History of contrast enhanced ultrasound (CEUS)

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Abstract

The 50th year of the European Federation of Societies in Ultrasound in Medicine and Biology (EFSUMB) has been celebrated 2022 publishing articles on the history of US. Contrast enhanced ultrasound (CEUS) allows to visualize blood flow and tissue perfusion. CEUS has proven to be safe without risk of nephrotoxicity. The availability of a contrast agent (tracer) for ultrasound imaging allows for the first time a dynamic assessment of tissue perfusion (blood flow and wash-in/wash-out pattern) which is an essential part for the detection and characterisation of pathological tissue and abnormal organ function. It was an outstanding achievement of academic centers in close cooperation with EFSUMB to investigate and validate the clinical potential of this new technology for the diagnosis and monitoring of various diseases and to develop clinical guidelines based on an in-depth assessment of the existing scientific publications. An important part of the implementation of CEUS in clinical practice was the development of contrast-specific imaging modes on the ultrasound scanners (in close cooperation with the machine manufacturers), the optimization of the machine setups for contrast imaging and the education provided to clinical users in form of workshops, webinars, textbooks and scientific congresses.

Keywords: Contrast enhanced ultrasound; guidelines; contrast agent

Introduction

The 50th year of the European Federation of Societies in Ultrasound in Medicine and Biology (EFSUMB) has been celebrated 2022 publishing articles on the history of ultrasound (US) [1-4]. Contrast enhanced ultrasound (CEUS) allows to visualize blood flow and tissue perfusion. CEUS has proven to be safe without risk of and in many cases can replace other imaging examinations using ionizing radiation. The rapid elimination of the active compound of ultrasound contrast agents by exhalation allows repeated examinations in short intervals, not possible with CT and MRI examinations. The aim of the current article is to summarize the history of CEUS and the characteristics of the different ultrasound contrast agents commercially available.

Development of microbubble contrast

The first reported clinical use of echo contrast was performed by Joyner, who observed contrast enhancement during M-mode studies of the mitral valve after rapid injection of saline solution into the left ventricular outflow tract. The contrast effect is based on microbub-
bles created at the catheter tip during rapid injection of fluids [5]. Gramiak and Shah published the first report on contrast enhancement after injection of indocyanine green solution during examinations of the aortic root, caused by tiny air bubbles contained in the injected fluid [6].

In the following years, various solutions including saline solution, Renografin-76, dextrose solution and sorbitol solution were used after manual agitation or sonication. The problem of the destruction of larger microbubbles in the pulmonary circulation was circumvented by Japanese authors in the late 1980s and 1990s by using microbubbles produced by forming a solution of glucose and albumin with CO$_2$ to be infused directly intra-arterially via the coeliac trunk into the hepatic and pancreatic circulation (“sonographic angiography”). This made it possible for the first time to describe typical enhancement patterns of benign and malignant hepatic and pancreatic tumors [7-10]. Feinstein discovered that sonication of an albumin solution results in bubbles of smaller size and prolonged persistence [11], which is essential to allow passage of the pulmonary circulation and enhancement of the left heart cavity after intravenous administration [2]. Hand agitated saline is still frequently used today in clinical practice for detection of right-to-left cardiac shunts, although the injected gas volume and bubble size is difficult to control, and this technique has never been approved by a regulatory authority.

Size of microbubbles

Ultrasound Contrast agents (UCA) consist of tiny microbubbles, which create an acoustic interface to the surrounding blood. The size of the microbubbles is restricted by two factors. First, the size needs to be small enough to allow a free passage of microbubbles through the capillary bed. Usually, an upper limit of 10 µm should be achieved based on the physicochemical properties of the suspension. Secondly, the size of the microbubbles should provide a resonance frequency in the range of the ultrasound frequencies used for imaging, allowing to induce an oscillation of the microbubbles in the ultrasound field, creating a specific signal to create the contrast-specific images. Therefore, the intended microbubble size is between 1 and 10 µm. Although some formulations of mono-sized microbubbles were developed in research labs (providing the best signal at a specific frequency) formulations with a distribution of different microbubble sizes are preferred to allow the use with transducers of different frequencies used in clinical practice.

Contrast enhanced ultrasound (CEUS)

The term CEUS was introduced as an acronym by members of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) [12]. CEUS was initially intended to enhance Doppler signals but thereafter, contrast specific techniques were developed [2]. Important multicenter CEUS studies include the SonoVue® approval study in Europe [13], the DEGUM (Deutsche Gesellschaft für Ultraschall in der Medizin) trial to show the value of CEUS for focal liver lesion characterization in a practical clinical setting evaluating 1349 patients with focal liver lesions [14]. Sub-analyses have been published as well [15-18]. Similar studies have been published by French [19] and Romanian authors of the respective societies [20].

Commercial development of ultrasound contrast agents

After the initial experience with “self-made” hand-agitated or sonicated bubble suspensions, several pharmaceutical companies started the development of commercial ultrasound contrast agents. It became clear, that for broader clinical use the bubbles had to be standardized in size and stabilized for a longer period in vivo [2] (Table I).

The first agent to enter commercial development was Echovist® (Schering AG Berlin, Germany) [2]. In the United States, Albunex® was developed by Molecular Biosystems Inc. San Diego, USA, based on the sonication technique introduced by Feinstein.

Meanwhile, Schering in Germany, developed an improved formulation of their galactose-based microbubbles called Levovist®, where the air microbubbles were stabilized by a coating of palmitic acid. Using Levovist®, left ventricular enhancement could be obtained in all patients with normal pulmonary artery pressure, while in patients with pulmonary hypertension, the enhancement was only minimal or absent [21]. In the peripheral circulation, Levovist® enhanced the intensity of Doppler signals, allowing detection of Doppler signals even in small vessels of the parenchymal organs [22]. Levovist®

Fig 1. Stimulated acoustic emission (SAE) using Levovist in a dog before 1995.
obtained regulatory approval in 1995 in Europe. It was detected by chance that Levovist® also shows some enhancement in the liver in the post-vascular phase (after clearance from the blood stream), owing to an uptake by phagocytosing cells (Kupffer cells in the liver sinusoids) [23-26]. This was helpful in discriminating hepatic from non-hepatic tissue [25,27] (fig 1-3).

Although these first-generation contrast agents with air-based microbubbles were promising, they had major limitations in stability and enhancement duration. Air is highly diffusible with a high solubility in blood, resulting in a rapid escape from the bubbles into the blood circulation. Therefore, second generation microbubbles were developed, containing high molecular weight lipophilic gases with low solubility in the bloodstream.

The first second generation agent on the market was Optison®, which obtained regulatory approval in USA in 1998. Optison® was an improved formulation of Albunex®, with perfluorin gas instead of air.

The next second generation agent entering the market was SonoVue®, developed by Bracco. SonoVue® obtained regulatory approval in Europe in 2001 for use in echocardiography (left ventricular enhancement), macrovascular imaging (cerebral, carotid and peripheral arteries) and microvascular imaging (characterization of liver and breast lesions) (fig 4). In the USA, this agent is marketed under the brand name Lumason®. SonoVue® consists of microbubbles with a very flexible phospholipid shell, with a highly echogenic response over a broad range of frequencies from 1-10 MHz [28]. SonoVue® has also obtained regulatory approval for the use in children for liver imaging (USA) and detection of vesico-ureteral reflux in children (USA, Europe, China) [29,30]. The use of SonoVue has been reflected by EFSUMB and WFUMB guidelines and position papers in hepatic and non-hepatic indications [12,31-38]. Data on the use of SonoVue® in pediatric patients are collected in the EF-SUMB pediatric registry [39].

Another agent with an outer phospholipid shell is Definity®, which was developed by ImaRx Pharmaceutical Corp in Tucson, USA and subsequently acquired by DuPont Merck, and Bristol-Myers Squibb Medical Imaging which today operates as Lantheus Medical Imaging.

### Table I. Ultrasound contrast agents with regulatory approval for human use.

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>Gas</th>
<th>Shell</th>
<th>Approved indications</th>
<th>Distribution compartments</th>
<th>First approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echovist®</td>
<td>Schering (Bayer)</td>
<td>Air</td>
<td>Galactose</td>
<td>Cardio, Venous vessels, Fallopian tubes</td>
<td>Right Heart</td>
<td>1991</td>
</tr>
<tr>
<td>Albunex®</td>
<td>Molecular Biosystems</td>
<td>Air</td>
<td>Galactose</td>
<td>Cardio</td>
<td>Blood Pool</td>
<td>1993</td>
</tr>
<tr>
<td>Levovist®</td>
<td>Schering (Bayer)</td>
<td>Air</td>
<td>Galactose + Lipid</td>
<td>Cardio, Vascular, Cancer vascularisation, Urinary tract</td>
<td>Blood Pool RES Uptake</td>
<td>1995</td>
</tr>
<tr>
<td>SonoVue®/Lumason®</td>
<td>Bracco</td>
<td>Sulphurhexafluorid</td>
<td>Phospholipids</td>
<td>Cardio, Vascular, Breast Urinary tract</td>
<td>Blood Pool</td>
<td>2001</td>
</tr>
<tr>
<td>Definity®/Luminty®</td>
<td>Lantheus Medical Imaging</td>
<td>Perfluorpropane</td>
<td>Phospholipids</td>
<td>Cardio</td>
<td>Blood Pool</td>
<td>2001</td>
</tr>
<tr>
<td>Imagent®</td>
<td>Alliance Pharmaceutical</td>
<td>Perfluorhexane</td>
<td>Phospholipids</td>
<td>Cardio</td>
<td>Blood Pool</td>
<td>2002</td>
</tr>
</tbody>
</table>

Fig 2. B-mode (a) and stimulated acoustic emission (SAE, b) using Levovist of metastases.
period of attenuation if it is administered diluted in saline as infusion [40].

The most recent agent to receive regulatory approval for human use is Sonazoid®, developed by Nycomed in Oslo, Norway and then acquired by GE Healthcare. Sonazoid® has a more rigid shell of hydrogenated egg phosphatidylserine embedded in an amorphous sucrose structure, requiring a higher insonation power to produce non-linear signals [41]. Sonazoid® is also taken up by cells of the reticulo-endothelial system (RES) in the liver (also known as the Kupffer phase) [42]. Sonazoid® was approved in 2006 in Japan for assessment of focal liver lesions, where it was marketed by Daiichi-Sankyo. It has also obtained approval for assessment of focal breast lesions. In Norway and South Korea, Sonazoid® was also granted regulatory approval and is marketed by GE Healthcare (fig 5).

There have been several other contrast agents which were in clinical development e.g., SHU 563A (Sonovist; Schering) is a third generation UCA that is phagocytosed by the cells of the reticuloendothelial system (RES) in the liver and spleen. Further commercial agents were in development (Quantison®, Myomap®, AI700, CardioSphere®, BR14 and PESDA in between others) but never obtained regulatory approval for human use (fig 6). One of these agents, Echogen® managed to get regulatory approval but was subsequently withdrawn by the manufacturer owing to side effects [43-45].

**Contrast specific ultrasound techniques**

CEUS is highly dependent on the interaction of microbubbles with the ultrasound wave. In fact, the evolution of CEUS is closely correlated with the development of contrast-specific imaging techniques on ultrasound.
Scanners. Even in the early days, researchers tried to delineate contrast enhancement within parenchymal tissue rather than utilize it as a Doppler enhancer, e.g. for assessment of myocardial perfusion [46]. Two major problems however had to be solved: 1) the attenuation caused by high bubble concentration in the cardiac cavities and 2) the overlay of tissue signals from the cardiac wall. Shapiro therefore used an intracoronary administration to avoid cavity contrast and achieve a high local microbubble concentration. In the next phase, Doppler techniques were used to obtain the selective signals from microbubbles distinguishing it from the overlying fundamental echoes from tissue. This cancellation of tissue signals was based on velocity, so that only flowing microbubbles (e.g. in the heart cavity or large vessels) could be displayed. Tissue movement artifacts are limiting the display of small vessel blood flow. Contrast ultrasound at this time had been introduced purely to enhance or rescue Doppler studies [47].

It was fortuitous during development that it was discovered that Doppler signals could also be obtained from stationary microbubbles, when they were destroyed (“burst”) by insonation at higher power. The disappearance of the bubble signal from one frame to another was interpreted by the color Doppler autocorrelation algorithm as movement of the bubble. Thus these contrast signal existed only for a very short moment (like a “flash”, or “scintillation”) and this technique was termed stimulated acoustic emission (SAE) [48]. This technique was limited in that there was only one pass that could be used for diagnosis rather than the various phases of enhancement that is currently the norm to characterize focal lesions.

The final goal to display the microbubble signals and allow separation from tissue signals continuously, came with insonation at significantly reduced power (low-MI imaging) minimizing the destruction of microbubbles in the sound field. This causes contraction and expansion of the microbubbles leading to production of harmonic signals separate from the fundamental tissue signals.

The separation of the microbubble from tissue signals was challenging, but finally achieved by the introduction of frequency filtering and later pulse-summation techniques, taking benefit from the characteristic acoustic response of microbubbles oscillating in the ultrasound field (non-linear signals with harmonic frequency components) [49]. The capability of low MI imaging allowed real-time imaging of contrast wash-in and wash-out within parenchymal tissue. Today most ultrasound manufacturers have a contrast mode available for clinical use and these are typically based on the summation of pulses with inverted phase (phase inversion, phase modulation), modified amplitude (amplitude modulation, power modulation) or a combination of both [2]. Additional contrast enhancing modes have been used as well using manufacturer specific terminology, e.g., vascular recognition imaging mode (VRI) (fig 7).

**Dynamic contrast enhanced ultrasound**

Dynamic Contrast Enhanced Ultrasound (DCE-US) is a technique to quantify tissue perfusion down to the capillary level based on phase-specific enhancement after injection of microbubble contrast agents for diagnostic ultrasound. In addition, the quantitative analysis of the dynamics of contrast enhancement overcomes its subjective comparison between normal and abnormal pa-
renchyma, or between a focal lesion and the surrounding tissue [33,37,50]. In 1998, Wei et al [51] were the first to introduce the method of disruption-replenishment and the development of the mono-exponential model. Krix et al [52-54] used a similar approach however, the modified formulas were no longer based on empiric assumptions and based on a multi-vessel model and it incorporated differences in the acoustic field properties when using high and low-MI imaging. This model was found to be at least equivalent to the mono-exponential model, but it is nevertheless much less used. An improvement to Wei’s model was Arditi’s model [55], which later on was further improved by Hudson et al [56]. This model has 3 components that were not present in Wei’s model: it accounts for tissue perfusion through realistic microvascular geometry (Lognormal perfusion model), it considers the ultrasound field properties of the destruction beam, and also considers the ultrasound imaging field. With the Arditi-Hudson model, it is possible to calculate the relative mean flow rate [50].

**Assessment of tumour response**

Neoangiogenesis is essential for tumour growth and novel antiangiogenesis treatments have become an important facet of oncology therapy. Because microbubbles are pure microcirculation markers DCE-US has become an important tool in the quantitation of antiangiogenic tumour response [50]. Traditionally tumour response has been assessed by size (Response Evaluation Criteria in solid Tumours RECIST). However, antiangiogenetic therapies may not result in a decrease in tumour size until late and RECIST cannot identify non-responders early, unlike DCE-US, which would allow a prompt change in therapy that was not efficacious [57]. Two methods can be employed using DCE-US:

- Following a bolus injection of an ultrasound contrast agent single plane scanning is performed during the phase of enhancement. Using a region of interest (ROI) a time intensity curve can be recoded from which many parameters of wash-in and wash out can be derived. The majority of studies use this technique.
- Using a constant infusion of microbubbles initially scanned at low MI using a ROI, a few frames of high MI pulses are given to destroy the bubbles. Following this low MI scanning is performed and reperfusion of the ROI is measured. A reperfusion curve is measured [51]. Some of the indices measured include peak intensity (PI), area under the curve (AUC) which corresponds to blood volume, time to peak intensity (TPI) and slope of wash-in (SWI) curve both corresponding to blood flow. Studies on tumours have shown that the area under curve on the TIC corresponds with tumour vascularity and that this reduces before the tumour shrinks in those responding to antiangiogenesis drugs [58]. Thus, the vascular response precedes the decrease in volume that forms the conventional RECIST criteria for response and this allows treatment to be tailored to the vascular response earlier than when using conventional criteria [59].

**Contrast enhanced endoscopic ultrasound**

Similar to the term CEUS, contrast enhanced endoscopic ultrasound (CE-EUS) is generally used as an accepted acronym for all contrast-enhanced techniques using endoscopic ultrasound, independent of the specific physical principles. Similar to conventional transcutaneous ultrasound, CE-EUS can be performed with either a high or low mechanical index (MI). Therefore, the acronyms for endoscopic contrast use were CEHMI (contrast enhanced high MI EUS) first used in 1997 [60] and CEL-MI (contrast enhanced low MI EUS) in 2003 [61]. An alternative terminology differentiates between contrast-enhanced harmonic EUS (CEH-EUS) for the application of low MI technologies and contrast-enhanced Doppler EUS (CED-EUS) for the endosonographic amplification of color Doppler signals while maintaining the high mechanical indices. The terminology of different manufacturers techniques have been recently summarized [62]. CE-EUS is primarily used for the differential diagnosis of focal pancreatic solid and cystic lesions, the differentiation between gastrointestinal stromal tumors and benign gastrointestinal subepithelial lesions [31,32,36,63,64], to guide local ablative treatment and determine treatment
response [65-69]. The ability to distinguish very accurately between ductal adenocarcinomas and alternative tumors, some of which require only follow-up or non-radical surgery, even in very small pancreatic tumors with CE-EUS was an advance of high prognostic and therapeutic significance [70-72]. Of similar clinical relevance is the possibility of risk stratification of cystic pancreatic lesions by non-invasive differentiation between tiny true neoplastic nodular proliferations and nodular mucin plugs using CE-EUS [73,74].

Three dimensional (3D) CEUS

3D CEUS was first described and clinically applied in 2001/2002 [75] followed by CE EUS 3D techniques in 2010/2011 [76,77]. While this technique has been around for many years it has yet to find its true clinical utility and advantage over 2D CEUS (fig 8, fig 9). One potential application is the quantitative evaluation of tumor response which has shown some promise in research studies [37].

Contrast enhanced extravascular and intracavitary ultrasound

Extravascular (intracavitary) CEUS (EV-CEUS) using e.g., saline has been used for a long time for the imaging of physiological and non-physiological body cavities [e.g., peritoneal cavity, pleural cavity, biliary tract, gastrointestinal tract, urinary tract, hystero-salpingo-sonography (CE-HyCoSy), salivary gland duct imaging etc, and pathological cavities including fistula tract imaging and abscess delineation as well as many other applications [65,66,78-83]. In this article we refer to commercially available contrast agents (UCA). It is important to note, that the ultrasound contrast agent has to be significantly diluted. In intravenous administration, the contrast dose administered is distributed throughout the whole blood volume (about 5 litres in adults) after mixing within the cardiac chambers. For intracavitary use, the administered dose is distributed only within the cavity. Therefore a very dilute amount of the contrast agent (about 1:500) in 0.9% saline solution has to be used to avoid shadowing. The UCA is administered through a needle or catheter into the cavity. However, UCAs can also be given orally or as an enema for imaging the upper and lower gastrointestinal tract [33,36,65,66,78-84], or as a negative ultrasound contrast agents given orally to neutralize air artefacts [85]. Most studies have been performed using SonoVue® (fig 10, fig 11). Voiding vesicoureteral reflux sonography has also been introduced over a decade ago [84]. The shape of the urinary tract and a potential backflow of urine during micturition can be assessed. Percutaneous nephrostomy [86], biliary tract imaging via percutaneous transhepatic cholangiography and drainage (PTCD) [87-90] or via endoscopic retrograde cholangiography (ERCP) [91,92], as well as an oral CEUS swallow for imaging Zenker’s diverticulum
have been described and of proven utility in select case studies.

Safety

UCAs are safe with a very low incidence of side effects. As there are no cardio-, hepato, or nephro-toxic effects, it is not necessary to perform laboratory checks to assess liver, renal or thyroid function before administration [33]. The incidence of severe adverse events is lower than with current X-ray contrast agents and is comparable to those encountered with MR contrast agents. Life-threatening anaphylactic reactions in abdominal applications have been reported with a rate of 0.001%, with no death in a series of >23,000 abdominal patients [94]. Further studies have reproduced this very low adverse event rate [95,96]. Nonetheless, investigators should be trained in resuscitation and have the appropriate facilities available to react in cases of adverse events [33]. In particular, each center should be prepared with a crash trolley and the ability to treat anaphylactic shock [33]. Prolonged heterogenous liver enhancement [97] and other harmless contrast agent dependent artefacts have been described in detail [98,99].

CEUS history reflected in guidelines and important statements

• The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) published 2004 the first guidelines on the use of CEUS [12].
• The primarily pure CEUS liver guidelines were expanded in 2008 to include non-liver indications [38].
• In 2012 CEUS, non-hepatic guidelines were published by WFUMB - EFSUMB [36] and more recently updated in 2017 [31,32].

Fig 10. Combined contrast enhanced ultrasound using intravenous and intracavitary endoscopic ultrasound techniques (Sonovue) in a patient with peripancreatic pseudocyst drainage using microbubble tracing imaging (left side). The cavity and distally splenic artery are indicated.

Fig 11. Intracavitary biliary drainage. The UDCA fills a biliary liver abscess via the pigtail drainage and empties into the small intestine via the biliodigestive anastomosis.

• In 2013 pure CEUS liver guidelines were published by EFSUMB and the World Federation for Ultrasound in Medicine and Biology (WFUMB) and were updated in 2020 [34,35].
• How to perform contrast enhanced ultrasound [33,100-102].
• Dynamic CEUS has been introduced describing the technique of time intensity curve analysis and its potential utility [37,50].
• The use of standardized terminology including liver imaging reporting and data system (LI-RADS) [103-108].
• Asian Federation of Societies for Ultrasound in Medicine and Biology (AFSUMB) guidelines on contrast enhanced endoscopic ultrasound (EUS) [109].
• CEUS does not influence elastography evaluation (single center study) [110].
• UCAs are safe with a very low incidence of side effects [94-96].
• Cardiac contrast enhanced ultrasound guidelines (cCEUS) have been published [111,112]. The history of cardiac ultrasound has been recently summarized [4] and the history cCEUS will be described in more detail elsewhere.

Conflict of interest: Some of the authors declare that they have received lecture honoraria and/or support for ultrasound courses from Bracco and GE. Christian Greis was employee of Bracco Imaging.

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History of contrast enhanced ultrasound (CEUS)


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History of contrast enhanced ultrasound (CEUS)


