Ultrasound contrast media in the characterization of soft tissue lesions: ongoing research

M. Averkiou Department of Mechanical Engineering, University of Cyprus, Nicosia, Cyprus.
J. Powers Philips Ultrasound, Philips Medical Systems, Bothell WA, U.S.A.

Important note:
This article describes ongoing research. To date no ultrasound contrast agents have received approval from the FDA for general radiological applications in the United States and only two are approved for cardiac left ventricular opacification. In Canada, Europe and Asia, however, there are ultrasound contrast agents approved for both cardiology and general radiology.

CT and MR imaging modalities have long used intravenously injected contrast material to visualize blood flow in the microcirculation and larger vasculatures. The use of microbubbles enables ultrasound to complement CT and MR in a number of clinical areas where perfusion is an important clinical differentiator. In many countries, ultrasound contrast agents are transitioning from research to clinical use as another tool in the characterization of liver and kidney lesions. The portability and real-time nature of ultrasound combined with contrast is finding new clinical utility in interventional therapies with the liver. The spatial and temporal resolution obtainable with ultrasound contrast provides new physiologic and pathophysiologic information not previously available.

Despite continuing advances in the sensitivity of diagnostic ultrasound systems, Doppler-based imaging techniques are unable to detect low-velocity blood flow in the microcirculation or smaller vessels. The chief difficulty these techniques share is that blood is a weak reflector of ultrasound with received amplitudes 40 to 60 dB smaller than that of tissue, so that Doppler-based techniques rely solely on the movement of red blood cells to differentiate blood flow from tissue. The removal of the tissue signal places a lower limit on the ability to detect low-velocity blood flow (<1 cm/s). A method to overcome these difficulties is to inject brighter reflectors than blood into the vascular system. Gas-filled microbubbles are one such reflector.

Microbubble contrast agents for use with diagnostic ultrasound have been an active area of research since 1968, when Gramiak observed opacification of the right ventricle following an injection of saline [1,2]. The earliest microbubbles were unable to pass through the lungs, and were only able to opacify the right ventricle [3,4]. However, over the last three decades several major pharmaceutical companies have been actively engaged in the development of stabilized microbubbles capable of transpulmonary passage for left-side blood-pool enhancement [4-7]. During the same time period there have been enhancements of the ultrasound equipment that have provided researchers with the ability to visualize microbubbles within the parenchyma of the liver, kidney and other organs following an intravenous injection [8-11].

This article outlines the improvements in ultrasound imaging systems that have taken place over the past decade that enhance the visualization of contrast microbubbles[1]. It begins with a brief review of ultrasound physics, in order to show how these new imaging developments work, and ends with a summary of some of the clinical uses of contrast agents in general imaging.

It must be noted here that to date no contrast agents have received approval from the FDA for radiological applications in the United States and only two are approved for cardiac left ventricular opacification. In Canada, Europe and Asia, however, there are contrast agents approved for both cardiology and radiology. This article is intended to provide those involved with ultrasound contrast research with a deeper insight into this continually evolving field.

Ultrasound contrast agents

One approach to making blood easier to detect with ultrasound is to introduce scatterers into the blood in order to increase the backscatter signal of the blood. To circulate freely and pass from the venous to the arterial side of the circulation, these particles must be smaller than the capillaries in the lungs (about 7-10 μm).

[1]Philips, who pioneered many of these imaging methods, optimizes the iU22 ultrasound system for specific clinical applications using the various techniques described, choosing the optimum technique for each application, based on extensive clinical evaluation. Philips does not specify the technique used for each application, as they may be changed from one release to another to keep pace with developments.

While being small enough for the circulatory system, the particles must still be efficient acoustic reflectors. The compressibility of gas enables microbubbles to be such an efficient scatterer. Unfortunately, free gas bubbles small enough to pass through capillaries are unstable in the blood and dissolve in a fraction of a second due to the combined effects of surface tension and diffusion. To prevent dissolution, the bubbles are stabilized by encapsulation within a shell, and most use a low-solubility, high molecular weight gas such as a perfluorocarbon (PFC). This shell is often coated with a biocompatible surfactant to minimize reaction.

Ultrasound contrast agents for various applications have been developed by GE/Amersham, Point Biomedical, Bracco Diagnostics, Bristol Myers Squibb, Alliance and Schering. Approval of specific contrast agents and their applications differs from country to country, so users should check with their local Regulatory source for approved agents/applications.

Microbubble nonlinearity

This section briefly discusses the nonlinear properties of microbubbles [12].

An acoustic wave generated by an ultrasound system consists of alternating high and low pressures at frequencies of 1.2-15 MHz. When an acoustic wave encounters a microbubble, it alternately compresses the microbubble on the positive pressure, and expands it on the negative pressure. Due to the physical properties of the gas, the compression during the positive portion of the wave is much smaller than the expansion in the negative portion. In fact, during the expansion phase of oscillation, a gas bubble's radius can increase by as much as several hundred percent. During the compression phase of oscillation, the contraction of the gas bubble is limited, due to the gas inside the bubble rapidly increasing in density as the molecules are forced closer together, making it less compressible, whereas the expansion is only limited by the elasticity of the shell. This results in an asymmetric nonlinear bubble oscillation.

Instead of producing a sinusoidal echo signal with a clean frequency spectrum like the transmitted signal in Figure 1a, it produces an odd-looking echo signal with asymmetric top and bottom as shown in Figure 1b. This asymmetry produces harmonics that can be utilized to enhance the signals from the bubbles and effectively distinguish them from the surrounding tissue. Figure 1c shows the frequency spectrum of the bubble echo signal in Figure 1b. The first major hump is the fundamental, and the subsequent ones are the second, third and fourth harmonics.

Bubbles are stabilized by encapsulation within a shell.

Microbubble disruption

Bubbles in a liquid tend to diffuse and disappear unless they are stabilized by some form of a shell. Once the shell is disrupted the gas inside will diffuse into the surrounding fluid. The Mechanical Index (MI), originally defined to predict the onset of cavitation in fluids, also gives an indication of the likelihood of bubble disruption. The MI is defined as:

MI = peak negative pressure ÷
SQRT (ultrasound frequency)
MI = peak negative pressure *
SQRT (period of U/S wavelength)

The more effort is put into trying to expand the bubble (peak negative pressure) and the longer the effort is applied (period of ultrasound wavelength) the more likely the bubble is to burst. This is also affected by the properties of the microbubble shell. The more elastic the shell is, the less likely it is to burst, as it can expand during the negative pressure without rupturing. It has been well established that the acoustic power level used during routine examinations destroys most contrast microbubbles [13,14].

The more elastic the shell is, the less likely it is to burst.

The blood flow in a normal capillary bed is on the order of 1 mm/s, and a typical capillary is about 1 mm long [15]. Thus, if the contrast within a capillary is destroyed, it will take about a second or more to refill the capillary. Given the branching structure of the microvasculature and the thickness of a typical scan plane, as well as

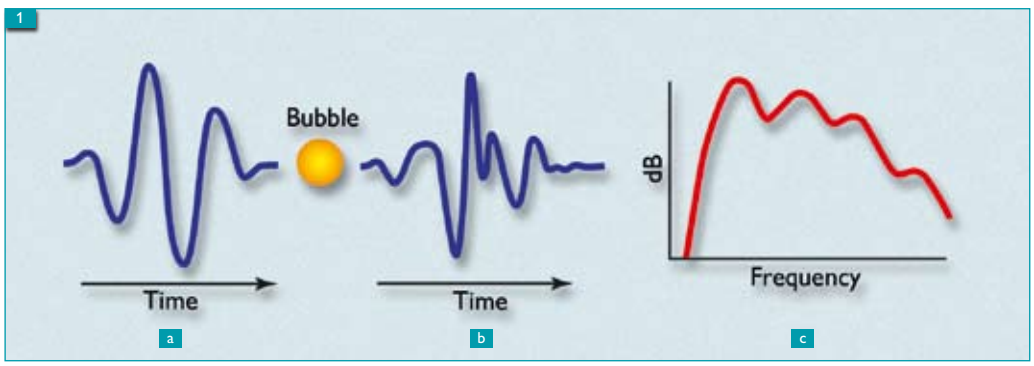

Figure 1. Nonlinear acoustic properties of microbubbbles:
a. Incident acoustic wave (transmitted signal)
b. Nonlinear echo signal
c. Frequency spectrum of bubble echo signal.

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the flow rate to the organ, it can take several seconds to replenish the contrast in the scan plane.

During real-time scanning at normal output power levels, the contrast is never given a chance to fill the microvasculature. This was first observed by Porter when he found that triggered imaging allows much better visualization of contrast within the myocardium [16,17]. This led to the widespread use of ECG triggering during myocardial contrast echo, with users often triggering only once every four or more cardiac cycles. Similar techniques have been used to image flow in the parenchyma of abdominal organs [18-20].

In recent years new non-linear imaging techniques have been developed that are far more sensitive to very small signals from microbubbles, making it possible to image them relatively non-destructively in real time at very low acoustic pressures. Low MI real-time scanning is currently the operating mode of choice for GI contrast imaging.

Low Mechanical Index imaging

Low Mechanical Index (MI) scanning is important for two reasons. First, at low MI bubble destruction is avoided. Although microbubbles differ in their shell composition, our work to date indicates that at an MI of about 0.1 or below, there is no significant destruction of microbubbles, while the harmonic contrast signal is good. The second major reason for low MI scanning is the reduction of the harmonic component in the tissue echoes relative to bubble echoes. While tissue harmonics have benefited routine diagnostic scanning, the contrast signal still has to rise above the background noise. Because tissue is less nonlinear than bubbles, it requires a higher MI than the contrast microbubbles for a certain harmonic response. Therefore, at low MI, the contrast-to-tissue ratio is higher than at high MI, helping to remove the tissue signal and leave only the contrast signal.

Non-linear imaging methods

Non-linear behavior of microbubbles can be utilized to enhance the contrast relative to tissue.

The nonlinear behavior of microbubbles in an acoustic field can be utilized to enhance the contrast relative to tissue. A number of techniques have been developed to help distinguish bubbles from tissue, all of which rely on the higher nonlinearity of bubbles when compared to tissue. All of these techniques have their advantages and disadvantages for any particular clinical application, depending largely on whether sensitivity or resolution is the driving factor for that application. In addition, as the use of contrast matures in the various applications, and the requirements are better understood, user preferences may change over time.

Harmonic imaging

"Conventional" harmonic imaging relies on transmitting at a fundamental frequency f_0 and forming an image from the second harmonic component $2f_0$ of the backscattered echoes by the use of filters to remove the fundamental component. While effective, this restricts the bandwidth available for imaging to ensure that the received harmonic signal can be separated from the fundamental signal. If the bandwidth of the fundamental signal overlaps with that of the second harmonic, they cannot be completely separated in the receiving process. Thus, in conventional harmonic imaging a narrower transmit bandwidth is used. To increase the harmonic signals from bubbles, higher MIs are used and this causes bubble destruction. Harmonic imaging has traditionally been used as a high MI technique and this required triggered (or delayed) imaging to allow enough time for fresh bubbles to refill the region of interest. Originally it was believed that harmonic imaging would allow complete separation of contrast from tissue, as it was assumed that tissue was completely linear. While it has long been known that tissue does produce nonlinear energy [21] it was believed that the higher frequency harmonics would be eliminated by attenuation. However, it was soon found that tissue did produce significant harmonic energy and the high sensitivity and bandwidth of modern ultrasound equipment could detect it. In fact, the harmonic image produced by tissue alone has beneficial qualities such as reduced clutter in the image and improved resolution [22, 23]. Therefore, a tissue image is present even in the absence of a contrast agent, so that perfect separation is not achieved.

Pulse Inversion imaging

As mentioned above, harmonic imaging uses relatively narrow bandwidths to prevent fundamental and harmonic component overlap. Pulse Inversion (PI) imaging avoids these bandwidth limitations by subtracting rather than filtering out the fundamental signals [24]. Consequently, PI can separate the fundamental component of the bubble echoes from the harmonic even when they overlap. This allows the use of broader transmit and receive bandwidths for improved resolution, and increased sensitivity to contrast agents.

In Pulse Inversion harmonic imaging two pulses are transmitted down each ray line, instead of only a single pulse as is done with conventional harmonic or fundamental imaging. The first is a normal pulse, the second is an inverted replica of the first, so that wherever there is a positive pressure on the first pulse there is an equal

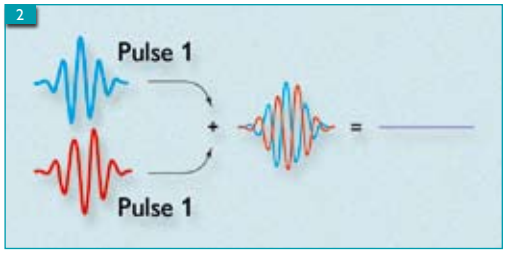


Figure 2. By adding two consecutive bubble echoes from a normal (blue) and an inverted pulse (red), Pulse Inversion cancels out fundamental echoes without filtering.

negative pressure on the second. Any linear target that responds equally to positive and negative pressures will reflect back to the transducer equal but opposite echoes. These are then added and all stationary linear targets cancel out, as shown in Figure 2.

Unlike stationary linear targets, microbubbles respond differently to positive and negative pressures and do not reflect identical inverted waveforms. Figure 3 illustrates the effect changing phase has on nonlinear components generated by microbubbles. Pulse 1 excites a microbubble, generating a linear fundamental response along with higher harmonic components. The inverted pulse 2 generates the same frequency components, however with different phases. The fundamental and other odd harmonic components experience a 180° phase shift relative to the first pulse components. The second harmonic and other even harmonic components experience a 360° phase shift, which is equivalent to a 0° phase shift. As a result of these relative phases between the bubble responses, the fundamental component cancels out and the second harmonic component constructively adds when the responses are added together.

Figure 4 shows a hemangioma in the liver using conventional imaging (a) and pulse inversion harmonic imaging with a contrast agent (b). Much greater contrast sensitivity is obtained and the lesion is better delineated than with previous technologies. The lack of microbubble destruction is also demonstrated well here, in that the blood flow to a hemangioma is extremely low and can take up to several minutes to fill with contrast. The fact that contrast in a hemangioma can be imaged in real time indicates that there is very little bubble destruction.

Although PI is mostly used as a low MI technique, as in Figure 4, in some cases it is also used as a high MI technique. For example, PI is used in clinical studies of the liver with Levovist® agent to destroy the microbubbles and form a high-resolution image from the harmonic response of

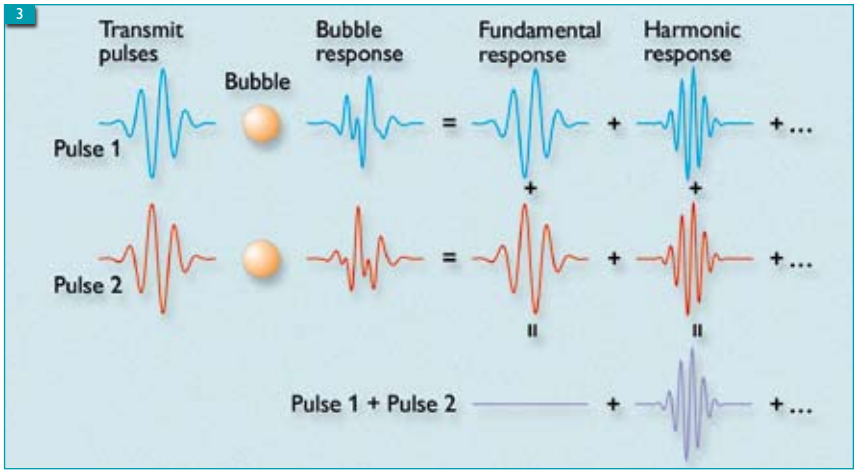


Figure 3. Pulse Inversion Harmonic Imaging signal processing.

the bubble echoes [25]. As mentioned above, research indicates that a normal liver that contains bubbles has a bright appearance in the image, whereas the metastases are black (i.e. have no signals).

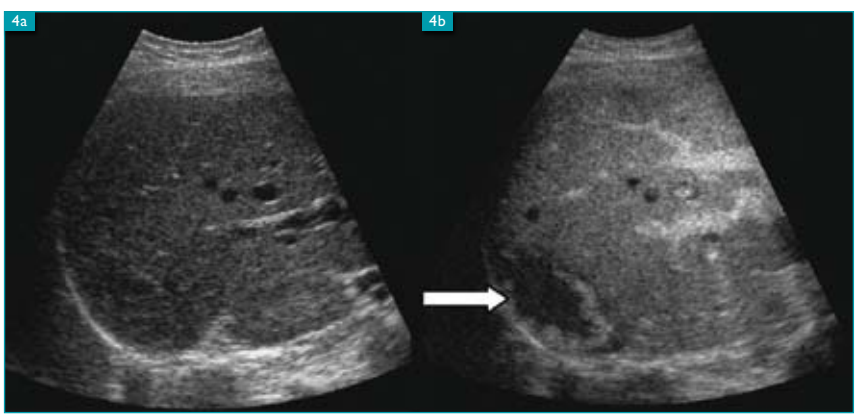
Power modulation imaging

An alternative to changing the phase of each successive pulse is to change the amplitude of each successive pulse in a group of transmit pulses. This technique is referred to as Power Modulation Imaging (PM). PM detects the differential nonlinear response generated from two different excitations. In PM, a low amplitude pulse is transmitted to estimate the linear response of a target volume. Then a slightly higher amplitude pulse is transmitted to elicit a nonlinear response from the target volume. Upon reception, the lower amplitude is rescaled by the factor between transmit pulses and subtracted. The resulting difference at the fundamental frequency represents energy which has leaked out of the first pulse into the higher harmonics. Figure 5 illustrates the presence of nonlinear fundamental energy in the resulting subtracted spectrum. This lower frequency nonlinear signal has the luxury of lower attenuation upon return to the transducer relative to second harmonic imaging approaches. Additionally, any nonlinear responses, such as

Figure 4. Liver hemangioma. Comparison of conventional and pulse inversion harmonic imaging.

Figure 4a. Conventional imaging.

Figure 4b. Pulse inversion harmonic imaging with contrast agent.



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higher order harmonics, are detectable in the bandwidth of the transducer. One drawback of power modulation is that the resolution of the nonlinear fundamental signal is lower than that of pulse inversion.

Power modulated pulse inversion imaging
In some cases combining Pulse Inversion with Power Modulation Imaging has benefits. This is sometimes called Contrast Pulse Sequence, or CPS. In this case, both the phase and amplitude are altered between pulses. The pulses are again scaled upon receive, but added. This method has the advantage that the second harmonic energy generated by both pulses can be preserved due to the phase inversion (see Pulse Inversion above). In PM, the second harmonic energy generated on the higher amplitude pulse is reduced by the subtraction of the second harmonic energy generated on the lower amplitude pulse. As a result, PMPI detects nonlinear signals at both the fundamental and second harmonic frequencies.

Agent detection imaging
When microbubbles are interrogated with high MI ultrasound, the backscattered signal is very large and has a broad bandwidth (many harmonic components). Interrogation of microbubbles at high MI also disrupts their encapsulated shell, leaving the gas to diffuse into the surrounding fluid. With high MI multi-pulse techniques, microbubble disruption leads to pulse-to-pulse changes (<mS), while tissue signal can be removed based on its coherence from pulse to pulse. In recent years, high MI imaging techniques for investigational radiological applications have been referred to as Agent Detection Imaging (ADI).

Figure 5. Power Modulation signal processing.

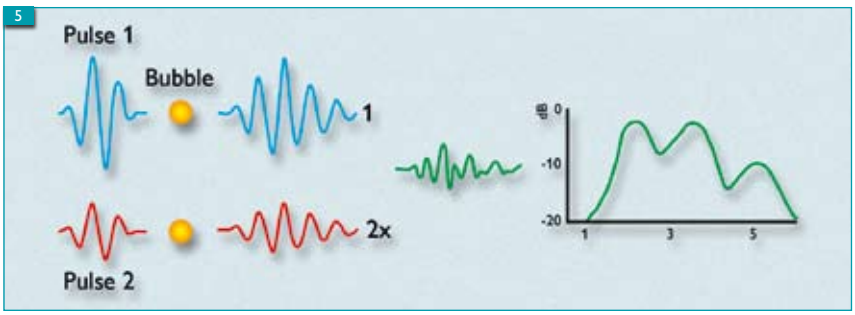
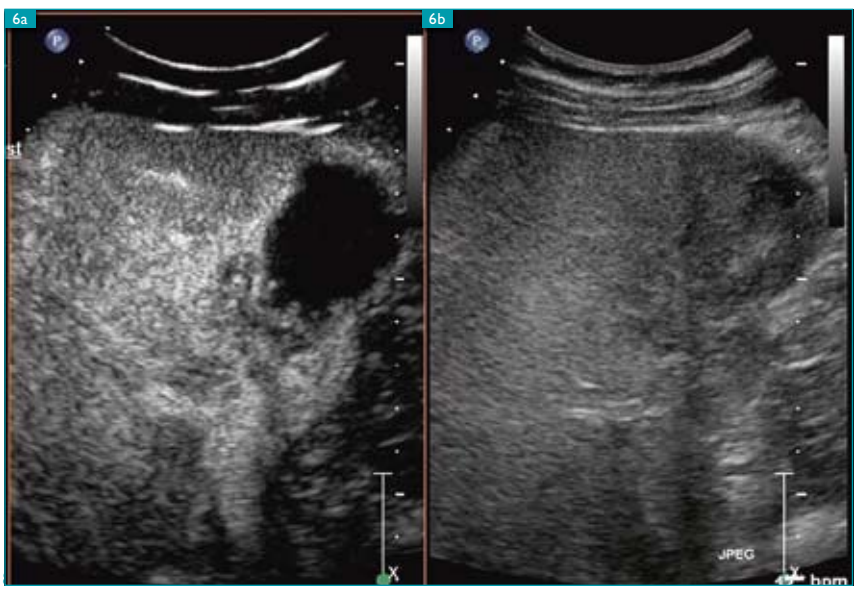


Figure 6. Contrast Side-by-Side imaging of recurrence on the edge of a previously ablated metastasis. Image by courtesy of O. Kolokythas, USA.
Figure 6a. Contrast image.
Figure 6b. Tissue image.



One clinical research application that helped in the wider use of ADI is liver metastasis detection with agents such as Levovist® and SonoVue® that tend to remain in the liver parenchyma after the vascular phase. These agents collect in the normal liver but not in the metastases. In studies with ADI, a bubble destruction image of the liver is formed, with the normal liver bright and the metastases black without any signal [25]. The bubble destruction signals are usually strong and, as a consequence, ADI is very sensitive. However, a region in the liver can only be scanned once (just one frame) because once the bubbles are destroyed ADI images will have no signals at all. ADI is performed by sweeping the whole liver and then freezing the system and reviewing the loop frame-by-frame to find any possible lesions. One disadvantage is that the contrast microbubbles may be destroyed accidentally while trying to find the correct view, and the injection must then be repeated.

Nonlinear imaging mode comparison
Due to the higher frequency components used, Pulse Inversion tends to have higher spatial resolution but less penetration than Power Modulation. Pulse Inversion is also more sensitive to tissue harmonics, due to factors of implementation. Power Modulated Pulse Inversion tends to be a compromise between the two. In many cases, the PMPI signal has roughly the same amount of energy as either PI or PM, but about half of it is at the fundamental and half at the second harmonic, making it more sensitive than PI, but with a higher resolution than PM. Any of the modes may also be used for ADI.

Contrast Side-by-Side display
As imaging techniques have improved in their ability to image contrast separately from tissue, it has become difficult to visualize lesions in a contrast imaging mode prior to the arrival of contrast at the site. For this reason "Contrast Side-by-Side" display has been developed, with the contrast imaging mode on the left, and conventional (tissue) imaging on the right. The

tissue image gives the user landmark information for guidance before and during a contrast injection. The tissue image can be used to ensure a lesion is in the scan plane, with the simultaneous display of contrast in the lesion (Figure 6). The tissue image is also acquired at low MI (<0.15) so as to not destroy additional microbubbles.

Flash contrast imaging

While the ability to visualize microvascular blood flow in real time without contrast disruption is a significant advancement, the ability to disrupt contrast can also be useful. The techniques described above can detect nearly stationary microbubbles in the microcirculation. Flash contrast imaging enables visualization of the arterial vasculature of a lesion after the microcirculation fills. Flash refers to the transmission of a few high MI frames to clear a plane of contrast agent followed by a return to low MI imaging.

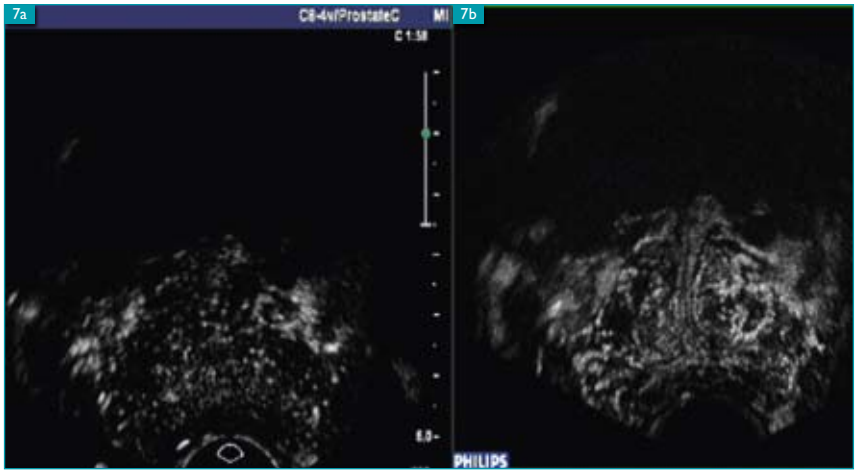
When an IV bolus of contrast first arrives in the arterial vessels, it provides visualization of the arterial vasculature. However, once the microcirculation fills with microbubbles, the larger arterial vasculature is obscured. Flash contrast imaging is often employed to visualize arterial vasculature structure after contrast has arrived in the microvasculature. Flash contrast imaging also holds promise as a quantification technique by creating a localized negative bolus of contrast, followed by measurement of the refill kinetics. This use is described below under Contrast quantification techniques.

MicroVascular Imaging

It has long been known that malignant tumors force the host to grow new blood vessels to supply nutrients to support the rapid growth and spread of the tumor [26,27]. This process of angiogenesis starts with very small microvasculature, growing larger feeding vessels over time as the tumor grows. The ability to image angiogenesis is important in cancer diagnosis, as well as therapy assessment research.

The ability to visualize microbubbles in real time, combined with improvements in sensitivity, has led to the ability to image microbubbles in small vessels (<1 mm) in lesions with low blood flow rates (<1 cm/s). In some vessels the flow rate is so low that a bubble may pass through only every few seconds. It might be visible for several frames, but still gives only a fleeting glimpse of the vasculature, as shown in Figure 7a.

MicroVascular Imaging (MVI) tracks the passage of microbubbles traversing lesional vasculature.



▲ Figure 7. Prostate. Image by courtesy of H. Wijkstra, the Netherlands.

Figure 7a. Individual bubbles in still frame of live loop.

Figure 7b. Processed MVI image capturing tracks of many bubbles.

This processing measures changes in the image from frame to frame, suppressing any background tissue signal and capturing the bubbles as they pass through the vasculature. Research has shown that this dramatically enhances vessel conspicuity, showing tracks of single bubbles flowing through the microvasculature as shown in Figure 7b. This software is available using Philips QLAB quantification software either on the Philips iU22 ultrasound system, or on a workstation with exported data, and will soon be available in real time.

Contrast quantification techniques

Contrast ultrasound provides opportunities for quantification that may lead to improved diagnosis, therapy monitoring, and prognosis. There is a great deal of literature on indicator dilution techniques using a contrast bolus [28-31]. Absolute measurements of volumetric blood flow with contrast ultrasound using indicator dilution techniques is not yet possible, due to the requirement of knowing the absolute concentration of the agent. However, measurements of bolus kinetics such as arrival time, time to peak, or time to wash-out do hold promise for diagnosing several disease states [32-34].

Contrast Cineloops can be analyzed to investigate lesion vasculature with Philips QLAB. This software enables visualization and analysis of regions of interest over a Cineloop segment. An example of a bolus passing through an HCC (hepatocellular carcinoma) is shown in Figure 8. The red ROI illustrates early enhancement from arterial-venous shunting and a higher arterial vasculature supply, as well as early wash-out. In QLAB, a gamma-variate model can be fitted to bolus curves, providing access to various parameter estimates such as wash-in rates, time to peak, or area under bolus curve.
Flash contrast imaging also holds promise for flow quantification. Contrast enhancement in an image actually represents the volume of contrast

▶ **Imaging angiogenesis is important in cancer diagnosis and therapy assessment.**

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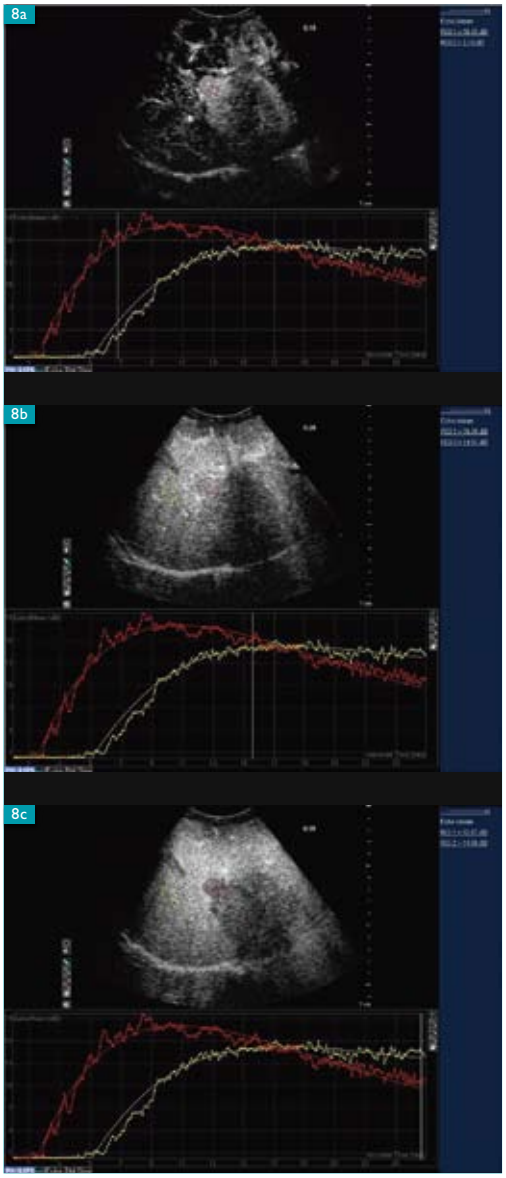


Figure 8. Bolus kinetics through normal liver parenchyma (yellow ROI) and HCC (red ROI) using QLAB. The white line on the graphs denotes the time of the frame above. Images by courtesy of M. Chen, China.

Figure 8a. Early arterial phase.

Figure 8b. Portal venous phase.

Figure 8c. Late portal venous phase.

within the image, not the flow rate. Blood volume can be fairly constant, even in regions of widely varying flow rates. So, once a vascular bed has filled with contrast, it will be difficult to differentiate altered flow rates.

Contrast within a scanplane can be cleared using Flash (see Flash contrast imaging above). A "negative bolus" of contrast is then created locally. The time it takes for contrast to refill the scanplane is an indicator of the local blood flow velocity. Parameters from an exponential model curve fit (A*(1- exp (β-t)) can be used to estimate A, which is related to contrast blood volume, and the time constant β, which is related to blood flow velocity [35]. This has been proposed as a method for quantification of myocardial perfusion [35-37] and is under investigation for general imaging applications such as renal artery stenosis and angiogenesis quantification and monitoring. A contrast infusion is used to provide a stable contrast concentration over the time of the exam.

Clinical applications in contrast radiology

The use of ultrasound contrast agents has grown with advances in imaging and widening regulatory approval. The clinical application of contrast has begun in areas where presence, absence or structure of vascularity is of clinical value. The clinical use of contrast has gained widest utilization in the liver. The following section describes different uses of contrast in the management of focal liver lesions. A wide variety of other applications are under development [38-41]. Developing examples of contrast use in prostate, gynecology and breast will be discussed. As noted above, approval of specific contrast agents and their applications differs from country to country, so users should check with their local Regulatory source for approved agents/applications.

Applications in the liver

The most effective treatment of malignant liver lesions is surgical resection or local ablation therapy. These treatments are most successful when the lesions are small. Consequently, the early diagnosis of malignant liver lesions is a critical component of a positive prognosis. Most early detection occurs through continual surveillance (every 3-6 months) of high-risk patients. Ultrasound contrast is an economical, sensitive and radiation-free tool for this surveillance. In addition, ultrasound contrast can be used for the characterization of lesions by providing additional vascular information not available with CT or MR. Examples of ultrasound contrast used for liver lesion detection, characterization and therapy guidance are described and shown below.

Characterization of liver lesions

Conventional ultrasound has been shown to be inferior to contrast-enhanced CT and MR for liver mass detection and characterization. Contrast enhanced CT and MR utilize differences in lesional blood flow for detection and characterization. Most of the clinically significant lesional blood flow is not detectable by ultrasound using current Doppler techniques. However, microbubbles enable ultrasound to visualize the same information that CT and MR provide, with improved temporal and spatial resolutions.

Microbubbles are first seen entering through the hepatic artery about 20 seconds after intravenous injection, depending on several factors such as cardiac output, speed of injection, and amount of contrast. This is referred to as the arterial phase. Only 20-25% of the blood supply to the liver is from the hepatic artery. The remainder is from the portal vein. The portal phase begins

approximately 20 seconds after the arterial phase and lasts for about 2-5 minutes, when the bubbles begin to disappear from the vascular system. Certain agents have a parenchymal uptake (late phase) and they persist in the liver after 3-5 minutes [8,25,42]. The contrast agents used today with associated imaging protocol followed for vascular and late phase are shown in Table 1.

Contrast agent	Vascular phase (scanning method)	Late phase (scanning method)
OPTISON®	Low MI	N/A
Definity®	Low MI	N/A
SonoVue®	Low MI	Low MI
Sonazoid®	Low MI	Low MI
Levovist®	High MI	Low MI

▲ Table 1. Contrast agents and imaging protocols during vascular and late phase.

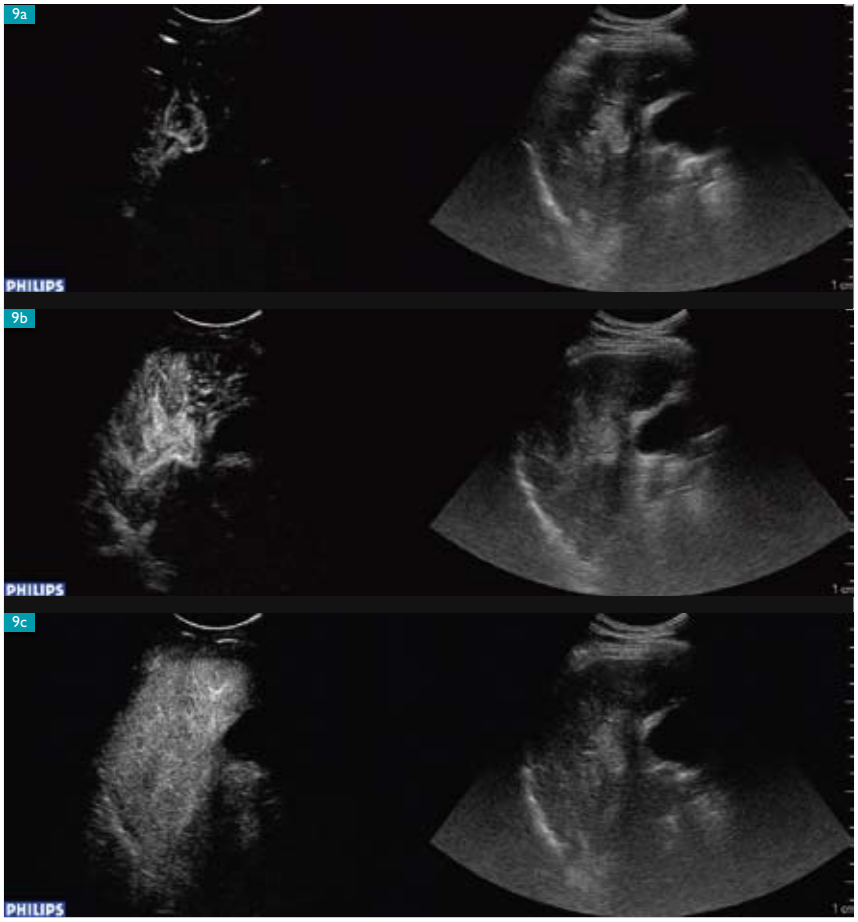
The vascular presentation of ultrasound contrast for the four most common liver lesions will be discussed in this section:
- hepatocellular carcinoma (HCC)
- metastasis from a primary tumor at some other location
- hemangioma
- focal nodular hyperplasia (FNH).

The first two are malignant while the latter two are benign. The additional differential diagnostic information ultrasound contrast provides over CT/MR will be discussed, with particular reference to low MI real-time imaging.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common liver malignancy in the world. The majority of HCCs develop in cirrhotic livers (resulting from damage) but may also arise in a normal liver. HCCs progress from a regenerative nodule to a dysplastic nodule, and finally to an HCC. The change in histologic types of the nodule is believed to be sequential and continuous, but distinction between these stages is not always clear, even with histopathology [43]. The early diagnosis of HCC is the most important factor for any of the treatment options [44].

HCC lesions have irregular arterial intratumoral and peritumoral vasculature which can be viewed in real time with the early arrival of a contrast bolus [44-46]. Figure 9a is an angiography-like image in the early arterial phase, using contrast, showing the complex arterial vasculature of an HCC. Figure 9b complete filling of the HCC.



▲ Figure 9. Example of HCC with SonoVue in low MI scanning. Images by courtesy of M. Chen, China.

Figure 9a. Early arterial phase.

Figure 9b. Complete filling of the HCC before portal venous enhancement of normal liver.

Figure 9c. Early late phase.

The whole tumor is enhanced, compared with normal liver, before arrival of portal venous flow. An HCC may remain hyperechoic in the portal phase, but cases where it becomes isoechoic or hypoechoic are also encountered.

A typical HCC will have little contrast enhancement in the late phase (Table 2), due to a reduction in lesional portal blood flow as an HCC matures (Figure 9c). CT and MR acquisitions are restricted to a few snapshots of the bolus passage (usually 30 s, 60 s, 3-10 minutes). Arterial and portal venous phase arrival times can vary due to cardiac output or cirrhosis, which can lead to suboptimal CT/MR results (due to the fixed acquisitions in time). Ultrasound contrast can capture the whole bolus with higher temporal and spatial resolutions, yielding new information about the lesional vascular morphology and blood flow dynamics.

Metastasis

The most common primary sites for metastases in the liver are the gastrointestinal tract (especially the colon), breast, and lung carcinomas. The arterial phase presentation varies depending on the primary. The arterial phase may be hyperechoic, sometimes with peripheral enhancement (colorectal metastases), or hypoechoic. The most characteristic signature of

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Lesion type	Characteristic features	Arterial phase	Portal phase	Late phase
Hepatocellular carcinoma	S-shaped vessels and vascular lakes	Hyperechoic	Hyperechoic	No contrast uptake
Metastasis	Ring enhancement in late phase	Hyperechoic or no change	Isoechoic or hypoechoic	No contrast uptake
Hemangioma	Progressive peripheral nodular enhancement	Peripheral nodular enhancement	Centripetal slow filling	Marked contrast uptake
Focal nodular hyperplasia	Radial vascularity and stellate central scar	Hyperechoic	Hyperechoic	Marked contrast uptake

Table 2. Lesion vascular behavior during contrast exam.

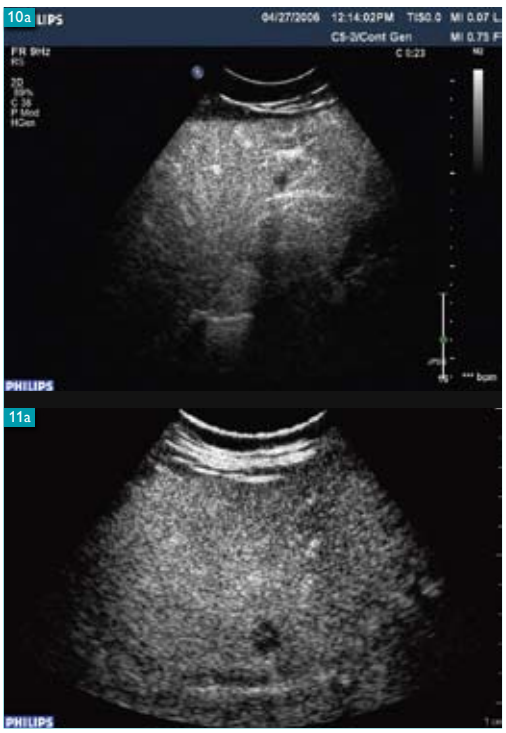


Figure 10. Examples of metastases with SonoVue® in low MI scanning. The 'black holes' in the image indicate metastases. Images by courtesy of O. Kolokythas, USA.

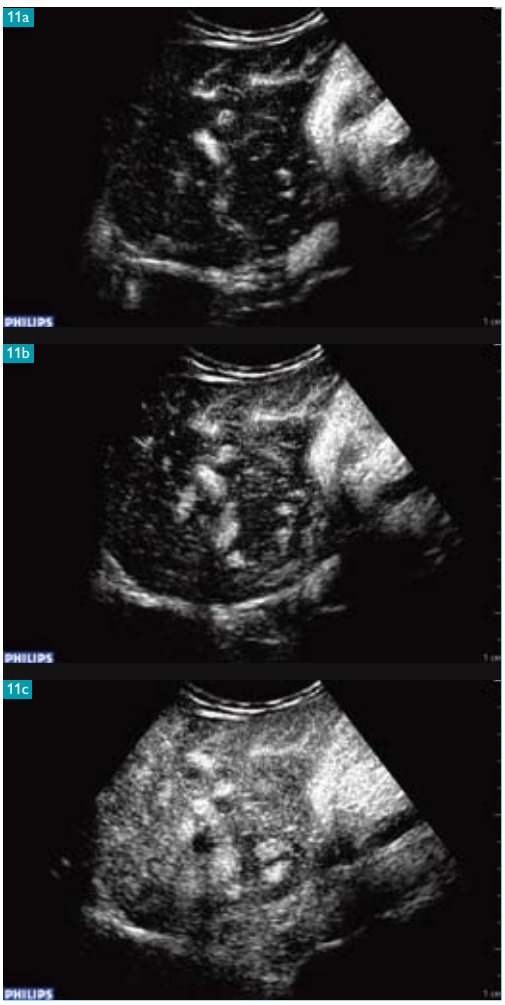


Figure 11. Example of hemangioma with SonoVue®. Images by courtesy of S. Wilson, Canada.

Figure 11a. Early peripheral enhancement.

Figure 11b. Slow inward filling and pooling

Figure 11c Complete filling.

these lesions is hypoechogenic presentations in both the portal and late phases due to the presence of vascular necrotic areas (Table 2) [47]. Figure 10 illustrates early wash-out of two small metastases from pancreatic and colorectal primaries.

The sensitivity of ultrasound contrast has been shown to be similar to that of CT for metastases [48]. Ultrasound contrast can detect smaller lesions (<1 cm) not detected by MR/CT, but may miss deeper lesions due to attenuation [48]. Intraoperative ultrasound with contrast has been shown to be the most sensitive imaging modality for detection (98%) [49]. The ability of ultrasound contrast to visualize the arterial enhancement of metastases, regardless of time of enhancement, might be an important tool for assessing response to therapy [50].

Hemangioma

Hemangiomas are the most common type of benign liver lesion. They are usually asymptomatic benign lesions, consisting of a large network of endothelium-lined vascular spaces. In conventional ultrasound, hemangiomas can often appear echogenic, with a variety of other presentations [45,48,51]. The main feature of hemangiomas during a contrast exam is progressive peripheral nodular enhancement (Figure 11) [20]. In the arterial phase, enhancement is seen only peripherally with a patchy appearance, and areas of pooling or filling centripetally over the course of the liver vascular phases (Table 2).

The rate of enhancement of hemangiomas varies greatly. A rapid-filling, high-flow

hemangioma is frequently seen as a complete enhancing nodule without the appearance of peripheral enhancement in the arterial phase of CT or MR scans [48]. It may be difficult to make a specific diagnosis of hemangioma because an HCC or hypervascular metastasis may show similar findings. Ultrasound contrast can be used as a problem-solving method, because its real-time nature and resolution are able to demonstrate early, strong peripheral nodular enhancement with rapid central filling, even in rapid-filling hemangiomas.

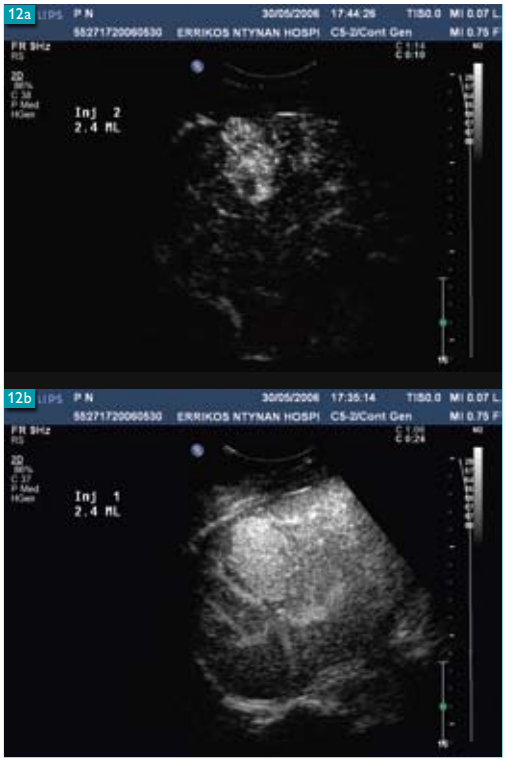
Focal nodular hyperplasia

Focal nodular hyperplasia (FNH) is a benign lesion consisting of abnormally arranged hepatocytes frequently associated with a central fibrous scar and anomalous arteries [46,51]. The main characteristic of FNH is radial vascularity and a stellate central scar, which can be visualized by contrast-enhanced CT or ultrasound [45,48,51]. Intratumoral enhancement often begins from the center and progresses to the periphery over time, i.e. centrifugal filling (Figure 12). Centrifugal filling is often used as a differential characteristic from HCC or adenoma [51]. In the case of sub-centimeter lesions, this differential characteristic is more often visualized with ultrasound contrast, due to the advantages in spatial resolution and arterial temporal resolution [52]. The lesion becomes isoechoic or slightly hyperechoic through the portal venous phase. A central scar is usually depicted in the late phase as a hypoechoic area in a hyperechoic lesion.

Therapy guidance

The use of ablation procedures for the treatment of HCC and metastatic lesions has grown with the development of radio frequency ablation (RFA). RFA offers treatment for non-surgical candidates and repeat treatments with lower morbidity and mortality compared with surgical resection. The portability and ability to visualize needle placement in real time make ultrasound the primary imaging modality used for RFA guidance [39].

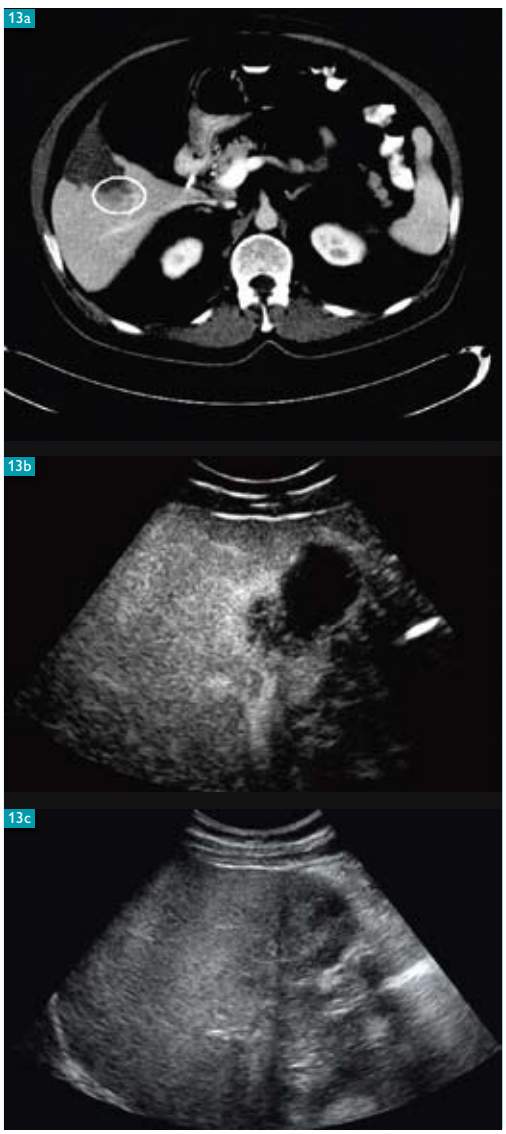
A pre-treatment ultrasound exam is done to locate the lesion and establish the ability of ultrasound to target the lesion for treatment. Ultrasound contrast increases the number of lesions detectable with ultrasound, especially metastases. As a result, ultrasound contrast increases the number of RFA procedures and benefits from the advantages ultrasound provides for needle guidance. Even for lesions seen with ultrasound, contrast can improve the confidence and reproducibility of their visualization. Contrast improves the assessment of size and



◀ Figure 12. Example of Focal Nodular Hyperplasia with SonoVue®. Images by courtesy of M. Averkiou, Cyprus.

Figure 12a. Central filling in atrial phase.

Figure 12b. Uniform hyperechoic portal phase.



◀ Figure 13. Recurrence of previous RFA metastasis. Images by courtesy of O. Kolokythas, USA.

Figure 13a. CT image initially detecting recurrence.

Figure 13b. Conventional ultrasound showing possible site of recurrence.

Figure 13c. Contrast image verifying location of recurrence and re-defining the extent of tumor.

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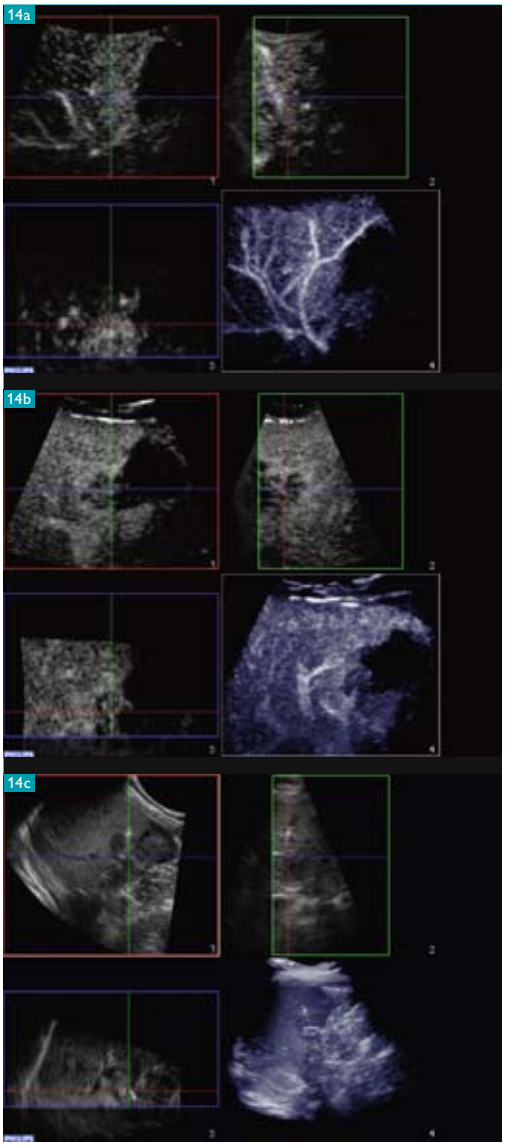

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Figure 14. Recurrence of previous RFA treatment. Images by courtesy of O. Kolokythas, USA

Figure 14a. 3D image of early portal flow.

Figure 14b. 3D image of portal venous phase showing enhancement of recurrence.

Figure 14c. 3D image of RFA needle tines and placement in lesion.

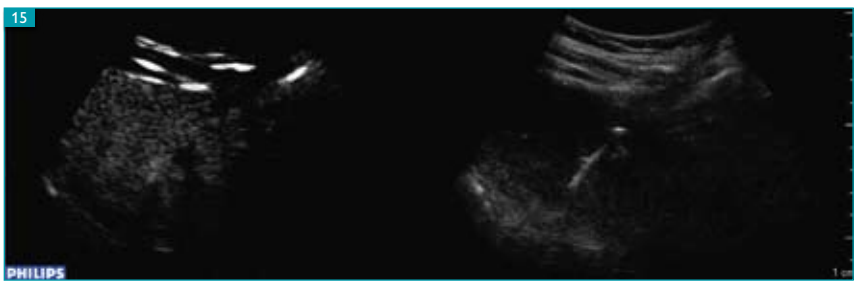

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Figure 15. The image on the left is a contrast image of 1 cm metastasis, while the image on the right shows the tissue image with the needle. The pathology results confirmed that a successful core sample had been acquired. Images by courtesy of O. Kolokythas, USA.

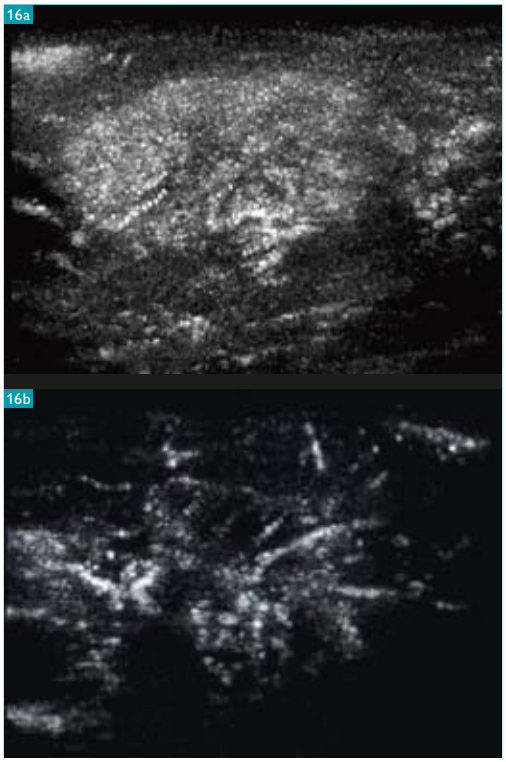

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Figure 16. Contrast-enhanced ultrasound can show the differences in microvascular morphology between benign and malignant lesions, improving the differential diagnosis of solid breast nodules. Images obtained with Optison® and MVI.

Figure 16a. Contrast-enhanced ultrasound image of a fibroadenoma. Image by courtesy of D. Murdali, Canada.

Figure 16b. Biopsy-proven invasive ductal carcinoma. Image by courtesy of B. Porter.

extent of active lesions, which can be important when planning treatment of recurrence of a previous ablation. Figure 13 shows how contrast first verifies the location of recurrence found on CT and, secondly, re-defines the boundaries of the active tumor.

Three-dimensional (3D) imaging with contrast has begun to be used to aid in the planning of RFA. The use of 3D aids in planning the needle approach by visualizing the spatial relationships between the lesion and surrounding structures such as bile ducts, diaphragm and other vasculature. Defining the true 3D extent of the lesion enables improved needle selection for treatment volume and selection of the most advantageous lesion axis to follow for needle insertion.

Visualization of the needle in 3D also aids in the evaluation of the needle placement in the lesion relative to surrounding structures, such as diaphragm, stomach, etc. (Figure 13c).

As contrast agents increase the number of lesions detectable with ultrasound for RFA, the number of lesions targetable with ultrasound for biopsy is also increased. Figure 14 illustrates the use of ultrasound contrast in the guidance of a needle biopsy of a 1 cm metastasis, not detectable with ultrasound without contrast.

Other applications

Breast

Breast cancer is the second most common cause of cancer death in women worldwide.

Ultrasound has an established and important role in breast cancer diagnosis for the evaluation of palpable masses, as an adjunct to X-ray mammography, and for biopsy guidance. Contrast-enhanced breast ultrasound has the potential to further improve the differential diagnosis of solid masses and lymph nodes by evaluation of microvascular morphology and contrast kinetics. For example, Figure 16 illustrates the distinctly different microvascular patterns between a benign fibroadenoma and an invasive ductal carcinoma.

Likewise, contrast-enhanced ultrasound has shown the potential to identify changes in axial lymph nodes due to metastasis in patients with breast cancer. These changes, which are recognizable (but often subtle) in conventional grayscale imaging as erosion of the fatty hilum, are obvious as a characteristic "ring enhancement" in the microvascular image of a metastatic node, as shown in Figure 17. Furthermore, contrast-enhanced breast ultrasound may have additional applications beyond diagnosis, including improved assessment of lesion size and extent for staging and pre-surgical planning, detection of residual tumor or recurrence after surgical resection, and monitoring response to neo-adjuvant chemotherapy. Figure 18 illustrates the use of contrast for assessment of the size and extent of an indistinct hypoechoic lesion, which could be useful for staging and pre-surgical planning.

Prostate

Prostate cancer (PCa) is the second leading cause of death in men from cancer. Transrectal ultrasound (TRUS) is commonly used to guide biopsies of the prostate in patients with elevated PSA. The frequency of positive biopsies is as low as 25%. The addition of contrast to identify suspicious lesions for targeted biopsies could reduce the number of negative biopsies. Staging PCa at initial diagnosis, tumor localization with biochemical recurrence and monitoring therapy are inaccurate with current imaging methods [53]. Imaging the prostate for these applications is an active area of research in MR, CT, PET and contrast ultrasound. Figure 19 illustrates the early enhancement of a lesion in the prostate in a patient with a moderate PSA of 4 ng/mL. A following targeted biopsy proved positive for PCa.

Brain

Stroke is the third leading cause of death worldwide. The only therapy for ischemic stroke is the thrombolytic drug tPA, which must be given within three hours of onset of symptoms. However, if the stroke is hemorrhagic in origin, as it is in about 6% of stroke patients, giving a thrombolytic drug is likely to be fatal. The CT exam required to rule out intracerebral hemorrhage (ICH) may take up to an hour or more, so that only 5-10% of stroke patients are diagnosed in time to receive thrombolytic therapy.

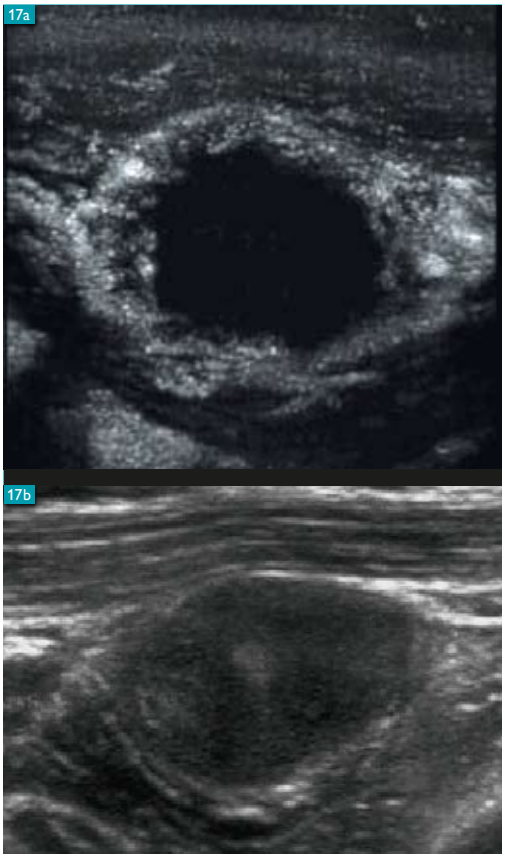

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Figure 17. Contrast-enhanced ultrasound shows a characteristic "ring enhancement" due to metastatic invasion of an axial lymph node in a patient with breast cancer. Images by courtesy of B. Porter, USA.

Figure 17a. Contrast-enhanced ultrasound image of the lymph node using Optison® contrast agent and MVI.

Figure 17b. Conventional high-resolution grayscale image of the same lymph node without contrast agent.

Figure 18. Breast lesion with indistinct margins, showing improved boundary delineation and depiction of lesion extent with contrast enhancement. Images by courtesy of Q. Dai, China.

Figure 18a. Contrast-enhanced tissue image.

Figure 18b. Non-enhanced image.

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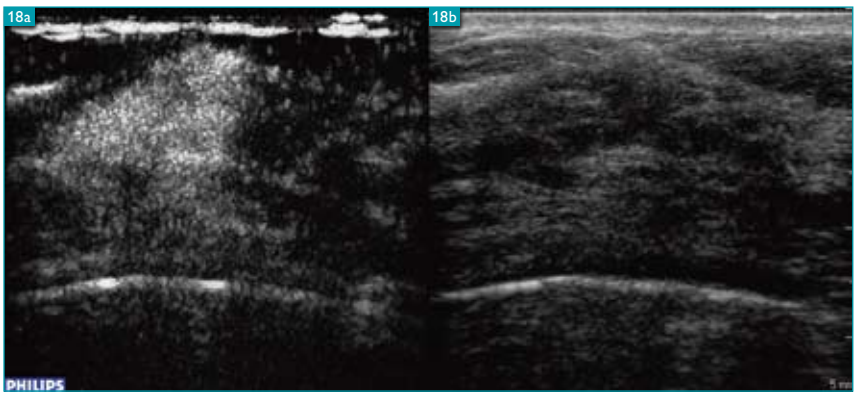

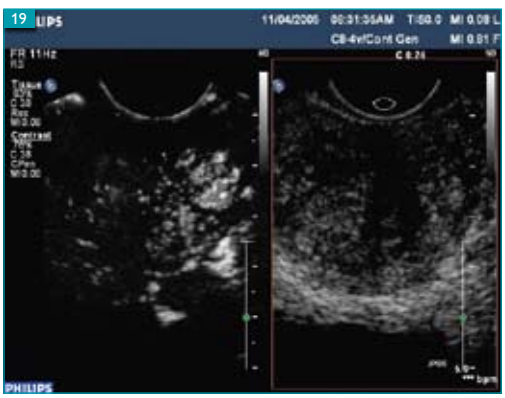

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Figure 19. Example of an early filling prostate lesion, which proved positive for prostate cancer by biopsy. The contrast image is on the left and tissue image is on the right. Images by courtesy of R. Barr, USA.

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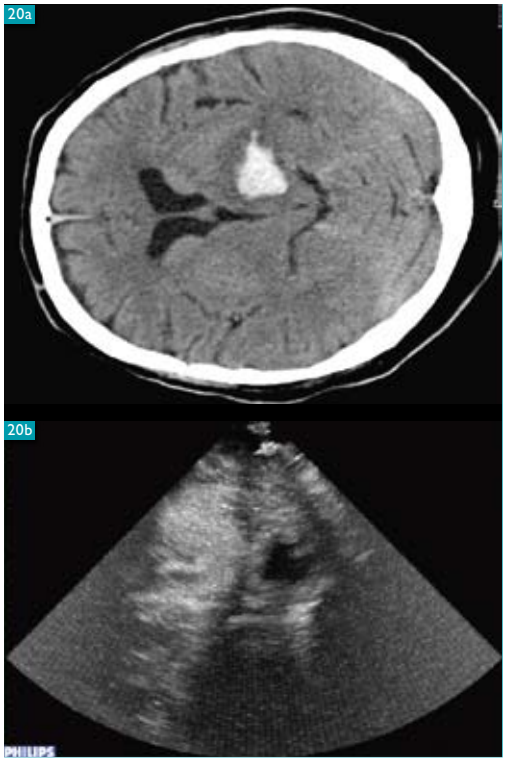

Figure 20. Example of intra-cerebral hemorrhage. Images by courtesy of S. Meairs, Germany.

Figure 20a. CT.

Figure 20b. Ultrasound with SonoVue® contrast agent and MVI.

Acknowledgement
This article is largely based on a White Paper prepared by Matt Bruce.

The ability to rule out hemorrhage with ultrasound would be advantageous in speeding up this process. Figure 20 is an image of an ICH with SonoVue® contrast agent showing the lack of contrast within the hemorrhage, surrounded by a bright halo possibly caused by normally perfused tissue being displaced by the ICH.

Conclusions

There is a great deal of research underway into the clinical applications of ultrasound contrast imaging. The use of ultrasound contrast agents in the liver for lesion characterization and therapy guidance has already entered routine clinical use in some countries. Many of the advances in this field over the past decade have been led by Philips Ultrasound.

Due to the length of time required to develop or change an existing contrast agent, clinical utility for broad routine use will be proven with existing agents. Further improvements to the imaging equipment will accelerate the adoption and the breadth of applications of ultrasound contrast agents. Extrapolating from the improvements seen over the past decade and our continued commitment, we expect Philips Ultrasound to continue a leadership role in this rapidly emerging discipline ■

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