Contrast-Enhanced Ultrasound

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KEYWORDS

• Ultrasound • Contrast-enhanced • Liver • Microbubbles • Abdomen

KEY POINTS

- Current ultrasound contrast agents are generally composed of a microbubble gas core and a stabilized biological shell.
- Studies have established the relative safety profile of ultrasound contrast agents, although precautions must be observed in patients with certain medical conditions.
- Ultrasound contrast agents can characterize anatomic structures, and visualize tumor vascularity, vesicoureteral reflux, and neovascularity in atherosclerotic carotid plaques.

INTRODUCTION

Ultrasound (US) imaging is the most used and widespread imaging technology in the world. US examination uses nonradiating energy and is an affordable modality compared with computed tomography (CT) and MR imaging. The many applications of US imaging in multiple body parts extending from the abdomen to the vasculature and breast makes US examination a versatile modality. Standard US imaging, including 2-dimensional B-mode and color flow Doppler imaging, has significant limitations in characterizing anatomic structures and slow flow vascularized lesions. Color flow Doppler imaging is appropriate for large vessel delineation and assessment of the degree of stenosis, as in the carotid artery, and iliac or saphenous veins. Contrast-enhanced US imaging is a technique that uses specific contrast agents, improving the characterization of anatomic structures with the visualization of small vascular beds. Furthermore, it enables the US measurement of perfusion parameters. US contrast agents are mainly microbubbles consisting mainly of a gas core and a stabilized biological shell.

These contrast agents have multiple microbubbles of approximately 1 to 10 μm in size, approximating the size of a red blood cell, permitting visualization not only of the macrovasculature, but also the microvasculature. It is precisely this visualization that permits assumptions regarding the perfusion of abnormal lesions and normal organs. The relative short half-life of US contrast agents also permits serial evaluation of organs, particularly in patients with renal insufficiency. These techniques are already used in many countries for diagnostic radiological purposes; however, the lack of both Food and Drug Administration (FDA) approval and reimbursement for noncardiac hospital-based imaging has delayed widespread use in the United States.

Contrast-enhanced US has the benefit of a high temporal resolution with the capability of detecting the contrast transit in the arterial, portal venous, and late phases. The arterial phase starts 10 to 20 seconds after contrast injection and lasts approximately 25 to 35 seconds. The portal venous phase starts a few seconds after the arterial phase. In this article, we describe the types of contrast enhancement agents, safety, and clinical applications.

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TYPES OF CONTRAST ULTRASOUND AGENTS

The application of contrast-enhanced US initiated in the 1960s in which agitated saline was injected into patients with an enhanced detectable signal during an US examination.[1] These microbubbles resulted in backscatter of the US wave; however, they had a short lifetime. Intense research has been ongoing to create more stable microbubbles to image for a prolonged period of time. Currently, the majority of the US contrast agents are microbubbles. These are bubbles between the range of 1 and 10 μm. This is the approximate size of a red blood cell, permitting the visualization of small vascular structures.

There are 2 different types of shell materials. These are soft and hard shell bubbles. Hard shell bubbles result in increased mechanical stiffness, which reduces the compliance of the bubble as well as the internal gas. Softer shells result in increased compressibility of the internal gas, and these differences in compressibility changes the US properties of the microbubble.[2]

Initially, the internal gas of these microbubbles was air or nitrogen; however, it has been demonstrated that this gas provides a very short lifetime and limits the continued evaluation of the circulation. The discovery of perfluorocarbon, a more stable gas core that resulted in a consistent microbubble, provided an ideal prolonged lifetime of approximately 10 minutes, which increases the scan time for diagnostic procedures.

HARD SHELL MICROBUBBLES

Hard shell microbubbles are mainly used for higher intensity US applications, because soft shell microbubbles may rupture during insonation. Natural polymer shell microbubbles are one type of hard shell microbubbles. Gelatin was the first natural polymer used; however, quickly its use was dropped given the uneven production of microbubble size.

Synthetic polymers are usually filled with perfluorocarbon(s) (PFC) or air. Cyanoacrylate polymer is a synthetic polymer shell with air.[3] The first commercially available microbubble with the synthetic polymer is Sonovist (Schering AG, Berlin, Germany); these microbubbles are able to last for more than 10 minutes eventually taken up predominantly the Kupffer cells of the liver and phagocytosing cells of the spleen.[4] poly(n-butylcyanoacrylate) (PBCA), poly L-lactic acid (PLLA) poly glycolic acid (PGA), and poly(D,L-lactic-co-glycolicide) (PLGA) are other microbubble with synthetic polymer shell. These have been used in multiple trials and result in significant enhancement of up to 20 dB in suspension.[5]

PROTEIN-SHELLED MICROBUBBLES

This contrast media is less resistant to US waves than synthetic polymer-coated microbubbles. Optison and Lumason (Sonovue, Bracco Imaging, Milano, Italy) are protein shell microbubbles. The diameter of these microbubbles is between 2 and 5 μm with a small proportion of albumin in the shell, which enhances the contrast as well as prolongs its lifetime in circulation. Optison primarily has been used thoroughly for left ventricular echocardiography.[3,6] Optison has a bubble concentration of 5 to 8×10^8/mL, with a mean diameter of 3.0 to 4.5 μm and 95% less than 10 μm. It is filled with a gas with a half-time elimination rate of 1.3 minutes and it is completely eliminated in 6 to 10 minutes.[7]

SOFT SHELL MICROBUBBLES

Soft shell microbubbles are composed of phospholipids or stabilized surfactant and have better oscillation properties compared with hard shell microbubbles. This property is secondary to the improved compliance of the soft shell wall. Usually, under low-intensity US imaging, soft shell microbubbles undergo expansion and shrinkage; however, under high-intensity US imaging, soft shell microbubbles tend to divide into several smaller bubbles. In contrast, hard shell microbubbles burst under high-intensity US imaging.[8]

An example of a lipid base US contrast agent is Definity (Lantheus Medical Imaging, North Billerica, MA). This contrast agent has smaller size microbubbles between 1 and 2 μm and has been used for left ventricle and myocardial enhancement.

Another presentation of a phospholipid microbubble is Lumason, known globally as Sonovue (Bracco Imaging), which is a sulfur hexafluoride-filled phospholipid microbubble currently used in and approved for left ventricular opacification and endocardial border definition. In 2016, Lumason became the first US contrast agent to obtain FDA approval for use in liver imaging in adults and in the pediatric population. In 2017, Lumason became the first to be approved by the FDA for ultrasonography of the urinary tract (voiding ultrasonography) for the evaluation of suspected or known vesicoureteral reflux in pediatric patients (**Table 1**).

Surfactant-stabilized microbubbles are gas-filled liposomes with a diameter of 2 μm. Levovist (Schering AG) is an air-filled shell of saccharide and palmitic acid with a 6 μm diameter, which has been used for clinical echocardiography however lately has demonstrated great use in liver metastasis. This contrast agent has made possible to differentiate between cancer, hemangiomas, and fatty lesions of the liver.[9]