Guidelines and Good Clinical Practice Recommendations for Contrast Enhanced Ultrasound (CEUS) – Update 2008

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- transcranial US

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Ultrasound (US) contrast agents (UCAs), in conjunction with contrast specific imaging techniques, are increasingly accepted in clinical use for diagnostic imaging and post-interventional workup in several organs. To those not intimately involved in the field, the rapid advances in technology and techniques can be difficult to follow. In March of 2003, at the EUROSON Congress in Copenhagen, it was agreed that it would be useful to produce a document providing a description of essential technical requirements, proposed investigator qualifications, suggested study procedures and steps, guidance on image interpretation, recommended and established clinical indications and safety considerations.

Initially a set of guidelines for the use of ultrasonic contrast agents in the liver alone were developed. These were presented and discussed in detail at an EFSUMB special consensus meeting held in Rotterdam in January 2004. The resulting consensus document was published in the August 2004 edition of Ultraschall in der Medizin/European Journal of Ultrasound, and has also been published in French [1] and Chinese [2]. Time has however moved on, and EFSUMB and the group of experts who developed these first guidelines took the view in 2006 that they should be revisited and expanded to include recommendations for applications in the kidney, in vesico-ureteric reflux, in the pancreas, in trauma and in the cerebral circulation. In order to facilitate the production of these new guidelines and recommendations a further two meetings of experts were held, the first in Bologna in September 2006 in conjunction with the EUROSON/SIUMB meeting, the second immediately following the European Symposium on Ultrasonic Contrast Agent Imaging in Rotterdam in January 2007.

As previously these guidelines are based on comprehensive literature surveys including results from prospective clinical trials. On issues where no significant study data were available, evidence was obtained from expert committee reports or was based on the actual consensus of experts in the field of US and contrast enhanced Ultrasound (CEUS) during the consensus conferences. During the meeting of experts in Rotterdam many additional new and exciting developments were discussed, and whilst some are quickly entering clinical practice, it was felt too early to include them in the current recommendations.

These guidelines and recommendations provide general advice for the use of UCAs. They are intended to create standard protocols for the use and administration of UCAs and improve the management of patients. Individual cases must be managed on the basis of all clinical data available for that specific case. This second version will be subject to change to reflect future advances in scientific knowledge and the rapidly evolving field of US technology.

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1 General Considerations

1.1 Introduction

The development of ultrasound contrast agents (UCAs), which perform as blood pool tracers, have overcome the limitations of conventional B-Mode and colour or power Doppler US and enable the display of parenchymal microvasculature [3 – 5]. Dependent on the contrast agent and the US-mode, the dynamic lesion enhancement pattern is visualized during intermittent or continuous imaging. Enhancement patterns are described during subsequent vascular phases (e. g. arterial, portal-venous and late phase for liver lesions), similar to contrast enhanced computer tomography (CECT) and/or contrast enhanced magnetic resonance imaging (CEMRI). Contrast enhanced ultrasound (CEUS) and CECT or CEMRI are not equivalent as UCAs have different pharmacokinetics and are confined to the intravascular space, whereas the majority of currently approved contrast agents for CT and MRI are rapidly cleared from the blood pool into the extracellular space.

An inherent advantage of CEUS is the possibility to assess the contrast enhancement patterns in real time with a substantially higher temporal resolution than other imaging modalities, without the need to predefine scan-timepoints or to perform bolus-tracking. Furthermore, administration can be repeated due to the excellent patient tolerance of UCAs.

In addition to intravenous (IV) use, UCA intracavity applications such as intravesical administration can be performed.

UCA studies are subject to the same limitations as other types of ultrasound: as a general rule, if the baseline ultrasound is very suboptimal, CEUS may be disappointing.

1.2 Commercially Available Ultrasound Contrast Agents in Europe

Four transpulmonary UCAs are currently approved and marketed within European Countries:

- Levovist® (air with a galactose and palmitic acid as a surfactant) (Schering, introduced in 1996). Main indications include heart, abdomen, vesico-ureteric reflux and transcranial.
- Optison® (octafluoropropane (perflutren) with an albumin shell) (GE Healthcare, introduced in 1998). Sole indication is to date cardiac.
- SonoVue® (sulfur hexafluoride with a phospholipid shell)(-Bracco, introduced in 2001). Approved indications are cardiac (endocardial border delineation), macrovascular (cerebral and peripheral arteries, portal vein) and microvascular (characterisation of focal lesions in liver and breast).
- Luminity® (octafluoropropane perflutren with a lipid shell) (Bristol-Myers Squibb, introduced in 2006). Sole indication to date is cardiac.

The composition, packaging, storage, indications and contraindications of these agents are detailed in appendix 1.

There are other UCAs approved outside Europe or under investigation.

1.3 Imaging Techniques using Ultrasound Contrast Agents

1.3.1 Background on UCAs and contrast specific modes

The UCAs which are currently used in diagnostic US are characterized by a microbubble structure consisting of gas bubbles stabilized by a shell [3, 4, 6 – 8]. UCAs act as blood pool agents. They strongly increase the US backscatter and therefore are useful in the enhancement of echogenicity for the assessment of blood flow. While conventional ultrasound can detect high concentrations of microbubbles, in practice their assessment usually requires contrast-specific imaging modes.

Contrast specific US modes are generally based on the cancellation and/or separation of linear US signals from tissue and utilization of the nonlinear response from microbubbles [9 – 12].

Non-linear response from microbubbles is based on two different mechanisms:

- non-linear response from microbubble oscillations at low acoustic pressure, chosen to minimize disruption of the microbubbles,
- high energy broadband non-linear response arising from microbubble disruption.

Non-linear harmonic US signals may arise also in tissues themselves due to a distortion of the sound wave during its propagation through the tissue. The extent of this harmonic response from tissue at a given frequency increases with the acoustic pressure, which is proportional to the mechanical index (MI).

Low solubility gas UCAs (e. g. SonoVue®, Optison®, Luminity®) are characterized by the combination of improved stability with favorable resonance behavior at low acoustic pressure. This allows minimally disruptive contrast specific imaging at low MI and enables effective investigations over several minutes with the visualization of the dynamic enhancement pattern in real time.

Low MI techniques furthermore lead to effective tissue signal suppression, as the non-linear response from the tissue is minimal when low acoustic pressures are used [9, 12, 13].

US imaging with air filled microbubbles (e. g. Levovist®) at high pressure is dependent on microbubble disruption which is a significant limitation for real time imaging.

1.3.2 Intracavitary administration of UCAs

In addition to intravenous use, UCAs are suitable for intracavitary administration, particularly for performing contrast-enhanced voiding urosonography (VUS) [14 – 16]. After intravesical administration UCAs markedly enhance the US backscatter of bladder content. Consequently, refluxing microbubbles in the ureter and pelvicalyceal system and flow in the urethra are easily visualized. Levovist® has been approved for this indication in children in a number of countries. A few clinical studies using SonoVue® for sonographic reflux examination have been published recently [17 – 20].

1.3.3 Assessment of Anti-angiogenic Treatment

Since anti-angiogenic treatment very frequently induce lesion necrosis with no change in the volume of the initial tumor, new functional imaging technologies are particularly suitable for the early assessment of the response to treatment [21], a task for which the RECIST and WHO size criteria [22, 23] appear inappropriate. Studies of various types of tumor treated with targeted therapies have recently confirmed that the use of microbubble contrast agents enable early prediction of the response to treatment, demonstrating changes in tumor parenchymal perfusion and emergence of necrosis with no change in tumor volume [24, 25]. Early detection of the emergence of secondary resistance could also be demonstrated 6 to 9 months prior to the increase in lesion bulk, thus providing an opportunity for rapid adjustment of the therapeutic strategy [26].

1.3.4 Equipment and Technical Requirements

See systems specification in appendix 2.

1.4 Investigator Training

The EFSUMB minimal training requirements for the practice of medical ultrasound in Europe define three levels of training requirements [27]. It is likely that most CEUS examinations would be performed by level 2 or 3 investigators. Specific minimum training recommendations will be developed for the use of UCAs.

It is recommended that investigators wishing to undertake CEUS examinations should gain experience by observing contrast studies being performed by experts in this field. They should also ensure that their equipment is optimised for contrast examination by discussion with their equipment manufacturers. It is also important that in their own department there are sufficient numbers of examinations being performed and different types of pathological processes being observed to acquire and maintain their skills.

Practitioners need to be competent in the administration of contrast agents, familiar with any contra-indications and be able to deal with any possible adverse effects within the medical and legal framework of their country.

1.5 Safety Considerations

In general, UCAs are very safe with a low incidence of side effects. They are not nephrotoxic and do not interact with the thyroid and therefore it is not necessary to perform laboratory tests of renal function before administering them. UCAs are not licensed in pregnancy and breastfeeding is a contra-indication in some countries.

The incidence of severe hypersensitivity or allergic events is lower than current X-ray and comparable to MR contrast agents. Life threatening anaphylactoid reactions in abdominal applications have been reported with a rate of 0.001 % [28]. Investigators, therefore, should take the necessary precautions.

A few fatal events in critically ill patients who have undergone also contrast enhanced echocardiographic examinations have been reported. Contraindications for the use of Sonovue® were defined with the EMEA in 2004. In October 2007, the Food and Drug Administration issued a warning which cautions the use of Definity® and Optison® in patients with severe cardiopulmonary disease (FDA Alert 10/2007): the basis of this alert is currently under evaluation by the scientific and clinical communities, as well as other regulatory agencies, as of December 2007.

In echocardiographic applications, premature ventricular contractions have been described when high MI ultrasound and end-systolic triggering have been used together [29, 30], and the release of subclinical myocardial bio-markers has been reported in high MI clinical studies [31].

There is a theoretical possibility that the interaction of diagnostic ultrasound and UCAs could produce bioeffects. In vitro cellular effects that have been observed include sonoporation, haemolysis and cell death. Although observed in vitro, such bioeffects may have relevance for the in vivo situation as they result from interactions between single gas bodies and single cells. Data from small animal models suggest that microvascular rupture could occur when microbubbles are insonated. This might be a potential safety issue in special situations where such vascular damage would be clinically important such as ocular and brain US.

The MI provides a useful, albeit very rough, on-screen indicator of the potential for non-thermal effects. The potential for non-thermal bioeffects exists in all modes, including conventional 2D imaging and 3D methods.

Users should balance the potential clinical benefit from the use of UCAs against the theoretical possibility of associated adverse bioeffects in humans.

Some general recommendations are:

- Resuscitation facilities should be available.
- Caution should be considered for off label use of UCAs in tissues where damage to microvasculature could have serious clinical implications, such as in the eye, the brain and the neonate.
- As in all diagnostic ultrasound procedures, the operator should be mindful of the desirability of keeping the displayed MI and Thermal index (TI) low, and of avoiding unduly long exposure times.
- Caution should be exercised when using UCAs in patients with severe coronary artery disease.
- The use of contrast agents should be avoided 24 hrs prior to extra-corporeal shock wave therapy.

2 Liver

Focal liver diseases have evolved into the single most important application of CEUS (setting aside the applications in echocardiography) because of the marked improvement over conventional ultrasound in both their detection and characterisation. Subject to some limitations that are detailed in the following sections, CEUS now equals CECT and in some instances exceeds it in accuracy. Partly this is because of the real-time nature of modern contrast ultrasound which reveals important rapid flow phenomena; CT, with its intermittent imaging, sometimes misses these. Partly also the persistence of microbubbles beyond the large vessel enhancement period (the late phase) provides a marker for the sinusoidal space; lesions that lack this vascular space, notably metastases, appear as late phase defects.

Thus the late phase is mainly used for detection of malignancies and the arterial phase mainly for characterising focal liver lesions. In this section, characterisation is covered first, followed by detection. While this may seem illogical, it reflects the order of usage dictated by the liver's haemodynamics.

2.1 Characterisation of focal liver lesions (FLL)

2.1.1 Background

Due to the dual blood supply of liver tissue by the hepatic artery (25 – 30%) and the portal vein (70 – 75%), three overlapping vascular phases can be defined and visualized using contrast enhanced sonography. Depending on individual circulatory status, enhancement resulting exclusively from the hepatic artery supply usually starts from 10 – 20 seconds post-injection into a peripheral vein and lasts for approximately 10 – 15 seconds. This is followed by the portal venous phase, which usually lasts until 2 minutes after UCA injection. The late phase lasts until the clearance of the US contrast agent from the hepatic parenchyma, up to approximately 4 – 6 minutes post injection for SonoVue®. This late phase differs from the equilibrium phase of extracellular CT and MRI agents. The origin of this late phase is subject of ongoing scientific discussion; suggested mechanisms include sinusoid pooling and RES/Kupffer cells uptake [32, 33] (**Table 1**).

The arterial phase provides information on the degree and pattern of vascularity. The portal and late phases provide information about the wash out of UCA from the lesion compared to normal liver tissue.

Table **1** Vascular Phases in Contrast Enhanced Ultrasound of the Liver. The individual global haemodynamic situation in a given patient will influence the time of onset of the three vascular phase times

	visualization post-injection time (seconds)	
phase	start	end
arterial	10 – 20	25 – 35
portal-venous (PV)	30 – 45	120
late	> 120	bubble disappearance (approx. 240 – 360)

Portal and late phase enhancement can provide important information regarding the character of the lesion: most malignant lesions are hypo-enhancing while the majority of solid benign lesions are iso- or hyper-enhancing [34 – 59].

2.1.2 Study Procedure

2.1.2.1Low Mechanical Index (MI) Techniques

Low MI contrast specific techniques allow dynamic imaging with subsequent evaluation of the three different vascular phases using a low solubility gas UCAs.

The steps recommended in the study procedure are as follows:

- Baseline investigation in B-Mode, potentially including Doppler techniques.
- After identification of the target lesion(s) the transducer is kept in a stable position while the imaging mode is changed to low MI contrast specific imaging.
- Using low MI contrast specific imaging modes, it is crucial to provide sufficient tissue cancellation with maintenance of adequate depth penetration (a function of MI and gain, both of which must be adjusted). Adequate cancellation of tissue signals is characterized by disappearance of the B-Mode parenchymal liver structures. Major vascular structures and some anatomical landmarks such as the diaphragm remain barely visible.
- UCA is administered as a bolus injection followed by a 5 – 10 ml saline flush. It is adviced to use a needle diameter of at least 20 Gauge whenever possible to avoid loss of bubbles due to mechanical impact during injection. The needle diameter should not be smaller than 20 Gauge to avoid loss of bubbles due to mechanical impact during injection. A stop clock should be started at time of UCA injection.
- Because of the dynamic nature of real time CEUS, it is recommended to document the investigation on video or digital media (essential clips for each vascular phase should be stored).
- Note: In some contrast specific US modes a simultaneous display of tissue and contrast signals has been implemented. This modality is particularly useful for small lesions to ensure that the target lesion is kept within the scanning field during CEUS.
- A single bolus is usually adequate, but further injections can be used if the examination after the first bolus was inconclusive.
- Continuous scanning for 60 – 90 seconds is recommended to continuously assess the arterial and portal-venous phase. For assessment of the late phase scanning may be used intermittently until the disappearance of the UCA from the liver microvasculature has been observed.

2.1.2.2 High Mechanical Index (MI) Techniques

High MI techniques in which microbubbles are deliberately destroyed, have been initially used for characterisation of FLLs. When required, intermittent scanning of the lesion is performed during all 3 phases. Such high MI techniques are no longer recommended.

2.1.3 Image Interpretation and Evaluation (Enhancement Patterns of FLL)

2.1.3.1 Benign Lesions

Sustained enhancement in the portal-late phase characterizes most benign solid liver lesions. They can be further characterized by enhancement patterns during the arterial phase: e.g. enhancement of the whole lesion (typical of focal nodular hyperplasia [FNH]) or initial peripheral globular-nodular enhancement (haemangioma).

The typical enhancement patterns are summarized in **Table 2** for the following lesions: haemangioma, FNH, focal fatty sparing, focal fatty change, regenerative nodule, simple cyst, adenoma, abscess.

2.1.3.2 Malignant Lesions

Hypoenhancement of solid lesions (darker than the surrounding liver) in the late phase characterizes malignancies: all metastases show this feature and no exception has been reported to date. A typical HCC is characterized by arterial phase hypervascularity and wash-out in the late phase. Atypical variations occur, especially in well-differentiated tumours, as are described in the table. The arterial phase is important for demonstrating hypervascularity of HCC and of hypervascular metastases.

Bland (blood) thrombus is usually avascular, though when well organised, venous recanalisation channels may form. Since they are formed of at least partly viable tumour tissue, tumour thrombus in the portal or hepatic veins contains malignant neovascularity which can be demonstrated with CEUS. The enhancement patterns are different (a tumour blush rather than discrete vessels) and the arterial signals in tumour can be confirmed on contrast enhanced spectral Doppler [60]. A marked wash out in the portal and late phases may occur in metastatic portal vein thrombosis, up to anechoic appearance, resembling bland thrombus in this vascular phase [61].

The enhancement patterns used for the characterization of malignant lesions (HCC, hypovascular Mets, hypervascular Mets, cholangiocarcinomas) are summarized in **Table 3**.

2.1.4 Recommended Uses and Indications

CEUS should be performed and interpreted with knowledge of clinical and laboratory data. With typical enhancement patterns on CEUS and in an appropriate clinical setting, characterization of haemangioma, focal nodular hyperplasia, metastasis and HCCs can be obtained at a high level of probability and confidence. Focal liver lesions with atypical enhancement patterns or technical suboptimal studies require further investigation.

2.1.4.1 Recommended Indications

CEUS is indicated in the following clinical situations (**Fig. 1a, b**):

- Incidental findings on routine US.
- Lesions or suspected lesion in chronic hepatitis or liver cirrhosis.

Table **2** Enhancement (E) patterns of benign focal liver lesions

tumor entity	arterial phase	PV phase	late phase
haemangioma			
typical features	peripheral-nodular E, no central E	partial/complete centripetal filling	complete E.
additional features	small lesion: complete, rapid centripetal E		non-enhancing areas
	rim enhancement		
FNH			
typical features	hyper-enhancing, complete, early	hyper-enhancing	iso/hyper-enhancing
additional features	spoke-wheel arteries, centrifugal filling	hypo-enhancing central scar	hypo-enhancing central scar
	feeding artery		
focal fatty sparing			
typical features	iso-enhancing	iso-enhancing	iso-enhancing
focal fatty change			
typical features	iso-enhancing	iso-enhancing	iso-enhancing
regenerating nodule			
typical features	iso-enhancing	iso-enhancing	iso-enhancing
other features	hypo-enhancing		
simple cyst			
typical features	non-enhancing	non-enhancing	non-enhancing
adenoma			
typical features	hyper-enhancing, complete	iso-enhancing	iso/hypo
additional features	non-enhancing areas	hyper-enhancing	
		non-enhancing areas	non-enhancing areas
abscess			
typical features	rim E, no central E	hyper/iso-enhancing rim, no central E	hypo-enhancing rim, no central E
additional features	enhanced septa	hypo-enhancing rim	
	hyper-enhanced liver segment	enhanced septa	
		hyper-enhanced liver segment	

Table **3** Enhancement patterns of malignant focal liver lesions

tumour entity	arterial phase	PV phase	delayed phase
HCC			
typical features (in cirrhosis)	hyper-enhancing, complete	iso-enhancing	hypo/iso-enhancing
	non-enhancing areas	non-enhancing areas	
additional features	basket pattern/chaotic vessels		
	enhancing tumor thrombus in PV and/or HV		
atypical features	non-enhancing lesion	non-enhancing lesion	non-enhancing lesion
HCC in non cirrhotic liver	hyper-enhancing	hypo/non enhancing	hypo/non enhancing
hypovascular mets			
typical features	rim E	hypo-enhancing	hypo/non enhancing
additional features	complete E	non-enhancing areas	
	non-enhancing areas		
hypervascular mets			
typical features	hyper-enhancing, complete	hypo-enhancing	hypo/non enhancing
additional features	chaotic vessels		
cystic metastasis			
typical features	hyper-enhancing nodular/rim component	hypo-enhancing	hypo-enhancing
cholangiocarcinoma			
typical features	rim E	hypo/non enhancing	hypo/non enhancing
additional features	non-enhancing		

- Lesions or suspected lesion in patient with a known history of malignancy.
- Patient with inconclusive MRI/CT or cytology/histology results.
- Characterization of portal vein thrombosis.

2.1.4.2 Limitations

- Specificity and sensitivity are markedly reduced in attenuating livers and for deep-sited lesions.

2.2 Detection of focal liver lesions

2.2.1 Background

Conventional US is the most frequently used imaging procedure for the primary diagnosis of abdominal organs and the liver, but is less accurate in detection and staging of liver lesions than contrast-enhanced CT and MRI or intraoperative US. The main reasons for this are problems in the detection of small sized and/or isoechoic lesions, especially for deep lesions or in difficult anatomical areas (e.g. in the subdiaphragmatic areas).

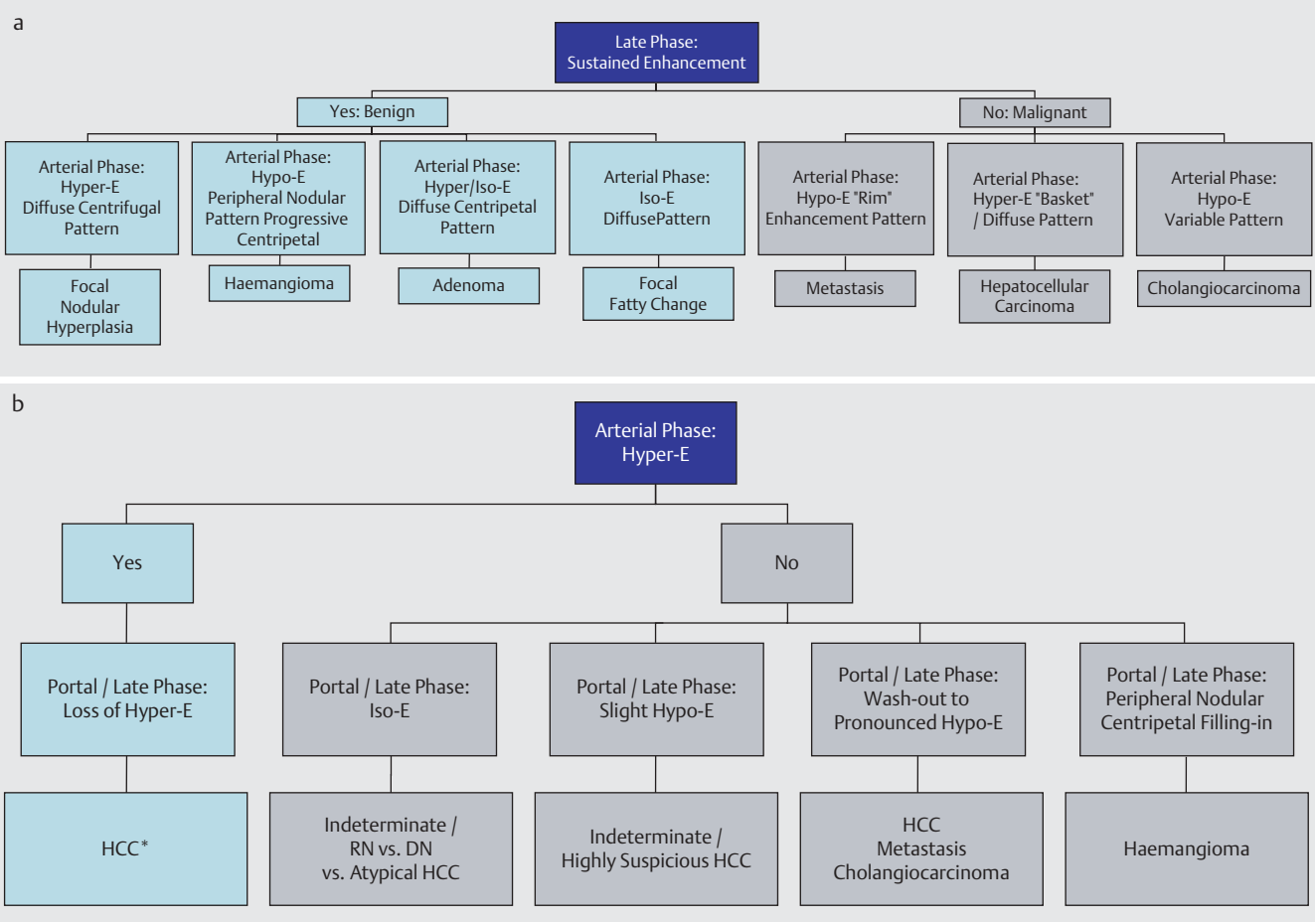

Fig. 1 **a** Characterisation Algorithm for FLL in Non-Cirrhotic Liver. **b** Characterisation Algorithm for FLL in Cirrhotic Liver.The diagnostic of HCC for lesions > 2 cm, newly emerged during surveillance in cirrhosis, can be established on CEUS alone. In addition to CEUS, a confirmation of arterial hypervascularisation and subsequent wash out by CT/MR is requested to establish the diagnostic of HCC in FLL 1 – 2 cm detected during surveillance, or in FLL > 2 cm emerged out of surveillance programs. HCC = Hepatocellular Carcinoma; DN = Dysplastic Nodule; RN = Regenerative Nodule.

Based on the published literature [62 – 64] there is clear evidence that CEUS improves detection of metastases compared to conventional US. Some studies have shown that the accuracy in the detection of liver metastases is comparable to CECT [65, 66] provided scanning conditions allow a complete investigation of all liver segments. Cholangiocarcinomas behave in the same way as hypovascular metastases and are well shown as late phase defects, even when they are not visualised on baseline ultrasound [56].

It has also been shown that CEUS can detect metastases not visible on CT [63, 65, 67, 68]. On the other hand, CEUS can also miss lesions shown on CT. The overall performance of both modalities is comparable.

Recent studies have shown that the addition of USCA improves the sensitivity and specificity of intraoperative US [69, 70] Contrast enhanced Intraoperative US (IOUS) is emerging as the new reference method for liver imaging in selected cases.

2.2.2 Study Procedures

2.2.2.1 Low Mechanical Index (MI) Techniques

The steps recommended in the study procedure are as follows:

- Baseline investigation in B-Mode, potentially including Doppler techniques.
- Change to low MI contrast specific imaging mode.
- Using low MI contrast-specific imaging modes, it is crucial to provide sufficient tissue cancellation with maintenance of adequate depth penetration (a function of MI and gain, both of which must be adjusted). Adequate cancellation of tissue signals is characterized by disappearance of the B-Mode parenchymal liver structures. Major vascular structures and some anatomical landmarks such as the diaphragm remain barely visible.
- UCA is administered as a bolus injection followed by a 5 – 10 ml saline flush. The needle diameter should not be smaller than 20 Gauge to avoid loss of bubbles due to mechanical impact during injection. A stop clock should be started at time of UCA injection.
- Because of the dynamic nature of real time CEUS, it is recommended that the investigation is to be documented on video or digital media (essential clips for each vascular phase should be stored).
- Note: In some contrast-specific US modes a simultaneous display of tissue and contrast signals has been implemented to ensure that a lesion seen on CEUS can be concurrently detailed on convention B-mode.
- A single bolus is usually adequate, but further injections can be used if the examination after the first bolus was inconclusive.

- Complete examination of the liver using various sweeps is possible within a time frame of approximately 4 – 5 min including all vascular phases.
- Scan in sweeps to cover the whole liver. The left lateral decubitus and sometimes the standing position improve liver coverage.
- For detection of hypovascular metastasis, the benefit of scanning before 90sec is debatable and some experts would avoid scanning before this time. On the other hand, if a lesion is visible on the baseline scan, this lesion should be scanned during the arterial and portal phase for characterisation (in addition to detection of other lesions) (for details see under 2.1.2 Characterisation, Investigation procedure).

2.2.2.2 High Mechanical Index (MI) Techniques

Due to the difficult examination technique, the routine use of high MI techniques and Levovist is no longer recommended.

2.2.3 Image Interpretation

2.2.3.1 Metastases

In the portal-venous and the late phase, metastases show as hypo-enhancing defects and these phases are the most useful time to detect them. In comparison, most benign lesions show uptake at this time and are therefore not likely to be confused with metastases.

The appearance of metastases in the arterial phase is variable. Hypovascular metastases show in CEUS as hypoechoic lesions with or without an additional rim enhancement, while hypervascular metastases show as brightly enhancing hyperechoic lesions.

2.2.3.2 HCC

Detection of HCCs, especially in the cirrhotic liver, may be difficult. They may be visualised as areas of increased enhancement in the arterial phase, but the short duration of this phase can make full surveillance of the whole liver impossible. The late phase appearances are variable, as previously described, but in a proportion of patients, HCCs are well shown as relative defects at this time and this can facilitate detection. There is currently no data to support the routine use of USCA in the detection of HCC. (For characterisation of indeterminate lesions in cirrhotic livers, see above.)

2.2.3.3 Inflammatory mass and abscess

Inflammatory masses and abscesses usually show arterial phase enhancement, which is rim-like in abscesses. Thereafter they wash out to appear as relative defects on late phase imaging. Detection and size assessment are thereby improved.

2.2.3.4 Trauma

Traumatic liver lacerations and haematomas are well demonstrated in all phases as non-enhancing defects. The same method is of value in other solid organs such as the spleen and kidney (for details see section 6 on trauma).

2.2.4 Recommended Uses and Indications

2.2.4.1 Recommended Indications

- All liver ultrasound scans to “rule out” liver metastases or abscess, unless conventional ultrasound shows clear evidence of these lesions.
- In selected cases, when clinically relevant for treatment planning, to assess the number and location of liver metastases as a complement to CECT and/or CEMRI.
- Surveillance of oncology patients where CEUS has previously been useful.
- Suspected cholangiocarcinoma where other imaging is inconclusive or not scheduled.
- Suspected liver trauma in some situations (see section 6.3 for details).

2.2.4.2 Limitations

- Although often readily shown, very small metastases (< 5 – 10 mm) may be overlooked as they may be too small to produce visible defects in the portal and late phases.
- Subdiaphragmatic lesions, especially those in segment 8, may not be accessible to conventional or contrast enhanced US. Intercostal scanning and positioning the patient in the left decubitus position can help reduce this limitation.
- Since CEUS has limited penetration, especially in the case of hepatic steatosis or cirrhosis, deep-sited lesions may not be accessible. Scanning in the left lateral decubitus position brings the liver forward and closer to the transducer and can help overcome this limitation and should be part of the routine survey.
- The falciform ligament and surrounding fat can cause an enhancement defect that may be confused as a metastasis.
- A potential pitfall is that small cysts, which were undetected on unenhanced US are sometimes detected on late phase scanning. These can often be distinguished from metastases as they characteristically show increased through transmission on CEUS. Careful re-evaluation with conventional US may help to show the cystic nature of these lesions.

2.3 Monitoring of Local Ablative Treatment

2.3.1 Background

Percutaneous ablation therapies play a key role in the management of patients with liver malignancies, both HCC and metastases [71 – 77].

Diagnostic imaging in patients undergoing local ablative treatment includes US, CECT and/or CEMRI during pretreatment diagnostic work-up and at distinct time points within the follow-up of the patient (usually within the first week post treatment and after 1, 3, 6 etc. months).

Unenhanced US, even when combined with color/power Doppler, does not provide any reliable information about the outcome of ablation treatments. The assessment of vascularization and tissue perfusion is crucial to differentiate necrosis from residual viable tumor. Biphasic helical CT or dynamic gadolinium-enhanced MRI can predict the extent of the coagulation area to within 2 – 3 mm.

When US is used as the imaging modality for guiding ablations, the addition of UCA can provide important information in each of the following procedural steps [78 – 85]:

- pre-treatment assessment of lesion vascularity in order to compare pre- and post-ablation patterns at the end of ablation and for better delineation of lesions poorly visualized on baseline US scans,
- guidance of the ablation needle/probe into lesions not visualized or not well delineated with unenhanced US,
- immediate assessment of the therapeutic result to detect residual viable tumour areas,
- post-ablation follow-up to assess treatment response.

2.3.2 Study Procedures

2.3.2.1 Pre-treatment Contrast-Enhanced Ultrasound

- For procedure, refer to 2.2.
- Accurate pre-treatment size assessment (measurement of the three largest diameters in two orthogonal scan planes) of every mass to be treated is mandatory. Either real-time volumetric (4 D) studies or post-processing volume reconstructions for volume calculation of every target are highly recommended. This enables accurate treatment planning: number of needle/probe insertions needed to thoroughly treat each tumor mass, path of every insertion and in case of large tumors, modality of overlapping contiguous ablation volumes [86, 87]. This procedure is to be performed under CEUS imaging only when CEUS and conventional US provide significantly different identifications of the mass borders. Field depth, selected scan plane, acoustic gain and mechanical Index (MI) (or acoustic power) used for the pre-treatment CEUS study of each lesion must be pre-defined.
- Images and/or movie clips are to be video- or digitally stored for precise comparison with immediate post-ablation studies.

2.3.2.2 Positioning of probe/needle (only when the lesion is not visible on unenhanced US).

- For procedure, refer to 2.2.
- Probe/needle is inserted during the vascular phase in which the target is optimally depicted.
- Periprocedural Assessment of Treatment Response (for thermal ablation).
- Unenhanced US is used to monitor the reduction of the hyperechoic "cloud" due to gas formation caused by ablation. This usually requires 5 –15 minutes.
- For procedure, refer to 2.2.
- For each treated lesion, the same system settings and scan planes must be used as for the pre-ablation assessment.
- Images and/or movie clips are to be digitally stored for comparison with previously stored pre-ablation images.
- If additional probe/needle insertions are performed, repeated doses of UCA can be given.

2.3.2.3 Follow-up Investigation to Assess Tumor recurrence

- See procedure described at 2.2.

2.3.3 Image Interpretation – Definition of Complete Treatment Response

The most important imaging finding that indicates complete ablation is the disappearance of any previously visualized intralesional enhancement on contrast-enhanced images. This must be assessed throughout the whole volume of each tumor which has undergone ablation. The size of the post-treatment avascular volume of the necrosis achieved should be compared with the size of pre-treatment volume of tumor(s). The simultaneous display of tissue and contrast signals, available on some equipment, is of particular value for short and long term follow up of treated lesions, to ascertain whether persistent enhancing portions of tissue are inside or outside the ablated lesion.

In hypoenhancing lesions (e.g. most liver metastases), completeness of treatment can be assessed by comparing the pre-treatment lesion volume and location with the volume and location of the post-treatment coagulated or necrotic region. This also determines whether if a sufficient perilesional "safety" margin has been achieved. Due to the reported high incidence of satellite nodules around small HCCs (5 – 10 mm range of distance from the main tumor [88]), it is strongly recommended to assess the presence and thickness of the "safety margin" following ablation not only for liver metastases but also for HCCs.

In the early (e.g., within the first 30 days) post-ablative evaluation using CEUS, a thin and uniform enhancing rim can be visible along the periphery of the necrotic area, similar to findings on CECT. Misinterpretation of this perilesional hyperemic halo as residual viable tumour can be avoided by comparing post-ablation images with pre-ablation scans.

2.3.4 Recommended Uses and Indications

- As a complement to CECT and/or CEMRI for pretreatment staging and assessment of target lesion vascularity. Pretreatment optimized CECT and/or CEMRI are recommended.
- Facilitation of needle positioning in cases of incomplete or poor lesion delineation on unenhanced US.
- Evaluation of immediate treatment effect after ablation and guidance for immediate re-treatment of residual unablated tumoral areas.
- Assessment of tumour recurrence, when follow-up CECT or CEMRI are contraindicated or not conclusive. Although CECT and/or CEMRI are considered to be the standard techniques for assessment of treatment outcome, CEUS may be used in the follow-up protocols.

3 Kidney

▼

In most centres, ultrasound is the preferred first imaging modality in patients with known or suspected renal disease. Main objectives are to measure renal size, to prove or rule out focal lesions, to detect obstruction of the collecting system and to look for vascular disorders by means of Doppler techniques [89]. Often unexpected findings like anatomic variations or focal lesions are detected and need further clarification.

The differentiation between simple cyst and solid or complex tumour can often be made by greyscale US. However, acoustic properties do not contribute in distinguishing between different types of tissue and therefore benign and malignant lesions may be difficult to distinguish. Pulse wave and color Doppler techniques help to characterize renal blood flow, with limitation because of attenuation, lack of sensitivity, blooming, and angle dependency. A benefit from using CEUS can therefore be expected [90].

The following recommendations deal with the uses of ultrasound contrast agents for the evaluation of the micro- and macrovasculature of the kidneys, including the characterization of focal renal lesions, the detection of lesions and the monitoring of local treatment. The use of CEUS in this indication has not yet obtained regulatory appoval and thus represents an off-label use, which should be justified by an individual risk/benefit assessment for the respective patient, based on the available scientific data.

3.1 Characterization of Focal Renal Lesions

3.1.1 Background

The kidneys receive 20 – 25% of the cardiac output. The renal cortex tissue receives 90% and the medulla the remaining 10%. Medullary blood flow is slower than cortical flow.

Unlike CECT or CEMRI, CEUS may be performed in patients with impaired renal function or uretric obstruction that may

be contraindications to performing contrast CT or Gadolinium enhanced MR examinations. UCAs have no reported clinical side effects on the kidneys in humans to date. Two contrast boluses are usually necessary in order to examine both kidneys. Although several papers describe the use of Levovist® with intermittent imaging, today most centres use low solubility gas agents such as SonoVue® with real time, low MI imaging.

As UCAs are confined to the vascular bed, CEUS can not provide information about the excretory function of the kidneys. The wash in phase can be divided into a short cortical enhancement phase, beginning 10 to 15 seconds after bolus injection, followed by a medullary enhancement phase which progresses much more slowly via the vasa recta, and proresses from the outer to the inner portion of the medulla. The duration of parenchymal enhancement depends on the vascular status and age of the patient, renal blood flow and the sensitivity of the US device used. Because of the high perfusion in the cortex, high microbubble concentration in the superficial parenchyma may cause attenuation in deeper portions of the kidney. This can be avoided by reducing the dose of contrast agent. In slim, easy to scan patients with superficial kidneys the dose may be reduced to 1 – 1.5 ml of contrast agent. The wash out phase is first recognized by a decrease in medullary enhancement, followed by a slower cortical wash out.

3.1.2 Study Procedure

3.1.2.1 Low Mechanical Index (MI) Techniques

Low MI contrast specific techniques allow dynamic imaging with evaluation of the different vascular phases using a low solubility gas UCAs.

The steps recommended in the study procedure are as follows:

- Baseline investigation in B-Mode, potentially including Doppler techniques.
- After identification of the target lesion(s) the transducer is kept in a stable position while the imaging mode is changed to low MI contrast specific imaging. For comparison, both normal and suspected abnormal renal tissue should be included in the scan plane.
- The MI setting should be adjusted to provide sufficient tissue cancellation with maintenance of adequate depth penetration. Major vascular structures and some anatomical landmarks should remain barely visible.
- UCA is administered as a bolus injection followed by a 5 – 10 ml saline flush as described in the liver chapter above. The needle diameter should not be smaller than 20 Gauge to avoid the loss of bubbles due to mechanical impact during injection. A stop clock should be started at time of UCA injection.
- Real time scanning performed for up to 180 seconds is recommended to continuously assess the wash in and wash out phases.
- In some contrast specific US modes, simultaneous display of tissue and contrast signals has been implemented. This modality is particularly useful for small lesions to ensure that the target lesion is kept within the scanning field during CEUS.
- Because of the dynamic nature of real time CEUS, the investigation should be documented on video or digital media.
- In patients with suspected vascular diseases (mainly small vessel diseases) or trauma, long and short axis views should be obtained during both the cortical and medullary phases.

3.1.2.2 High Mechanical Index (MI) Techniques

Due to the difficult examination technique, the routine use of high MI techniques is no longer recommended.

3.1.3 Image interpretation and evaluation

3.1.3.1 Benign and malignant renal lesions

Dinstinguishing between developmental anomalies (eg septa of Bertin) and neoplasm can be helped by a contrast study: the haemodynamics of pseudotumours are identical to the remainder of the kidney whereas true tumours usually show spatial or temporal differences from normal tissue.

So far there are no reliable criteria to distinguish malignant from benign tissue, for example renal cell carcinoma from renal metastasis, angiomyolipoma, oncocytoma and leiomyoma. Therefore, the value of CEUS in distinguishing different solid tumour entities is limited [91].

Some CEUS findings may be of clinical benefit in the work up of renal tumours. The proof of vascularization by showing tissue enhancement can demonstrate that the tissue is viable. This finding may be useful in evaluating echoic material within the collecting system or the urinary bladder, or in differentiating benign thrombus from venous tumor extension into the renal vein or the vena cava.

As in hepatic abscess, renal abscess shows an early rim enhancement and quicker wash out compared to normal renal cortex. Usually the pararenal tissue appears hypervascularized [92].

3.1.3.2 Complex cystic lesions

Complex cysts, which are classified as type 2F, 3 or 4 according to the Bosniak classification [93], are probably the best indication for renal CEUS [94]. So called complex cysts, a term adapted from CT and MR, are characterized by a thickened or irregular wall, calcifications, septa or solid components. UCA helps to characterize these lesions by demonstrating vascularization which suggests that the lesion is malignant. Therefore, CEUS may help in characterizing lesions in which CT and/or MRI studies are inconclusive or contraindicated.

3.1.3.3 Vascular diseases

The diagnostic value of CEUS in detecting or grading renal artery stenosis (RAS) is still controversial and so far probably not superior to established Doppler techniques in most patients. However, it may help to enhance backscatter signals from the renal arteries and thus decrease the number of inadequate Doppler studies [95 – 98]. Detection of segmental or subcapsular renal infarction and cortial necrosis are strongly improved by CEUS [99].

3.1.3.4 The transplant kidney

In the transplant kidney, CEUS can help in diagnosing arterial and venous thrombosis as well as infarction with great confidence [99, 100]. It can be employed to identify post interventional complications such as bleeding, hematomas, AV shunts or large false aneurysms in angiomyolipoma [101].

3.1.3.5 Renal trauma patient

See trauma chapter 6.

3.1.4 Recommended uses and indications

3.1.4.1 Recommended Indications

CEUS is indicated in the following clinical situations:

- Evaluation of anatomic variations mimicking a renal tumor ("pseudo-tumor").
- Characterisation of complex cystic lesions and suspected cystic renal carcinoma.
- Characterization of thrombus within the renal vein and vena cava.
- Suspected vascular disorders, including renal infarction and cortical necrosis.
- Renal trauma and follow up.
- Patients with contraindications for the use of contrast agents for CT or MR.

3.1.4.2 Limitations

- The short enhancement time limits the diagnostic window.
- Due to high bubble concentration during the corticomedullar phase, attenuation may cause shadowing in the deepest parts of the kidney.

3.2 Detection of Focal Renal Lesions

Despite the fact that today most renal tumours are detected by greyscale US, the sensitivity of CEUS is rather low in small tumours when being compared to contrast enhanced CT or MR. Except for a small group of patients with an increased risk of renal cell carcinoma (i.e. patients with Von Hippel Lindau disease and patients with end stage renal disease), routine use of CEUS for detection purpose can not be recommended.

3.3 Monitoring of local ablative treatment and after surgery

Ultrasound contrast agents may be useful in the immediate assessment of residual tumor after radiofrequency ablation (see liver chapter 2.3). They may also be helpful in demonstrating postoperative local complications such as bleeding or hematoma that may mimic a solid renal tumor.

4 Vesico-ureteric reflux

▼

4.1 Background

In addition to intravascular use, UCAs are suitable for intracavitary administration. Other than hysterosalpingography, the main application in this regard is for diagnosis of vesicoureteric reflux (VUR) after intravesical instillation [15]. This is the most commonly performed contrast-enhanced US examination in children. UCAs markedly boost the US backscatter of bladder content. Consequently, refluxing microbubbles in the ureter and pelvicalyceal system and flow in the urethra are easily visualized. Levovist® is approved for this indication in children in a number of countries.

A few clinical studies using SonoVue® for sonographic reflux examination have recently appeared though it is not approved yet for paediatric use [17]. No clinical side effects of intravesical administration of UCAs have been reported since their introduction over a decade ago.

The intravesical administration of UCAs for diagnosis of vesicoureteric reflux (VUR), called voiding urosonography (VUS), has become part of the routine diagnostic imaging modality options in children [15]. It is used in conjunction with or as a complete replacement for reflux examinations using ionizing radiation i.e. voiding cystourethrography (VCUG) and radionuclide cystography (RNC). Comparative studies, particularly between VUS and VCUG, have revealed the significantly higher sensitivity of VUS in reflux detection [14, 16, 17, 19, 102 – 109]. The time needed to perform a VUS may be longer than for a VCUG but this can be reduced by using advanced contrast imaging techniques [14, 16, 19]. When VUS is employed in routine practice there is the potential of more than 50% reduction of the number of children undergoing reflux examinations using ionising radiation [110].

The higher cost of UCAs compared to X-ray contrast agents is an impediment to the widespread use of VUS. With the newer UCAs such as SonoVue® there is potential for marked dose reduction with the possibility of performing several reflux examinations using just one vial, where permitted [17 – 20]. This would reduce the cost of the VUS examinations.

4.2 Study Procedure

4.2.1 Preparation

The UCA can be administered via a bladder catheter or suprapubic puncture. For the latter, a full bladder is necessary and it is advisable to apply an anaesthetic plaster at the site of puncture about an hour prior to the examination.

4.2.2 Procedural steps

The steps recommended in the study procedure are as follows [14 – 16]:

- Pre-contrast urosonography: baseline documentation of the whole urinary tract in supine (± prone) positions, paying particular attention to the terminal ureters and pelvicalyceal system.
- Intravesical administration of UCA and 0.9% normal saline [111] via transurethral catheter, suprapubic puncture/catheter. UCA – Levovist® concentration 300 mg/ml; dose 5 – 10% of bladder volume. 0.9% normal saline – volume is age-dependent.
- Post-contrast urosonography: monitor UCA administration; scan terminal ureters and alternatingly – going from side-to-side – both renal pelves.
- Post-contrast voiding urosonography: repeat above scan during and after voiding; the patient can be examined during voiding in one of the following positions: supine, prone, sitting or standing.
- ± Urethrosonography: transperineal scan of the urethra during voiding.

4.2.3 Procedural remarks

- When using Levovist®, fundamental US scanning may suffice for the diagnosis of reflux. The additional use of colour Doppler can increase the sensitivity of reflux detection [108, 112, 113]. Harmonic imaging has proved to be of considerable advantage in VUS as it markedly increases the conspicuity of the microbubbles and the detection rate of reflux [114 – 116]. Dedicated high MI imaging incorporating colour overlay of the microbubbles, subtraction and dual imaging brings about even more practical improvements.
- The air in the microbubbles of Levovist® diffuses out very rapidly when 0.9% saline from a vacuum-sealed container is infused into the bladder. This is because of the low saturation of the solution with air and results in marked shortening of the duration of contrast. Physiological saline solutions from plastic containers are saturated with air, but those from glass bottles are very rarely so [117].

- SonoVue® is not approved for VUS. Initial clinical studies have demonstrated that the dose necessary for intravesical administration is less than 1% of the bladder volume [17–20].
- Urethrosonography can be performed as part of VUS. Comparative studies have shown its high diagnostic accuracy compared to VCUG in both boys and girls [118–120].

4.3 Image interpretation

- Reflux diagnosis: reflux is diagnosed when echogenic microbubbles are detected in one or both ureters and/or the pelvicalyceal system.
- Reflux grading: the severity is graded into 5 degrees (Grade I–V) similar to the international reflux grading system of VCUG [121].

4.4 Recommended use and indications

4.4.1 Recommended indications

The main factor influencing the selection of VUS as the primary diagnostic imaging modality has been the necessity of depicting the urethra [110, 122, 123]. The additional scan of the urethra, even though technically feasible, is not commonly performed. Accordingly, the common selection criteria for VUS are as follows:

- Follow-up examination for reflux after conservative or surgical therapy.
- First reflux examination in a girl.
- Screening for reflux e.g. siblings, transplant kidney.

4.4.2 Limitations

VUS is not recommended, particularly as the primary imaging modality for reflux, in the following conditions:

- The bladder or one of the kidneys is not depicted on US e.g. in severe scoliosis.
- Routine evaluation of urethra (first reflux examination in boys).
- Assessment of bladder function.

5 Pancreas

▼

5.1 Background

The study of the pancreas is a new and promising application of contrast-enhanced ultrasonography (CEUS), including contrast-enhanced endoscopic ultrasound, and some recommendations may be now proposed.

Contrast-enhanced ultrasonography (CEUS) is not indicated to date to improve the detection of pancreatic lesions. CEUS can be used to improve delineation of pancreatic lesions compared to conventional ultrasound (US) or to characterize lesions already visible at US [124–127]. The use of CEUS in this indication has not yet obtained regulatory appoval and thus represents an off-label use, which should be justified by an individual risk/benefit assessment for the respective patient, based on the available scientific data.

5.2 Study procedure

The blood supply of the pancreas is entirely arterial. Enhancement of the pancreatic gland begins almost at the same time as aortic enhancement. After this early phase (arterial/pancreatic; from 10 to 30 sec) the venous/late phase persists for a short time (from 30 to approximately 120 sec) [124–126].

Dynamic observation of a given lesion during the arterial, parenchymal and venous phases should allow a better characterization and evaluation of its relationship with the peripancreatic arteries and veins.

After completion of the pancreatic study, an evaluation of the liver in the late phase should be performed exploiting the same injection [38, 124–126, 128–131].

5.3 Image Interpretation and Evaluation

5.3.1 Pancreatic carcinoma

Ductal adenocarcinoma is the most frequent pancreatic solid lesion and the most common tumour of the pancreas. At CEUS, ductal adenocarcinoma is typically hypoenhanced compared to the adjacent pancreatic tissue in all phases. This pattern is reported in 88 to 93% of cases [125, 126, 132–140]. The lesion size and margins are better visualized, as well as the relationship with peripancreatic arteries and veins [125, 126, 135].

Endocrine tumor are characterized by hypervascularization appearing typically hyperenhanced at CEUS [124, 127].

5.3.2 Pancreatitis

Focal pancreatitis has been reported to have similar enhancement features to the normal pancreatic parenchyma [133].

5.3.3 Pseudocysts and cystic tumors

CEUS improves the ultrasonographic differential diagnosis between pseudocysts and cystic tumors of the pancreas (e.g. mucinous cystadenoma, cystadenocarcinoma) by revealing vascularization of intralesional inclusions.

Pseudocysts, the most common cystic lesions of the pancreas, are non-vascularised: they do not show any signal at CEUS and remain completely anechoic in all phases, even when they are inhomogeneous on US. In some cases, peripancreatic vessels may be seen trapped inside the pseudocyst. Cystic pancreatic tumors usually have vascularized septa and parietal nodules [141].

The reported sensitivity and specificity of CEUS in characterising pseudocysts is up to 100% [138].

5.4 Recommended uses and indications

All the pancreatic lesions, in the absence of clear cut signs of malignancy (e.g. liver metastases), found at US should be studied with CEUS in order to improve:

- depiction of the dimensions and margins of the lesion including its relationship with adjacent vessels,
- characterization of the lesion (e.g. ductal adenocarcinoma, endocrine tumor),
- differential diagnosis between pseudocyst and cystic tumors,
- differentiation of the vascular (solid) or avascular (liquid/necrotic) components of the lesion.

6 Blunt abdominal trauma

▼

6.1 Background

Contrast enhanced CT (CECT) is the obvious modality of choice for the detection of parenchymal, skeletal and neurological damage, haemorrhage and thoracic injuries in all cases of high-energy multitrauma. However, there is a wide range of severity among trauma patients who are admitted to an emergency unit, and positive findings on CECT decrease with lower trauma energy. Many patients who have suffered low energy trauma are

haemodynamically stable and are able to cooperate. A large sub-group of low energy trauma patients have suffered blunt trauma to one abdominal flank. In this group the liver, spleen and kidneys are the parenchymal organs that are by far the most prone to injury, and a substantial proportion of these patients have no injuries on CECT. This should be weighed against the negative implications of CECT, which are the exposure to ionizing radiation and the injection of iodinated contrast. These negative implications become even more important as many of these patients are young and otherwise healthy.
Conventional greyscale ultrasound (US) is used around the world for assessment of free fluid in the abdomen in cases of trauma (FAST, or Focused Assessment with Sonography in Trauma). However, US has major limitations for the detection of parenchymal lacerations and even large lacerations can be undetectable.

6.2 Study procedures

Befor the CEUS exam begins, a US according to a FAST protocol is performed in order to detect or exclude the presence of free fluid. The liver, spleen and kidneys are examined with US. If it is determined that these can not be fully visualized, CEUS is not performed and CT is recommended.
Contrary to malignant or benign solid lesions, there is no circulation at all in haematomas or lacerations unless there is ongoing bleeding. This means that the detection of injuries is possible in all circulatory phases of the organs. Repeated small doses of UCA give the examiner more time for a thorough examination.

6.2.1 The liver

Active bleeding is best seen during the arterial phase, and lacerations are best seen when there is homogenous enhancement in the liver in the late phase. Two to three minutes after the first injection, a second administration of half the amount of the first bolus may be given to provide more time for scanning.

6.2.2 The spleen

The spleen generally enhances intensely for a long time, which may cause self-shadowing of the deepest parts by the UCA. Initially about one-fourth of a normal liver dose of UCA is recommended. The parenchyma of the spleen initially enhances in a patchy pattern, and the parenchyma is generally not evenly enhanced until about 40 seconds following the bolus. Once the parenchyma is evenly enhanced there is usually ample time for a thorough examination of the spleen without a reinjection. After a few minutes the veins of the spleen have been washed out and may mimic lacerations, but the veins can easily be defined as veins from to residual UCA signals and their typical anatomy.

6.2.3 The kidneys

Normally there is intense enhancement of the renal parenchyma, and initially one-fourth to one half of a normal liver dose of UCA is recommended. There is a fast turnaround of the UCA in the kidneys so that the enhancement usually results in only about two minutes of effective scanning. Scanning for injuries may begin immediately since most lacerations include the cortex. Since the kidneys are limited in size and can usually be covered in two planes fairly quickly, two minutes is usually enough for thorough scanning. If not, a reinjection of about half the original bolus prolongs the available examination time.

6.3 Recommended uses and indications

Since CEUS is not capable of screening the entire abdomen as it is possible with CECT, care must be taken not to perform CEUS instead of CECT as the first hand modality in cases where there is a clinically appreciable risk of injury to organs other than the spleen, liver or kidneys. Isolated low energy trauma to one flank very rarely involves other organs, but the trauma pattern must be assessed by the clinician in charge of each clinical case. The use of CEUS in this indication has not yet obtained regulatory appoval and thus represents an off-label use, which should be justified by an individual risk/benefit assessment for the respective patient, based on the available scientific data.
CEUS can sometimes be successfully used as an adjunct to multitrauma CECT in trauma cases where the CECT exam is of poor quality due to artefacts. Focused CEUS of an organ with equivocal results on CECT may establish or rule out injury in the particular area of interest.
CEUS should be considered for initial detection of lacerations, fresh subcapsular haematomas and fluid collections around the organs. It can also be useful to follow up known parenchymal injuries in order to avoid unnecessary repeat CECT with its risks. Thus, an initial CEUS examination may be useful at the time of the CECT when follow-ups can be expected.

6.3.1 Recommended indications

- CEUS is recommended in addition to FAST and US in the evaluation of traumatic parenchymal injuries to the liver, spleen and kidneys.

7 Transcranial Ultrasound

7.1 Background

The general indication for the use of transpulmonary UCAs in investigations of the cerebral arteries is a poor signal-to-noise ratio with unenhanced Doppler. Moreover, difficult diagnostic problems are often encountered in unenhanced transcranial color-coded sonography (TCCS) such as apparent “no flow, slow flow or low flow” phenomena. In such cases, administration of UCA enables differentiation between vessel occlusion and poor insonation conditions as well as detection of very slow blood flow velocities and low blood volume (**Table 4**).
Contrast-enhanced transcranial color-coded duplex sonography (CE-TCCS) is the best ultrasound technique for contrast imaging, as it provides simultaneous B-mode depiction of brain anatomy, which can be optimized without the Doppler signal. After UCA administration, the contrast agent can be detected simultaneously in several vessels.
UCAs can also be used to image brain perfusion in patients with cerebrovascular disease. This is because UCA can be detected in the cerebral microcirculation through a unique interaction with the ultrasound energy, thus allowing UCAs to serve as surrogate markers for blood. Of the approaches that have been developed for brain perfusion imaging, most clinical experience has been obtained with bolus kinetics. Other methods, which can be classified as experimental, include refill kinetics and diminution kinetics. Real-time, low mechanical index imaging with UCA is a particularly promising new application for evaluation of brain perfusion.

diagnostic problem	clinical example	
	intracranial	extracranial
poor ultrasound penetration	– poor temporal acoustic window – insonation of arteries at the contralateral hemisphere	– ultrasound attenuation by calcified carotid artery stenosis or postoperative edema (carotid-TEA) – anatomy: deeper arteries at the skull base (ACI-dissection)
slow blood flow velocity	– subtotal stenosis – aneurysm/AVM – vein/cerebral sinus	– subtotal stenosis (intra- or poststenotic)
low signal intensity	– detection of small vessels – detection of cerebral micro-circulation (tissue perfusion)	– residual lumen of a subtotal stenosis with high blood flow velocity

Table 4 Indications for the application of UCAs in neurovascular imaging of extra- or intracranial brain supplying arteries

7.2 Study Procedures

There are two general procedures using UCA bolus application.

7.2.1 Vascular imaging

- Transtemporal or transnuchal insonation in the axial planes with an insonation depth of 10 to 12 cm (transtemporal arterial investigation site ipsilateral to the probe). Coronal transtemporal insonation planes may also be used.
- After optimizing the acoustic bone window, the UCA is administered as a bolus injection:
  - Levovist®: the UCA is injected intravenously as a bolus (5 – 10 ml at the concentration of 400 mg/ml), followed by 10 ml saline flush,
  - SonoVue®: the UCA is injected intravenously as a bolus of 1 – 2 ml (up to 4.8 ml) followed by 10 ml saline flush.

7.2.2 Perfusion imaging

- Transtemporal insonation in the axial plane with an insonation depth of 10 to 12 cm (ischemic lesion ipsilateral to the probe). Other insonation planes may also be used.
- After optimizing the acoustic bone window with conventional B-Mode imaging, UCA is administered as a bolus injection:
  - Levovist®: the UCA is injected intravenously as a bolus (10 ml [1 – 2 ml/s], 400 mg/ml), followed by 10 ml saline flush.
  - SonoVue®: the UCA is injected intravenously as a bolus (2 ml [up to 4.8m]) followed by 10 ml saline flush.

7.3 Image Interpretation and Evaluation

7.3.1 Vascular Imaging

In most cases, CE-TCCS is used to differentiate between vessel occlusion and poor insonation conditions as well as for the detection of very slow blood flow velocities and low flow volumes (small vessels, vessel pseudo-occlusion). Beside the color information of the CE-TCCS the simultaneous Doppler frequency spectrum recording adds important haemodynamic information for the interpretation of the investigation.

Several technical artifacts should be considered when using CE-TCCS. Bolus application leads to peak concentrations of UCA that overload the ultrasound system with an overshoot of color signals (``blooming''). Doppler spectra cannot be measured in this early phase. The blooming artifact can be reduced by choosing a lower signal amplification or by using an UCA infusion. It decreases with falling UCA concentration. UCA injection leads to an artificial increase (15 – 36%) in maximum blood flow velocity [142, 143]. This technical artifact should be considered when using velocity criteria in the classification of stenoses.

7.3.2 Perfusion imaging

After UCA bolus injection, time intensity curves (TICs) with wash-in and washout phases can be generated using contrast-specific imaging and further analyzed. Different parameters of these curves can be extracted, such as time to peak intensity, peak width, or area under the transit curve.

7.4 Recommended Uses and Indications

7.4.1 Examination of the anterior circulation

Insonation through the temporal bone window can be impaired by a poor signal-to-noise ratio, especially in elderly patients in whom the bone is thickened. This can be overcome in most patients with CE-TCCS. After administration of UCA, over 85% of examinations of the middle cerebral artery, the anterior cerebral artery, the P1 and P2 segments of the posterior cerebral artery, and the supraclinoid portion of the internal carotid artery siphon are satisfactory.

7.4.2 Examination of the posterior circulation

Examinations of the intracranial vertebral arteries and the basilar artery are also facilitated by UCA. CE-TCCS through the foramen magnum can increase the depth at which vessels can be identified and improve the number of pathologic findings not seen in unenhanced scans and improve diagnostic confidence. UCA can also improve the detection of cerebellar artery segments.

7.4.3 UCAs in patients with internal carotid artery (ICA) stenosis

Particularly in patients with ICA stenosis and insufficient bone windows, characterization of collateral flow in the circle of Willis with UCA is important for estimating the hemodynamic risk of borderzone infarction in the ipsilateral cerebral hemisphere. When undergoing carotid endarterectomy, patients with absence of collateral flow are particularly vulnerable during carotid artery cross clamping. Thus, the use of UCA in patients with carotid stenosis and poor temporal bone windows can provide valuable information for patient management.

7.4.4 UCAs in stroke patients

Recent studies in stroke patients have documented successful examination of the basal cerebral arteries in only 55% with unenhanced TCCS. Fortunately, reliable diagnosis can be obtained in 90% of acute stroke patients after contrast enhancement. Correspondingly, in patients eligible for recombinant tissue-type plasminogen activator (rt-PA) thrombolysis, it may be advantageous to administer UCA without prior unenhanced scanning.

In patients with successful CE-TCCS exams receiving correlative angiography (MR, CTA or conventional angiography) the findings are identical in over 95%.

7.5 Limitations

- Despite administration of UCA, only the proximal segments of the basilar artery can be investigated. The distal portion can be examined using the transtemporal approach which leaves the middle portion of the basilar artery as a diagnostic gap in CE-TCCS.
- The quality of transtemporal precontrast scans is strongly predictive of the potential diagnostic benefit from administration of an UCA. In patients whose intracranial structures are not visible on B-mode imaging and whose vessel segments are not depicted with color Doppler, there is little chance that a contrast agent will provide diagnostic information. On the other hand, precontrast identification of any cerebral artery strongly predicts a conclusive investigation with an UCA.
- The main limitation to the bolus technique for evaluation of brain perfusion is the fact that it requires one UCA bolus injection per investigation plane. Therefore, the amount of contrast agent needed as well as the time for the investigation increases with the number of planes investigated. This limitation may be alleviated by new real-time, low mechanical index imaging protocols. The impact of current perfusion imaging parameters is limited by both physical (depth dependence of the signal intensity, microbubble destruction by ultrasound) and technical (low frame rates used in conventional harmonic imaging) factors. Until now, they can only describe but not actually measure cerebral perfusion or blood flow (due to bolus shape variations between subjects).

8 Technical Appendices

See appendices under www.efsumb.org.

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