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Breast

Lymphatic Mapping with Contrast-enhanced Ultrasound for Lymphaticovenous Anastomosis Surgery: How We Do It

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Summary: Lymphaticovenous anastomosis (LVA) surgery is an effective surgery for the treatment of lymphedema in the extremities. Indocyanine green lymphography is the reference standard for visualizing lymphatics for LVA surgery, but it has several limitations; most notably, superficial dermal congestion can mask deeper lymphatic vessels. To overcome the limitations, we add contrast-enhanced ultrasound (CEUS) lymphography. We have previously reported that CEUS lymphography can identify lymphatic vessels for LVA surgery that indocyanine green lymphography does not. Here, we describe how we perform CEUS lymphography, including workflow, technique, and documentation. Before informed consent, the patient must be screened for possible adverse reactions to microbubbles. The procedure involves multiple intradermal injections of the microbubble agent at various sites along the extremity. After each injection, imaging for microbubble uptake by lymphatic vessels is performed using an ultrasound scanner with contrast-specific software. We use sulfur hexafluoride lipid-type A microspheres (Lumason/SonoVue; Bracco Suisse SA), but we are investigating the performance of other Food & Drug Administration–approved microbubble agents for CEUS lymphography. Having a systematic approach to marking the skin can mitigate the hindrance of marking over ultrasound coupling gel. Another benefit of CEUS lymphography is the rapid identification of neighboring veins compatible in size and location for anastomosis. We hold regular scheduled multidisciplinary meetings for coordination of care, discussion of outcomes, quality assurance, and ongoing innovation. *(Plast Reconstr Surg Glob Open 2023; 11:e5328; doi: 10.1097/GOX.0000000000005328; Published online 12 October 2023.)*

TECHNIQUE

Successful contrast-enhanced ultrasound (CEUS) lymphography involves a team of plastic surgeons, radiologists, sonographers, and nurses. When lymphaticovenous anastomosis (LVA) surgery is indicated and scheduled, the patient is screened for history of allergic reactions to microbubble-based contrast agents, blood products, albumin, polyethylene glycol, or eggs,[1] and informed consent is obtained. A clinical order for CEUS lymphography is usually entered several weeks in advance for scheduling purposes. A dedicated radiology team ensures the availability of staff and resources to perform the procedure. Monthly multidisciplinary meetings are held for coordination of care, discussion of outcomes, quality assurance, and ongoing innovation.

Outpatient CEUS lymphography can be performed close to the day of surgery, and topical anesthetic gel or spray can be used to reduce the pain from needle injections. We generally perform CEUS lymphography intraoperatively before indocyanine green (ICG) lymphography and LVA surgery. Before the procedure, the correct patient, site, and side are confirmed. The patient's extremity is prepared with ethanol or chlorhexidine; we have found that betadine-based agents fluoresce slightly under near-infrared imaging used in ICG lymphography. The microbubble agent is prepared according to manufacturer instructions. A total of 15–20 intradermal injections of microbubbles are performed throughout

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the extremity on both the dorsal and ventral surfaces by the radiologist, one or two sites at a time. (**See figure, Supplemental Digital Content 1,** which displays potential sites of microbubble injection in the upper extremity. Intradermal injections of microbubbles are performed at multiple sites in the extremities. The stars on the upper extremity show the potential sites of microbubble injection. Analogous sites can be injected in the lower extremity. The sites of injection are guided by prior experience, patient positioning, and the duration of the procedure. Although the specific sites of injection can vary among patients, the optimal sites of injection that may demonstrate the highest yield are being investigated. **http://links.lww.com/PRSGO/C809**.)

Each injection consists of 0.3–0.4 mL of microbubble solution injected through a 25-gauge needle to create a skin wheal. We found that the 25-gauge needle provides the most effective intradermal administration without spillage while providing diagnostic images. It is important to use a Luer-Lock syringe, as pressure from the intradermal injection can dislodge the needle from a slip-tip syringe. After firmly massaging the skin wheal for 10–15 seconds, sterile ultrasound coupling gel is applied, and scanning is performed with an ML6-15 (4.5–15 MHz) transducer using the thyroid scanning model on a GE Logiq E9 scanner (General Electric Healthcare, Wauwatosa, Wisc.), scanning proximally from the injection site. The transducer is oriented perpendicular (transverse plane) to the long-axis of the arm. The B-mode and CEUS screen are displayed side by side to differentiate fascial planes that can seem echogenic on the CEUS screen. A mechanical index of 0.06-0.08 is used. Microbubble uptake by lymphatic vessels is seen as a focal echogenic dot extending from the injection site in the transverse plane and as a linear channel in the longitudinal plane (Fig. 1). An injection site could reveal no lymphatic vessels or vessels of variable length, sometimes longer than 30 cm.

Microbubble uptake by lymphatic vessels is marked on the skin to complete the procedure. As ultrasound coupling gel considerably hinders marking the skin with ink-based markers, we use an approach that minimizes the wipe-and-write frequency. As lymphatic vessels are

Takeaways

Question: How do you perform contrast-enhanced ultrasound lymphography for lymphaticovenous anastomosis surgery preoperative mapping?

Findings: The preparation, the procedure, and the documentation for performing contrast-enhanced ultrasound lymphography in the extremities are described. A systematic approach to mark the skin is needed. A video tutorial is included.

Meaning: Ultrasound with intradermal injection of microbubbles can identify lymphatic vessels and potential recipient veins for lymphaticovenous anastomosis surgery in the extremities.

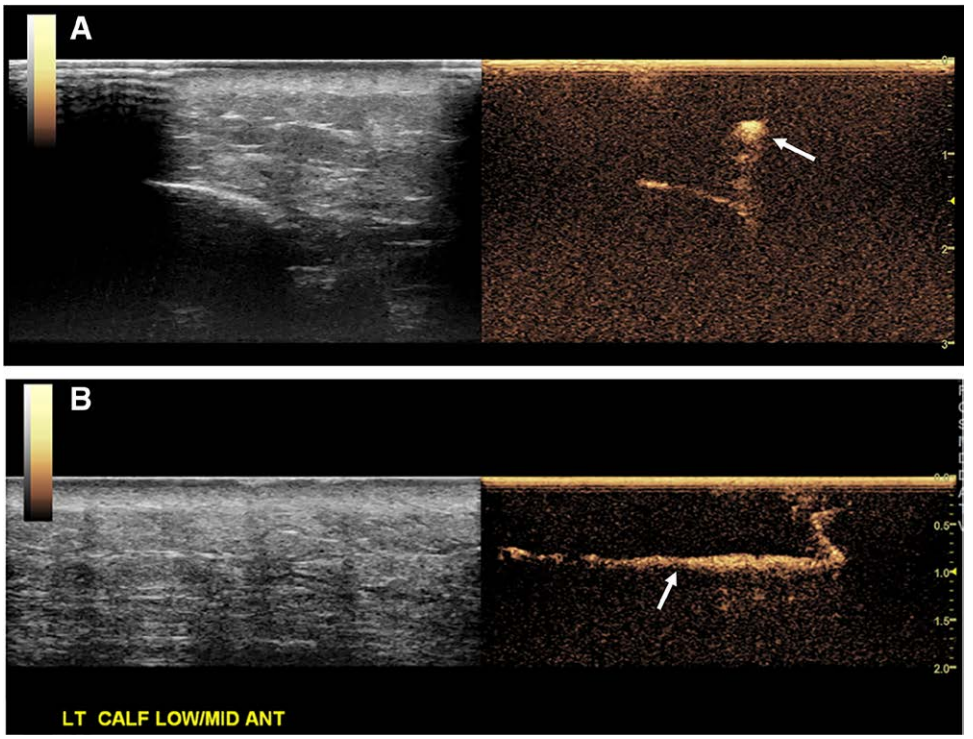

Fig. 1. Dual display of B-mode and contrast-enhanced ultrasound screens. After intradermal injection of microbubbles, their uptake by a lymphatic vessel (arrows) is shown in the transverse (A) and the longitudinal (B) planes. Sometimes, the lymphatic vessels branch into numerous smaller branches, and the most robust channels are usually marked on the skin at the discretion of the radiologist.

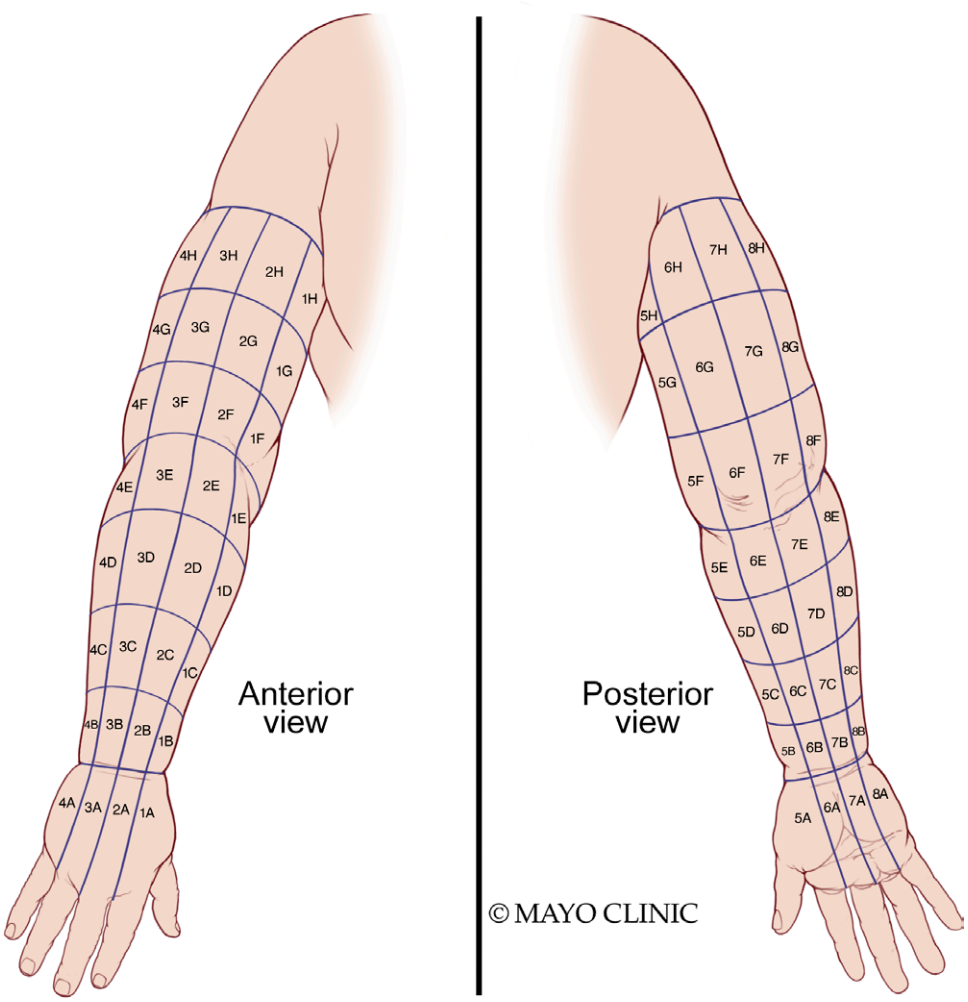

Fig. 2. Alphanumeric upper extremity grid. It is often difficult to document and communicate the exact locations of surgical incisions and anastomosis creation. An 8×8 alphanumeric grid system that encompasses the entire extremity in the surgical position may improve the communication of anastomoses created during LVA surgery. Documenting as such provides later proceduralists and surgeons a precise location of the LVA and potentially aids in follow-up evaluation of anastomosis patency. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved).

identified, the sonographer will pause every 3–5 cm, and the radiologist will make an indentation in the skin with a small blunt object, such as the end of an alcohol swab stick. After wiping off the coupling gel, indelible ink is used to connect the indented skin marks. Finally, the trajectories of the identified lymphatic channels are reimaged with an L6-24D (6–24 MHz) transducer to identify similar-sized veins within 1 cm of the lymphatic vessel. Candidate anastomotic veins are marked with indelible ink. CEUS lymphography image acquisitions include a cine clip and static images taken at each injection site. [**See Video 1 (online),** which displays a CEUS cine clip at a microbubble injection site. A video tutorial demonstrates the entire CEUS lymphography procedure.] [**See Video 2 (online),** which displays a CEUS lymphography video tutorial in the upper extremity.]

CEUS lymphography results are reviewed with the plastic surgeon. The surgeon documents the locations of the anastomoses and how the target lymphatic vessels were identified (CEUS, ICG, or both) in the operative note once the LVAs are created. An alphanumeric grid (Fig. 2) can be used to report the anastomotic locations accurately and consistently for follow-up evaluations and future providers. Photographs of the extremities are taken before lymphatic mapping, after CEUS lymphatic mapping and ICG lymphography, and immediately after surgery. The microbubble injection sites are assessed for any adverse reactions. [**See figure, Supplemental Digital Content 2,** which displays examples of marked skin after lymphatic mapping with CEUS and ICG lymphography. In our practice, CEUS lymphatic mapping is performed before ICG lymphography. Sometimes, the same lymphatic vessels are identified by both methods. CEUS lymphatic mapping may reveal lymphatic vessels not identified by ICG lymphography and vice versa. In these photographs, lymphatic channels identified by CEUS (dotted and solid blue

lines), lymphatic channels identified by ICG lymphography (green lines), and potential recipient veins (red dots and lines) are marked on the skin. **http://links.lww.com/PRSGO/C810**.]

DISCUSSION

LVA surgery, also known as lymphovenous bypass, is an effective surgery for the treatment of lymphedema in the extremities.[2,3] LVA surgery relies on identifying lymphatic vessels and their recipient veins. ICG lymphography is the reference standard for visualizing lymphatics for LVA surgery. Its limitations include the inability to detect lymphatic vessels masked by superficial lymphatic congestion, especially in later stages of lymphedema, and contraindication in patients with iodine sensitivity. Our early experience demonstrated that CEUS could identify lymphatic channels not seen by ICG lymphography, leading to additional successful anastomoses, including in patients where no targetable lymphatic vessels were visualized by ICG lymphography.[4,5] In addition to ICG lymphography, CEUS lymphography is the standard of care examination at our institution because of its clinical benefits before performing LVA surgery. As with other sonographic examinations, the result may vary by operator experience.

The safety profiles of commercially available microbubble agents are well published. In the United States, there are three FDA-approved microbubble agents: sulfur hexafluoride lipid-type A microspheres (Lumason/SonoVue), perflutren protein-type A microspheres (Optison), and perflutren lipid microspheres (Definity/Luminity). Perfluorobutane microspheres (Sonozoid), although not available in the United States, are widely used in Europe and parts of Asia, and have shown uptake by lymphatic vessels in the extremities of healthy volunteers.[6] Microbubbles are not labeled for intradermal injection by the FDA. For intravenous injections, microbubbles impose a very low risk of adverse reactions;[1] intradermal injections of microbubbles have an even lower risk profile. CEUS has been described for mapping sentinel lymph nodes in breast cancer at least since 2006 in thousands of patients in the research setting.[7] After appropriate exclusion of patients with significant comorbidities or history of allergy to ultrasound contrast agents, many studies report no adverse reaction or minor skin irritation in extremely low numbers of patients related to the intradermal injection of microbubbles.[8–10] At our institution, CEUS lymphatic mapping is performed with Lumason, primarily because of availability, prepared according to the manufacturer instructions without dilution. The utility of other microbubble agents for lymphatic mapping is currently under investigation.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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