Benefits of contrast enhanced ultrasound in intervention

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ABSTRACT

For evaluating unclear tumorous lesions, CEUS is an important imaging modality besides contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI) and may provide valuable insights into the microvascularization of tumors by its dynamic examination. In interventional procedures, CEUS can make a valuable contribution in pre-, peri- and post-interventional settings, reduce radiation exposure and, under certain circumstances, the number of interventions for the patient.

Keywords: contrast-enhanced ultrasound, lesion, tissue vascularization, real-time imaging

Introduction

Contrast-enhanced ultrasound (CEUS) enables the physician to dynamically assess the vascularization of tissues and vessels in a real-time manner. For this purpose, a contrast agent is injected intravenously, which allows the assessment of the precise contrast dynamics of suspicious lesions. The lesions are evaluated during the arterial phase (15-30 seconds after injection), the portal venous phase (30-70 seconds after injection) and the late phase (>70 seconds after injection) (1-3) which can be transferred as cine loops (5-10 second intervals) to the local memory of the ultrasound unit and subsequently to the local institutional archiving system of the institute. Typical malignant characteristics of a suspected hepatic metastasis are a pronounced early arterial hypervascularization, an early wash-out in the portal venous phase and a persistent wash-out in the late phase (figure 1) (4-7). The higher spatial resolution of ultrasound imaging compared to CT and MRI enables the physician to safely characterize lesions even smaller than 1 cm which can be used for pre-interventional planning, peri-interventional monitoring and post-interventional treatment response assessment (8).

Overview of the use of contrast media with specific outlook on Sonazoid®

The recommended volume of contrast medium varies between 1.0 and 2.4 ml, depending on the ultrasound system and the tissue to be examined, and is followed by a bolus of up to 10 ml of sterile saline (0.9% NaCl) (1, 9-11). Modern contrast agents (e.g. SonoVue®, Bracco, Milan, Italy) are small gas-filled microbubbles that generate a nonlinear tissue independent contrast which allows dynamic evaluations at the level of capillary microcirculation with a spatial
resolution superior to those of CT and MRI (8, 12, 13). In order to gain sufficient imaging quality a low mechanical index (<0.2) is preferably used to prevent early destruction of the oscillated microbubbles induced by the emitted ultrasound waves. Unlike the contrast agents usually based on iodine (CT) or gadolinium (MRI), most ultrasound contrast agents like SonoVue® have a purely intravascular distribution pattern which underlines the benefits of CEUS especially for small lesions (14-17). In addition, ultrasound contrast agents have extremely low risk profiles and can be administered to a wider range of patients due to its lack of influence on the kidney or thyroid gland function (18, 19). First studies demonstrated a safe application of intravenous contrast agents during CEUS examinations in pregnant women (20, 21). Safe applications in children and young adults is already widely used in daily routine (22-24).

Sonazoid® (GE Healthcare, Waukesha, WI, USA) has a unique characteristic in the field of second-generation ultrasound contrast agents. It was first approved and launched in Japan in 2007 and is nowadays, next to Japan, also available in Korea, Norway, Singapore, Taiwan and China. So far, Norway was the first and only country in Europe to approve Sonazoid® in 2014. The lack of broad availability can be explained by the number of adverse events (AEs) in early studies. In a prospective study from 2009, AEs were registered in 49.2% of cases, with fever, nausea and diarrhea as the three most common clinical symptoms. Adverse drug reactions occurred in 10.4 %, however, all of them only were mild (25). In a study from 2019 with an investigation period between 2014 and 2015 a markedly lower rate of AEs has been described, but at 24.1% it is still inferior to the approved contrast media (26).

Sonazoid®, a perflubutane-based contrast agent, enables the acquisition of a parenchyma-specific Kupffer phase. The 2-3 μm microbubbles are phagocytosed by the Kupffer cells which represent the liver-specific macrophages, allowing the examiner to evaluate the hepatic parenchymal enhancement of up to 60 minutes (27, 28). Lesions such as HCC or abscesses show no or only a markedly decreased enhancement in the postvascular phase due to the lack of regular Kupffer cells (29). The physician can also generate a defect reperfusion image in which both the arterial and the Kupffer phase can be assessed by repeated administration of Sonazoid® in the same slice (15, 30). When comparing their diagnostic value, current studies indicate that Sonazoid® is noninferior to established contrast media such as Sonovue (31).

In a consensus statement and recommendation for the Clinical Practice of Contrast-Enhanced Ultrasound using Sonazoid® in 2020, the Asian Federation of Societies for Ultrasound in Medicine and Biology (AFSUMB) expects a further introduction of Sonazoid® in the rest of
Europe in the near future due to its low rate of AEs (0.5% and 6.3%), its advantages regarding a stable time window of up to 60 minutes with a possible improvement of the whole-liver imaging quality and its advantages within the framework of liver intervention (32).

**CEUS in the framework of liver intervention**

**Puncture and biopsy**

Advantages of ultrasound-assisted biopsy compared to CT or MRI intervention include the possibility of acquiring real-time imaging, multiplanar image acquisition and its superior cost-effectiveness. One of the main benefits of performing an CEUS-guided punctures or biopsies is the ability to obtain morphological information regarding the microvascular blood supply and blood flow in lesions that could otherwise only be obtained by CECT or CEMRI (32-34). This advantage enables the physician to differentiate between vascularized and non-vascularized tumor tissue in order to perform a targeted puncture/biopsy and, conversely, to obtain a higher quantity of tissue for histopathological analysis. This fact is highly relevant in partially necrotic lesions which can be analyzed more accurately than in non-dynamic examinations like the CT or MRI. Modern ultrasound devices also provide additional hardware to enable automatic needle guidance to the target lesion, thus increasing safety for especially for less experienced examiners (35). For this purpose, a steering device can be attached to the transducer containing a channel for the needle that can be aligned at different angles. For a safe performance of the interventional procedure, it is recommended to first mark the location on the skin which allows a good access path while avoiding risk structures such as vessels. In comparison to the free-hand technique, the reduced mobility and adjustment of the needle position during the procedure may be regarded as possibly disturbing. Overall however, there is a significant time advantage with similar success rates especially for less experienced examiners (36-38).

In interaction with CEUS, the contrast medium cannot only be applied via the peripheral venous access, but it can also be administered directly via the inserted needle in order to increase the diagnostic accuracy, e.g. in cystic transformed lesions. In addition, it could be shown that CEUS has a positive impact on diagnostic accuracy in fusion imaging and may safely visualize lesions that are not visible in the native B-mode ultrasound (39, 40).
**Minimal invasive ablative therapies**

The primary goal of thermal ablation is to induce cell death, e.g. by intense heat or high radiation induction to obtain a devascularization of the suspected lesion with subsequent necrosis. This requires a targeted placement of an ablation probe under imaging guidance which can, using grayscale US, cause difficulties in purely visualized small lesions even for the most experienced examiners (41). According to a study by Rim et al., tumors could not be visualized by conventional US in 30% of the patients referred for percutaneous radiofrequency ablation (RFA) (42) which underlines the importance and additive value of CEUS.

In the context of interventional therapy planning, CEUS can enable real-time imaging of the topographic anatomy of the lesion to be treated such as the distance to the surrounding vessels, the liver capsule or other intra- or retroperitoneal organs such as stomach, intestine or kidney. The latter could achieve periinterventional insertion of an inflatable balloon to displace the intestines from the radiation field (43). The possibility of real-time imaging and image fusion can also provide the interventionalist with important information during the intervention (44, 45). While conventional B-mode US can sometimes be of limited value in the perinterventional setting, for example due to intralesional gas formation (e.g. during RFA), CEUS can provide additional information if there are contraindications to the use of contrast media in CT or MRT imaging (46). In consideration with a previous study, the use of Sonazoid® showed a significant reduction in RFA sessions when the hepatic lesion was not well-delineated on native B-mode US and ablation used to be performed based on the information from CT (47). Peri-interventional CEUS can also have a positive effect on the detection of residual tumor, which makes it possible to treat these lesions during the same session (48). However, the investigator must carefully differentiate between residual tumor and peri-ablational hyperemia or gas bubbles at the ablation site in the course of a RFA (49, 50).

After histopathological acquisition of tumorous material and an interdisciplinary decision regarding the implementation of a locally invasive therapy, CEUS offers the possibility of a radiation-free procedure to evaluate the success of the performed therapy. Early stage postinterventional CEUS imaging in combination with preoperative CECT/CEMRI can determine the safety margin after for example RFA or transarterial chemoembolization (TACE) with a high sensitivity of 80-100% and thus provide information on the success of the LAT (figure 2) (51-53). Thus, the investigator has the possibility to preclude tumor recurrence.
by assessing the lack of revascularization in the follow-up examinations (54). According to the literature, several reports have raised concerns about tumor recurrence after RF ablation in HCC whereby the underlaying exact mechanism is not yet fully understood. One possible explanation is an intravascular tumor spread due to a sudden increase of the intracellular pressure in the ablated tissue (55, 56). According to the work by Jeong et al., Sonazoid® shows a significant suppressive effect on the popping phenomenon without, however, affecting the clinical outcomes (57). In general, ultrasound imaging is useful in all pre-, peri- and postinterventional settings and may provide valuable information on the success of local ablative therapy.

**Drainage in biliary intervention**

In biliary interventional therapy, CEUS can be installed in the therapeutic placement of a percutaneous transhepatic biliary drainage (PTBD) which displays a common procedure in benign or malignant biliary diseases (figure 3). CEUS-PTBD was first described in 2009 and displays a typical indication in ultrasound-guided diagnostics (58). Both the native B-mode imaging and CEUS provide a high anatomical accuracy in the evaluation of the correct drainage position. However, the field of view can sometimes be limited in native B-mode ultrasound since an intraluminal tip position can lead to artifacts caused by physiological intestinal gas accumulation. In many cases, additive fluoroscopic cholangiography is required for correct visualization of the catheter tip, which is associated with radiation exposure to the patient. To avoid exposure to ionizing radiation, CEUS can overcome the limitations of native B-mode imaging and thus provide additional information on the drainage position. For this purpose, contrast medium can be applied via the primarily placed drainage. Hereby a direct location of the tip in relation to the bile ducts or the small intestine can be established. This is particularly useful if the bile ducts are not dilated or if the question of an accidentally dislocation of the drainage arises (figure 3c) (59). Another potential complication that can be assessed by CEUS is for example the presence of a biliary-arterial fistula (60). In summary, CEUS represents a radiation-free examination technique which can provide valuable information on the correct drainage position, possible complications and enables the physician to perform the examination at the patient's bed side (41).
Handling of image fusion in ultrasound imaging

In order to expand the application field, image fusion was implemented in modern ultrasound devices. By enabling the sonographer to better visualize small lesions in B-mode ultrasound, image fusion facilitates pathological clarification or, in the interventional setup, punctures or biopsies of these small lesions (61, 62). Further areas of application include the field of post-interventional perfusion analyses in the assessment of locally ablative procedures (46).

In the early stages, the co-registration in the context of image fusion was considered difficult for the unexperienced users, but now runs largely automatically in up-to-date ultrasound machines by often using a rigid transformation matrix (17). In the case of manual co-registration, clear and easily found anatomical structures such as large vessels or cysts can be used for better handling. Necessary equipment includes an extra-magnetic field generator and an additional position sensor. The sensor registers the position of the ultrasound probe in interaction with the extra-magnetic field generator and sends the acquired data to the ultrasound device to enable the most accurate co-registration possible. In addition to B-mode imaging, the ultrasound imaging system can also make use of Doppler sonography and CEUS, which covers the entire range of ultrasound imaging and thus allows optimal detection of the microvascularization of the tumorous tissue to be examined. The display of the images after successful image fusion can be differentiated between a side-by-side mode (figure 1 e-g), in which the cross-sectional CT or MRI examination is compared to the ultrasound imaging, and an overlay technique, which combines the CT or MRI examination with the currently generated ultrasound examination to bundle the image information from the different examination modalities into one image. Despite its partially automated procedure, the image fusion ultrasound examination requires certain experiences in handling the technical precautions and protocols. A disadvantage of the present method is that image fusion adjustment during patient movement or breathing is not always adequately possible and may result in an ineffective co-registration. Therefore, it is recommended to perform the examination in a breathing position identical to the comparative examination.

Conclusion

CEUS displays a diagnostic procedure that can play an important role in planning, performing, monitoring or in follow-up imaging. Thus, this technique represents an examination with a wide range of possible clinical applications in daily routine. CEUS and image fusion
combines the general advantages of contrast-enhanced ultrasound imaging with the possibility of combined access to information from additive CT or MRI imaging for detection, therapy and follow-up.

References

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**Figure legend**

Figure 1: 54-year-old female patient with metastatic colorectal cancer. B-mode ultrasound reveals a 12 mm peripheral hypoechoic lesion in liver segment IVa cranially adjacent to the portal trunk (a) without evidence of hypervascularization in duplex sonography (b). CEUS indeed shows an early arterial contrast medium accumulation (c) with a wash-out in the portal venous and late phase (d) (5 minutes after injection of contrast medium) indicating a singular liver metastasis.

Image fusion of the same patient (e-g) comparing B-mode sonography and CEUS to a previous MRI (3 months ago) reveals a new demarcated liver lesion with the sonomorphological features as described above (a, c, d).
Figure 2: Same patient as in figure 1. MRI imaging shows, in analogy to sonography, a liver metastasis in segment IVa with a defect (a) in the hepatobiliary phase (contrast agent: Primovist ®). CT-morphologically, the lesion shows a wash-out in the venous phase (b) followed by an RFA with placement of a RFA probe (c). In B-Mode ultrasound, the lesion shows a slightly progressive hypoechoic rim 5 minutes after RFA (d).

In the follow-up examination 5 months after performing the RFA, CEUS shows an early arterial enhancement (e) and wash-out (f) at the cranial rim of the treated lesion. In MRI the lesion shows, analogous to CEUS, a shallow contrast-medium enhancement (g) with a restricted diffusion (h, i), revealing local recurrence.

Figure 3: 62-year-old patient with a percutaneous transhepatic biliary drainage (PTBD) (red arrow) showing a contrast uptake in the biliary system (yellow arrow) after injection of contrast agent via the drainage, indicating the correct position of the PTBD (a). Increasing contrast of bile ducts seven seconds later than image a (b). Same patient showing a displacement of the PTBD after 5 days (c) (yellow arrow).
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Figure 3b

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