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Contrast-enhanced ultrasound for lymphatic mapping: a comprehensive review

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Abstract

Contrast-enhanced ultrasound (CEUS) offers vascular-based real-time visualization of anatomy and pathology while maintaining the advantages of ultrasound: no radiation exposure and cost-effectiveness. This review provides an overview of the past, the current technology, and the future prospects of using CEUS to evaluate the lymphatic system. It has been demonstrated that lymphatic vessels and the lymph nodes they drain to can be successfully identified in patients who have undergone CEUS lymphography. For lymphaticovenous anastomosis (LVA) surgery planning, CEUS has shown capability in identifying target lymphatic vessels, sometimes outperforming conventional indocyanine green (ICG) fluorescent lymphography. While these preliminary findings are encouraging, further research is needed to establish standardized protocols and validate long-term outcomes. This review suggests that CEUS technology holds significant potential for advancing lymphatic imaging and improving surgical outcomes in lymphedema management.

Keywords: Contrast-enhanced ultrasound (CEUS), ultrasound, lymphatic vessels, lymph nodes, lymphedema, microsurgery, microbubbles

EVOLUTION OF ULTRASOUND TECHNOLOGY IN LYMPHATIC IMAGING: FROM CONVENTIONAL IMAGING TO CONTRAST-ENHANCED APPLICATIONS IN LYMPHATIC VISUALIZATION

Ultrasound (US) is commonly used in clinical practice, primarily due to its advantages, including real-time imaging, lack of radiation, accessibility, ease of use, and cost-effectiveness. Advancements in ultrasound technology have enhanced its capabilities, enabling high-resolution anatomical imaging and detailed blood flow analysis within regions of interest (ROI), broadening its applications across various medical fields. Ultrasound is now particularly effective for visualizing microvessels and provides superior resolution compared to current magnetic resonance imaging (MRI) and CT technologies, making it a valuable tool for lymphatic imaging[1-6]. While traditional limitations of ultrasound, such as user dependence, depth penetration, and limited contrast, still apply, its small footprint makes it especially useful for point-of-care applications, including intraoperative settings. Unlike MRI or computed tomography (CT) lymphangiography, which are better suited for imaging larger lymphatic vessels like the thoracic duct, ultrasound offers unique advantages in microvessel visualization and can be used in a more dynamic, hands-on environment.

The early 2000s marked a significant advancement in medical imaging with contrast-enhanced ultrasound (CEUS) significantly enhancing the capabilities of traditional US[1-3]. CEUS is a vascular-based imaging technique providing real-time blood flow and visualization of tissue vascularization[4].It has broad applications, including cardiac imaging for assessing structural and functional heart characteristics, liver and renal imaging for characterizing various masses, and vascular applications, including the evaluation of endografts[1,2,5,6]. Recently, CEUS has been utilized to identify sentinel lymph nodes and lymphatic mapping[7-19] CEUS offers safe complementary imaging, delivering dynamic imaging and allowing for repeat contrast administration without concerns for nephrotoxicity[4].

Overview of CEUS technology

Definition and components

CEUS is comprised of two fundamental elements: the ultrasound contrast agent (UCA) and the contrast-specific imaging technique. These elements allow a noninvasive imaging procedure for real-time blood flow and tissue vascularization assessment[1].

Development of UCAs

First-generation UCAs - including agitated saline, hydrogen peroxide, air, and carbon dioxide -could not pass through the pulmonary circulation, limiting their use to right-heart imaging. Second-generation UCAs, however, are stabilized with substances like phospholipids, albumin, or polymers and have a mean diameter of less than 8 μm, allowing these agents to pass through the pulmonary circulation and reach multiple organs. These newer UCAs also have increased stability due to lower water solubility and produce a strong harmonic response, extending their effectiveness in imaging applications[3,4]. Recent advancements in UCA development have focused on targeted contrast agents, which are engineered to bind to specific molecular markers, potentially enabling more precise diagnostic imaging and therapeutic applications.

Pharmacology of contrast agents and diffusion

Recent clinically used microbubble-based agents typically consist of particles 1-5 μm in diameter. They consist of a shell containing a fluorinated gas core, such as sulfur hexafluoride lipid-type A microspheres (Lumason®/SonoVue®), perfluoro protein-type A microspheres (Optison™), perflutren lipid microspheres (Definity®), and perfluorobutane microspheres (Sonazoid®). When exposed to ultrasound at low power (low mechanical index), these microbubbles undergo compression and rarefaction in a nonlinear fashion[1,4]. This behavior creates harmonic signals that can be separated from most background tissue signals, enabling real-time tissue subtraction imaging[1,4].

One of the key advantages of microbubble contrast agents is their status as true intravascular blood pool agents[4]. Their relatively large size restricts their diffusion into the extravascular space, making them ideal for vascular imaging. Moreover, since these agents are cleared through the respiratory system rather than the kidneys, they are suitable for patients who cannot undergo contrast-enhanced CT or MRI due to impaired renal function[4]. The phospholipid component of the microbubbles undergoes hepatic metabolism, while the gas core is eventually excreted via the pulmonary system. The use of microbubbles combined with CEUS through intradermal injection presents an innovative approach to visualizing lymphatic vessels. Although this approach is considered off-label, meaning it is being used for a purpose not specifically approved by regulatory bodies like the FDA, these microbubbles travel through lymphatic vessels when injected intradermally, allowing for real-time, high-resolution visualization of lymphatic flow patterns and vessel architecture.

Indications

The regulatory framework for CEUS has progressed significantly. In October 2014, the U.S. Food and Drug Administration (FDA) approved Lumason® (known internationally as SonoVue®) for use in adults with suboptimal echocardiograms to enhance opacification of the left ventricular chamber and improve delineation of the left ventricular endocardial border. Subsequently, in 2016, Lumason® became the first ultrasound contrast agent to receive FDA approval for liver imaging, specifically enhancing the sensitivity and specificity of ultrasonography in distinguishing between malignant and benign focal hepatic lesions.

As of November 2024, the FDA has approved the following microbubble-based ultrasound contrast agents as described in Table 1:

1. Definity® (Perflutren lipid microsphere): It is composed of octafluoropropane gas encapsulated in a lipid shell and is indicated for use in echocardiography to enhance the opacification of the left ventricular chamber and improve the delineation of the left ventricular endocardial border in adult and pediatric patients with suboptimal echocardiograms[20].

2. Optison™ (Perflutren protein-type A microspheres): This agent consists of octafluoropropane gas within a human serum albumin shell. It is approved for use in echocardiography to enhance the left ventricular chamber and improve endocardial border delineation in patients with suboptimal echocardiograms[21].

3. Lumason®/SonoVue® (Sulfur Hexafluoride Lipid-Type A Microspheres): It is also known as SonoVue® outside the United States. It contains sulfur hexafluoride gas encapsulated in a phospholipid shell. Its FDA-approved indications include:

1) Echocardiography: For left ventricular chamber opacification and endocardial border delineation in adults with suboptimal echocardiograms.

2) Liver imaging: Characterization of focal liver lesions in both adult and pediatric patients

Urinary tract imaging: Evaluation of suspected or known vesicoureteral reflux in pediatric patients via intravesical administration.

3) In Europe and Asia, SonoVue® has broader approved applications, including lymphatic imaging. When used for lymphatic visualization, intradermal injection of SonoVue® enables identification of superficial lymphatic vessels and sentinel lymph nodes, particularly beneficial in preoperative mapping for

Table 1. Characteristics and properties of FDA-approved ultrasound contrast agents (UCAs)

Name	FDA-approved	Composition	Outer shell	Mean microbubble size range (μm)	Polyethylene glycol	Iodine
Lumason (SonoVue)[22]	Yes	SF_6	Lipid-type A	1.5-2.5	Yes	No
Definity[20]	Yes	C_3F_8	Perflutren lipid microsphere	1.1-3.3	Yes	No
Definity RT[20]	Yes	C_3F_8	Perflutren lipid microsphere	1.1-3.3	No	No
Optison[21]	Yes	C_3F_8	Protein-type A	3.0-4.5	No	No
Sonazoid	No	C_4F_{10}	Phospholipid monolayer	2.0-3.06	No	No

SF_6: sulphur hexafluoride; C_3F_8: octafluoropropane; C_4F_{10}: perflubutane; RT: room temperature; FDA: Food and Drug Administration.

lymphaticovenous anastomosis (LVA) surgery in lymphedema patients[22].

4. Sonazoid® (Perfluorobutane Microspheres): While not FDA-approved in the United States, Sonazoid® is widely used in Europe and Asia, particularly for liver imaging. It has shown unique capabilities in lymphatic imaging due to its high affinity for reticuloendothelial cells and prolonged retention in lymph nodes. Studies have reported 100% sentinel lymph node detection rates in early-stage breast cancer applications. Its extended imaging window has proven particularly valuable for intraoperative sentinel lymph node biopsy procedures[4,23].

These agents enhance ultrasound imaging by increasing blood echogenicity, thereby improving the visualization of cardiac structures and blood flow. It is important to note that while these microbubble contrast agents are FDA-approved for specific indications, their use in other applications should be based on clinical judgment and current medical guidelines[24,25].

Complications

The safety profiles of commercially available microbubble agents are well-published[2,4,5,8,25]. 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 (Sonazoid®), 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[9].

In 2007, the FDA mandated a black box warning - their strictest labeling requirement - for all approved UCAs in response to reports of serious cardiopulmonary reactions, including fatalities. However, subsequent investigation revealed that many of these adverse events were not definitively attributed to UCAs and may have been related to underlying medical conditions or other medications. Cumulative scientific literature continues to demonstrate a favorable safety profile for these agents, leading to an ongoing citizen petition from ultrasound societies for the removal of these boxed warnings[26].

While microbubbles are not FDA-approved for intradermal injection, they impose a very low risk of adverse reactions for intravenous injections, and intradermal injections of microbubbles may have an even lower risk profile. The most common adverse reactions using Definity® reported in > 0.5% of subjects are headache, back/renal pain, flushing, nausea, chest pain, injection site reactions, and dizziness. Adverse events reported in < 0.5% of subjects who received Optison™ included arthralgia, back pain, body or muscle

aches, induration, urticaria, dry mouth, eosinophilia, palpitations, paresthesia, photophobia, premature ventricular contraction, pruritus, rash, irritableness, hypersensitivity, tinnitus, tremor, visual blurring, wheezing, oxygen saturation decline due to coughing, discoloration at the Heplock site, and burning sensation in the eyes[1,4-6,8].

A study published in 2023 used four stress echocardiography databases, which included 26,539 Definity® and 11,579 Lumason® administrations; isolated back pain or headache occurred more frequently with Definity® (0.49% *vs.* 0.04%, $P < 0.0001$). However, these symptoms were less common with Definity® infusion than with bolus administration (0.08% *vs.* 0.53%, $P = 0.007$). Across all sites, there were 201,834 Definity and 84,943 Lumason® administrations. While severe and critical adverse drug reactions remain rare, they were observed more frequently with Lumason®, and their incidence has increased in recent years[5].

Our experience

At our institution, we use Lumason® (Bracco, Suisse) microbubble suspension for CEUS. We administer intradermal injections at the interdigital web spaces, proceeding distally before moving proximally in a circumferential pattern. After each injection, the site is gently massaged for 5-15 s. Ultrasound imaging is then performed using an ML6-15 transducer (4.5-15 MHz). Supplementary Videos 1-3 demonstrate CEUS lymphography of the left lower extremity. The sequence shows intradermal injections of microbubbles, which effectively highlight lymphatic vessels. These enhanced vessels represent potential lymphatic channels that could be valuable for diagnostic assessment or surgical planning.

CEUS IN LYMPHATIC IMAGING

Sentinel lymph node detection

The lymphatic system's ability to uptake intradermally injected microbubbles was first demonstrated in a swine model of melanoma[27]. CEUS with microbubbles has shown potential in the identification of sentinel lymph nodes (SLN), as demonstrated in Table 2. In Malone *et al.*'s study, microbubbles injected peritumorally were taken up by the lymphatic channels, allowing for accurate identification of SLN via ultrasonography in 90% of cases[2]. Subsequent studies have shown promising results in SLN detection for breast cancer. Sever *et al.* demonstrated that microbubble contrast SonoVue® (Bracco Imaging, Milan, Italy) readily enters breast lymphatic channels and can be visualized clearly in draining SLN by CEUS, successfully identifying SLN in 89% of patients[11]. In a subsequent study, they identified SLN in 71 (89%) of the 80 patients using a microbubble contrast SonoVue® (Bracco SpA, Milan, Italy)[10]. *Li et al.*, using SonoVue® (Bracco SpA, Milan, Italy), demonstrated the sensitivity, specificity, positive predictive value, and negative predictive value of SLN-CEUS for the diagnosis of SLN being 96.82%, 91.91%, 87.54%, and 98.01%, respectively[28]. Similarly, Xie et al. used SonoVue® (Bracco SpA, Milan, Italy) in patients with early breast cancer for SNL identification[13]. The sensitivity of predicting SLN metastases by CEUS enhancing pattern was 81.8 %, the specificity was 86.2%, and the positive and negative predictive values were 75.0 and 90.3 %, respectively[13]. Furthermore, Cui *et al.* used SonoVue® (Bracco SpA, Milan, Italy) and successfully identified sentinel lymph nodes in 96.3% of patients, showing it to be a highly effective technique[7]. The study found that there was a 100% concordance between the CEUS-guided SLN and those identified by the blue dye method, indicating that CEUS could reliably match the results from traditional sentinel lymph node biopsy (SLNB)[7]. In contrast, Hao *et al.* demonstrated that CEUS with percutaneous injection of Sonazoid can successfully identify SLN with a rate of 100% in early breast cancer patients, higher than 95.59% of blue dye[9]. It also noted that Sonazoid has a high affinity with reticuloendothelial cells, increasing the imaging time of SLNs and facilitating biopsy intraoperatively better than SonoVue® as a lymphatic tracer[9].

Table 2. Studies evaluating CEUS applications in the identification of sentinel lymph nodes (SLNs).

Article	Year	Sample size	Characterization	Adverse events	Microbubbles
Sever *et al.*[11]	2009	54	Identified sentinel lymph nodes (SLNs) in 89% of patients (48/54)	Burning sensation, superficial bruising	SonoVue (Bracco SpA, Milan, Italy)
Sever *et al.*[10]	2011	80	Preoperatively localized SLNs in 89% of 80 patients	Burning sensation, superficial bruising	SonoVue (Bracco SpA, Milan, Italy)
Xie *et al.*[13]	2015	100	Demonstrated feasibility of SLN tracing in 100 patients, with a 97.03% identification rate (98/101)	Not reported	SonoVue (Bracco SpA, Milan, Italy)
Hao *et al.*[9]	2020	68	Achieved 100% SLN identification (68/68)	No adverse events noted	Sonazoid (GE Healthcare, Oslo, Norway
Li *et al.*[28]	2019	453	Successfully detected enhanced lymphatic channels in 445 of 453 patients, resulting in a 98.2% identification rate. SLN-CEUS identified a total of 765 sentinel lymph nodes, averaging 1.72 per patient	No adverse events noted	SonoVue (Bracco SpA, Milan, Italy)
Cui *et al.*[7]	2023	109	CEUS successfully identified sentinel lymph nodes in 96.3% of patients, showing it to be a highly effective technique. The study found that there was a 100% concordance between the CEUS-guided SLNs and those identified by the blue dye method, indicating that CEUS could reliably match the results from traditional SLNB	No adverse events noted	SonoVue (Bracco SpA, Milan, Italy)

CEUS: contrast-enhanced ultrasound; SLNB: sentinel lymph node biopsy.

Preoperative mapping for lymphatic surgery

CEUS has shown potential in preoperative mapping of lymphatic vessels for LVA surgery, as demonstrated in Table 3. While indocyanine green (ICG) fluorescent lymphography is the reference standard for visualizing lymphatics for LVA surgery, recent studies have demonstrated that CEUS with intradermal injections of microbubbles can effectively identify more target lymphatic vessels in the extremities[14-17].

For instance, in a study exploring the capabilities of CEUS for preoperative identification of lymphatic candidates lymphedema patients, Jang *et al.*[16] demonstrated that lymph vessels for LVA were successfully mapped in 33% of patients [8 of 24; 95% confidence interval (CI): 16-55] using both CEUS with intradermal microbubble injections (Lumason®; Bracco Suisse) and ICG fluorescent lymphography. CEUS alone identified lymphatics for LVA in 58% of patients (14 of 24; 95%CI: 37-78), while ICG fluorescent lymphography alone identified lymphatics for LVA in 8% of cases (2 of 24; 95%CI: 1-27)[16]. Similarly, Lahtinen *et al.* studied 30 healthy volunteers, and CEUS imaging of superficial lymphatic vessels was successful in 59 of 60 upper limbs (98.3%)[17].

Further, Xiahou *et al.* established that CEUS with SonoVue® can be a viable alternative to ICG lymphatic imaging, showing superior visualization and localization of superficial lymphatic vessels[14]. In a study of 20 patients, the average diameter of lymphatic vessels identified in the CEUS group was significantly greater than that in the ICG group (0.78 ± 0.06 *vs.* 0.52 ± 0.05mm; $p < 0.001$)[14]. Moreover, one study used SonoVue® (Bracco SpA, Milan, Italy) and the CEUS technique for preoperative localization for LVAs in a case of lymphocutaneous fistula, demonstrating that microbubbles and CEUS can identify

Table 3. Studies evaluating CEUS applications in lymphatic imaging and surgery

Article	Year	Sample size	Characterization	Adverse events	Microbubbles
Jang *et al.*[16]	2022	11	A total of 35 explorations were conducted (median of three per patient, range 2-4), leading to the creation of 24 LVAs (median of three per patient, range 0-4). Among the anastomoses, 33% (8/24) were mapped using both CEUS and ICG, 58% (14/24) with CEUS only, and 8% (2/24) with ICG only	No adverse events noted	(Lumason, Bracco Suisse)
Lahtinen *et al.*[17]	2022	30	Successfully imaged lymphatic vessels in 98.3% of 30 cases.	No adverse events noted	Sonazoid (GE Healthcare, Oslo, Norway
Zhu *et al.*[15]	2023	1	The study demonstrated the effectiveness of microbubbles in identifying deep lymph vessels, with successful treatment of severe lymphorrhea through lymphatic vessel anastomosis (LVA), which addresses the underlying pathophysiology and restores lymphatic flow	Not reported	Not mentioned
Xiahou *et al.*[14]	2024	20	The CEUS group had a significantly greater average diameter of lymphatic vessels (0.78 ± 0.06 mm *vs.* 0.52 ± 0.05 mm, $P < 0.001$), a shorter operation duration (4.47 ± 0.37 min *vs.* 6.70 ± 0.45 min, $P < 0.001$), and fewer anastomosed lymphatic vessels (5.0 *vs.* 9.5, $P < 0.001$	Not reported	SonoVue freeze-dried powder (Bracco),
Jang *et al.*[19]	2024	9	Lymphatic vessels were visualized in eight of nine upper extremities, with a 100% success rate for Lumason (3/3) and Optison (3/3), and a 67% rate for Definity (2/3). Overall, lymphatic vessels were identified in 57% (36/63) of the injections in the study	No adverse events noted	Lumason, Optison and Definity

deep lymphatic vessels and better evaluate their function[15].

Several CEUS agents, including Lumason® and SonoVue®, have been studied for lymphatic imaging[15-19]. Jang *et al.* detailed the technique for using intradermal injection of micro-bubbles to identify lymphatic vessels and potential recipient veins for LVA surgery in the extremities[18]. Building on this foundation, a recent study by Jang *et al.* demonstrated the feasibility of two other FDA-approved intravenous microbubble agents for visualizing lymphatic vessels in the upper extremity: perflutren lipid microspheres (Definity® /Luminity, Lantheus) and perfluoro protein-type A microspheres (Optison™, GE HealthCare). The study demonstrated lymphatic vessel visualization using either Definity® or Optison™ in 57% (36 of 63) of the injections.[19] Broadening the range of available microbubble agents for CEUS lymphography could improve accessibility to the procedure and provide potentially safer alternatives[19].

In terms of safety, Rames *et al.* reported a minor adverse effect in one of their 51 patients, who developed site-specific wheals around the forearm and hand after repeat intradermal contrast exposure[29]. Their protocol for CEUS lymphography uses Lumason® sulfur hexafluoride lipid-type A microspheres as a contrast agent to identify potential sites for LVA[29].

CONCLUSION

CEUS has significantly advanced the scope of ultrasound, further expanding its role in clinical practice. CEUS offers real-time, radiation-free imaging with the potential for repeat dosing and infrequent adverse reactions, providing clinicians with new opportunities for investigation.

This review explores the emerging role of microbubble technology, which has been well established in applications such as echocardiography and renal and hepatic imaging, and its expanding utility in lymphatic interventions. In recent years, microbubble-enhanced visualization has shown promise in LVA for lymphedema treatment, enabling improved lymphatic vessel identification during surgery, allowing for more efficient and precise dissection and anastomosis, which is critical for optimizing outcomes in lymphedema management. Additionally, CEUS has demonstrated particular value in SLN identification and mapping, representing a crucial advancement in oncologic staging and surgical planning.

Based on the preliminary findings, microbubble-assisted techniques are valuable in preoperative planning for LVA, potentially improving patient outcomes through enhanced visualization and mapping. However, while early results are promising, further large-scale studies are necessary to validate these benefits and establish standardized clinical protocols. As research progresses and new applications are explored, CEUS is poised to expand its role in diagnostics and therapeutics across diverse medical specialties, particularly in sentinel node detection and lymphatic mapping. The ongoing development of CEUS technology and contrast agents will continue to refine and broaden its capabilities, solidifying CEUS as a vital component of medical imaging.

DECLARATIONS

Authors' contributions

Study design, data collection, manuscript writing, and revision: Bustos S
Data collection, manuscript writing, and revision: Rios-Sanchez M
Data collection, manuscript writing, and revision: González-Barreto E
Manuscript writing and revision: Hesley G, Lee C, Fahradyan V, Tran N

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Not applicable.

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