Contrast Evaluation of Liver Masses

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KEYWORDS

• CEUS • Ultrasound • Contrast • Liver • Review • Microbubble

KEY POINTS

- Contrast-enhanced ultrasound (CEUS) is highly useful in the detection and characterization of focal liver lesions (FLLs) as well as in monitoring of ablation therapy.
- Ultrasound contrast agents (UCAs) are pure intravascular tracers with excellent safety profiles, ideally suited for evaluating perfusion changes.
- Limitations include poor penetration and nonlinear propagation artifacts.

Videos of color Doppler demonstrating feeding artery and spoke wheel configuration of an FNH, CEUS of the same FNH in the arterial phase, and typical appearance of hypervascular liver metastases on CEUS accompany this article at http://www.ultrasound.theclinics.com/

INTRODUCTION

There are an estimated 782,000 diagnoses and 746,000 deaths attributed to primary liver cancer annually.[1] The liver is also the second most common site for metastatic spread, with significantly more patients suffering from liver metastases than primary cancer.[2]

Ultrasound is the most commonly used imaging modality of the liver.[3] It is inexpensive, portable, nonionizing and has an excellent safety record.[4,5] Traditional gray-scale and color Doppler ultrasound imaging have inherent limitations. First, detection of FLLs is complicated by similar echogenicity of the lesion and the surrounding liver parenchyma. Second, accurate characterization of FLLs is problematic with different pathologic lesions having overlapping or nondiscrete gray-scale imaging features. Last, although color and spectral Doppler imaging allows visualization of gross blood flow characteristics, it cannot determine microvascular status or enhancement qualities.[6]

The advent of UCAs has improved characterization of liver masses by comparing the altered enhancement dynamics of a lesion with the adjacent liver parenchyma.[7] In addition, the ability to perform real-time evaluation of FLLs in all vascular phases has conferred CEUS a temporal resolution superior to most other imaging modalities.[8,9] CEUS is highly useful in differentiating FLLs, with reported accuracies of up to 92% to 95%.[10–14] Its use has reduced the need for further imaging or biopsies.[15]

In 2012, the World Federation for Ultrasound in Medicine and Biology (WFUMB) and European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) in conjunction with the Asian Federation of Societies for Ultrasound in Medicine and Biology, American Institute of Ultrasound in Medicine, Australasian Society for

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Ultrasound in Medicine, and International Contrast Ultrasound Society published a set of guidelines to standardize the use of CEUS in liver imaging.[8]

This review article covers the technical considerations of CEUS, UCA evaluation of common liver masses, and its use in ablation therapy, limitations of technique, pitfalls, and future prospects.

PART 1: TECHNICAL CONSIDERATIONS

Ultrasound Contrast Agents

Physical properties

UCAs contain gas bubbles, referred to as *microbubbles*. Most of the UCAs in current clinical use belong to the second-generation. The typical second-generation microbubble has a stable outer shell comprising a thin (10–200 nm thick) biocompatible material (eg, phospholipids) and an inner core of hydrophobic gas (eg, perfluorocarbon, sulfur hexafluoride, or nitrogen), which has a high molecular weight, reduced solubility, and diffusivity.[16] These properties increase resistance to arterial pressure, preventing microbubbles from dissolving in the bloodstream.

A microbubble is approximately 3 to 5 μm in diameter, slightly smaller than a human red blood cell but much larger than the molecules of CT and magnetic resonance (MR) contrast agents. They are confined within the blood pool because they cannot extravasate through the vascular endothelium into the interstitium. They remain, however, small enough to move into the microcirculation of the pulmonary capillaries for safe excretion.[13] The gaseous component of UCAs is respired out in the lungs after approximately 10 to 15 minutes, whereas the shell is either broken down in the liver or excreted by the kidney.[17]

Most UCAs are gradually cleared from the blood pool after the fifth minute. An exception is Sonazoid (Daiichi-Sankyo, GE Tokyo, Tokyo, Japan), which remains in the human liver for several hours. This is because the Sonazoid microbubbles are phagocytozed by Kupffer cells, long after it is cleared from the blood pool. Sonazoid has thus been compared with superparamagnetic iron oxide agents used for MR hepatic imaging. It is the only commercial available UCA with an effective postvascular phase.[18]

Microbubble interaction with ultrasound

Although microbubbles increase the backscatter of ultrasound beams and produce highly echogenic signals, oscillating microbubbles are required for effective contrast imaging.

The natural resonance frequencies of microbubbles (where they are driven into maximal oscillations) are between 3 and 5 MHz. This is coincidentally similar to frequencies used in abdominal imaging.[13] On exposure to ultrasound waves of low acoustic pressure, a microbubble volumetrically expands and contracts in a controlled manner, undergoing stable cavitation. At high acoustic pressures, the microbubble reaches an unstable size and collapses, undergoing inertial cavitation (**Fig. 1**).

Oscillating microbubbles produce asymmetric, nonlinear signals. Human tissue returns largely linear signals and a minimal amount of nonlinear signals at low acoustic pressure. The harmonics arising from the nonlinear signals of the oscillating microbubbles are processed by specialized contrast ultrasound software to produce an image solely depicting microbubble echoes.[19]

Commercially approved UCAs

- SonoVue (Bracco SpA, Milan, Italy) consists of a sulfur hexafluoride gas contained within a phospholipid shell. It is currently approved for use in Europe, China, Korea, Hong Kong, Singapore, India, New Zealand, and Brazil.
- Sonazoid consists of perfluorobutane within a phospholipid shell. It is licensed for use in Japan and South Korea.
- Definity/Luminity (Lantheus Medical, Billerica, Massachusetts) consists of perflutren within a lipid shell. It is licensed in Canada, Mexico, Israel, New Zealand, India, Australia, Korea, Singapore, and United Arab Emirates.
- Optison (GE Healthcare, Princeton, New Jersey) consists of human serum albumin with a perflutren core. It is currently being trialled for liver imaging.
- Levovist (Bayer AG, Schering AG, Berlin, Germany) consists of galactose, palmitic acid, and air. It is a first-generation UCA, which has been approved for liver imaging. It is currently no longer available, although production has recommenced in Japan.
- To date, no UCAs have been approved by the US Food and Drug Administration (FDA) for evaluation of abdominal abnormalities. Optison and Definity are FDA approved, however, for cardiac imaging and can legally be used off-label in the abdomen.

Enhancement phases

The normal liver has a dual blood supply, with approximately one-third coming from the hepatic artery and two-thirds from the portal vein.[20] Vascular phases of a CEUS liver study are similar to CT and MR imaging, progressing from the arterial to portovenous phase and ending with the late (delayed) phase. The enhancement pattern of an