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REVIEW ARTICLE

Lymphovenous shunts in the treatment of lymphedema

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Abstract

Lymphedema is a progressive disease with no known cure. Characterized by the accumulation of lymphatic fluid and subsequent swelling in the affected limbs, it often poses significant challenges to those living with it. Although various conservative treatments have been used to manage lymphedema, such as compression therapy and physical rehabilitation, surgical interventions have emerged as promising avenues for more substantial relief. Lymphovenous shunts have been described since the 1960s and have garnered much attention in the recent two decades due to technological advances in optics, imaging, and surgical instruments. This review article explores the use of different lymphovenous shunts such as lymphatic implantation, lymph node-to-vein anastomoses (LNVAs), dermal-adipose lymphatic flap venous wrapping (DALF-VW), and supermicrosurgical lymphovenous anastomoses (LVAs) as treatment modalities for lymphedema. We will discuss the underlying principles, indications, techniques, and potential benefits. By examining the current state of knowledge and ongoing research in the field, we aim to provide insights into the role of lymphovenous shunts in the comprehensive management of lymphedema and shed light on the prospects for this treatment option.

Keywords: Dermal-adipose lymphatic flap venous wrapping; Lymph node-to-vein anastomosis; Lymphatic implantation; Lymphovenous shunt; Supermicrosurgical lymphovenous anastomosis

1. INTRODUCTION

Advances in in-vivo imaging technology have allowed researchers to gain more insights into the interstitium. We now understand that afflictions of the interstitium, and their drainage system, the lymphatics, account for some of the pathologies we encounter today. Benias et al[1] described a network of submucosal channels known as the submucosal interstitium in the digestive and urinary tracts that facilitates the transmission of tumor cells once luminal invasive tumors reach the submucosa. Metastasis is then promoted through the lymphatics and lymphovenous shunts (LVSs) in the body. A LVS or lymphovenous communication connects the lymphatic and venous systems. They can be classified as physiological, pathological, or iatrogenic/surgical based on their etiology.[2]

Physiological LVSs exist in individuals with normal lymphatics. The anastomoses between the thoracic duct and the subclavian vein represent well-known LVSs. Hidden et al[3] stated that there is a physiological necessity for LVS in points other than the terminal entry of the thoracic duct into the superior caval system. LVSs between the thoracic duct and the azygous system have been reported in the literature,[4] although their physiological or physiological etiology is still up for debate. Some authors believe physiological shunts only open when lymphatic pressure exceeds a certain threshold.

Pathological LVSs exist as artificial connections between the lymphatic and venous systems due to abnormalities in the lymphatic system, like primary lymphedema or diseases like malignancies which result in the invasion of lymph nodes and destruction of their local architecture. Most of the time, these LVSs occur peripherally. Edwards et al[5] did a study involving the lymphography of 700 patients. He found that LVSs other than the termination of the thoracic duct were all pathological. They noticed that the presence of LVSs in the primary lymphedema group may protect a limb from the overt development of edema. These shunts were found in limbs with definite lymphatic abnormalities yet were clinically normal. This observation would further advance the concept of surgical LVSs.

The conceptualization of surgical LVSs began as early as 1962 when Jacobson[6] performed experimental lymphovenous anastomoses in animals. This led to the birth and evolution of numerous techniques reconstructive surgeons are currently using for lymphatic shunting. Our review article will do a deep dive into these techniques, namely, lymphatic implantation, lymph node-to-vein anastomoses (LNVAs), dermal-adipose lymphatic flap venous wrapping (DALF-VW), and supermicrosurgical lymphovenous anastomoses (LVAs).

2. LYMPHATIC IMPLANTATION (LYMPHOVENOUS IMPLANTATION)

During the early days of microsurgical lymphatic reconstruction, surgeons were limited by the technology of sutures and microscopes. Hence, early surgical LVSs comprised of implantation

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of healthy lymphatic vessels into relatively large veins. These were initially termed lymphovenous anastomoses in the literature, which causes a substantial amount of confusion today. The correct nomenclature should be lymphovenous implantation (LVI). Using U-shaped microvascular sutures, one or more lymphatic vessels and their surrounding adventitia and adipose tissue were often introduced and telescoped into the large lumen of the recipient vein. Degni[7] described an innovative method of implanting multiple lymphatic vessels end-to-side (ES) into the great saphenous vein using a venous needle and double arm 7-0 nylon sutures. However, Degni's[7] technique is accompanied by a high probability of thrombus formation and subsequent embolism into the pulmonary circulation. Refinement of the method was followed by Campisi et al[8] and Yamamoto and Sugihara,[9] reporting end-to-end (EE) implantation into a vein with an intact valve. Implantation offers several advantages:

1. Implantation requires a shorter duration of time compared to intima-to-intima lymphovenous anastomosis. Less preparation of the lymphatic vessel is needed, and fewer stitches are placed to obtain a water-tight seal.
2. Technically less demanding technique.
3. Implantation does not require supermicrosurgical instruments and optics to perform.

Although these tangible benefits have attracted many surgeons to attempt LVI, it is essential to consider what are the potential risks involved:

1. No prospective human studies have shown the long-term patency of LVI.[10] Exposure to collagen-rich lymphatic adventitia surfaces may increase the probability of thrombosis.
2. When implantation is performed to a large vein, thrombus formation may propagate proximally and increase the risk of thromboembolic events.

Boccardo et al[11] would further popularize the LVI concept with the lymphedema microsurgical preventive healing approach (LYMPHA). This approach utilized prophylactic LVI to prevent secondary lymphedema in breast cancer patients requiring axillary dissection. In some countries, this approach is also known as immediate lymphatic reconstruction. Nineteen patients who underwent axillary dissection had severed lymphatic collectors telescoped EE into branches of the axillary vein. The LVI was performed 8-0 nylon U-shaped stitches (Fig. 1). These lymphatic vessels were visualized using blue dye injection into the medial upper arm lymphosome. Two to four implantations were done per patient, and their outcomes were followed up for 1 year. At 1 year follow-up, no patients had secondary clinical lymphedema, whereas lymphoscintigraphy showed moderate to marked improvement of the lymphatic transport index. The group would publish data based on 4 years of follow-up in 2014. Of 74 patients who underwent LYMPHA, 71 had no signs of secondary lymphedema, and volumetry coincided with the preoperative condition. However, only three patients were deemed to have developed secondary lymphedema, and 14 developed cellulitis. Five of the eight patients who received radiotherapy had temporary edema, and the remaining three had permanent edema. Their published lymphedema incidence was 4.05% in LYMPHA patients.

Although the LYMPHA approach is widely adopted by many centers for use in the prevention of secondary lymphedema, more high-quality data are required to determine its effectiveness. Several meta-analyses and systematic reviews have been published on this topic.[12–14] Unfortunately, many studies were

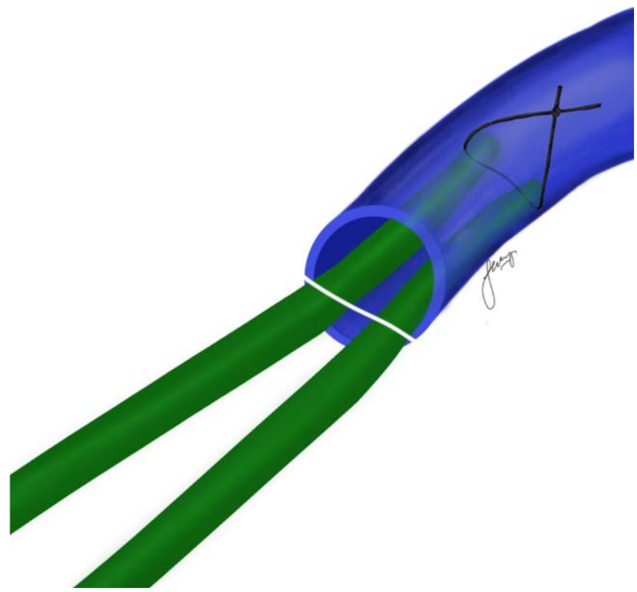

Fig. 1 An example of lymphovenous implantation is shown where two lymphatic vessels are telescoped into the vein via a U-shaped stitch.

plagued with small sample sizes, a lack of a consistent control group, and nonstandardized outcome measures. The follow-up duration for many studies was shorter than 2 years in more than two-thirds of the studies, which limited the utility of the data. A minimum follow-up of 3 years after starting oncologic treatment should be contemplated to identify patients suffering from cancer–related lymphedema satisfactorily. As for patency assessment, Boccardo et al's[11] and Buchan et al's[15] had postoperative patency assessment via lymphoscintigraphy and indocyanine green (ICG) lymphography, respectively. Although Buchan et al[15] did demonstrate maintenance of linear patterns on ICG lymphography in most of their patients, a late-phase scan was not performed; hence a definite exclusion of dermal backflow in their cohort cannot be made.

Recently, Levy et al[16] published a well-designed retrospective study involving 45 women in both LYMPHA and non-LYMPHA cohorts. This study would prove controversial as the study failed to show statistically significant benefits of the LYMPHA group. The LYMPHA group had a 31.1% incidence of lymphedema, whereas the non-LYMPHA group had 33.3%.

Chen et al[17] described a modification to the conventional LVI technique. In this modification, called the "octopus" technique, small (often <0.5 mm) and superficial lymphatics are skeletonized and implanted into large veins at multiple distal sites of the limb. This technique is technically less demanding than LVA and creates multiple channels of bypasses using better-preserved distal lymphatic vessels. In their series, nine consecutive patients had the "octopus" shunts formed, and all patients experienced disease regression as demonstrated by clinical disease down-staging.

Although there is no strong long-term data comparing the patency rates of LVI vs supermicrosurgical LVA in humans, animal studies have given some insight into this topic. Ishiura et al[18] compared 12 Wistar rats randomized into two arms; LVI and supermicrosurgical LVA. Patency was evaluated intraoperatively with patent blue dye and 1 week postoperatively with ICG lymphography.[18] The postoperative patency rate in the supermicrosurgical LVA group was significantly higher than that in the LVI group, 100% (six of six) vs 33.3% (two of six; $p = 0.014$). Given the paucity of high-level data surrounding the longevity and effectiveness of LVI, it is best to consider its use when an intima-to-intima style of supermicrosurgical LVA is technically too challenging because of the small diameter of the lymphatic vessel.[18–20]

3. LYMPH NODE-TO-VEIN ANASTOMOSES

Nielubowicz and Olszewski[21] were the first to experiment with implanting mesenteric lymph nodes with intact afferent vessels into the inferior vena cava as a surgical LVS on a dog. The shunts were shown to be patent for up to 1 year, and the group published a small series shortly after involving four patients with secondary lymphedema of the lower extremity (Fig. 2). In their limited series, every patient experienced a reduction in leg circumference and was able to have some form of symptomatic relief.[22] Olszewski[23] continued performing surgical LVS such as LNVA and LVA for the next 45 years and published his experience with more than 1100 patients. The most significant improvement was shown in patients with early stages of lymphedema.

Although the practice of LNVA is less widespread than LVI or LVA, there continue to be scattered reports of good outcomes when LNVA was used to treat post-filariasis lymphedema and protein-losing enteropathy. Recently Pak et al[24] described a modification to the conventional LVNA technique. Instead of transecting the lymph node in a transverse plane to expose the lymph node's afferent lymphatics and draining systems, the group uses a 16-gauge needle to bore a hole down to the medulla of the node. A recipient vein is then anastomosed to the puncture hole in the capsule of the lymph node using 9-0 or 10-0 nylon. The group opines that preservation of the afferent and efferent lymph nodes helps to optimize the shunting capabilities of the LNVA. In their retrospective study, the treatment of 160 International Society of Lymphology (ISL) stages II and III patients with secondary lymphedema of the lower extremity were divided into two groups: one with LNVA and LVA and the other group with just LVA alone. Their results showed statistically significant improvement of the LNVA and LVA group over the LVA alone group regarding the lymphedema reduction rate. This was consistent for both ISL stage II and stage III patients. This method may represent a refinement of the traditional LNVA technique where sectioning a large portion of the lymph node may expose thrombogenic parts of the node to the venous blood. Furthermore, using small vein branches or venules limit the adverse effects if a thrombus were to form at the anastomosis, as the potential for embolism is lower in small caliber veins than in large femoral vein tributaries.

The evidence surrounding LNVA and similar nodo-venous shunt techniques is limited to retrospective studies and small case series. As such, the efficacy of such techniques is still a subject of ongoing research. Furthermore, LNVA is often combined with other procedures such as LVA, liposuction, and other surgical debulking methods confounding the actual effectiveness of the procedure. The lack of direct visualization of the shunt effects and the limited evidence of its effectiveness as a sole treatment for lymphedema prevents its widespread adoption amongst reconstructive surgeons.

4. DERMAL-ADIPOSE LYMPHATIC FLAP VENOUS WRAPPING

This novel shunt technique described by Yamamoto et al[25] is mainly used in treating severe upper extremity lymphedema refractory to previous LVA surgeries. Unlike LVI or LVA, this procedure utilizes the dermal lymphatic capillaries for LVS. In contrast, procedures like LVI and LVA aim to achieve this shunting effect via collecting lymph vessels draining into venous circulation; those of the dermal lymphatic capillaries are diverted in DALF-VW. In chronic lymphedema, lymphosclerosis progresses in the collecting lymph vessels. The lumen of these vessels gradually undergoes stenosis and occludes. When the collecting lymph vessels' lumens are obstructed, lymph flows retrogradely through the dermal lymphatic capillaries. This makes LVI and LVA ineffective but creates a compelling case for DALF-VW to work. Dermal lymphatic capillaries are too small for anastomosis, so a narrow dermal-adipose tissue, DALF, is wrapped with a recipient vein's wall; VW method. As in LVI and LNVA, it is crucial to use a reflux-free vein, as thrombosis is inevitable when venous blood comes into contact with a DALF.

In this retrospective study, 37 patients underwent the procedure, and 98 shunts were created (an average of 2.6 per patient). Patient characteristics and outcomes such as upper extremity index, cellulitis frequency, and quality of life score (LeQOLiS)

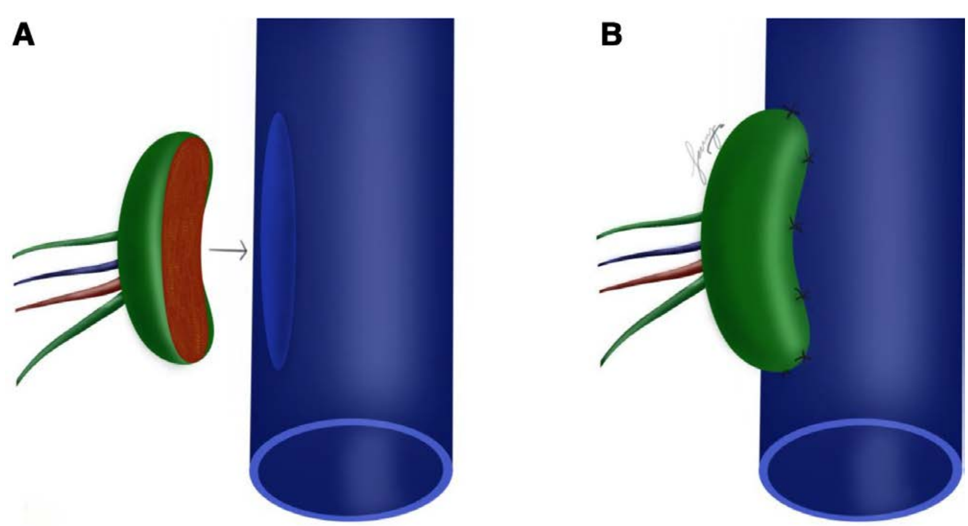

Fig. 2 Lymph node-to-vein anastomosis is shown here. A lymph node is partially transected to expose the substance of the lymph node (A). The capsule surrounding the cut surface is then anastomosed end-to-side to the vein (B). The transected lymph node can also be anastomosed end-to end-to a venous branch.

Table 1

Statistically significant improvement after DALF-VW in the upper extremity index, LeQOLiS, and the number of cellulitis episodes

	Before DALF-VW	After DALF-VW
Upper extremity index	103-196 (131.9)	91-150 (121.8)
LeQOLiS	12-94 (45.6)	0-77 (31.0)
Cellulitis frequency	0-5 (0.8)	0-2 (0.2)

DALF-VW = dermal-adipose lymphatic flap venous wrapping; LeQOLiS = quality of life score.

were measured before and after surgery. Statistically significant improvements in these three outcomes were demonstrated in this study and summarized in Table 1.

The patients recruited for this procedure are classified as stage V on ICG staging with severe lymphosclerosis and absent linear lymphatic channels on ICG lymphography. They were also refractory to multiple attempts of LVA. Vascularized lymph node transfer will be the natural therapeutic progression for these patients. Hence, DALF-VW represented a last-ditch effort to improve or retard the progression of upper extremity lymphedema. The procedure is quick, with an average time of 23.5 minutes for each shunt creation, and can be performed under loupe magnification.

The technical details are as such:

1. Shunts are sited on the most edematous portions of the upper limb where ICG demonstrated gross dermal backflow (the most severe dermal backflow pattern being "Diffuse").
2. Preoperative ultrasound is used to localize 2 to 3 mm recipient veins. Veins with intact valves are chosen during the procedure and are considered a critical factor in the success of the shunt.
3. Under local anesthesia, a 2 cm incision is made, and meticulous hemostasis is secured.
4. The recipient vein is localized and traced proximally to include as many valves as possible.
5. The vein is transected distally, and transcommissural valvuloplasty is performed if venous reflux is noted.
6. A 15 mm truncated cone-coned shape DALF, slightly larger than the diameter of the recipient vein, is fashioned from one of the cut sides of the incision. A wide-based pedicle is preserved.
7. Deepithelialization of the DALF is performed with meticulous hemostasis afterward.
8. Ten millimeters of the anterior aspect of the vein is laid open, and the DALF is placed inside the lumen of the vein (Fig. 3).
9. 10-0 nylon suture is used to close the vein over the DALF and secure it intraluminal (Fig. 3B).
10. Wound closure is performed with care to not strangulate the base of the DALF.
11. Postoperative compression garments are applied.

The limitations to the DALF-VW are:

1. Improvement was only shown in upper extremity lymphedema as lower extremity shunts are subjected to more significant venous reflux, causing early thrombosis and limiting their effectiveness.
2. This procedure should not be done in patients with high venous pressure and reflux.
3. The longevity of this procedure and the duration of such improvements were not proven.
4. No direct visualization of the shunting effects postoperatively.

As such, this technique may be helpful as a bridging procedure before vascularized lymph node transfer in patients where no patent lymphatics could be found due to severe lymphosclerosis. It can also be an alternative to supermicrosurgical LVA when the LVA site is incised but no suitable or patent lymphatic is found. Rather than closing the wound without creating any shunts, a DALF-VW can be performed quickly in its place.

5. SUPERMICROSURGICAL LYMPHOVENOUS ANASTOMOSIS

Lymphovenous anastomosis can also be termed lymphovenular anastomosis or lymphovenous bypass. At times, they may be referred to as lymphaticovenous anastomosis as well. The first description of intima-to-intima lymphovenous anastomosis was by Yamada.[26] He performed his experiment in 80 live canine specimens where EE and ES anastomoses were performed with a 10-0 monofilament tetron suture. He managed to demonstrate patency via direct lymphangiography using a radio-opaque contrast medium. There was 90.9% patency of the EE anastomosis at 1 week, which dropped to 72.7% at 8 weeks, and 44.4% at 6 months. The patency of ES anastomoses were lower across the board at 85.7% at 1 week, 55.6% at 8 weeks, and 35.7% at 6 months. Yamada[26] utilized the concept of a temporary internal splint through a polyethylene catheter placed intraluminal to prevent the vessel from collapsing and catching the back wall whereas placing the stitch.

Yamada's[26] work inspired O'Brien et al[27] to publish their article utilizing microsurgical principles for lymphovenous anastomoses. They experimented on 100 canine lymphedema models and achieved patency rates of 74% at 1 week, 66% at 6 to 12 weeks, and 84% at 6 months, even without any temporary internal splinting. This was followed by a case series of 22 patients that underwent LVA in the upper limb for radical mastectomy–related lymphedema. Most of their patients experienced a mean excess volume reduction of 38%. The group stressed specific points about LVAs:

1. Meticulous microvascular technique is required for patency as they concluded that the common feature in thrombosed anastomoses was the presence of poorly opposed edges of the vessels. Thrombosis always stems from the venous component.
2. More than one anastomosis is required to achieve meaningful reduction. Patients with three or more anastomoses increased the probability of significant volume reduction in their case series.
3. LVAs alone were insufficient in redistributing the edema fluid back into the venous system. Compression therapy and manual lymphatic drainage synergized with LVAs in reducing excess volume. When the improvement had plateaued for many months postoperatively, these conservative measures were gradually reduced without any adverse effect.
4. Based on their experimental canine model, they believed that LVAs in lymphedema patients with even higher lymphatic pressure could achieve reasonable long-term patency rates.
5. The group believed that progressive and permanent changes to the lymphatics occurred at the onset of the disease and advocated for early disease intervention.
6. The risk of causing an increase in edema precludes using postoperative lymphangiograms (lipiodol) to assess patency in clinical cases.

O'Brien et al[27] did mention that lymphatic pressures tend to be higher than venous pressures at normal physiological states.

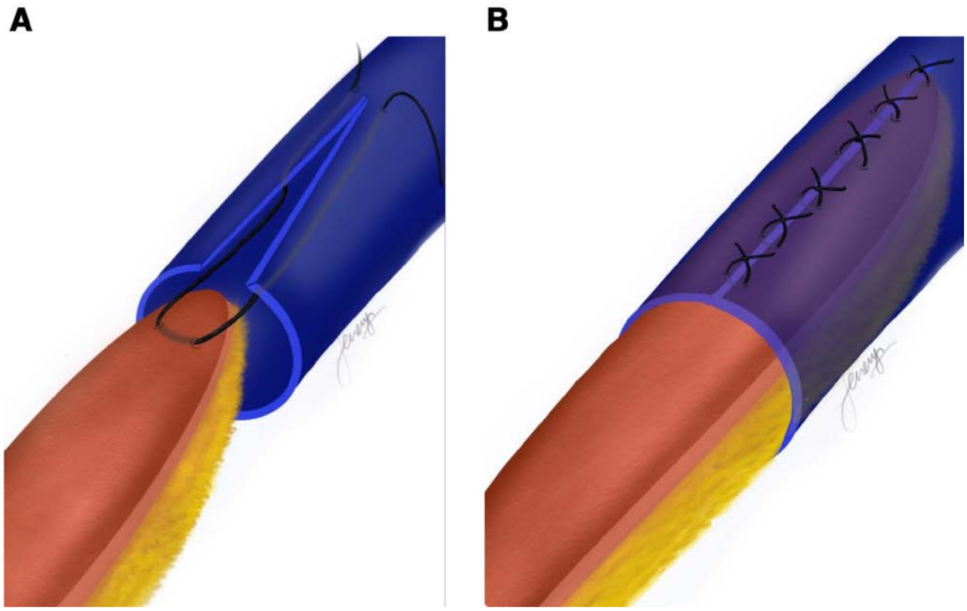

Fig. 3 DALF-VW is shown here. A 15 mm truncated cone-coned shape DALF slightly larger than the diameter of the recipient vein, is fashioned from one of the cut sides of the incision. The recipient vein is laid open, and the deepithelialized flap is telescoped into the lumen using a U-shaped stitch (A). The vein is then closed over the DALF with interrupted sutures (B). DALF-VW = dermal-adipose lymphatic flap with venous wrapping.

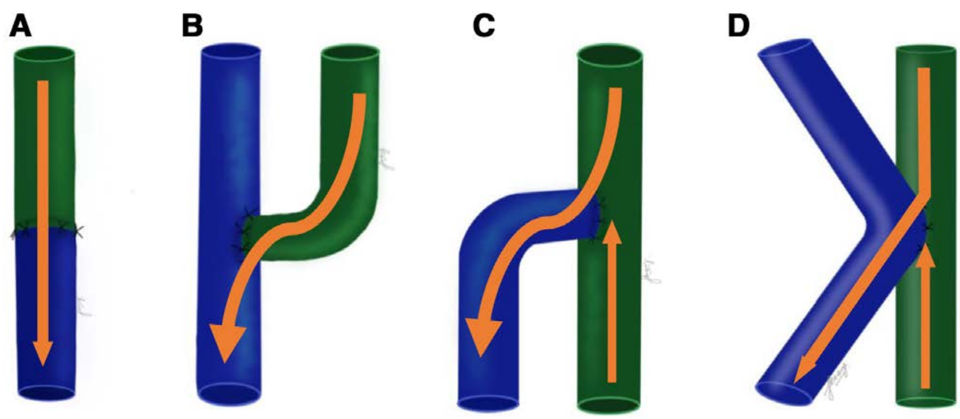

Fig. 4 Different anastomotic configurations for supermicrosurgical lymphovenous anastomosis. End-to-end anastomosis (A), end-to-side anastomosis (B), side-to-end anastomosis (C), and side-to-side anastomosis. C and D, Preserve the original lymphatic flow.

This was exaggerated when muscle activation compressed the lymphatics. However, Baumeister et al[28] expressed concern that cutaneous venous pressure can be higher than lymphatic pressure in some situations. These are patients with venous reflux and patients with lymphedema where lymphosclerosis has destroyed the smooth muscles of the lymphatics. This would lead to thrombosis of the venous blood at the anastomosis.

LVAs would remain an enigma to reconstructive surgeons for many years, even after the articles from Yamada[26] and O'Brien et al.[27] This was due to the limitations in optics and suture technology. Furthermore, lymphography techniques were either cumbersome or carried some unacceptable risk of adverse outcomes, and hence postoperative assessment of patency was difficult. This gradually changed since the late 90s when the concept of supermicrosurgery was adopted. Although the anastomoses of small caliber vessels have been performed for many years, Koshima et al was the first to use the term "supermicrosurgery" to describe the anastomosis of small vessels around 0.5 mm.[29] Supermicrosurgical LVA was first described by Koshima et al[30] in 1996 and heralded the rise of LVAs in treating lymphedema. The modifications to previous protocols involved using an operating microscope with a higher magnification of X20-X30, subdermal venules as recipient veins, and a smaller micro-suture of 11-0 nylon with a 50-micron needle.

These modifications aimed to improve the opposition of vessel edges and reduce the probability of thrombosis at the anastomosis site. Since Koshima et al's[30] article, many extensions and advancements of his technique have been reported in the literature.

Lymphography techniques improved with ICG advent. Initially developed during the Second World War by Kodak Research Laboratories as a photoimaging dye, ICG was approved by the US Food and Drug Administration in 1959 and was primarily used in hepatic function diagnostics. In 2007, Ogata et al[31] and Unno et al[32] independently reported the first reports of ICG lymphography for lymphedema evaluation. Yamamoto et al[33] reported the first classification of lymphedema severity based on four characteristic ICG patterns seen during

ICG lymphography. Linear, splash, stardust, and diffuse patterns were described in the article, the last three being pathognomonic for dermal backflow in lymphedema. The modified dermal backflow staging system was also created based on the initial articles ICG patterns and distribution.[34] ICG lymphography enabled surgeons to understand the level of obstruction by visualizing patent lymphatics in real-time in relation to the areas affected most by edema. LVA sites are then planned based on the most proximal linear channels seen within the areas of dermal backflow. Ultrasonography and ICG lymphography are often used hand in hand in the planning of LVA sites. High-frequency and, more recently, ultra-high-frequency ultrasound can be utilized to find patent and sizable lymphatics where the ICG fluorescence signal terminates.[35] It is essential to understand the ultrasonographic features of lymphatic vessels:

1. Location: lymphatic collectors of interest are often found in the deep subcutaneous fat just under the superficial fascia.
2. Shape: hypoechoic, spicular, and misshapen. No bright echogenic texture around them.
3. Flow: no flow is seen on the color Doppler mode.
4. Collapsibility: lymphatics are less likely to collapse than veins when the transducer is pressed against the skin.

While performing LVAs, it is crucial to consider the type of anastomotic configuration to be used. The four basic configurations are EE, ES, side-to-end (SE), and side-to-side (SS) (Fig 4). In our center, EE anastomosis represents the most basic and technically least demanding configuration with the highest patency rate. Hence, EE anastomosis is recommended in most cases and situations. As sclerotic lymphatic vessels often have retrograde flow, it is ideal for performing a double EE anastomosis that bypasses both antegrade and retrograde flow; a lymph vessel is transected, and both stumps are anastomosed EE to two veins. The SS and SE anastomoses have the theoretical advantage of maintaining bidirectional lymphatic drainage without proximally transecting and ligating lymphatic vessels. However, these configurations are technically challenging to perform, especially in sclerotic lymphatics, and are often unfeasible due to the anatomical positions of the lymphatic vessel and venule. ES anastomoses have the lowest patency rates, and when attempted, an EE anastomosis should be added to create the lambda-shaped anastomosis to allow for bidirectional lymphatic flow.[36]

Utilizing efferent lymphatics emerging from the lymph nodes for anastomosis is another variation of LVA. Efferent lymphatic vessel anastomosis (ELVA) was first described by Yamamoto et al[37,38] for the treatment of subclinical early-stage lower extremity lymphedema secondary to pelvic cancer treatments. The efferent lymphatics from the lymph node represent the most proximal lymphatic shunting achievable via LVA. It is theoretically more physiological than LNVA, LVI, and LVA, as lymph can still be filtered through the lymph nodes. As ELVA relieves lymphatic hypertension, inguinal lymph nodes are decongested, and their function can be preserved. With the help of ICG lymphography and ultrasound, the lymph nodes are localized and carefully dissected. Gentle and atraumatic technique is used to dissect down to the inguinal lymph node, paying close attention not to damage the lymph nodes and their accompanying vessels, which will exacerbate lymphedema. Efferent lymphatics tend to be larger and deeper than the lymphatic collectors described in LVA. Drainage veins from the hilum of the lymph nodes should not be used in ELVA as this will lead to venous congestion and eventual necrosis of the lymph node.

In conclusion, LVS offer potential benefits such as reducing limb volume, reducing symptoms and enhancing patients' overall quality of life. Although further research is needed to fully understand the long-term efficacy and patient selection criteria, current studies have shown encouraging results. As this field continues to evolve, advancements in surgical techniques and a deeper understanding of lymphatic physiology hold great promise for improving the management and outcomes of lymphedema through LVS. In the meantime, LVAs will likely remain the primary therapeutic option for surgical treatment of lymphedema of the extremities.

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