Sonazoid contrast-enhanced ultrasonography for diagnosis of hepatic tumors

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Learning objectives

The purpose of our educational exhibits is to:

1. understand properties of Sonazoid contrast-enhanced ultrasonography (CEUS) and realize the differences of other contrast agents.
2. learn the typical enhancement patterns of the most common FLLs using Sonazoid CEUS in comparison with CT or MRI findings.
3. understand Sonazoid CEUS improve not only for the diagnosis of FLLs, but also for the assessment of treatment efficacies of FLLs.

Background

Sonazoid (Daiichi-Sankyo, GE Tokyo, Japan) is a ultrasound contrast agent that is composed of perfluorobutane microbubbles with a hard phospholipid shell. By visualizing microbubbles non-destructively, Sonazoid CEUS allows prolonged enhancement, which lasts over 60 minutes, and clear vascular imaging in real-time, that improves both the characterize FLLs and treatment efficacy assessment. In addition, Sonazoid microbubbles taken up by Kupffer cells. Therefore tumors which lack Kupffer cells tend to appear as contrast defects during the Kupffer phase [1-2]. Stable Kupffer imaging improves the detection of FLLs as lesions of contrast defect, that shows similar information in the hepatocyte phase observed on gadolinium ethoxybenzyl-diethylenetriamine pentaacetic acid enhanced MRI (EOB-MRI). For all of these reasons, Sonazoid CEUS is expected to facilitate the qualitative diagnosis and characterization of FLLs and to contribute considerably to improving the accuracy of treatment efficacy assessment [3-9].

Findings and procedure details

Sonazoid CEUS procedure

The ultrasound devices equipped with low mechanical index (MI) contrast-specific imaging, such as pulse-inversion imaging, should be used.

Sonazoid microbubbles are not destroyed under a low-MI of 0.20-0.25 imaging, which are stable for over 60 minutes after intravenous injection, and provide continuous vascular imaging with high spatial resolution in real-time [Fig. 1.]. Also Sonazoid microbubbles are phagocytized by Kupffer cells, and FLLs without Kupffer cells tend to appear as contrast
defects during the Kupffer phase [Fig. 2.]. Sonazoid is the only contrast agent with these characteristics.

Sonazoid is administered intravenously as a bolus of 0.0075 ml/kg followed by flushing with 10 ml of normal saline. After injection, each vascular phase is recorded and evaluated: the arterial phase (i.e., 10-40 seconds from beginning of injection), the portal venous phase (i.e., 40-120 seconds from beginning of injection), and the Kupffer phase (post vascular phase (i.e., 2-15 minutes from beginning of injection). When FLLs is detected as a defect during the Kupffer phase for the first time, then Sonazoid is administered again for an enhancement pattern assessment. This technique, named defect reperfusion imaging is quite useful to make a qualitative diagnosis [9].

**Sonazoid CEUS findings of FLLs**

**Hemangioma** [Fig. 3-4]

Hemangioma of the liver is the most common benign liver tumor. The typical Sonazoid CEUS findings of liver hemangioma is peripheral nodular enhancement during the arterial phase, with centripetal progression during the portal venous and the Kupffer phases. These findings are similar to the perfusion pattern of CT or MRI. However, unlike CT or MRI findings, about half of hemangiomas show washout during the late Kupffer phase. These findings are characteristic of Sonazoid. This difference seems to be by the presence or absence in the interstitial space of the contrast media.

**Focal nodular hyperplasia (FNH)** [Fig. 5-6]

The typical Sonazoid CEUS findings of FNH is rapid central spoke wheel-shaped enhancement during the early arterial phase [Fig. 1], that becomes homogeneous hyperecho during the late arterial phase. Homogeneous hyper- or isoechoic enhancement persists during the portal venous and the Kupffer phases. A hypoechoic central region corresponding to a central stellate scar is observed during the Kupffer phase. Because of its stability, a washout phenomenon is not observed in the Kupffer phase using Sonazoid.

**Hepatocellular carcinoma (HCC)**

Sonazoid CEUS findings of HCC vary according to the degree of differentiation. The typical Sonazoid CEUS findings of moderately or poorly differentiated HCC shows diffuse enhancement during the arterial phase that decreases during the portal venous and the Kupffer phases. Among HCC with high degree of differentiation, enhancement persists for a long time. Therefore, for the patient for the HCC search, observation should be performed over 10 minutes as an additional late Kupffer phase. When tumors are detected as contrast defects during an additional Kupffer phase for the first time, the
diagnostic technique of defect reperfusion imaging is quite useful for the differentiation of moderately or well differentiated HCC from early HCC or precancerous dysplastic nodules.

**Cholangiocellular carcinoma (CCC) [Fig. 10-11]**

About 30% of CCC shows diffuse heterogeneous enhancement during the arterial phase that decreases during the portal venous phase. This washout pattern is similar to that of metastasis. Delayed enhancement is not seen in the late phase of CEUS unlike that of CT or MRI findings.

**Liver Metastasis [Fig. 12-13]**

As hepatic malignancies generally do not involve Kupffer cells, Sonazoid CEUS has made it possible to detect hepatic metastases as contrast defects in real time. Liver metastasis shows various enhancement patterns during the arterial phase, that depends on the primary focus. An enhancing peripheral rim and variable intralesional enhancement are observed during the early arterial phase that decreases immediately during the late arterial and the portal venous phases. As Sonazoid CEUS can observe the lesion in real time and consecutively, findings of the arterial phase may vary with that observe on CT or MRI.

**Treatment efficacy assessment [Fig. 14-15]**

Sonazoid CEUS allows real-time evaluation of FLLs after several treatment methods such as ablation therapy or systemic chemotherapy, which improves treatment efficacy assessment, compared to CT or MRI. Sonazoid CEUS can detect the small locoregional recurrence after local therapy such as ablation therapy or trans-catheter arterial chemo-embolization (TACE) that other modalities cannot detect. Sonazoid CEUS can depict slight intratumoral blood flow in real time, that is superior by treatment efficacy assessment.

**Images for this section:**
**Fig. 1:** Vascular assessment of focal nodular hyperplasia (FNH) by Sonazoid CEUS. A feeding artery from the center to outwards produce a spoke-wheel appearance and strong hyper-perfusion. This microflow imaging, composed of a flash replenishment and a maximum intensity holding sequence, shows the micro structure in the scanning area.
**Fig. 2:** Detection of small liver metastasis from pancreas cancer. During the Kupffer phase (a)(5 min.), a small metastasis (arrow) depicts near the gallbladder. Photograph during the surgery (b), a liver metastasis is found on surface of the liver as a small yellowish nodule.

**Fig. 3:** Sonazoid CEUS findings of cavernous hemangioma. On the unenhanced phase (a) the lesion (asterisk) is slightly hypoechoic with ill-defined margins. During the early arterial phase (b)(18 sec.), hyperdense peripheral nodular enhancement is seen, which progresses centrally during the arterial phase (b)(30 sec.). During the Kupffer phase (d) (3 min.) shows complete fill-in. The lesion appears slightly heterogeneously hypoechoic during 8 minutes after injection (e).
**Fig. 4:** Dynamic CT findings of hemangioma. The same case as shown in Fig. 3. The enhancement patterns are similar in Sonazoid CEUS with peripheral nodular enhancement in the arterial phase and gradual filling of the entire mass with contrast agent as time passes. (a) plain, (b) the arterial phase, (c) the portal venous phase, (d) the equilibrium phase.

**Fig. 5:** Sonazoid CEUS findings of focal nodular hyperplasia. The same case as shown in Fig. 1. On the unenhanced phase (a) FNH is slightly hypoechoic to the liver. During the arterial phase (b) (12 sec.), the nodule enhances rapidly with feeding arteries (arrow) from the periphery to the center in real-time. In the portal venous and the Kupffer phase (c. and d. respectively) the FNH appears isoechoic compared to background normal liver parenchyma. In the Kupffer phase, the central stellate scar (arrow) is revealed as hyperechoic spot.
**Fig. 6:** Dynamic CT findings of focal nodular hyperplasia. The same case as shown in Fig. 5. The enhancement patterns are similar in Sonazoid CEUS. However, FNH enhances rapidly, the centrifugal enhancement is usually undetected. (a) plain, (b) the arterial phase, (c) the portal venous phase, (d) the equilibrium phase.

**Fig. 7:** Sonazoid CEUS findings of hepatocellular carcinoma. On B-mode image (a), the lesion (arrow) is slightly hypoechoic with central hyper-echo. During the arterial phase (b), 22 seconds after injection, the nodule enhances form a doughnut shape rapidly, which appears isoechoic relative to the adjacent liver parenchyma during the portal venous phase. Twelve minutes after injection, the nodule shows complete washout (c).
Fig. 8: Dynamic CT findings of hepatocellular carcinoma. The same case as shown in Fig. 7. The enhancement patterns are slightly different from that of Sonazoid CEUS. A hypervascular nodule is seen on the arterial phase (b), but is no longer seen in the portal venous phase (c). (a) plain, (b) the arterial phase, (c) the portal venous phase, (d) the equilibrium phase.
Fig. 9: Defect reperfusion imaging. A small nodule locates near the surface of the liver is detected as a defect during the Kupffer phase, 14 minutes after injection. Then Sonazoid is administered again for an enhancement pattern assessment in real-time to make a qualitative diagnosis.
Fig. 10: Sonazoid CEUS findings of peripheral cholangiocellular carcinoma. On the unenhanced phase (a) the lesion is hypoechoic with well-defined margins. During the arterial phase (b)(21 sec.), heterogeneous enhancement is seen, which gradually washout during the portal venous phase (c)(41 sec.). Complete washout is seen during the Kupffer phase (d)(200 sec.).

Fig. 11: Peripheral cholangiocellular carcinoma. The same case as shown in Fig. 10. The tumor appears hypointense on unenhanced GE T1-weighted image (a). Peripheral enhancement is seen on images acquired during the arterial (b) and the portal venous (c) phases after the administration of Gd-EOB. A peripheral hypointense rim is seen on the hepatocyte phase image (d) and the lesion appears hypointense compared to the surrounding parenchyma.
**Fig. 12:** Hypervascular metastasis from colon cancer after Sonazoid CEUS. On the unenhanced phase (a) the lesion (asterisk) appears hypoechoic with well-demarked margins. Rapid enhancement during the arterial phase (b) (17 sec.) is seen. The subsequent portal venous phase image (c) (43 sec.) reveals the rapid washout with rim-like enhancement. These findings are characteristic of metastasis.

![Fig. 12](image)

**Fig. 13:** Metastasis from colon cancer. The same case as shown in Fig. 12. On the unenhanced GE T1-weighted image (a), a small hypointense lesion is seen. During the arterial phase (b), the lesion shows less vascularity than that in the surrounding liver parenchyma after the administration of Gd-EOB. The lesion appear hypointense with increased conspicuity in the portal venous phase (c) and the hepatocyte phase (d).

![Fig. 13](image)

**Fig. 14:** Treatment efficacy assessment of hepatocellular carcinoma treated with transarterial chemoembolization (TACE) by dynamic CT. The judgment of the presence or absence of viable cells is difficult with these CT images. (a) plain, (b) the arterial phase, (c) the portal venous phase, (d) the equilibrium phase.
**Fig. 15:** Treatment efficacy assessment of hepatocellular carcinoma treated with transarterial chemoembolization (TACE) by Sonazoid CEUS. The same case as shown in Fig. 14. An intratumoral blood flow from bottom of the nodule (arrow) is seen in real-time.
Conclusion

Sonazoid CEUS improves both the diagnostic accuracy and the assessment of treatment efficacy for FLLs.

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