

Application of Contrast-Enhanced Ultrasound in the Digestive System

CME
Credits

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INTRODUCTION

Ultrasound has important roles in the diagnosis and management of diseases in the digestive system. Although Doppler ultrasound can be used to obtain dynamic information concerning blood flow, it is usually used to observe blood flow within larger vessels due to the limitations of the signal-to-noise ratio. Doppler technology is, therefore, not suitable for evaluating the tissue reperfusion. Contrast-enhanced computed tomography (CT) or magnetic resonance (MR) is widely used to obtain dynamic information for the reperfusion of tissues such as focal liver lesions. Since the introduction of ultrasound contrast agents (USCA) in the 1990s, ultrasound has been able to provide dynamic images of the reperfusion of tiny vessels and tissues, and its clinical use has been gradually extended to diseases of the digestive system.

Contrast-enhanced ultrasound

Contrast-enhanced ultrasound (CEUS) obtains the enhanced images provided by microbubbles, which perfuse the target tissues after being injected into the bloodstream. The gas in microbubbles is poorly soluble in blood, and the gas bubbles are coated with a layer of small molecules as the gas inside will be released after this coating dissolves in the blood. The outer shell of the microbubbles enhances the reflection of ultrasound signal, which is then used to create the enhancement on images. The microbubbles are generally $<3-5\ \mu\text{m}$ in size. Bubbles of this size cannot pass through the vascular endothelium and will remain within the vessels. Different USCAs have varied composition of the inner gas as well as the outer shell; thereby, the characteristics of USCAs and their clinical applications may differ.

The advantages of CEUS for the digestive system compared to CT and MR imaging (MRI) include the small size of the ultrasound machine which allows the use in a variety of situations, real-time observation, excellent resolution, low

radiation, and the ease of eliminating contrast agents. Most limitations on CEUS, similar to the case of conventional ultrasound, are imposed by the restrictions of physical characteristics. The acoustic window will be affected by interference from air in the lungs and intestines when performing liver scans. The newer generation of ultrasound machines is capable to perform ultrasound with low mechanical index (MI), which greatly limits the penetrating power, and affects the assessment of deep liver lesions and deep abdominal lesions such as the pancreas. In addition, CEUS cannot simultaneously observe multiple focal liver lesions if they are widely separated from each other.

Earlier generation of CEUS is performed with higher MI similar to that of conventional ultrasound. Acoustic waves with a high MI will quickly destroy microbubbles, lasting only for several seconds. This restricts its clinical use. The newer generation of USCAs can be performed with a very low MI ($\text{MI} < 0.3$), and the microbubbles can persist for several minutes, or even an hour. This allows acceptable observation period for continuous imaging and recording. Regarding the evaluation of focal liver lesions, CEUS can now provide images during arterial phase, portal phase, delayed phase, or even the much later hepatocyte phase (or Kupffer-phase) provided by Sonazoid. This further enhances the clinical application of CEUS for liver diseases.

The metabolism of USCA involves the release of the absorbed gases through the lungs, and the USCAs do not have significant liver or renal toxicity. Based on worldwide postmarket experiences, the most prevalent side effect of USCA is allergy to the USCA, which occurs approximately 1 in 10,000. The USCA can affect the capillaries, blood cells, and peripheral tissues during the irritation and destruction of microbubbles.

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It is generally recommended that apart from maintaining an appropriately low MI during the examination, the exposure of ultrasound energy should avoid areas that do not need to be inspected. While different USCAs may have somewhat different contraindications, they should be generally avoided in patients with impaired cardiopulmonary function, such as in patients with right-to-left shunts, severe pulmonary arterial hypertension, or acute respiratory distress syndrome. Due to the lack of sufficient evidence, the use of USCAs is not recommended in children, teenagers, and pregnant women.

Clinical applications of contrast-enhanced ultrasound in the liver disease

Among current experience of CEUS in the digestive system, its use in liver diseases has been most widely accepted and reported. The evaluation of focal liver lesions with CEUS is particularly the most common and mature. Multiple studies have indicated that CEUS offers better sensitivity and specificity than conventional ultrasound in the evaluation of focal liver lesions.^[1] The interpretation of dynamic imaging characteristics of CEUS regarding focal liver lesions is similar to contrast-enhanced CT or MR, which includes arterial phase, portal phase, and delayed phase.^[1] The arterial phase occurs about 30 s to 1 min after USCA injection, the portal phase begins close to 1 min after injection, and the delayed phase begins after 2–3 min. USCAs such as Definity or SonoVue can persist for approximately 5 min, allowing evaluation of all three phases. Sonazoid can last even longer for approximately 20 min, which allows the observation of the hepatocyte phase that occurs approximately 10–15 min after injection.^[2]

The typical imaging characteristics of CEUS for hepatocellular carcinoma (HCC) include hyperenhancement in arterial phase, washouts in early portal, and delayed phases [Figure 1], and nonenhancement in hepatocyte phase.^[1] If a lesion is hyperenhanced during the arterial phase, but without wash-outs in portal phase, delayed phase, or hepatocyte phase, the lesion is very likely to be benign [Figure 2]. While well-differentiated or early HCCs may be isoenhanced during the arterial phase, portal phase, or delayed phase, compared to that of nontumorous adjacent liver parenchyma, they are usually hypoenhanced during the hepatocyte phase. Thus, the hepatocyte phase provides additional information that can be beneficial for the differential diagnosis of focal liver lesions.

The enhancement pattern of metastatic liver lesions is closely related to the size and vascularity of tumors. The most common characteristics of CEUS images for metastatic cancer include late arterial phase enhancement, very rapid washout, and hypoenhancement after the portal phase.^[1] Benign liver lesions are generally carries a similar or increased enhancement relative to liver parenchyma during the delayed phase or even later hepatocyte phase, while malignant liver lesions carry a significantly lower enhancement or nonenhancement compared with the adjacent parenchyma. Researchers have proposed the defect reperfusion method which is based on

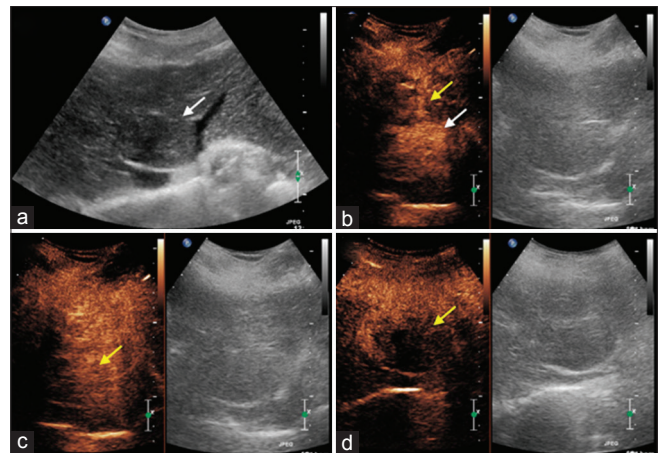


Figure 1: Typical enhancement pattern of hepatocellular carcinoma on contrast-enhanced ultrasound images. (a) An isoechoic tumor (white arrow) is seen at S4 on the gray-scale ultrasound image. (b) Hyperenhancement of this lesion (white arrow) can be seen during the early arterial phase (20 s after the injection of contrast agent), and the feeding vessel can also be seen clearly (yellow arrow). (c) Washout of the tumor can be seen during the early portal phase. (d) The tumor displays hypoenhancement or nonenhancement during the delayed phase

the characteristics of focal liver lesions during the hepatocyte phase.^[3] This method begins with an examination of the entire liver during the hepatocyte phase to check for hypoenhanced or nonenhanced liver lesions. The ultrasound probe then targets at those lesions, and USCA is re-injected to observe the dynamic enhancing patterns within the lesions. For example, if the lesion is hyperenhanced in arterial phase after re-injection, it is likely to be HCC.

There are controversies concerning the application of CEUS to differentiate HCC and intrahepatic cholangiocarcinoma (ICC) since several studies have suggested an overlapping feature of these two on CEUS. However, it is suggested that the arterial enhancement in ICC is frequently to be found at periphery. Compared with contrast-enhanced CT and MR, CEUS offers the advantage of being able to assess and record temporal quantitative dynamic signal intensities. By analyzing the temporal enhancing patterns, recent studies have suggested that the washout during the portal phase in ICC is even faster and more profound than in the case of HCC.

CEUS also has roles in the treatment of malignant liver lesions. Radiofrequency ablation (RFA) has demonstrated its effectiveness in the treatment of HCC and is considered as a first-line treatment for small early HCC. Clinically, the insertion of RFA probes is frequently guided with ultrasound. Without USCA, some small HCCs may be difficult for conventional gray-scale ultrasound to identify and treatment errors such as mistargeting can be made. CEUS can delineate small HCC that is obfuscated on conventional gray-scale ultrasound, improve the accuracy of probe insertion, and facilitate precise RFA treatment. Contrast-enhanced CT or MR is usually performed 1–3 months after RFA for HCC to determine the treatment efficacy. Recent studies have shown

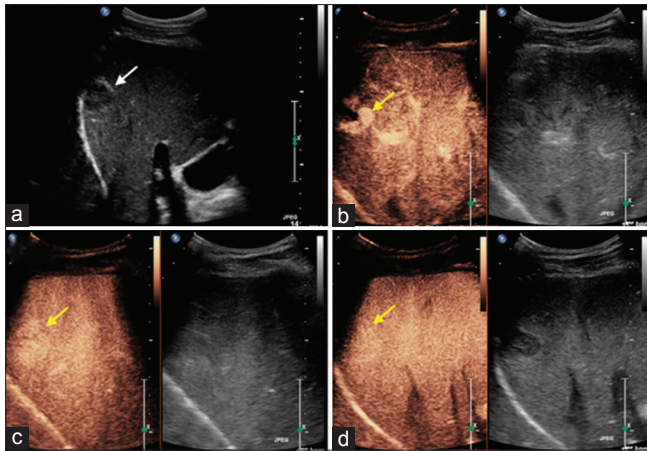


Figure 2: The enhancement pattern of hepatic hemangioma on contrast-enhanced ultrasound images. (a) A mixed-echoic lesion is visible at S7 on the gray-scale ultrasound image, and there is an acoustic halo around the lesion. (b) After injecting contrast agent, peripheral nodular enhancement (yellow arrow) has appeared during the arterial phase. (c) Centripetal fill-in of peripheral enhancement has occurred during the portal phase. (d) The lesion still has slightly hyperenhancement compared with the liver parenchyma during the delayed phase

that CEUS can be performed as early as several hours after RFA, which allows early assessment of whether complete ablation has achieved or the requirement of additional ablation is needed.

Clinical applications of contrast-enhanced ultrasound in the digestive system

Recently, CEUS has gradually expanded its clinical application from liver diseases to other digestive system organs. CEUS of the spleen can confirm splenic infarction or assess injury to the spleen in some trauma patients.^[4] CEUS can be performed in cancer patients who are not able to receive contrast-enhanced CT or MR for evaluation of spleen metastasis. In the case of the pancreas, CEUS can provide even more information to assist the identification and diagnosis of suspected cancerous lesions of the pancreas.^[5] CEUS has an important role in the identification of malignant pancreatic tumors, especially in the diagnosis of hypovascular pancreatic tumors, such as pancreatic ductal adenocarcinoma. However, the diagnosis of pancreatic neuroendocrine tumors can be difficult since pancreatic neuroendocrine tumors and inflammatory pancreatic lesions are often hypervascular. While CEUS can provide information of dynamic enhancement, current evidence from studies cannot support the use of CEUS to replace MR in the diagnosis for cystic tumors of the pancreas.

CEUS can be performed with endoscopic ultrasound (EUS) to assess pancreatic lesions. Many studies have found that the combined use of CEUS and EUS (CE-EUS) has an excellent diagnostic rate in the case of pancreatic tumors.^[6] Thus, several guidelines include CE-EUS among recommended

assessment tools for pancreatic disease. CE-EUS can be used for diseases of the intestinal tract. CEUS has been reported to differentiate between gastrointestinal stromal tumors (GIST) and intestinal tract leiomyoma based on the vascularity, as GIST is hypervascular and commonly accompanied by central necrosis, while intestinal tract leiomyoma is usually hypovascular.^[7]

CONCLUSION

CEUS offers better diagnostic performance compared with conventional ultrasound for focal liver lesions. CEUS is more accurate to differentiate between benign and malignant liver tumors. The quantitative dynamic signal intensities and patterns on CEUS have great value in the diagnosis of liver cancer. The newer generation of USCA allows the acquisition of hepatocyte phase images, which can greatly benefit the identification and diagnosis of focal liver lesions. CEUS can locate liver tumors not easily discovered using conventional ultrasound before hepatic intervention, can guide the intervention during the course of treatment, and can assess the effectiveness of RFA following treatment. In addition to liver diseases, the application of CEUS has been gradually extended to the evaluation of digestive system organs in recent years. The newer generation of USCA further improves CEUS in the application for diseases of the digestive system.

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Conflicts of interest

There are no conflicts of interest.

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