Wen-Ping Wang · Yi Dong
Christoph F. Dietrich
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Contrast-Enhanced Ultrasound Imaging of Hepatic Neoplasms

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Preface

Contrast-enhanced ultrasound (CEUS) has revolutionized the clinical practice of liver tumor in recent decades. Nowadays, ultrasound contrast agents (UCA) are usually well tolerated without hepatotoxic or nephrotoxic side effects. The advantages of CEUS include no radiation, wide availability, absence of contraindications, no adverse events, and good cost efficiency. In comparison to CT or MRI, CEUS is the only "real-time" imaging technique that allows accurate and precise observation of contrast enhancement in the arterial phase. Liver tumors are most commonly used area of CEUS clinically. CEUS has a high diagnostic accuracy in the preoperative diagnosis of various malignant and benign focal liver lesions. Up till now, a standard textbook of clinical experience focusing on CEUS liver tumor has not been published.

For the last few decades, Zhongshan Hospital, Fudan University, is one of the most famous and earliest application centers of liver CEUS throughout China. The editors have accessed a wealth of experience from their expert contributors, who present the subject matter as concretely as possible and offer vivid descriptions of their own clinical practical techniques and experiences. In this book, the editors and authors explore general aspects of CEUS features of various kinds of benign and malignant liver tumors. It has a high diagnostic accuracy in the differential diagnosis of focal liver lesions. Furthermore, CEUS is used for the detection of metastases and therapeutic monitoring after local ablative procedures. The authors also introduce specific dynamic CEUS analysis and future developments. The editors and authors regard patient's clinical background information, such as presence of liver cirrhosis, history of other malignancy, or incidental finding crucial for the correct interpretation of CEUS findings. Also, the examination procedure differs slightly depending on the specific clinical indications, such as detection, characterization, or treatment response follow-up.

This book is an expression of interdisciplinary and multi-professional viewpoints. The principle of "clinical practice" is expressed in everyday practice. Particular attention should be given to clinical significance. We hope that this book will be useful for medical researchers and clinicians—both students at the beginning of their careers and experienced investigators who are well established. We are particularly hopeful that those at the beginning of their liver CEUS careers will take this book as a way forward in understanding complex diseases, and this book will help them in this journey. We also hope that clinicians will find useful information here as well and explore new application areas of liver CEUS, which will lead to new treatment approaches and provide useful insights into future clinical practice.

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Contents

Contrast Enhanced Ultrasound: History and Basic Principles

1

Christoph F. Dietrich, Yi Dong, and Wen-Ping Wang

Abbreviations

AASLD	American Association for the Study of Liver Disease
AUC	Area under the (time intensity) curve
AUWI	Area under the wash-in curve
AUWO	Area under the wash-out curve
CCA	Cholangiocellular Adenocarcinoma
CECT	Contrast Enhanced Computed Tomography
CEMRI	Contrast Enhanced Magnetic Resonance Imaging
CEUS	Contrast Enhanced Ultrasound
CT	Computed Tomography
EASL	European Association for the Study of the Liver
FLL	Focal Liver Lesion
FNH	Focal Nodular Hyperplasia
HA	Hepatic Artery
HCA	Hepatocellular Adenoma
HCC	Hepatocellular Carcinoma
ICC	Intrahepatic Cholangiocellular Carcinoma
IO-CEUS	Intraoperative contrast enhanced ultrasound
IOUS	Intraoperative Ultrasound
IV	Intravenous
IVC	Inferior Vena Cava
MI	Mechanical Index
MRI	Magnetic Resonance Imaging
MTT	Mean transit time
PI	Peak Intensity
PV	Portal Vein
RECIST	Response Evaluation Criteria in Solid Tumours
SWI	Slope of the wash-in
TIC	Time Intensity Curve
TICA	Time Intensity Curve Analysis
TPI	Time to peak intensity
UCA	Ultrasound Contrast Agent
US	Ultrasound or ultrasonography
US-FDA	United States (of America) Food and Drug Administration

1.1 Historical Remarks

The first mention of "echo" might be in Greek mythology. Echo was a nymph who was punished for talking too much, by being prevented from initiating speech: she could only repeat what others had said. In the first century, the Roman architect Vitruvius first used the word echo in a scientific sense during his study of reflected sounds and building acoustics.

The French scientist/priest Marin Mersenne (1588–1648) had an interest in music, which led him to study the physics of a vibrating string. He measured the time of return of an echo and provided the first estimate of the speed of sound (published in *Harmonie Universelle* in 1636). The Swiss mathematician and physicist Daniel Bernoulli (1700–1782) studied the pressure, velocity and equilibrium of fluids (published in *Hydrodynamica* in 1738), and thus laid out the principles for fluid dynamics; a

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modified version of Bernoulli's hydraulic formula is used today in Doppler ultrasonography. Ultrasound itself was discovered in 1794 by Italian biologist Lazzaro Spallanzani (1729–1799), who observed that bats oriented themselves through echoes by emitting high frequency, inaudible sound. In 1842, Austrian mathematician Christian Doppler (1803–1853) made the important discovery that the perceived change in frequency of sound waves was due to the relative motion of observer and source; this is now called the Doppler effect. The ability to produce ultrasound depended on the 1880 discovery of piezoelectricity by Pierre and Jacques Curie, who noted that an electric charge was produced when certain crystalline materials were compressed. The reverse was also true, i.e. when a crystal was subjected to an electric potential, it oscillated and emitted high-frequency sound.

The concept of using an external contrast agent to provide "contrast", i.e. to increase the visibility of anatomical structures during a sonographic examination, was an accidental finding by Clause Joiner who made the discovery written up by Gramiak and Shah. The first echo contrast signals were detected in M-mode images of cardiac cavities and large vessels [1]. They injected indocyanine dye to study a patient's cardiac output at the level of the aorta, and at ultrasound they unexpectedly observed an area of intense echogenicity over the right ventricle. The initial experience included mainly self-made hand-agitated or sonicated bubble suspensions.

Much later the development of commercial ultrasound contrast agents (UCAs) was started. In 1982 W.F. Armstrong and colleagues used a microbubble contrast agent to assess myocardial perfusion. In the early 1980s, S.B. Feinstein and colleagues experimented with sonication to create small, stable microbubbles. This led the United States Federal Drug Administration in 1990 to approve **Albunex** (Molecular Biosystems), consisting of sonicated albumin, as the first commercial ultrasound contrast agent for visualisation of cardiac cavities by intravenous administration.

The first contrast agent with broader use was **Echovist®** (Schering AG Berlin, Germany). The Echovist® suspension of galactose microparticles releases air microbubbles after mixing with an aqueous solution for imaging of the right heart chambers and did not cross the pulmonary circulation. Therefore, Echovist® could not be used for liver imaging.

1.1.1 Contrast Enhanced Ultrasound

Contrast enhanced ultrasound/Computed Tomography/Magnetic Resonance Imaging (CEUS) was the term introduced by members of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) [2]. CEUS was developed to enhance Doppler signals, both with **Levovist®** (Figs. 1.1 and 1.2) and **SonoVue®** (Fig. 1.3). After the first clinical use contrast specific low mechanical index techniques were developed thereafter.

1.1.2 Ultrasound Contrast Agents for the Liver

The first important CA for the liver was **Levovist®**, where the air microbubbles are stabilized by a coating with palmitic acid allowing left ventricular opacification and liver imaging in patients with normal pulmonary artery pressure. Although Levovist® was developed to enhance the intensity of Doppler signals in the peripheral circulation, even in small vessels in parenchymal organs, Levovist® also showed some enhancement in the liver in the post-vascular phase (after clearance from the bloodstream), due to uptake by phagocytosing cells (e.g. the Kupffer cells in the liver sinusoids) (Fig. 1.4). This phenomenon allowed discrimination of hepatic from non-hepatic tissue in the late phase. Levovist® was approved in Europe in 1995. Although this first-generation CA with air-based microbubbles was exciting at that time, it showed major limitations in contrast duration due to the rapid escape of the bubbles from the blood circulation. This is explained by pressure instability since the air is highly diffusible with high solubility in the bloodstream. Therefore, there was a need for next-generation microbubbles, containing more stable and therefore, high molecular weight lipophilic gases with low solubility in blood.

The next generation and finally the most important contrast agent entering the European and Asian market was **SonoVue®** (in the USA marketed as **Lumason®**), developed by Bracco (Italy). SonoVue® consists of microbubbles with a very flexible and therefore, highly echogenic shell of phospholipids, with a response over a broad range of frequencies from 1 to 10 MHz. SonoVue® has obtained regulatory approval for the use in children for liver imaging (USA) and detection of vesico–ureteric reflux in children (China, Europe, USA). SonoVue® obtained European approval in

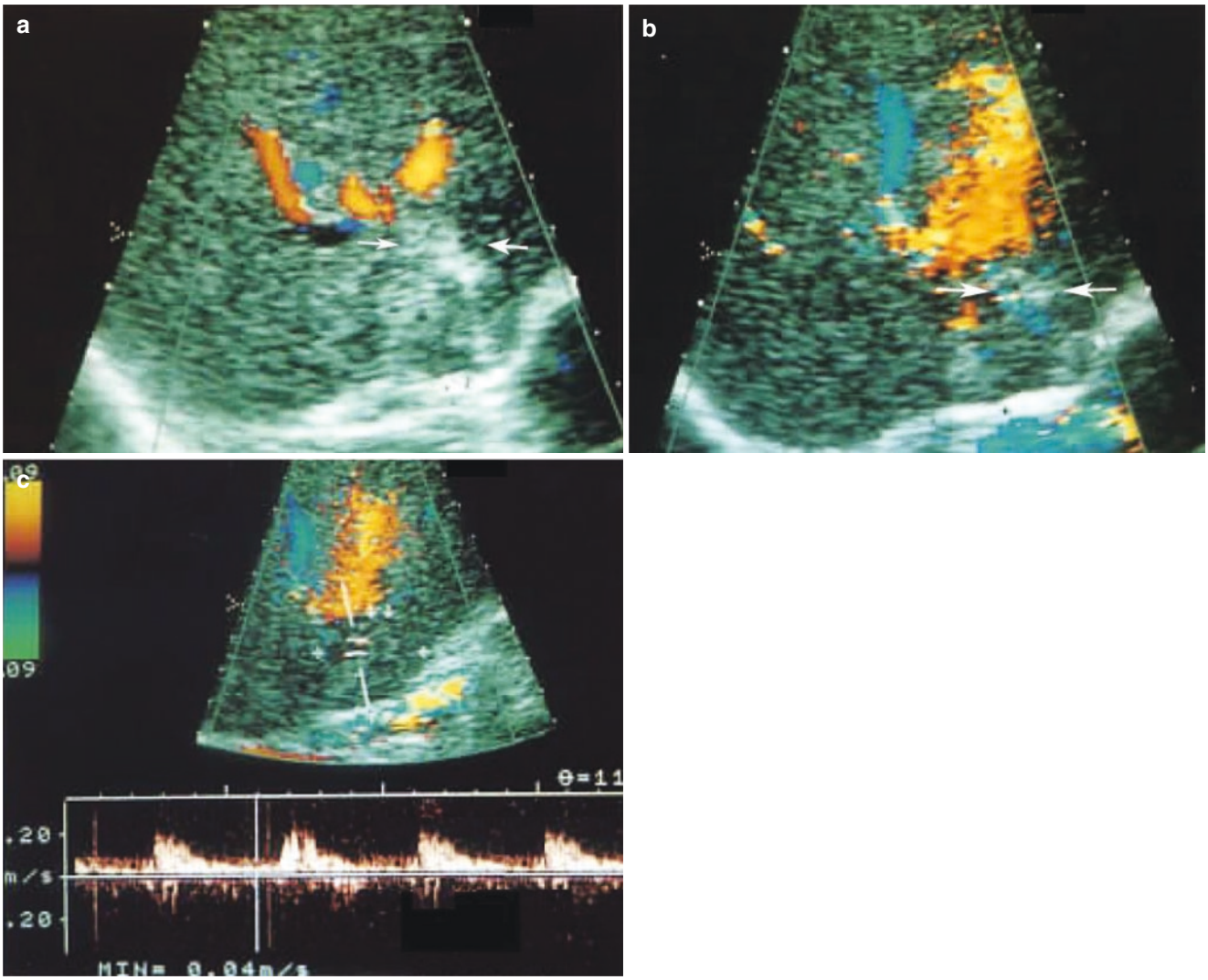

Fig. 1.1 Levovist® enhanced Doppler signals in liver contrast enhanced ultrasound. Hepatocellular carcinoma (HCC) smaller than 10 mm and located deeply in liver. Conventional colour flow ultrasound detected tiny blood flow signals inside the lesion (**a**). After injection of Levovist®, rich colour flow signals could be detected inside the lesion (**b**). Arterial spectrum with high RI (0.84) was measured afterwards (**c**)

2001 for the use in echocardiography (left ventricular opacification), macrovascular imaging (cerebral, carotid, and peripheral arteries) and microvascular imaging (characterisation of liver and breast lesions). **SonoVue®** is by far the most frequently used CA for CEUS liver imaging. **Echogen®** was approved for the liver but withdrawn from the market due to possible side effects.

In some Asian and European countries (Japan, South Korea, China, and Norway) **Sonazoid®**, developed by Nycomed in Oslo, Norway, has been licensed. Sonazoid® obtained national regulatory approval in 2006 in Japan and 2018 in China for assessment of focal liver lesions and is marketed by GE Healthcare and by Daiichi-Sankyo. The shell of Sonazoid® is more rigid and contains hydrogenated egg phosphatidylserine embedded in an amorphous sucrose structure, requiring a higher insonation power to produce non-linear signals. Similar to Levovist, Sonazoid® shows an uptake by cells of the reticulo-endothelial system (RES) resulting in a post-vascular phase enhancement in the liver (sometimes also called "Kupffer phase") [3, 4].

In an early comparative study focused on the detection of primary liver cancer with injection of CO_2 hepatic arteriosonography (**CO_2–HAS**) as ultrasound contrast agent, CO_2–HAS enhanced ultrasound and conventional ultrasound were compared in detection of primary liver cancer in 46 focal liver lesions (FLLs). Among which 22 FLLs were ≤3 cm, the other

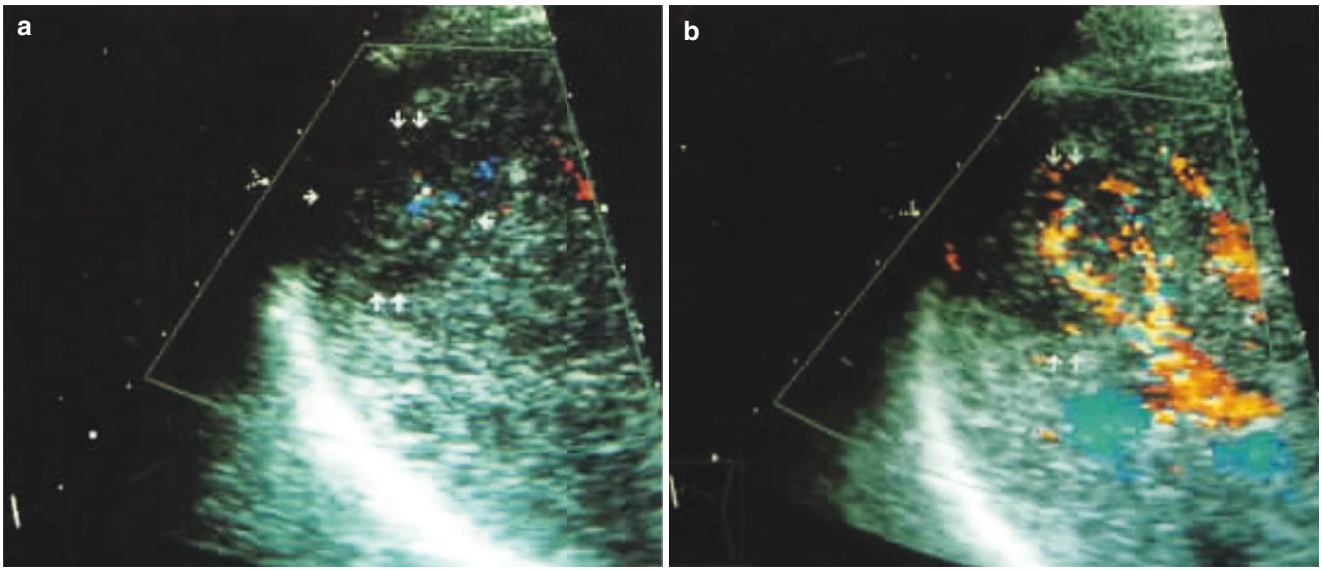

Fig. 1.2 Levovist® enhanced Doppler signals in a surgery and histopathologically proved hepatocellular carcinoma lesion. Conventional colour flow ultrasound detected tiny blood flow signals inside the lesion (**a**). After injection of Levovist®, rich colour flow signals could be detected inside the lesion (**b**)

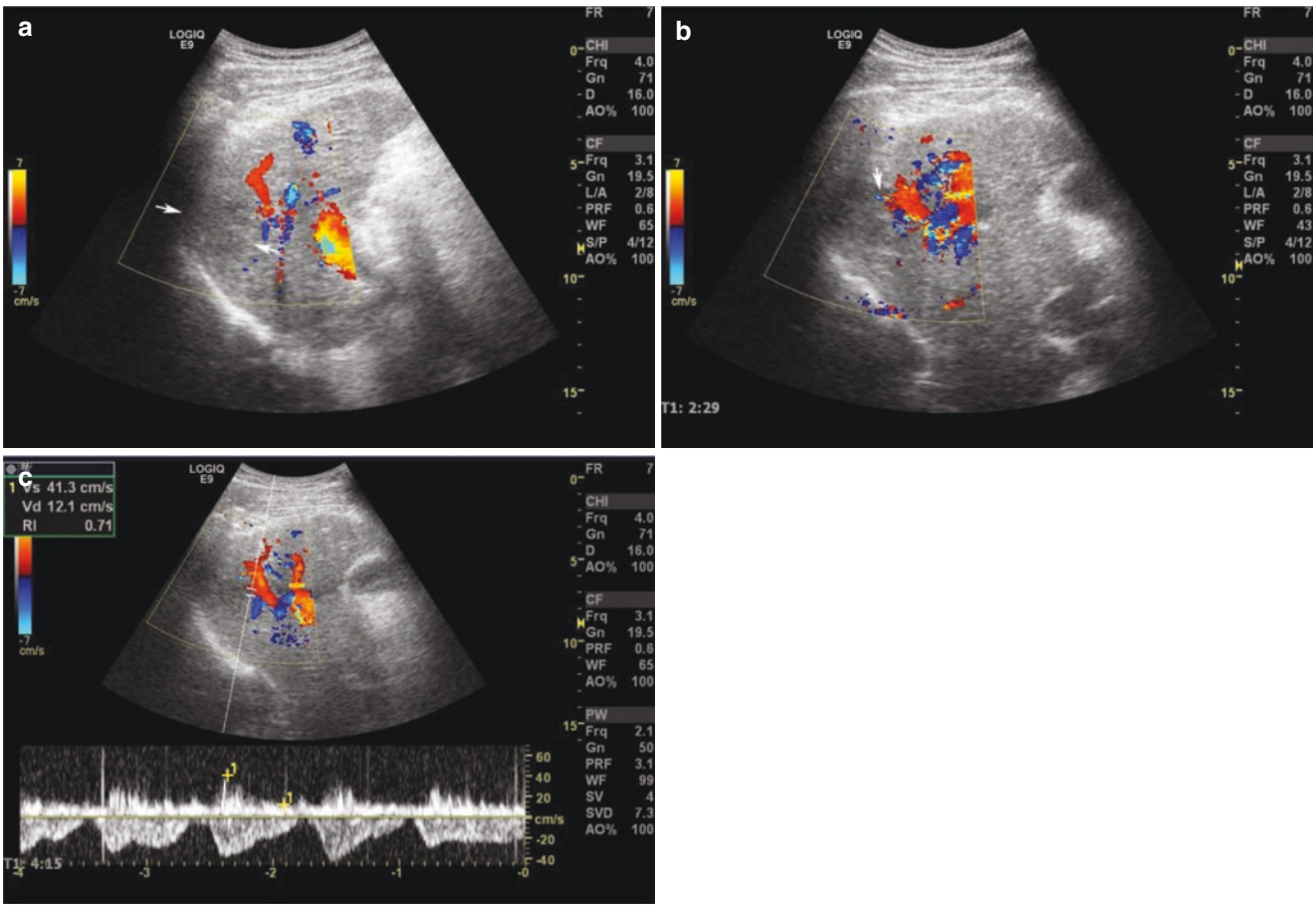

Fig. 1.3 SonoVue® enhanced Doppler signals in hepatocellular carcinoma (HCC) lesion. Conventional colour flow ultrasound detected no blood flow signals inside the lesion (**a**). After injection of Levovist®, rich colour flow signals could be detected inside the lesion (**b**). Arterial spectrum with high RI (0.71) was measured afterwards (**c**)

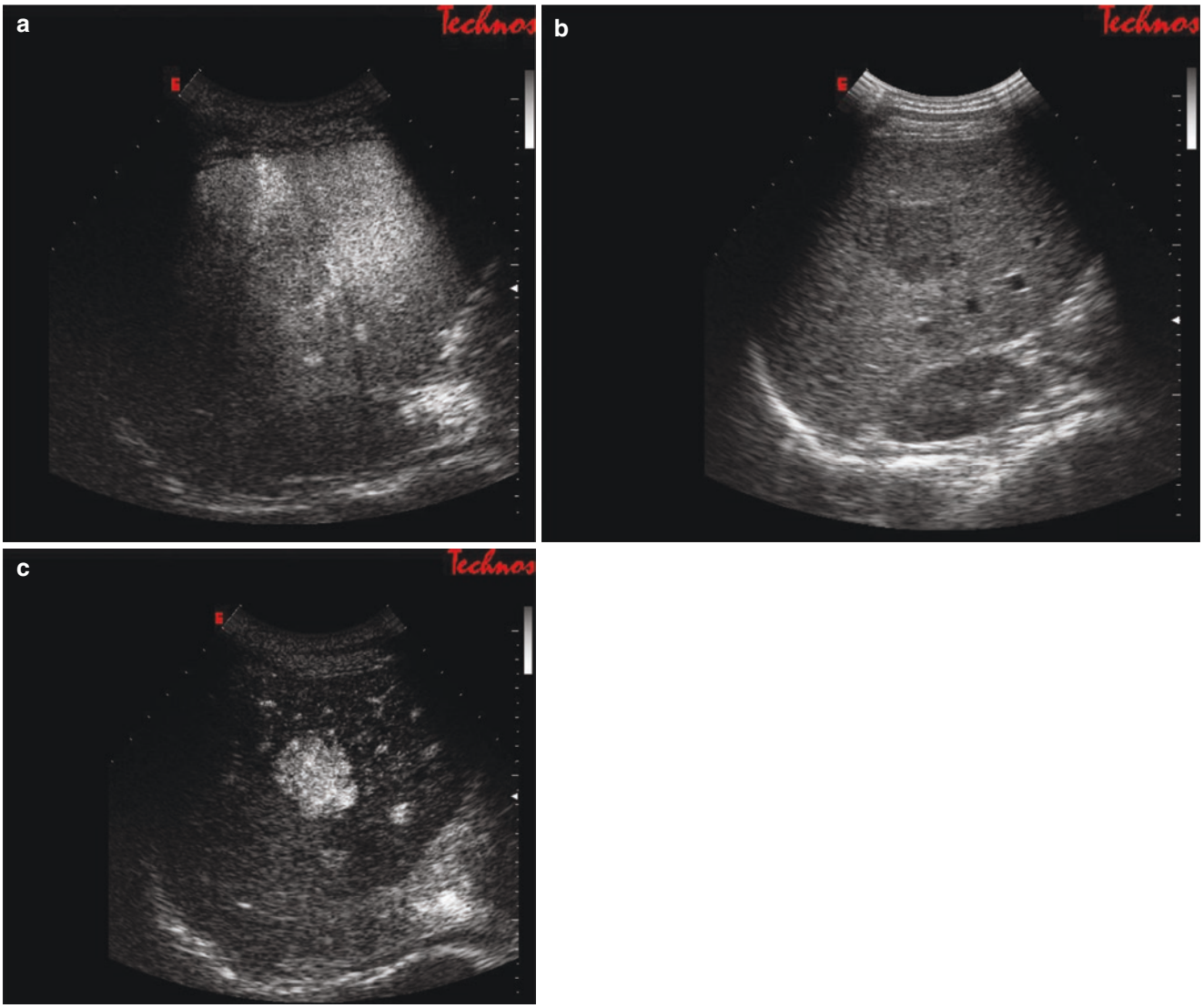

Fig. 1.4 Levovist® enhanced hepatocellular carcinoma (HCC) lesion during late phase (**a**). After clearance of microbubbles from the bloodstream (**b**), the lesion showed enhancement in the post-vascular phase due to uptake by phagocytosing cells (**c**)

24 were >3 cm in diameter. Their results demonstrated that CO_2–HAS enhanced ultrasound showed higher diagnostic accuracy and sensitivity in detection small (≤3 cm) FLLs while compared with conventional ultrasound (accuracy 54% vs. 91%, sensitivity 59% vs. 95%). The CO_2–HAS enhanced liver CEUS was a promising valuable imaging method in the detection of small primary liver cancer (Fig. 1.5).

1.1.3 Ultrasound Contrast Agents for Use Outside the Liver

Other UCAs on the market are used for different purposes. Such UCAs should be mentioned as well since a few off-label liver imaging studies have been reported in the published literature. Historically important for left ventricular enhancement is **Albunex®**, a dispersion of sonicated human albumin, containing air-filled microbubbles, which was developed by Molecular Biosystems Inc. San Diego, USA (regulatory approval in the USA in 1993). The follow-up contrast agent was **Optison®** (regulatory approval in the USA in 1998 for left ventricular opacification in echocardiography) with perflutren gas instead of air but otherwise similar to Albunex®. Optison® was developed by Molecular Biosystems Inc. and acquired later by Mallinckrodt and finally marketed by GE Healthcare. **Definity®** has been developed by ImaRx Pharmaceutical Corp in Tucson, USA, which today operates as Lantheus Medical Imaging. Definity® (containing a phospholipid shell) was approved in the USA in 2001 and in Europe in 2006 for left ventricular opacification in echocardiography but not for liver imaging. Definity® is marketed outside of the USA (Europe) as

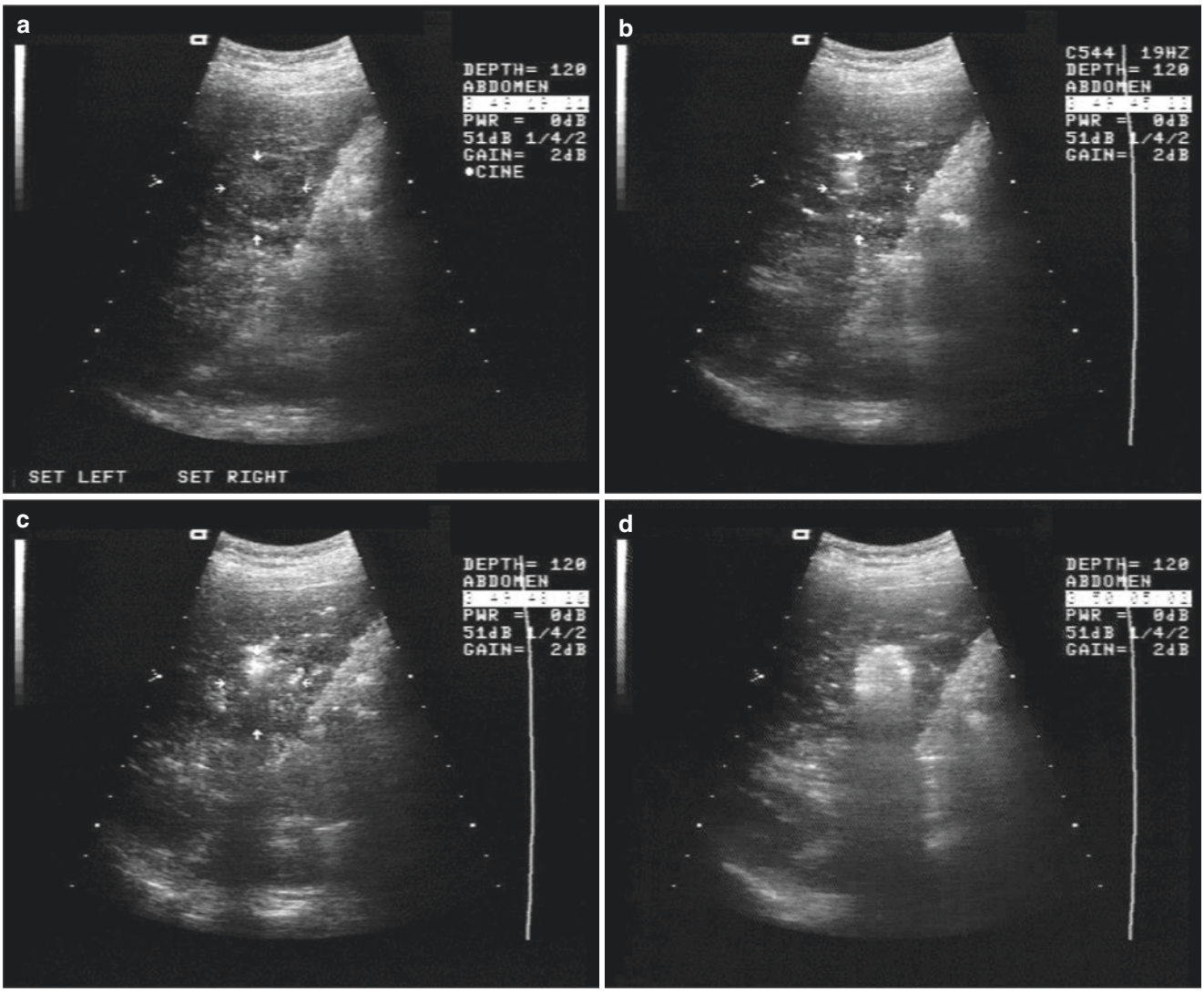

Fig. 1.5 CO_2–HAS enhanced liver contrast enhanced ultrasound. B mode ultrasound detected a hypoechoic focal liver lesion in the right lobe of liver (**a**). After injection of CO_2 hepatic arterio-sonography (CO_2–HAS) as ultrasound contrast agent, the lesion showed gradually hyperenhancement during arterial phase (**b**, **c**), until the whole lesion was completely hyperenhanced (**d**)

Luminity®. A further phospholipid shell agent **Imagent®** was approved by the FDA in 2002 for left ventricular border definition echocardiography but Imagent® has been withdrawn from the market. Many other UCAs have been studied in preclinical and clinical development (e.g. Quantison®, Myomap®, AI700, CardioSphere®, PESDA) but never obtained regulatory approval for human use [5].

1.2 The Introduction of a New Method

The introduction of a new diagnostic tool into clinical practice has always been a complex process. There is generally a first phase characterised by enthusiasm and optimism of the proponents proposing and performing the new technique and usually reporting convincing results, which seem to be significantly better than those achieved by previous techniques in the same field. The counterpart to this optimism is often the scepticism of the majority of clinicians not involved in using the technique. The subsequent phase, often occurring many years later is characterised by a more balanced evaluation, based on the accumulation of reliable data in the literature and extensive experience in clinical practice, leading to scientific societies producing clinical guidelines, where general agreement on the advantages and limitations of the technique and its diagnostic accuracy has been reached. At this stage and after 20 years of experience we discuss CEUS of the liver, which has been implemented into important international guidelines [2–4, 6–8].

1.2.1 Choice of Transducer

For liver imaging, curvilinear arrays are preferred for most cases. Linear probes with higher transmission frequencies may be useful for cases where there are superficial lesions and when more spatial resolution is necessary [9]. In this case, higher contrast doses may be beneficial, as the agents become less efficient non-linear scatterers at higher frequencies [10]. The settings are different compared to the conventional curved array abdominal scanners and readjusting the CEUS parameters is necessary. Different transducers have specific CEUS optimised settings (Figs. 1.6, 1.7 and 1.8).

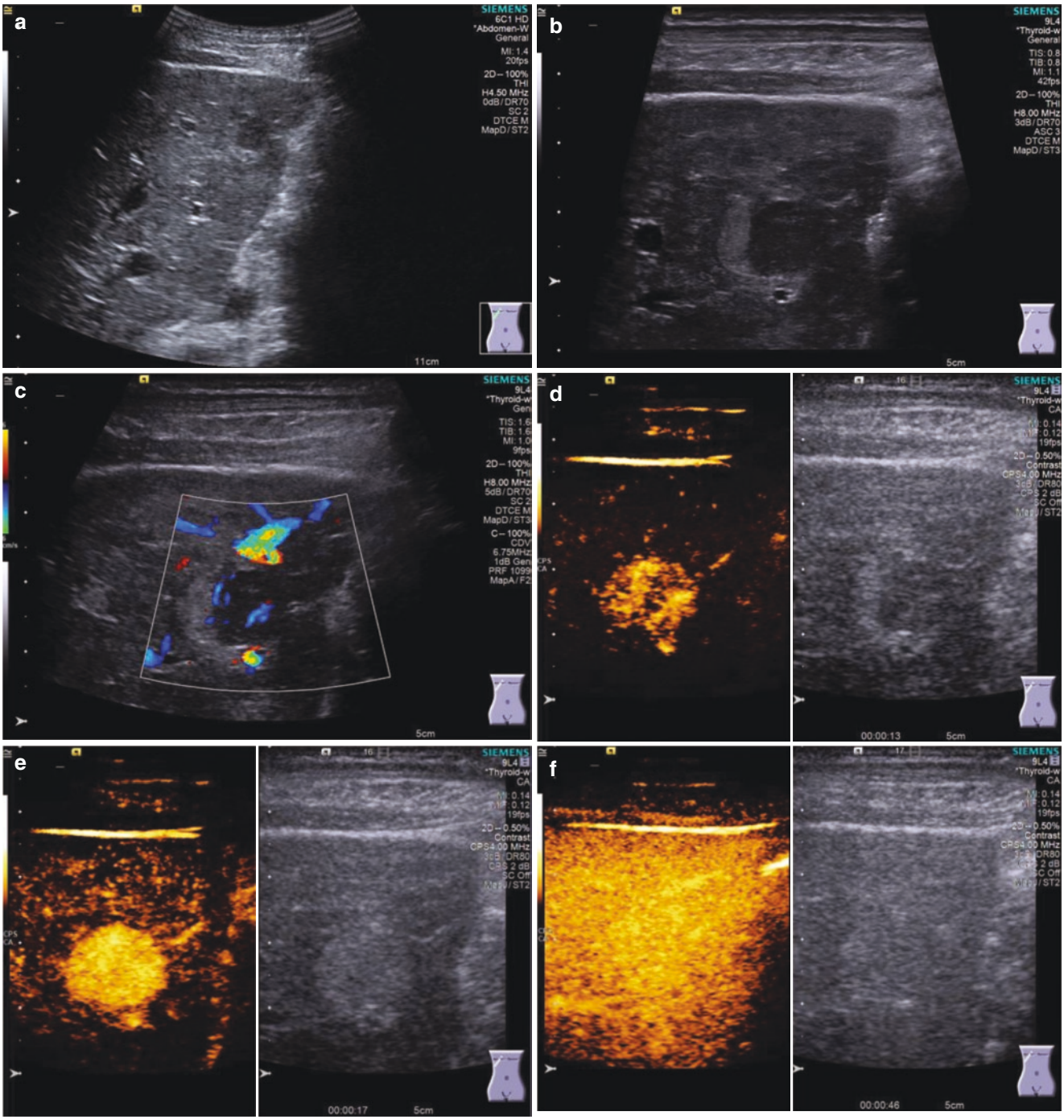

Fig. 1.6 SonoVue® enhanced liver contrast enhanced ultrasound. B mode ultrasound (BMUS) detected a small hypoechoic focal liver lesion in the right lobe of liver (**a**). By using high frequency linear transducer, the lesion was more clear on BMUS (**b**). Colour flow signals could be detected inside the lesion (**c**). After injection of SonoVue® as ultrasound contrast agent, the lesion showed rapid hyperenhancement during 13 s (**d**) and 17 s (**e**) in arterial phase. After 46 s, the lesion was completely isoenhanced until the late phase (**f**). Surgery and final histopathological results indicated it was a well-differentiated hepatocellular carcinoma (HCC)

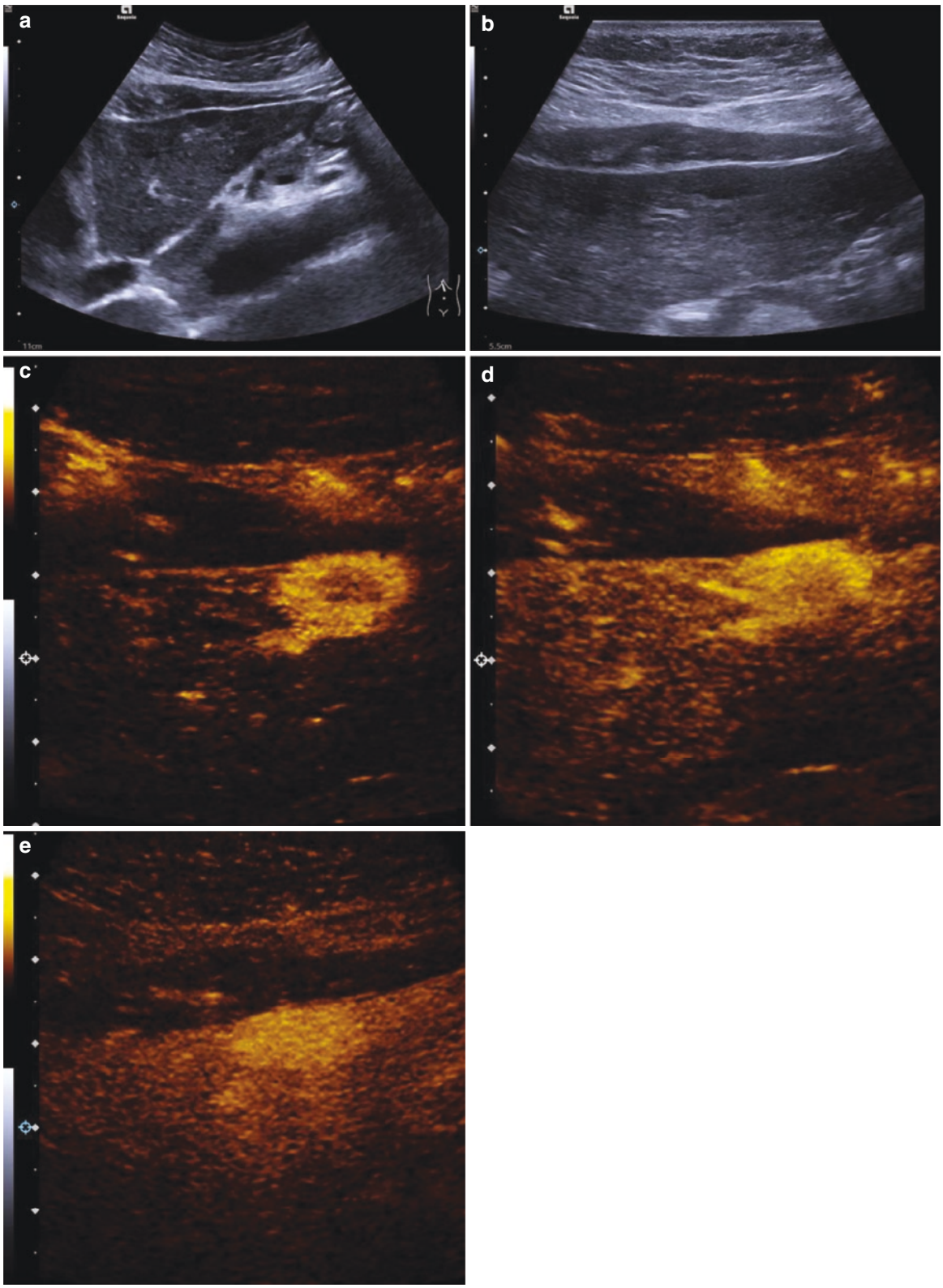

Fig. 1.7 SonoVue® enhanced liver contrast enhanced ultrasound. B mode ultrasound (BMUS) detected a small hypoechoic focal liver lesion in the superficial area of left lobe of liver (**a**). By using high frequency linear transducer, the lesion was more clear on BMUS (**b**). After injection of SonoVue® as ultrasound contrast agent, the lesion showed peripheral rim hyperenhancement during 13 s (**c**) and 27 s (**d**) in arterial phase. After 57 s, the lesion was completely hyperenhanced until the late phase (**e**). Imaging follow up indicted it was a liver heamengioma

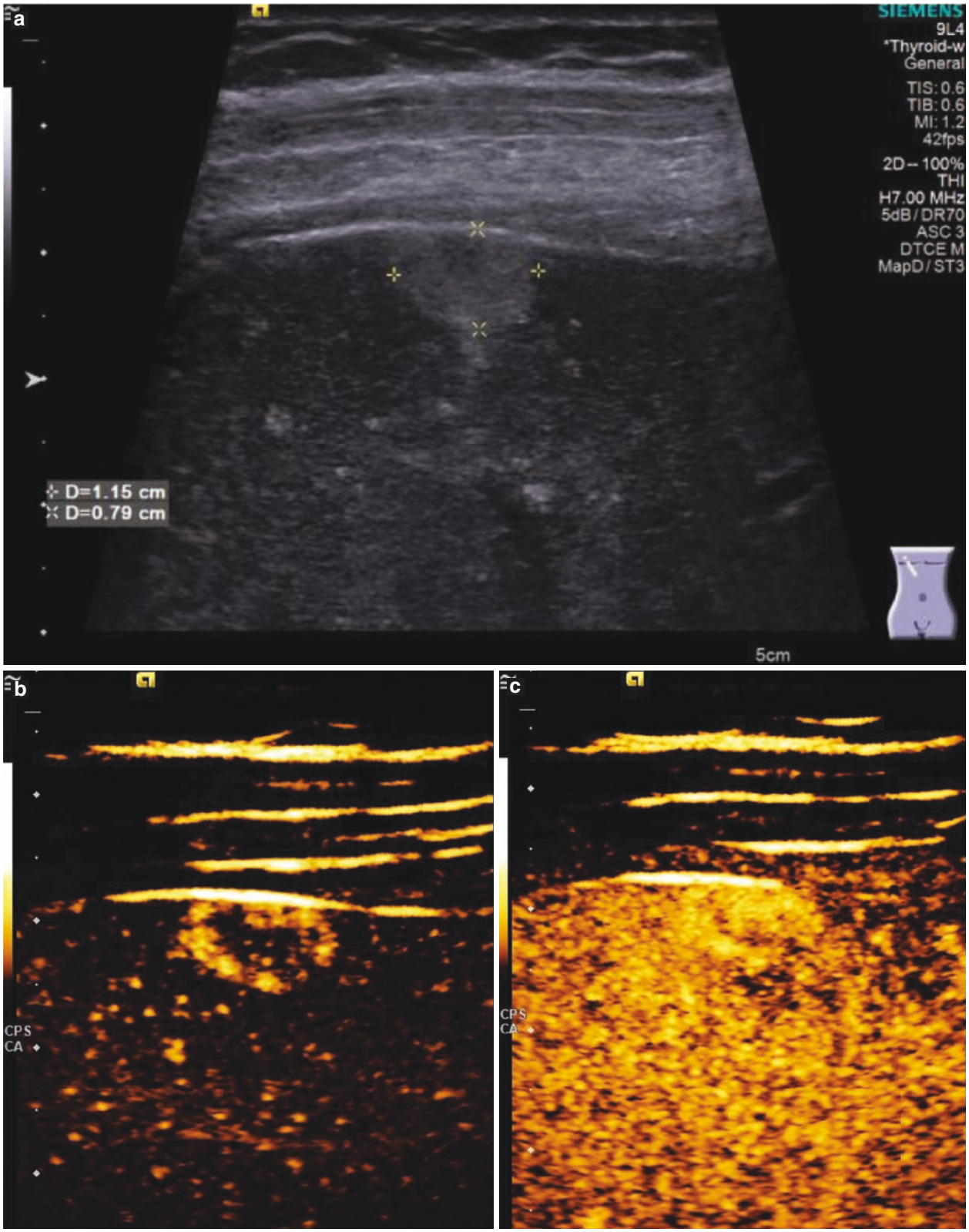

Fig. 1.8 SonoVue® enhanced liver contrast enhanced ultrasound. B mode ultrasound (BMUS) with high frequency linear transducer detected a small hyperechoic focal liver lesion in the superficial area of right lobe of liver (**a**). After injection of SonoVue® as ultrasound contrast agent, the lesion showed peripheral rim hyperenhancement during 17 s in arterial phase (**b**). After 47 s, the lesion was completely hyperenhanced until the late phase (**c**). Imaging follow-up indicted it was a liver heamengioma

1.3 Contrast-Specific Ultrasound Techniques

CEUS is highly dependent on the interaction of contrast microbubbles with the ultrasound wave. In fact, the evolution of CEUS is closely correlated with the development of contrast-specific imaging techniques. Early in its development researchers tried to display contrast enhancement inside parenchymal tissue, e.g. for assessment of myocardial perfusion.

However, two major problems had to be solved:

1. The attenuation caused by high bubble concentration in the cardiac cavities.
2. The overlay of tissue signals from the cardiac wall.

Shapiro, therefore, used intracoronary administration to avoid cavity contrast and achieve a high local microbubble concentration [11]. Then Doppler techniques were used to get selective signals from microbubbles without overlying tissue signals [12]. The cancellation of tissue signals was based on velocity, so that only flowing microbubbles (e.g. in the heart cavity or large vessels) could be displayed. Later it was detected, that Doppler signals could also be obtained from stationary microbubbles, when they are destroyed by high insonation power. The disappearance of the bubble signal from one frame to another is interpreted by the colour Doppler autocorrelation algorithm as movement of the bubble. However, this contrast signal exists only for a very short moment (like a flash) and was named stimulated acoustic emission [10]. The final goal, however, was to display the microbubble signals separated from tissue signals continuously, allowing real-time imaging of contrast wash-in and wash-out in parenchymal tissue. This requires insonation with highly reduced insonation power (low-MI imaging) minimizing the destruction of microbubbles in the sound field. The separation from tissue signals was achieved by the introduction of frequency filtering and later pulse-summation techniques, benefitting from the characteristic acoustic response of microbubbles oscillating in the ultrasound field (non-linear signals with harmonic frequency components) [13, 14]. Today most ultrasound manufacturers have a contrast mode available, based on the summation of pulses with inverted phase (phase inversion, phase modulation), modified amplitudes (amplitude modulation, power modulation) or a combination of both. CEUS does not influence elastography evaluation [15].

1.4 CEUS Phases

CEUS allows real-time imaging, recording and evaluation of the enhancement (wash-in) and wash-out phases of the ultrasound contrast agent (UCA) over time. The duration of signals depends on the UCA used and the technical equipment. The contrast imaging of the liver provides dynamic visualisation of four different phases explained by the specific dual blood supply to the liver: The arterial phase (AP), the portal venous phase (PVP), the late (sinusoidal) phases (LP) and the post-vascular phases (Fig. 1.9).

Microbubble destruction occurs by excessive ultrasound energy most often caused by continuous scanning in a single plane. The disrupted shell allows the gas from the microbubbles to diffuse and the microbubbles lose their scattering properties and are no longer effective contrast agents. Bubble destruction may mimic lesion wash-out.

Since microbubble destruction cannot be totally avoided the practical advice is to scan continuously for up to 60 s including the peak of arterial enhancement and record a cine loop. Thereafter scanning should be intermittent, with storage of single images or short loops to document hyperenhancement or the presence of wash-out.

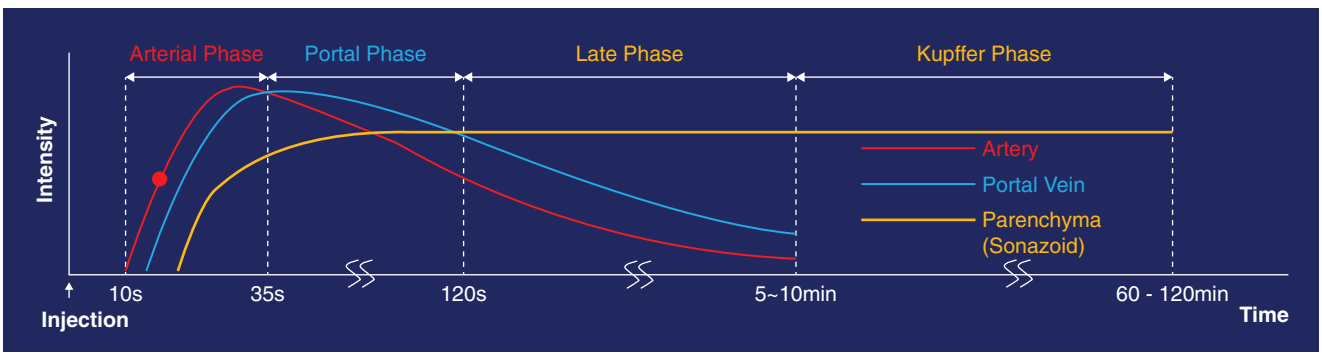

Fig. 1.9 Contrast enhanced ultrasound (CEUS) phases. The contrast imaging of the liver provides dynamic visualisation of four different phases explained by the specific dual blood supply to the liver: The arterial phase (AP), the portal venous phase (PVP), the late (sinusoidal) phases (LP) and the post-vascular phases

1.5 Comparison of Methods: CEUS, CECT and CEMRI

In general, the wash-in and wash-out of a contrast agent during contrast enhanced computed tomography (CT) using iodine chelate and magnetic resonance imaging (MRI) using gadolinium chelate, have phases that are comparable to those of CEUS. Nonetheless, several important differences must be taken into consideration. Firstly, during CT and MRI the contrast agent distribution is only sampled in a static manner at a few previously defined time points. The first phase (arterial) occurs >20 s after injection, so the very early contrast wash-in phase can be missed. Secondly, CT and MRI contrast agents leak out of the vascular bed immediately after wash-in and are distributed in the entire extracellular fluid space (equilibrium phase). This can result in discordant results compared to CEUS, e.g. in the case of varying degrees of vascularity in fat-containing lesions in comparison to the surrounding tissue ("observations" according to the Liver Imaging Reporting and Data System, LI-RADS) [16–19]. The detection of small lesions in the late phase can be significantly complicated by the diffusion of the contrast agent back into the lesion since wash-out of the contrast agent can be obscured [20, 21].

Thirdly, in some vascular Focal Liver Lesions (FLL) such as metastases of pancreatic neuroendocrine neoplasms, the enhancement occurs over only a few seconds and can easily be missed on CECT and CEMRI. Harmonic microbubble-specific software that suppresses the tissue echo signals, allows maximum contrast resolution, because the enhancement results only from the presence of microbubbles. Moreover, the dose of contrast agent (microbubbles) used is smaller than used in CT and MRI because the signal comes from the microbubbles' activity as a consequence of insonation, which is different from the other imaging modalities in which it is a passive process (absorbing the X-ray photons in CT or by influencing proton realignment on MR): the dose of contrast agent used on CEUS is about 2 mL in comparison to about 100 mL for CT and about 10 mL for MR.

UCAs are safe with a very low incidence of side effects and no cardio-, hepato- or nephrotoxic effects. Therefore, it is not necessary to perform laboratory tests to assess liver or kidney function prior to their administration [10].

1.6 Dynamic Contrast Enhanced Ultrasound, Time Intensity Curve Analysis

Dynamic Contrast Enhanced Ultrasound (DCE-US) is a quantitative diagnostic technique with microbubble contrast agents. Previous published EFSUMB guidelines in 2004, 2008 and 2011 established and recommended clinical indications of DCE-US, including technical requirements, training and investigational procedures, and essential image interpretation steps. DCE-US could make subjective comparison of the enhancement between normal and abnormal liver parenchyma, or between a focal liver lesion and its surrounding tissue. Meanwhile, DCE-US offers a better understanding of the microvascular perfusion of benign and malignant focal liver lesions.

Quantification of DCE-US is considered to be useful in evaluating data objectively or in comparison to imaging techniques. To quantify tissue and tumour enhancement is essential to the diagnosis of focal lesions, to limit clinical diagnosis variability, and to make objective and quantitative evaluation of therapeutic response of malignant tumours. Currently, imaging assessment of response to cancer treatment is mainly based on the Response Evaluation Criteria In Solid Tumours (RECIST). Unfortunately, RECIST only reflects tumour size changes, which are often delayed. RECIST is not sensitive to identify non-responders at an early time after treatment. A patient may be misclassified as a non-responder since there was no change in the tumour size. Tumor size may even increase in early stage after treatment, due to haemorrhage, necrosis and oedema [22].

1.7 How to Evaluate Treatment Response?

There are two different approaches for dynamic contrast enhanced ultrasound (DCE-US), which including bolus injection of microbubbles with TIC analysis used for clinical studies, intravenous infusion with disruption-replenishment analysis used for scientific purposes.

Initially, monitoring of tumor treatment response with contrast agents relied on qualitative analyses. In recent years, new methodologies using the raw linear data have been developed to produce more semi-quantitative and robust indices. With curve fitting, TIC analyses can be performed to reflect functional features. The main quantitative features including area under the curve (AUC); area under the wash-in (AUWI); slope of the wash-in (SWI); area under the wash-out (AUWO); peak intensity (PI); time to peak intensity (TPI) and mean transit time (MTT). This technique is highly recommended in the published EFSUMB and WFUMB guidelines for monitoring of treatment response in liver tumours [3, 4, 23].

1.8 Three-Dimensional (3D) CEUS

Three-dimensional CEUS was first described and clinically applied in 2001/2002 [24]. They concluded that CEUS might improve the detection rate and characterisation of liver and

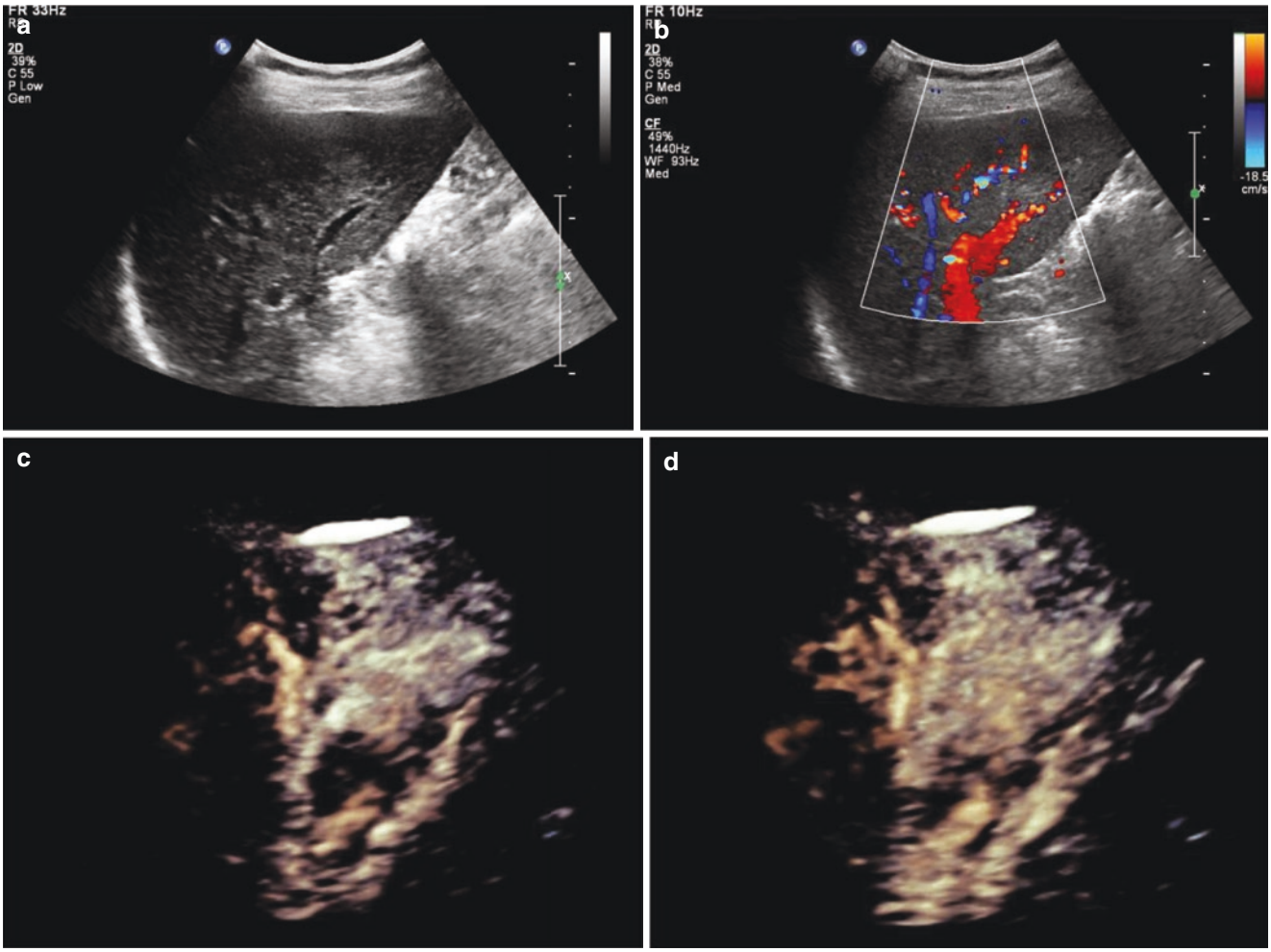

Fig. 1.10 Three-dimensional contrast enhanced ultrasound (3D-CEUS). B mode ultrasound detected a hypoechoic lesion in right lobe of liver, with indistinct margin (**a**). Dotted colour flow signals could be detected inside the lesion (**b**). 3D-CEUS showed a clear feeding artery of the lesion (**c**) and complete hyperenhancement of the lesion during arterial phase (**d**). The lesion was proved to be a hepatocellular carcinoma by surgery and histopathological results

splenic tumours. Future applications may include quantitative evaluation of tumour response evaluation [25, 26] (Fig. 1.10).

1.9 CEUS Guidelines

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) published 2004 the first guidelines on the use of CEUS [2]. The primarily pure CEUS liver guidelines were expanded in 2008 also to non-liver indications [6]. In 2012, CEUS non-liver guidelines were published by EFSUMB [27] and most recently updated [7, 8]. In 2013, pure CEUS liver guidelines were published by EFSUMB and the World Federation for Ultrasound in Medicine and Biology (WFUMB) [4, 28]. Dynamic CEUS has been introduced describing the technique of time intensity curve analysis [23]. Pioneering CEUS studies include the DEGUM (Deutsche Gesellschaft für Ultraschall in der Medizin) trial to show the value of CEUS for focal liver lesion characterisation in a practical clinical setting evaluating 1349 patients with focal liver lesions [29].

Current Chinese guidelines for diagnosis and treatment of liver cancer recommend application of CEUS for preoperative diagnosis and treatment follow up of liver cancers regarding patients with HCC in China to ensure optimum patient outcomes [30].

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Contrast Enhanced Ultrasound: How to Perform It in Liver Tumors?

2

Christoph F. Dietrich, Yi Dong, and Wen-Ping Wang

2.1 Introduction

Ultrasound (US) and contrast enhanced ultrasound (CEUS) are the most commonly used and first imaging modalities for detection and characterization of focal liver lesions (FLLs) [1–4]. The knowledge of the frequency of FLLs, the pathological classification, and the clinical presentation is critical for the management of both symptomatic and asymptomatic patients. The diagnostic work-up in patients with and without underlying malignant or inflammatory disease is often different. The preexamination decision tree is called "pretest probability" and should be used as a prerequisite before any kind of CEUS application. Knowing the pretest probability improves the diagnostic accuracy and enables rational decisions to be made as the appropriateness of undertaking the examination at all.

2.2 Machine Settings

The importance of the acoustic power and mechanical index (MI) should be highlighted first. Additional important factors are depth penetration, focus, gain, background signal (noise), dynamic range, frame rate, transmission frequency, and equipment software [5].

2.2.1 Acoustic Power and Mechanical Index

While using contrast agents for CEUS, the acoustic power and mechanical index (MI) are the most important physical determinant. Depending on the acoustic power, the MI is an estimate of the peak negative acoustic pressure in the tissue, which represents a measure of the energy deposited in the tissue. To put it simply, a higher MI indicates a higher acoustic pressure and consequently faster destruction of the microbubbles. Physically speaking, the MI is defined as:

$$\mathrm{MI} = \frac{\mathrm{PNP}}{\sqrt{F_c}}$$

where PNP is the negative value of the maximum pressure of the ultrasound wave. F_c is the center frequency of the ultrasound in MHz. A conservative correction factor for attenuation is applied, usually 0.3 dB/cm/MHz.

The MI relates to the highest value in the acoustic field. The mechanical index in the focus (MIF) provides this value for the focal zone. Based on multiple theoretical assumptions, the calculation of the MI is only an estimated value for the actual acoustic pressure in the tissue. The calculation algorithms are different among different manufacturers. For example, a mechanical index of 0.05 for unit A can correspond to a value of 0.2 for unit B. So, the same settings cannot be simply transferred from one manufacturer to another. A reasonable preset of the manufacturer provides a diagnostically sufficient image. Meanwhile, individual adaptation should be performed to optimize the presets in case of difficult imaging conditions, in order to obtain perfect image quality [5].

The correct acoustic power setting is decisive for effective contrast enhanced ultrasound. This is similarly true for [5]:

- Microbubble destruction.
- Penetration.

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- Signal separation between microbubbles and tissue, based on the assumption that the latter behaves in a perfectly linear fashion (i.e., the tissue responses follow the transmitted waveform exactly).

A higher MI results in a better penetration but also increases destruction of the microbubbles. The contrast agent dose balances the contrast enhancement intensity. In the early phase of CEUS, it prevents over enhancement of structures with shadowing. In the contrast enhancement duration, a sufficient contrast agent may concentrate in the late phase.

In practice, this perfectly linear model is not completely true since the transmitted waves become distorted as they are conducted through any medium and this produces harmonics, which are the basis for harmonic imaging widely used in B-mode scanning. It should be pointed out that microbubble harmonics are generated in a different way, by the fact that the microbubbles resist compression more strongly than expansion, so their response to a symmetrical ultrasound pulse is asymmetrical, generating harmonics.

2.2.2 Image Depth Penetration

The image depth penetration is determined by many factors including the manufacturer and transducer technology, transducer frequency, acoustic power (mechanical index), focus and other technology-dependent factors, and finally by the patient's condition. Limited depth penetration can be overcome by lowering the transmit frequency with the disadvantage of lower spatial resolution, eventually resulting in suboptimal imaging of small superficially located lesions. Increasing the MI may improve penetration but at the expense of microbubble destruction, especially in the nearfield [6]. Most importantly bubble destruction ("the circle of disaster") should be avoided. Regarding commonly observed artifacts we refer to the respective paragraph below [5].

2.2.3 Focus

Usually the focus should be positioned at the distal border of the target lesion but this might vary in some scanners. For detection, a deeper location of the focus (at least two-thirds of the screen) is recommended (Fig. 2.1).

2.2.4 Gain (Received Signal Amplification)

The gain should be usually set at or very slightly above the noise floor so that before microbubbles arrive, the image is dark. If the gain is set too low, sensitivity is too low and weak microbubble signals are not detected. If the gain is set too high signal saturation occurs possibly with acoustic shadowing (Fig. 2.2).

2.2.5 Background Signal (Noise)

A dual-image display format is often recommended since the nonlinear image is almost black making it difficult to focus on the lesion of interest, which is especially necessary when examining small and difficult to detect focal liver lesions. In the dual-image display, a conventional B mode fundamental image and a bubble-only contrast image are displayed side-by-side [6]. In contrast, it is also possible to overlay the contrast and B mode image, which doubles the screen size. For

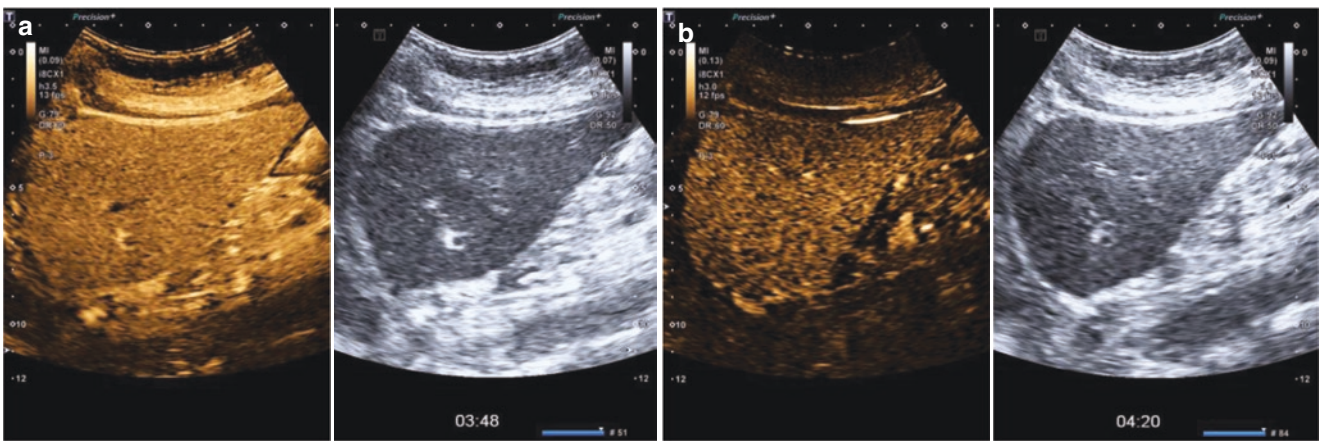

Fig. 2.1 Focal zone set during liver contrast enhanced ultrasound (CEUS). Normal CEUS of the liver showed an appropriately placed focal zone at the bottom of the image (**a**). Poor quality CEUS of a normal liver showed focal zone set in the near field (**b**), resulting in significant loss of contrast signal in the far field

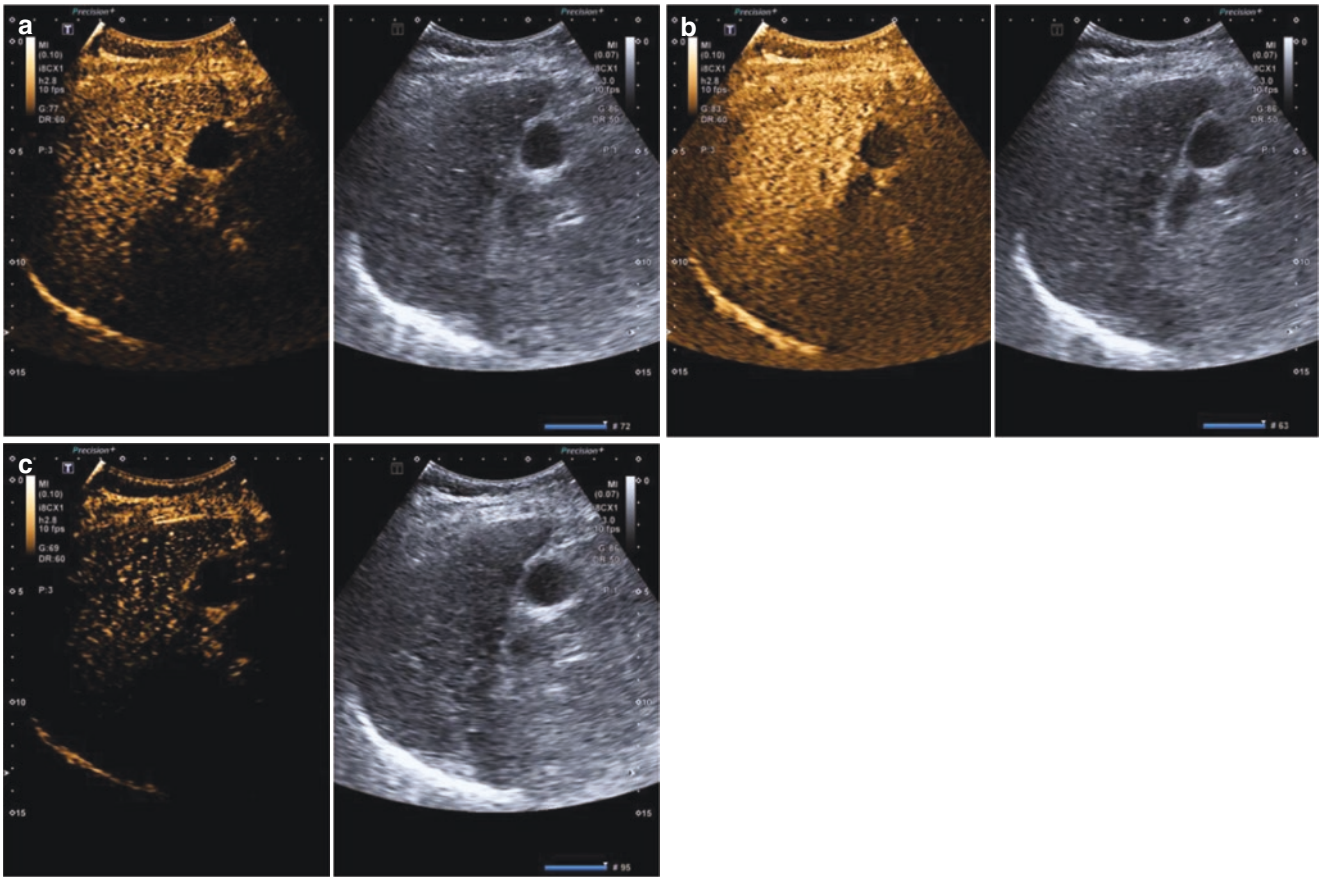

Fig. 2.2 Gain adjustments during liver contrast enhanced ultrasound (CEUS). CEUS with appropriately adjusted gain demonstrates normal enhancement of liver parenchyma (**a**). While too high (**b**) or too low (**c**) set of gain was not suitable for appropriate imaging

quantitative studies, the dual-image display is advantageous since it is important to keep the transducer at the same place and avoid motion. It should be mentioned that the quality of the B mode image in dual-image displays is inferior to that obtained in non-contrast mode with the same settings [6].

2.2.6 Dynamic Range

The dynamic range is the range of signal intensities to be displayed. It should be set to optimize the enhancement pattern. A small dynamic range will decrease the signal levels ("grey levels") in the image and increases visual contrast but can limit the differentiation between different degrees of enhancement. A wide dynamic range increases the number of "greys," allowing for better differentiation between different degrees of enhancement [6]. A large dynamic range allows to improve identification of the increased rim signal in patients with highly vascularized metastatic lesions. A narrow dynamic range is preferred for visualization of FLL with low perfusion. A wide dynamic range should be used in perfusion quantification studies to avoid signal saturation [6].

2.2.7 Frame Rate

For focal liver characterization with adequate visualization and recording the frame rate should be adjusted ≥10 Hz. Too high frame rates can augment bubble destruction and too low a frame rate does not allow real-time imaging [6] (Table 2.1).

2.3 CEUS of the Liver, Examination Technique

The pre-contrast examination preparations are important, which include the identification of the target focal liver lesion, the identification of the best position of the patient, and the optimal scan plane to minimize out-of-plane motion from respiration, usually longitudinal along the axis of the respiratory movements [6].

For injection of contrast agents, the cannula (20 gauge or larger) should be inserted in the antecubital vein of left arm, while avoiding interaction of the injector with the right-sided examiner (Fig. 2.3). Some important influencing factors should be avoided, e.g., avoid the side of the breast (or axillary) surgery to minimize the risk of worsening lymphedema.

Table 2.1 Ultrasound contrast agents in clinical use

Brand	Shell material	Gas core	Mean diameter (μm)	Concentration as prepared ($\times 1 \times 10^9$)/mL	(C)FDA approved	FDA approved indications
Definity	Lipid	Octafluoropropane	1.1–3.3	12.0	Yes	Left ventricular opacification
Optison	Sonicated albumin	Octafluoropropane	3.0–4.5	0.5–0.8	Yes	Left ventricular opacification
SonoVue (Lumason)	Lipid	Sulfur hexafluoride	1.5–2.5	0.15–0.56	Yes	Left ventricular opacification Characterization of focal liver lesions
Sonazoid	Sucrose	Perfluorobutane	2.1	1.2	Yes	Characterization of focal liver lesions

Fig. 2.3 Preparation for liver contrast enhanced ultrasound. Choose the most suitable contrast agent, SonoVue (**a**) or Sonazoid (**b**). Preparing for the contrast agents according to manual indications (**c**–**e**). The cannula (20 gauge or larger) should be inserted in the left arm, preferably the antecubital vein, to avoid interaction of the injector with the right-sided examiner (**f**)

Fig. 2.3 (continued)

Central line and port systems can be used as long as there is no filter requiring a high injection pressure, but be aware of a possible shorten contrast arrival time [6]. The catheter should be removed after the exclusion of any pseudoanaphylactic reaction. When multiple injections are anticipated, a three-way stopcock may be valuable and facilitates sequential administration of the contrast agent and then the saline flush, without removal of either syringe. The author almost never uses a three-way stopcock.

The timer should be started at the time of the beginning of the UCA injection. The application via a central venous line with a much shorter arrival time is a good reason for this [6].

The injection bolus for SonoVue™ is given at about 1–2 ml/s to avoid high pressure with the risk of microbubble destruction. Immediately after injecting the contrast agent, a 5–10 ml saline bolus should be given to flush the line with higher pressure >2 ml/s. The contrast dose depends on the quality of the machine and the machine setting. It is suggested to use lower dosages between 0.4 and 4.8 ml in small pediatric patients. Artifacts might appear in the early phases of enhancement with a too high contrast agent dose, including acoustic shadowing, over-enhancement of small structures, and signal saturation (Fig. 2.4). Meanwhile, too low a dose might cause the concentration of microbubbles to be subdiagnostic in the late phase, mimicking the detection of wash-out [6].

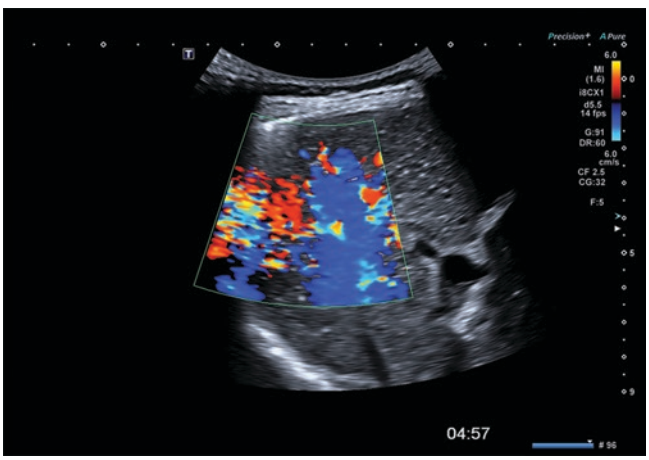

Fig. 2.4 Doppler blooming artifact. Following contrast administration, there is a marked increase in Doppler signal throughout the liver with color pixels displaying well beyond the expected vessel margins, indicating blooming artifact

Repeated injection is advised under the following circumstances [6]:

- There are additional FLL, which require characterization.
- The initial injection failed and did not provide the full answer to the detection and/or characterization of a FLL to allow for assessment of missing information.

- A wash-out region may be identified on sweeps of the liver in either the PVP or the LP to allow arterial enhancement characterization.

2.4 Improved Detection of Focal Liver Lesions

Conventional ultrasound is the most commonly used imaging modality for focal liver lesions, but is less sensitive in the detection of FLL while comparing with CECT, CEMRI, or intraoperative US. With the application of CEUS, it has dramatically increased detection rate of FLL before operation, especially in liver metastases ≤10 mm [7–18].

2.5 Characterization of Focal Liver Lesions

The contrast features of focal liver lesion (FLL) should be described in terms of the enhancement degree and enhancement phase. It is important to know in advance if the liver is normal or diseased (e.g., liver cirrhosis, fibrosis, or steatosis). This may affect the contrast enhancement features of the FLL and its surrounding liver parenchyma. Enhancement including isoenhancing, hyperenhancing, and hypoenhancing, which refers to the progressive intensity of the signal relative in FLL to the adjacent parenchyma. "Wash-out" is defined by the reduction in enhancement degree which follows peak enhancement. Sustained enhancement refers to the continuation of the iso- or hyperenhancement in the FLL relative to the adjacent parenchyma over time. Non-enhancing refers to the complete absence of enhancement [6].

The timing (early versus late onset, fast versus slow), degree (complete, incomplete), and pattern should be described in comparison to the surrounding "normal" parenchyma. The combined evaluation of the arterial contrast enhancement and portal venous and late wash-out of a lesion compared to the surrounding healthy liver parenchyma allows characterization of a FLL either as non-hepatic tissue (e.g., malignant, inflammatory, or fibrotic) if wash-out is present or as benign if iso- or hyperenhancement can be observed in comparison to the surrounding liver parenchyma.

In addition, analyzing the arterial vessel architecture in the early arterial wash-in phase allows further characterization, especially in benign focal liver lesions as hemangioma with peripheral nodular contrast enhancement and centripetal fill in [19] or as focal nodular hyperplasia with typical vascularity [20]. The vascular pattern of hepatocellular adenoma is more complex [21]. The characteristics are also valid for pediatric patients [22, 23].

The combined evaluation of the above diagnostic features makes it possible to characterize FLL in patients with liver cirrhosis as typical for HCC according to the Liver Imaging Reporting and Data System (LI-RADS) [24, 25].

2.6 Artifacts

Knowledge of the basic physical and technical principles of ultrasound is needed to understand sonographic images and findings and to be able to evaluate the possibilities and limitations of the method. Conventional and CEUS imaging are susceptible to multiple artifacts (imaging errors) since the properties assumed to be constant, such as straight-line sound propagation, attenuation (penetration), sound speed, acoustic field characteristics (the narrower the acoustic field, the better the suppression of side lobes not corresponding to wanted signals), acoustic attenuation, damping (due to reflection, absorption, refraction, scatter, and interference) (Fig. 2.5), and other factors, often deviate from the actual properties of the sound beam. Knowledge of such artifacts helps to avoid errors.

The visualization of the contrast agent signals is based on an interaction between the emitted ultrasound wave and the microbubbles, which depends on the equipment settings (acoustic power, image rate, focal zone, etc.). Wrong equipment settings are often the reason for CEUS artifacts that can result in uncertain diagnoses or even misdiagnoses in extreme cases.

Perhaps the most important CEUS artifact is bubble destruction (Fig. 2.6). The MI plays a crucial role here. It balances the signal intensity and penetration on the one hand and the stability of the microbubbles on the other hand. The CEUS "circle of disaster" is characterized by the following criteria: microbubble destruction → increase in contrast agent dose → attenuation (shadowing) → higher mechanical index → additional microbubble destruction. The secret is to find a good balance between the contrast agent dose and the equipment-specific settings.

Pseudoenhancement arises from nonlinear artifacts occurring in FLL that appear echogenic on conventional B mode ultrasound and eventually deep in location (Fig. 2.7). The presence of oscillating microbubbles in vascularized tissue between the transducer and the object of interest may create nonlinear echoes that can give the appearance of enhancement of a deep lesion relative to

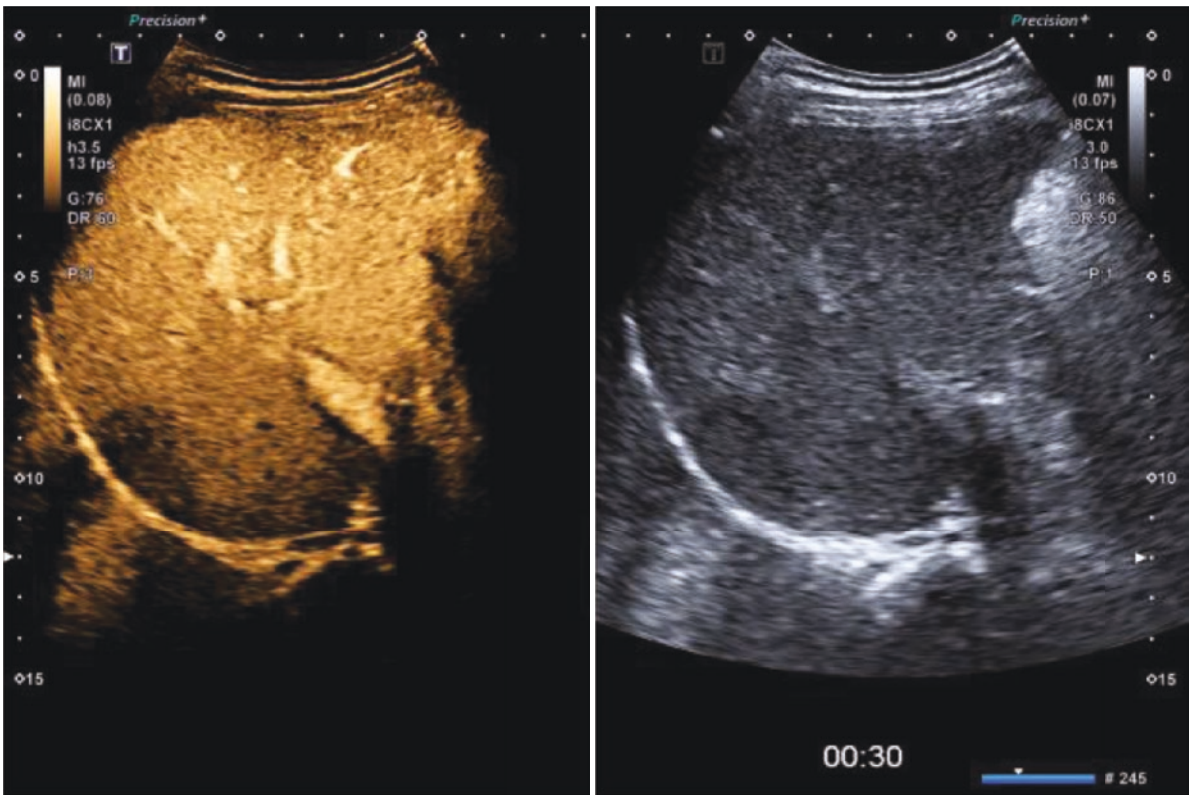

Fig. 2.5 Mirror Image Artifact. Contrast enhanced ultrasound (CEUS) of the liver showed a mass in the posterior right lobe with peripheral hyperenhancement adjacent to the inferior vena cava (IVC). A mirror image of the lesion and IVC was opposite the interface with the diaphragm and lung base

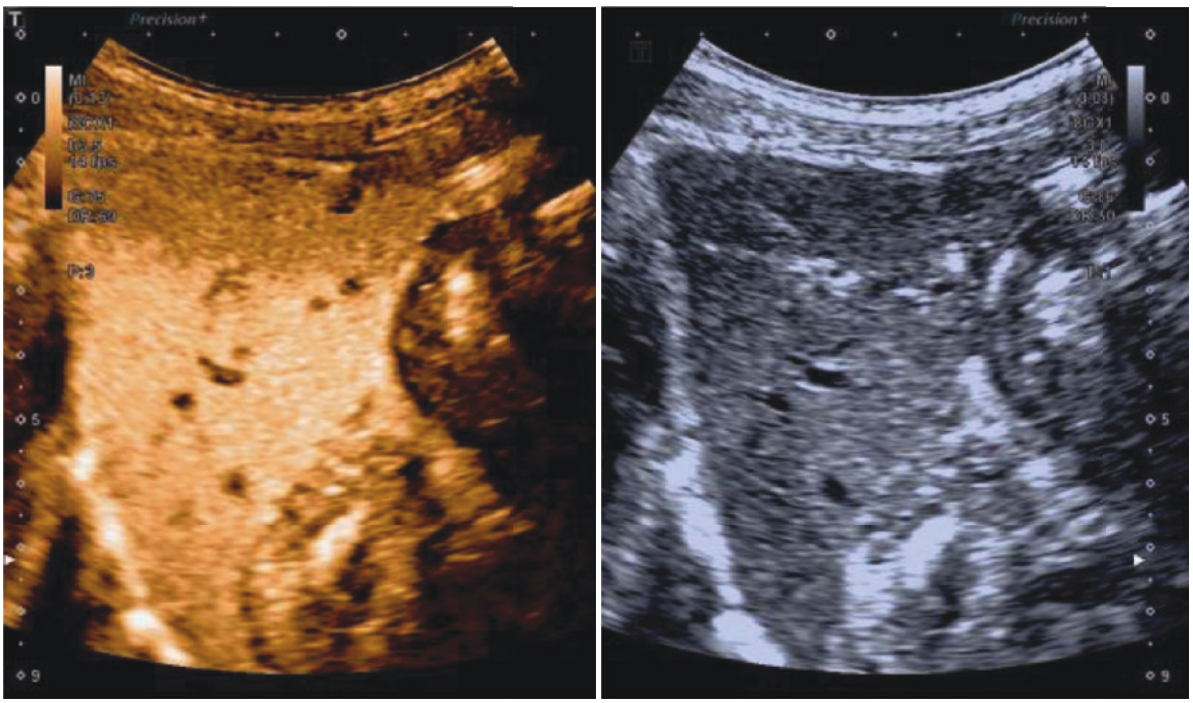

Fig. 2.6 Near field bubble burn-off artifact. A horizontal stripe of low signal in the near field due to inhomogeneous microbubble destruction (bubble burn-off)

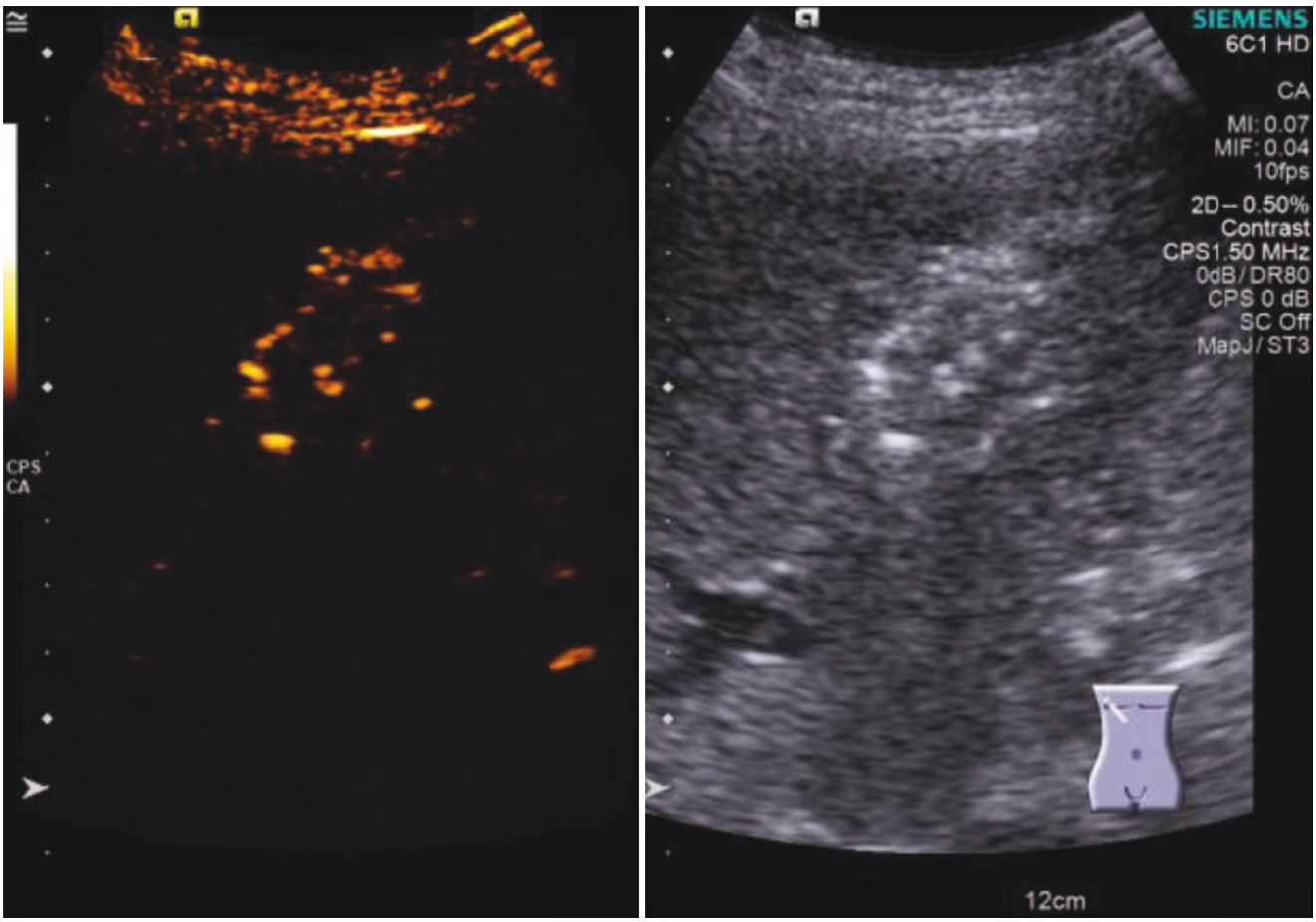

Fig. 2.7 Contrast ultrasound enhancement (CEUS) of a hepatocellular carcinoma lesion immediately after transarterial chemotherapy and radiofrequency ablation. CEUS prior to contrast administration showed the lipiodol deposition inside the lesion devoid of signal with a few echogenic foci

background tissue. This pseudoenhancement typically occurs in the late portal venous phase and progresses over time in distinction to real enhancement, which always initiates within the arterial phase [26]. This nonlinear propagation of the ultrasound beam increases with bubble concentration.

2.6.1 Long Liver Enhancement

Prolonged innocuous liver enhancement has been very rarely observed over the past decade after the bolus injection of microbubble contrast agents. It appears as a heterogeneous enhancement in the liver most often observed during the performance of the CEUS examination and often around 2 min and lasting up to 5 h after contrast injection on both B-mode and contrast-specific modes (Figs. 2.8 and 2.9). It is not destroyed by sonication at high MI. The enhanced signals can also be observed in the portal and superior mesenteric veins, though not in the systemic circulation. It is very simi-

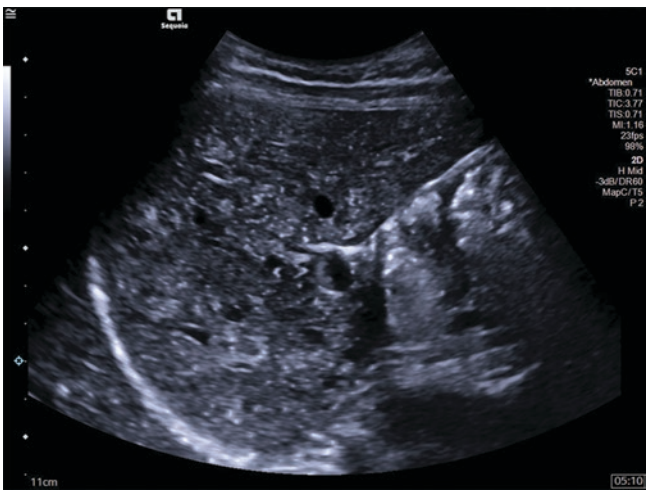

Fig. 2.8 Prolonged heterogeneous liver enhancement. B mode ultrasound through the liver following contrast administration (SonoVue) showed patchy, heterogenous areas of increased echogenicity. This appearance may last for several hours. However, it is likely not clinically significant and should not be confused for pathology