of the superficial circumflex iliac vein.

The vascular anatomy and perforator location of the TDAP flap is more variable than that of the SCIP flap. Thus, preoperative vascular imaging becomes even more important. Adequate perforators are commonly identifiable with Doppler ultrasound, 8-10 cm inferior to the axillary apex and 1-2 cm inside the lateral border of the latissimus dorsi. Perforators identified in this region may originate from intercostal and lateral thoracic vessels rather than from the thoracodorsal vessel, as shown in Figure 5. However, if adequate pedicle length can be achieved, harvesting the flap on these alternative vessels is acceptable[68,69]. Lymphatics are mapped with intradermal ICG injection of the fifth intercostal space in the midaxillary line to ensure their inclusion in the flap. By dissecting superficial to the superficial fascia, lateral thoracic lymph nodes are excluded from the flap.

For VLVT to be effective, the flap is placed closer to lymphatic edema, and in the proximity of relatively less degenerated lymphatics, both criteria are met in the distal part of the extremity (ankle/wrist). the flap is oriented to match its lymphatics vessels axiality to that of the recipient site lymphatics axiality to allow spontaneous lympholymphatic linkages, as shown by Yamamoto *et al.*[38]. Just as the minimum number of lymph nodes required for optimum performance of VLNT is not known, the minimum number of lymphatic channels needed for optimum efficacy VLVT is unknown. The density of lymphatic channels in the different flap donor sites has not been experimentally compared, and the minimum size (volume) of the flap required for desirable lymphatic decompression is unclear.

Decision-making: choosing between LVA and VLVT

Both LVA and VLVT are indicated for fluid-predominant lymphedema. Solid predominance, a state of bulky lipodystrophy and fibrosis, should be ruled out clinically (non-pitting edema, no significant volume reduction even after aggressive complex decongestive therapy)[4,70] as well as radiologically with MRI before proceeding.

Misconceptions surrounding LVA have hindered its acceptance amongst surgeons. It is assumed that LVA can only treat early lymphedema and that absence of "linear" patterns on ICG lymphography and/or the presence of venous insufficiency contraindicate its use. Additionally, a few studies have demonstrated inferior outcomes of LVA in lower extremity *vs.* upper extremity edema, thought to be due to the dependent position and higher venous pressure of the legs[71-75]. Finally, it is also believed that results of LVA take long to become noticeable and are short-lived. In the senior author's experience, none of the above holds true. The absence of "linear" ICG patterns simply indicates additional effort is needed to locate the lymph vessels, which, once located, are still of sufficient quality to perform LVA. The reduced lymphovenous pressure gradient in the lower extremity can be circumvented with postoperative bandage compression, which creates anterograde flow across the LVAs[53,69,73]. Finally, the senior author has witnessed

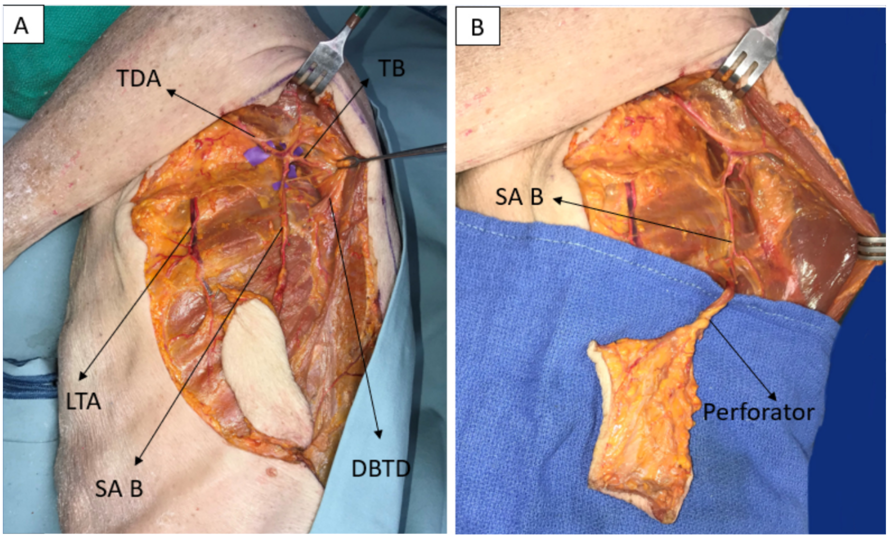

Figure 5. Anatomical dissection of the thin TDAP (thoracodorsal artery perforator) flap. The cadaver was pre-injected with red latex to highlight arterial anatomy. (A) Possible sources of skin perforators in the thoracodorsal region. Posterior intercostal vessels, which are another possible source of skin perforators in this region, are not shown here. (B) The perforator was located anterior to the lateral border of the latissimus dorsi muscle. A thin flap was elevated on this perforator, superficial to the superficial fascia. While the descending branch of the TDA is most commonly the source of the TDAP, proximal tracing of this perforator led to the serratus branch of the TDA. However, adequate pedicle length was still achieved. TDA: Thoracodorsal artery; TB: transverse branch of TDA; DBTD: descending branch of TDA; SAB: serratus anterior branch of TDA; LTA: lateral thoracic artery.

progressive improvement in patients for as long as 3 years post-surgery, which cannot be explained solely by the mechanical bypass provided by the LVAs. Following the initial lymphatic shunting, possible lymphatic regeneration is hypothesized to play an additional role in ultimately weaning patients off from compression garments.

Recent reports by Yang *et al.*[76], and growing experience in other high-volume centers has demonstrated that in the hands of experienced supermicrosurgeons, LVA can be successful in moderate-to-severe disease. With the limits of LVA getting pushed further along the spectrum of advanced lymphedema, deciding when to use VLVT instead of LVA becomes less straightforward. VLVT has less associated technical nuances and more predictable outcomes in the hands of less experienced surgeons but requires an additional surgical site. LVA, in contrast, has many technical variables. Even when optimized, its outcomes may not always be predictable. Yet, the minimally invasive nature of LVA outweighs its drawbacks. The success of VLVT depends on the patency of the pedicle anastomosis only, while the success of LVA depends on the quality (patency as well as pressure gradient across the anastomoses) as well as the quantity of the multiple anastomoses (number sufficient to decompress the distended lymphatic system). Discussing this dilemma at length with the patient can help them judiciously weigh the risks and benefits of both procedures and make an informed choice.

Controversy also surrounds the management of primary lymphedema. Many surgeons recommend VLNT over LVA due to theoretical concerns that the abnormal structure and function of lymphatics in these patients may decrease the efficacy of LVA[2,77,78]. However, in our experience, it is not uncommon for patients with primary lymphedema to exhibit global lymphatic dysfunction, as evidenced on ICG lymphography. It precludes any flap transfer procedure in such patients due to an elevated risk of iatrogenic donor-site lymphedema, leaving LVA as a safer alternative[64,79,80].

CONCLUSION

With recent technical refinements in LVA and the evolution of VLVT as a safer alternative to VLNT, outcomes of lymphedema surgery have dramatically improved. The encouraging results of LVA in advanced lymphedema have unveiled its unrealized potential while creating an overlap with the indications of VLVT/VLNT. Though more invasive than LVA, VLVT remains a valuable modality and should be investigated further.

DECLARATIONS

Authors' contributions

Conception and design of the paper: Chen WF

Manuscript writing: Pandey SK, Fahradyan VF, Orfahli LM, Chen WF

Final approval of manuscript: Pandey SK, Fahradyan VF, Orfahli LM, Chen WF

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication of de-identified images was obtained.

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