Ultrasound Quarterly
Vol. 19, No. 1, pp. 27–37

Ultrasound Contrast Imaging Research

Michalakis Averkiou, Ph.D., Jeff Powers, Ph.D., Dan Skyba, Ph.D., Matthew Bruce, M.S., and Seth Jensen, M.S.

Ultrasound Engineers, Philips Medical Systems/Philips Ultrasound, Bothell, Washington, U.S.A.

Summary: This article is a review of the research on ultrasound contrast agents in general imaging. While general imaging contrast agent applications are still undergoing investigation and waiting FDA approval in the United States, they are approved for clinical use in Europe and other countries. The contrast microbubble properties are described, including their nonlinear behavior and destruction properties. Imaging techniques like harmonic imaging, pulse inversion, power pulse inversion, agent detection imaging, microvascular imaging, and flash contrast imaging are explained. A connection is made between the aforementioned imaging techniques and the different contrast agents available. The blood flow appearance of different liver tumors in the presence of contrast agents is demonstrated with examples. **Key Words:** Ultrasound contrast agents—Nonlinear microbubble properties—Pulse inversion—Liver tumors.

Ultrasonic instrumentation has long used Doppler techniques for the detection of blood flow. Both color and spectral Doppler have assisted the medical imager in diagnosis by supplying blood flow information to augment morphologic features from grayscale imaging. Although there are many areas in which Doppler alone gives a definitive answer (e.g., in the evaluation of the carotid arteries), there are other areas in which Doppler performs inconsistently and does not always provide diagnostic information. This is especially true in the abdomen, where Doppler signals may be weak, and especially in the parenchyma of organs in which the blood is flowing too slowly in the microvasculature to be detected with Doppler methods.

To extend the utility of ultrasonic imaging in these more difficult areas, microbubble contrast agents for use with diagnostic ultrasound have been an active area of research since 1968 when Gramiak and others[1,2] observed opacification of the right ventricle after an injection of saline. The earliest microbubbles were unable to pass through the lungs, and so were only able to opacify the right ventricle.[3,4] The past two decades have seen very active development of stabilized microbubbles capable of transpulmonary passage for left-side blood pool enhancement by several major pharmaceutical companies.[5–8] During the same time period there have been enhancements of the ultrasonic equipment, such as harmonic imaging and low mechanical index imaging, that have provided researchers the ability to visualize microbubbles within the parenchyma of the liver, kidney, and other organs after an intravenous injection.[9–12]

We present the improvements in ultrasonic imaging systems that have taken place during the past decade to enhance the visualization of contrast microbubbles. We begin with a brief review of ultrasound physics to help understand how these new imaging developments work and end with a summary of some of the clinical uses of contrast agents.

It must be noted here that to date no contrast agents have received approval from the Food and Drug Administration for radiologic applications in the United States and only two are approved for cardiac left-ventricular opacification. In Europe and Canada, however, there are contrast agents approved for both cardiology and radiology. This paper is intended to help those involved with ultrasonic contrast research to understand this rapidly evolving field.

MICROBUBBLE NONLINEARITY

In this section we discuss briefly the nonlinear properties of microbubbles.[13] An acoustic wave generated by an ul-

The authors have disclosed that they have received research grants from and are employees of Philips Medical Systems/Philips Ultrasound.

Clinical application not yet approved in the United States. Supplied to U.S. researchers on request. This article is intended for use within Philips Medical Systems/Philips Ultrasound for informational purposes. Copyright ownership belongs to the authors of this article, not Lippincott Williams & Wilkins.

Address correspondence and reprint requests to Michalakis Averkiou, Ph.D., Philips Medical Systems/Philips Ultrasound, P.O. Box 3003, Bothell, WA 98041-3003. E-mail: mike.averkiou@philips.com

trasonic system consists of alternating high and low pressures at frequencies of 1.5 to 10 MHz. When an acoustic wave encounters a microbubble, it alternately compresses the microbubble on the positive pressure and expands it on the negative pressure. On the positive portion of the wave the microbubbles are compressed in a different fashion than the way they expand in the negative portion. This results in an asymmetric, nonlinear bubble oscillation. Instead of producing a sinusoidal echo with a clean frequency spectrum like the transmitted signal in Fig. 1A, it produces an odd-looking echo with an asymmetric top and bottom, as shown in Fig. 1B. It is this asymmetry that produces harmonics and can be used to enhance the signals from the bubbles. In Fig. 1C, the frequency spectrum of the bubble echoes (1B) is shown. The first major hump is the fundamental component and the subsequent ones are the second, third, and fourth harmonics.

MICROBUBBLE DESTRUCTION

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), defined originally to predict the onset of cavitation in fluids, also gives an indication of the likelihood of bubble destruction. The MI is defined as

MI = peak negative pressure/SQRT (ultrasound frequency) or equivalently

MI = peak negative pressure*SQRT (period of ultrasound wavelength)

The harder you try to expand the bubble (peak negative pressure) and the longer you expand it (period of ultrasonic wavelength), the more likely it is to break. It has been well established that the acoustic power level used during routine examinations destroys the contrast microbubbles.[14,15]

The blood flow in a normal capillary bed is on the order of 1 mm/second, and a typical capillary is approximately 1 mm long.[16] Thus, if the contrast within a capillary is destroyed, it will take approximately 1 second or more to refill the capillary. Given the branching structure of the microvasculature and the thickness of a typical scan plane, it can take several seconds to replenish the contrast in the scan plane, depending on the flow rate to the organ.

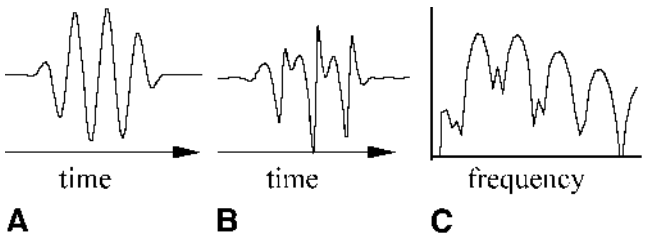


FIG. 1. **A.** Incident acoustic wave. **B.** Nonlinear bubble echoes. **C.** Frequency spectrum of bubble echoes.

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 et al.[17,18] when they found that triggered imaging allows much better visualization of contrast within the myocardium. This led to the widespread use of electrocardiographic triggering during myocardial contrast echo, 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.[19–21]

LOW MECHANICAL INDEX IMAGING

Until recently, visualization of flow in the microcirculation has required some form of triggering or low-frame rate imaging. To detect the bubbles, the ultrasound had to be strong enough to destroy them. However, the increased sensitivity provided by newer imaging techniques makes it possible to image contrast microbubbles relatively nondestructively in real time at very low acoustic pressures.

Low MI scanning is important for two reasons. First, at a low MI, bubble destruction is avoided. Although microbubbles differ in their shell composition, our work to date indicates that at an MI of approximately 0.15, the microbubbles examined are not destroyed markedly, yet give a good harmonic contrast signal. The second major reason for low MI scanning is the reduction of the harmonic component in the tissue echoes relative to bubble echoes. Although tissue harmonics have benefited routine diagnostic scanning, it is the background "noise" signal above which the contrast signal must rise. Because tissue is less nonlinear than bubbles, it requires a higher MI than the contrast microbubbles for a certain harmonic response. Therefore, at a low MI, the contrast-to-tissue ratio is higher than at a high MI, helping to remove the tissue signal and leaving only the contrast.

HARMONIC IMAGING

The bubble's nonlinear behavior can be used to enhance the contrast relative to tissue. "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. Although 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, it cannot be separated completely during the receive process. Thus, in 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 requires 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, because it was assumed that tissue was completely linear. Although it has long been known that tissue does produce nonlinear energy,[22] it was thought that the higher frequency harmonics would be eliminated by attenuation. However, it was soon found that tissue did produce notable harmonic energy, and the high sensitivity and bandwidth of modern ultrasonic 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.[23,24] Therefore, a tissue image is present even in the absence of a contrast agent, so that perfect separation was not achieved.

AGENT DETECTION IMAGING

When microbubbles are interrogated and destroyed with high-MI ultrasound, the backscattered signal is very large and has a broad bandwidth (many harmonic components). Studies have shown that the destruction of the bubbles allows even greater separation between tissue and contrast. When the bubbles are destroyed, the shell is cracked and the gas diffuses into the surrounding fluid or they are fragmented into smaller bubbles that follow the diffusion process even faster. In either case, the signal changes rapidly from pulse to pulse and Doppler techniques are well suited for detecting these changes. Power Harmonics (power Doppler at the harmonic frequency) was developed for contrast agents to detect pulse-to-pulse changes in the signal returned from microbubbles. It is effectively a topographic image of the destruction of microbubbles, thus indicating the regions where bubbles were present. Power Harmonics was pioneered by Philips Ultrasound (Bothell, WA) in the mid to late 1990s and has been used for both cardiologic and radiologic applications.

In recent years the high MI/destruction imaging technique for investigational radiologic applications has been referred to as agent detection imaging (ADI). As with other Doppler techniques, ADI is displayed as a color overlay over a grayscale tissue image. The overlay displays microbubble signals only. One clinical research application that helped in the wider use of ADI is liver metastasis detection with agents that tend to stick in the liver parenchyma after the vascular phase, like Levovist (Schering AG, Berlin, Germany) and SonoVue (Bracco Pharmaceuticals, Milan, Italy). 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 thus ADI is very sensitive. However, a region in the liver may 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 going back 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.

PULSE INVERSION HARMONIC IMAGING

As mentioned earlier, harmonic imaging uses relatively narrow bandwidths to prevent fundamental and harmonic component overlap. Pulse inversion harmonic (PIH) imaging avoids these bandwidth limitations by subtracting rather than filtering out the fundamental signals.[26] Thus, PIH imaging 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 PIH 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 and the second is an inverted replica of the first so that wherever there was a positive pressure on the first pulse there is an equal negative pressure on the second.

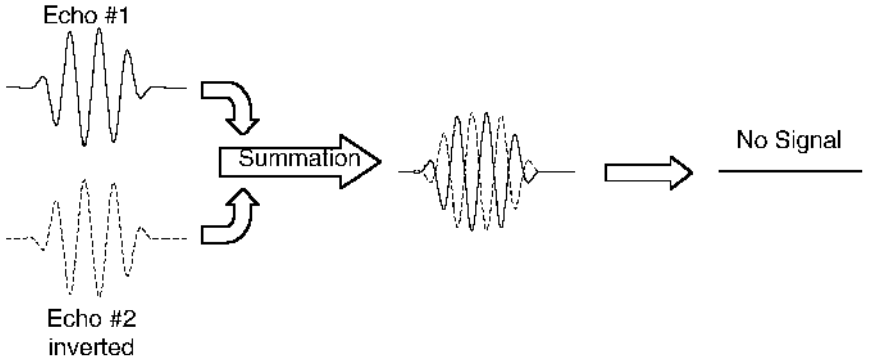


FIG. 2. By adding two consecutive bubble echoes from inverted pulses, pulse inversion cancels fundamental echoes without filtering.

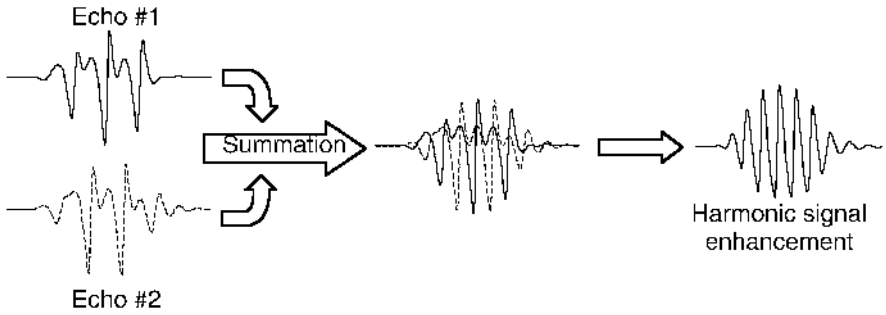


FIG. 3. Pulse inversion harmonic imaging signal processing.

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 in the beam former and all stationary linear targets cancel, as shown in Fig. 2.

Microbubbles respond differently to positive and negative pressures and do not reflect identical inverted waveforms as shown in Fig. 3. Echo 1 is identical to that shown in Fig. 1C. Echo 2 is from the same bubble when interrogated with an inverted pulse. Notice how different the positive portions of the echoes are from the negative portions. When these echoes are added, they do not cancel completely. The fundamental component of the echo cancels, as in Fig. 2, but the harmonic component adds, giving twice the harmonic level of a single echo.

Fig. 4 shows a hemangioma in a liver using conventional imaging (Fig. 4A) and PIH imaging with a contrast agent (Fig. 4B). Much greater contrast sensitivity is obtained and the lesion is much better delineated than without microbubbles.

Although PIH imaging is used mostly as a low MI technique, as in Fig. 4, in some cases it is also used as a high-MI technique. For example, PIH imaging is used in clinical studies of the liver with Levovist to destroy the microbubbles and to form a high-resolution image from the harmonic response of the bubble echoes.[25] As mentioned earlier, research indicates that the normal liver that contains bubbles has a bright appearance in the image whereas metastases are black (have no signals).

POWER PULSE INVERSION

To achieve greater sensitivity than PIH imaging, additional pulses of alternating polarity can be used. This also improves separation between tissue and contrast, and reduces motion sensitivity. Because PIH imaging uses two pulses to form each image line, anything that moves between the two pulses is not canceled completely, which leads to incomplete tissue removal. This is illustrated in Fig. 5, in which the simulated tissue signal has moved slightly between pulses. As seen, there is a motion component left at the fundamental frequency. This is similar to color Doppler motion artifacts, but because PIH imaging is a grayscale mode, the effect is to brighten the gray-scale image slightly.

To remove tissue motion artifacts while increasing sensitivity, a longer sequence of inverted pulses is used. Let's say three pulses are transmitted as $P1^+$, $P2^-$, and $P3^+$, where the + or − indicates a positive or inverted pulse, respectively. If the tissue is moving fairly uniformly, a good assumption at the PRF used, it will have moved approximately 10 μsec between $P1^+$ and $P2^-$, and then again between $P2^-$ and $P3^+$. Looking for a moment at only $P1^+$ and $P3^+$, we have two nearly identical waveforms that differ by

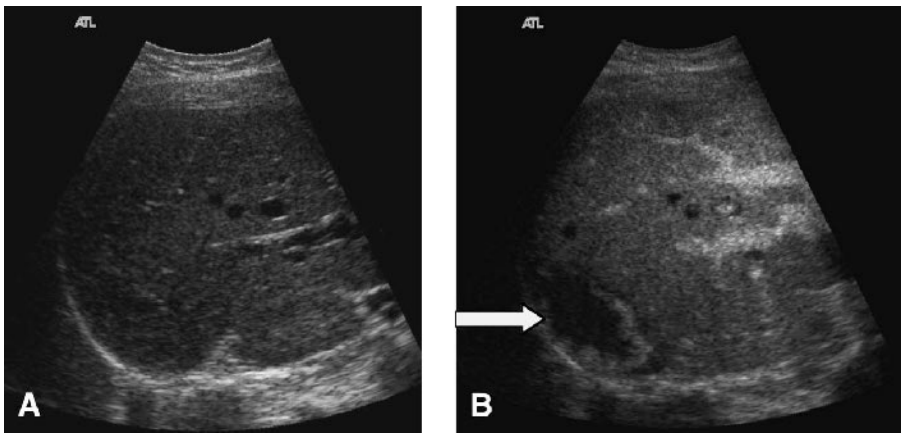


FIG. 4. A, B. A hemangioma with contrast scanned with conventional imaging (**A**) and pulse inversion harmonic imaging (**B**).

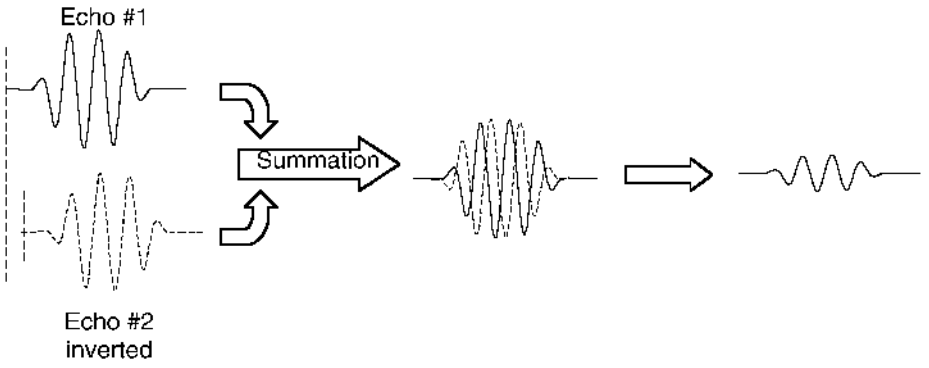


FIG. 5. Incomplete tissue echo cancellation with pulse inversion imaging resulting from motion between pulses.

only a slight phase shift of 20 μsec. If we add these two waveforms, we get a similar waveform with almost twice the amplitude but half the phase shift of the two original waveforms. This is based on the mathematical approximation that for small angles, ϕ,

$$\sin(\theta) + \sin(\theta + \phi) \approx 2*\sin(\theta + \phi/2).$$

This result gives us a new waveform with the same 10-μsec phase shift of $P2^-$. By multiplying $P2^-$ by two and adding these two waveforms, the tissue motion component vanishes, as shown in Fig. 6. The final sum is thus, $P1^+ + 2*P2^- + P3^+$.

Because the harmonic component of the echo is not inverted by inverting the transmitted pulse, the harmonic signals all add, giving four times the original harmonic signal, by extension of Fig. 3. More pulses can also be used, further increasing sensitivity and reducing motion artifacts.[27]

Power pulse inversion (PPI) also provides another very important benefit. As already described in a previous section, microbubbles are destroyed easily with normal imaging power levels, thus requiring very low transmit amplitudes. At these low amplitudes, tissue harmonics are nearly nonexistent, giving very little tissue signal for navigation. Presenting PPI as a colorized overlay on a conventional grayscale image results in a high-quality grayscale image for navigation and an extremely sensitive contrast image presented in color (Fig. 7).

PPI is used only as a low MI technique. Before contrast injection there are almost no signals present in the color overlay, whereas the background tissue image is in fundamental mode to ensure that we have an image even at the low MI used. Once the bubbles arrive, the overlay (foreground) displays the bubble signals while the background image may still be considered as a tissue image because the fundamental mode is not capable of showing the bubbles. In summary, we have a mode that shows a "bubble-only" image in the foreground and a "tissue-only" image in the background. The overlay may also be removed during acquisition or during review to view only the background tissue image for localization purposes.

MICROVASCULAR IMAGING

It has been known for some time that malignant tumors force the host to grow new blood vessels to supply nutrients to support the rapid growth and spread of the tumor.[28,29]

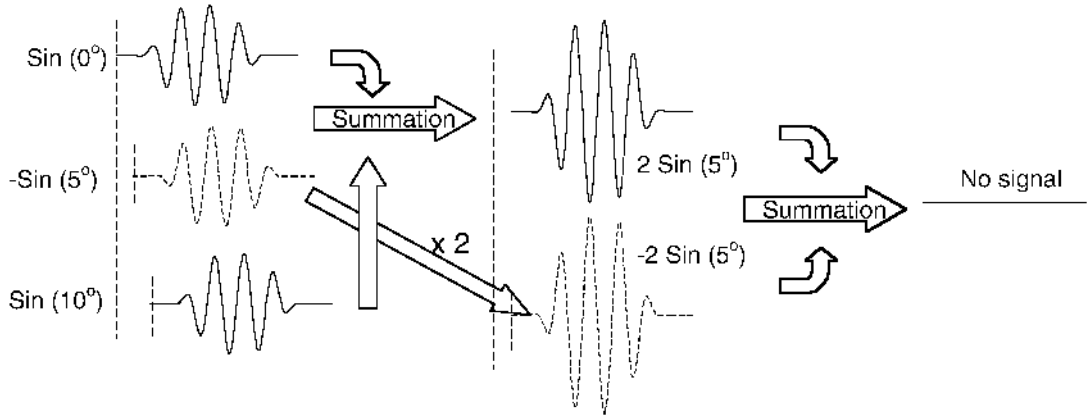


FIG. 6. Increased sensitivity and tissue motion cancellation with power pulse inversion imaging by summing multiple pulses.

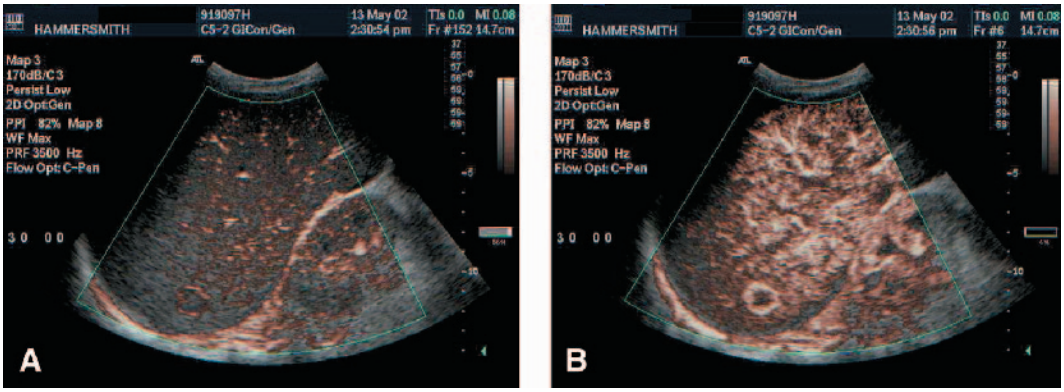


FIG. 7. A splenic hemangioma shown in power pulse inversion. **A, B.** Initial bubble arrival (**A**) and peripheral filling (**B**).

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 steady improvement in the ability to image microbubbles without destroying them has led to the investigator's ability to image individual bubbles in very small vessels in lesions with very low blood flow rates. In some of these 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 Fig. 8A.

Microvascular imaging has recently been introduced on the HDI 5000 system (Philips Ultrasound, Bothell, WA), which uses specially designed image-processing software to capture and track the bubbles as they go through these small vessels. This software 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 Fig. 8B.

FLASH CONTRAST IMAGING

Although the ability to visualize microvascular blood flow in real time is a substantial advancement, the ability to destroy contrast at will also has diagnostic potential. Contrast enhancement in an image actually represents the volume of contrast within the image, not the flow rate. Blood volume can be fairly constant distal to a stenosis, even if the flow rate is reduced. So, once a vascular bed has filled with contrast, it will be difficult to differentiate altered flow rates.

When flow rates are measured with indicator dilution techniques, a bolus is used, and the time to peak is an indicator of flow rate.[30,31] This is difficult to use with ultrasonic contrast because absolute concentration is unknown and the bolus spreads after an intravenous injection. By destroying the contrast within the scan plane, a "negative bolus" of contrast is created locally. Then, the time it takes for contrast to refill the scan plane is an indicator of the local blood flow velocity. This has been proposed as a method for quantification of myocardial perfusion[32–34] and is under investigation for general imaging applications such

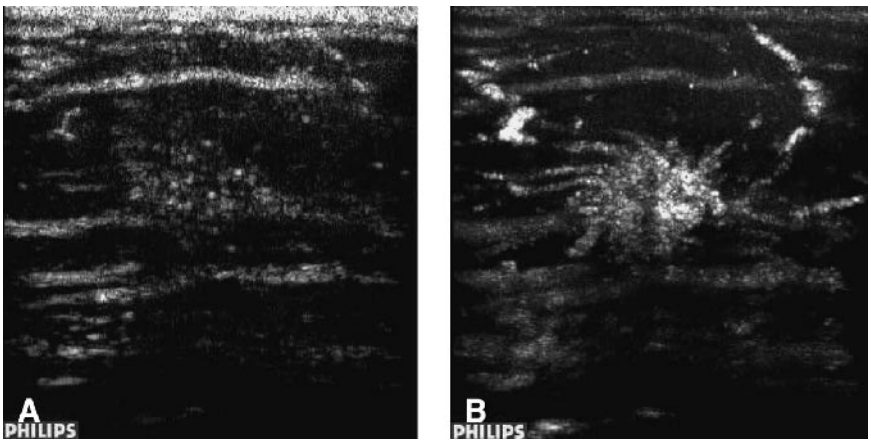
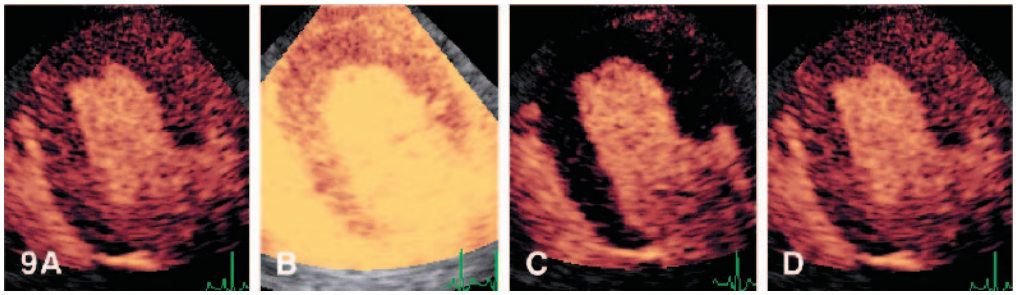
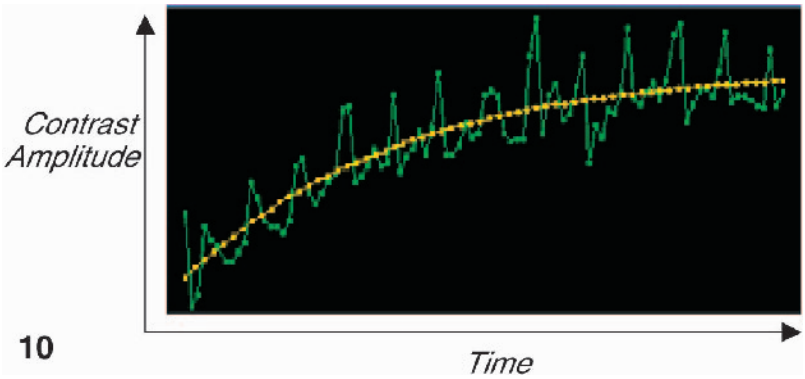
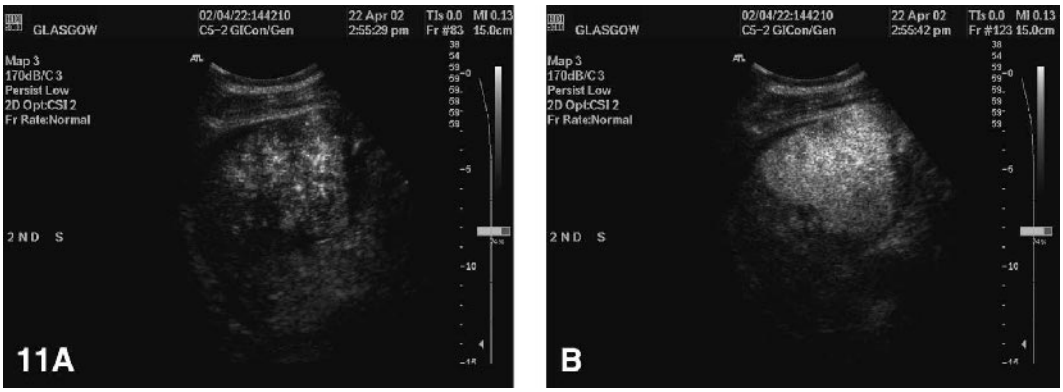


FIG. 8. A, B. Breast ductal carcinoma showing individual bubbles in a still frame of a live loop (**A**), and processed microvascular imaging capturing the tracks of many bubbles (**B**).







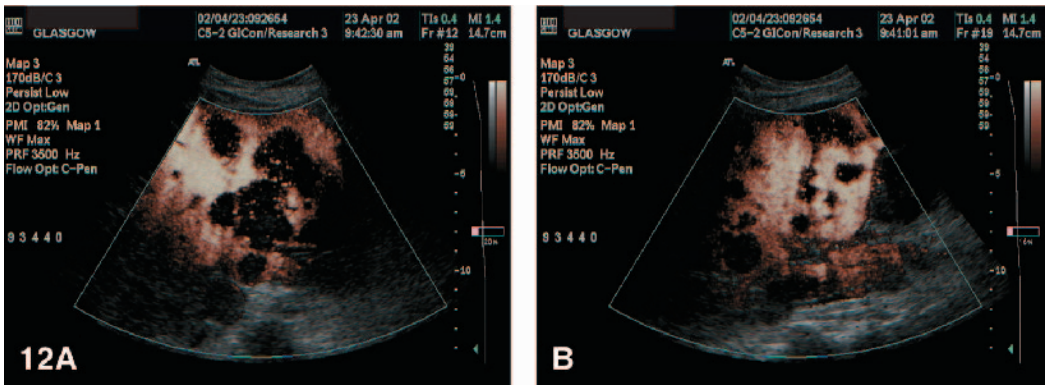


FIG. 9. Flash contrast imaging of myocardial perfusion. **A.** Stable perfusion before flash. **B.** High mechanical index flash to destroy agent. **C.** No agent in myocardium after flash. **D.** Seconds later the contrast has been replenished in the myocardium.
FIG. 10. Replenishment curve showing real-time data points from the full sequence shown in Figure 9 and curve fit to $C(t) = A^*(1 - \exp[-\beta t])$.
FIG. 11. Example of hepatocellular carcinoma with SonoVue (Bracco Pharmaceuticals) in low mechanical index scanning. **A.** Early arterial phase. **B.** Complete filling of hepatocellular carcinoma before portal venous enhancement of normal liver.
FIG. 12. Example of metastases with Levovist (Schering AG) in agent detection imaging. The black holes in the image indicate metastases.

TABLE 1. *Contrast agents and imaging protocols during vascular and late phase*

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	High MI
Imagent®	Low MI	N/A

as renal artery stenosis and angiogenesis quantification and monitoring.

Flash contrast imaging provides the tools required for this kind of research. By "flashing" the tissue with one or two frames at high MI and then switching automatically back to low MI, the replenishment can be watched in real time. This process is illustrated in Fig. 9 and a replenishment curve is shown in Fig. 10. The curve shown in Fig. 10 is the best fit to the equation $A^*[1 - \exp(-\beta t)]$, in which A is related to blood volume, and the time constant β is related to blood flow velocity. Although flash contrast imaging was developed for quantification research, it can also be used for other research purposes, such as clearing contrast out of the microvasculature to see the intermediate and larger size vessels.

CLINICAL APPLICATIONS IN CONTRAST RADIOLOGY

The largest application for contrast agents in radiology is liver lesion detection and characterization.[35–38] (Again, note that contrast agents are not yet cleared for these purposes in the United States.) Certain lesions may be seen with ultrasound before injection of contrast agents, but often lesions are not seen at all without them. Once a lesion is identified, it must be characterized. The main question to be answered is, what is the nature of the lesion, benign or malignant? The detection process is a visual observation of the size and location of the lesion during the ultrasonic examination.

The characterization process is a more involved process and requires observation of the different vascular phases (arterial, portal venous, and parenchymal uptake or late phase), the nature of vessels inside the lesion, and rate of filling. There are four main liver lesions discussed in this section: hepatocellular carcinoma (HCC), metastasis from a primary tumor at some other location, hemangioma, and focal nodular hyperplasia. The first two are malignant and the latter two are benign.

The microbubbles are first seen coming through the hepatic artery approximately 20 seconds after intravenous injection, depending on several factors like cardiac output, speed of injection, and amount of contrast. This is referred to as the *arterial phase*. Only 20 to 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 approximately 2 to 5 minutes. Subsequently 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 to 5 minutes.[11,25,39] The contrast agents used today and the imaging protocol followed for the vascular and late phases are shown in Table 1. Microbubbles that have a late phase are collected either in the sinusoids or in the reticuloendothelial system. They remain trapped there for some time (depending on the agent) or until high-MI insonification causes bubble disruption. The contrast enhancement characteristics of the different lesions are described next.

Hepatocellular Carcinoma

HCC is the most common liver tumor type in the world. It is found more often in men than women and usually in people with some degree of liver damage, like alcohol cirrhosis or hepatitis B or C. HCC has irregular vessels (S-shaped or corkscrew) that receive early arterial flow, and the overall tumor is hyperechoic compared with normal liver. HCCs may remain hyperechoic during the portal phase, but cases in which it becomes iso- or hypoechoic are also encountered. Fig. 11 shows an example of early arterial filling of HCC in low MI scanning with pulse inversion. The opposite behavior is seen during a late-phase examination (with an appropriate agent) in which HCC will have no contrast uptake and will show as a black void in a white liver (Table 2). Lesions may be characterized by the vascular enhancement patterns exhibited during the different circulation phases,[36] as shown in Table 2. The imaging technique used for vascular- and late-phase imaging (depending on the contrast agent used) may be chosen from Table 3.

Metastasis

The usual primary sites for metastases in the liver are the gastrointestinal tract (especially the colon), breast, and lung

TABLE 2. *Lesion vascular behavior during contrast examination*

Lesion Type	Characteristic Features	Arterial Phase	Portal Phase	Late Phase (only for certain agents)
HCC	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
FNH	Radial vascularity and stellate central scar	Hyperechoic	Hyperechoic	Marked contrast uptake

TABLE 3. *Imaging modes and their usage for low or high MI imaging*

Imaging Mode	Low MI (real-time imaging)	High MI (destruction)
Harmonic imaging	Yes (obsolete today)	Yes (obsolete today)
Pulse inversion	Yes	Yes
Power pulse inversion	Yes	No
Power harmonics/ADI	No	Yes

carcinomas. The most characteristic signature of these lesions is the late-phase appearance with contrast agents that have this property (Table 1).[40] A ring enhancement (vessels around the perimeter of the lesion) is often observed with the lesion itself being dark (no contrast uptake) and the surrounding normal liver being white. During the arterial phase the metastasis may be hyperechoic or show no change compared with the normal tissue. During the portal phase an iso- or hypoechoic appearance is observed. The agents with a late phase are Levovist (Schering AG), SonoVue (Bracco Pharmaceuticals), and Sonazoid (Amersham Health, Oslo, Norway), as shown in Table 1. When using Levovist, a high-MI protocol is followed and either interval delay (insonify after a fixed delay) during the vascular phase[19] or sweep of the whole liver during the late phase are used. The sweep method is needed with high-MI protocols because with every plane imaged the bubbles are destroyed, and subsequent frames will have no bubble information. Thus, by moving to a new plane, new bubbles are insonified and give information about lesions present there. At the end of the sweep the user freezes the system and reviews the loop to find all possible lesions. Fig. 12 shows an example of Levovist late-phase scanning in high-MI ADI. The voids in the images depict metastases. When using SonoVue or Sonazoid, as Table 1 suggests, a low MI protocol may be followed. And, as Table 3 shows, PIH imaging or PPI may be used. With those techniques, real-time scanning is permitted and the lesion is imaged continuously in all phases including the late phase (Fig. 13). Low MI scanning is easier to perform because the same area may be scanned repeatedly.

Hemangioma

Hemangioma is the most common type of liver lesion. Some clinicians refer to them as "birth marks." They are benign lesions and thus usually asymptomatic, consisting of a large network of endothelium-lined vascular spaces. They are usually found accidentally. In conventional ultrasound they are usually echogenic, but certain high-flow hemangiomas may be hypoechoic. The main feature of hemangiomas during a contrast examination is progressive peripheral nodular enhancement.[19] During the arterial phase, enhancement is seen only peripherally with a patchy appearance, and areas of pooling. Figs. 14A and B show an example of peripheral filling and areas of pooling. The enhancement progresses toward the center and continues during the portal phase. It may take as long as 2 minutes for complete filling and often looks brighter (hyperechoic) than the surrounding liver (Fig. 14C). Low MI protocols are used for real-time observation of the centripetal filling (e.g., PIH imaging or PPI, as shown in Table 3). For a real-time technique to work there must be very little bubble destruction; otherwise, the complete filling of a hemangioma may not be observed. Interval delay with a higher MI may also be used with techniques like PIH imaging or ADI. The choice of protocol (low or high MI) is determined by the type of contrast agent used.

Focal Nodular Hyperplasia

This type of lesion is more common with women than men and it is benign. Increased incidence in women using contraceptives has been observed. In ultrasonic images without contrast they are normally iso-or hypoechoic compared with the normal liver. With contrast agents their main characteristic is radial vascularity and stellate central scar.[35,41] Vessels are often observed that seem to connect the central point with the periphery, giving it the "spoke

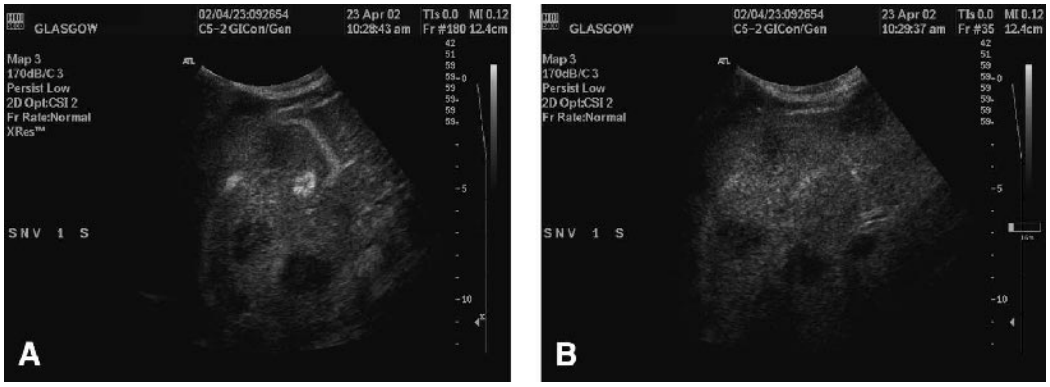


FIG. 13. Example of metastases with SonoVue (Bracco Pharmaceuticals) in low mechanical index scanning. The black holes in the image indicate metastases.

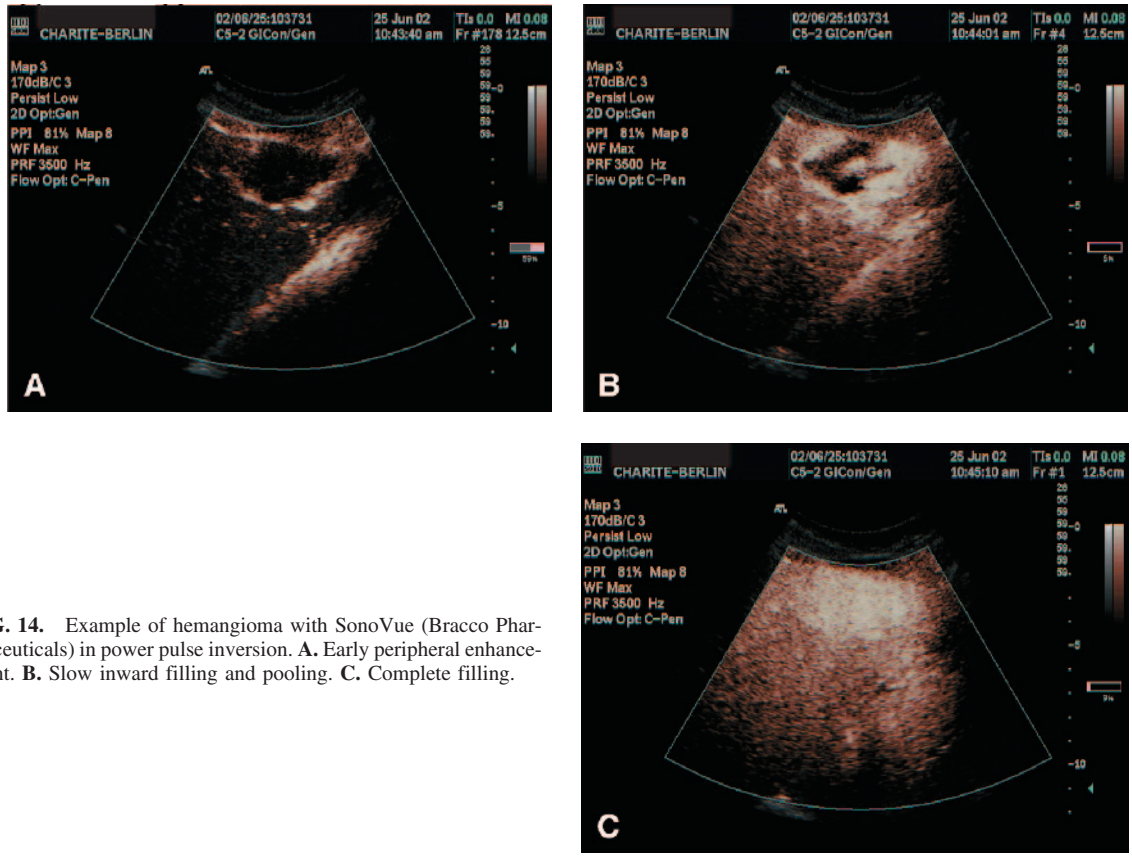


FIG. 14. Example of hemangioma with SonoVue (Bracco Pharmaceuticals) in power pulse inversion. **A.** Early peripheral enhancement. **B.** Slow inward filling and pooling. **C.** Complete filling.

wheel" appearance during the arterial phase. The lesion remains hyperechoic all through the portal phase and has a marked contrast uptake during the late phase. A central scar is usually depicted during the late phase as a hypoechoic area in a hyperechoic lesion. Focal nodular hyperplasia is best imaged with low MI protocols with PIH imaging and PPI techniques (Fig. 15).

Another clinical application of contrast agents is renal perfusion. For this type of study a low MI technique is preferable with either PIH imaging or PPI. The evaluation of the perfusion may be quantified with a destruction–replenishment protocol. With renal studies the main problems addressed are renal tumors, detection of renal artery stenosis, and early evaluation of kidney transplants.

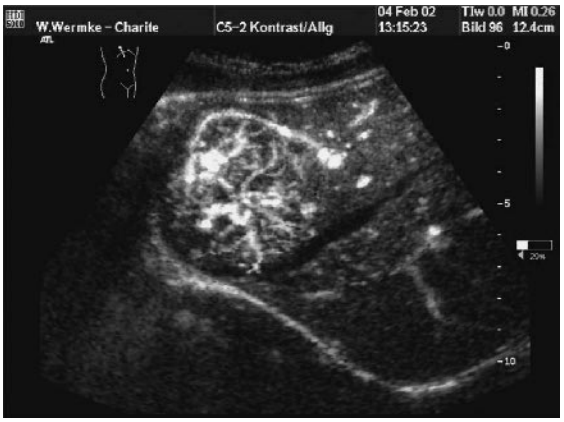


FIG. 15. Example of focal nodular hyperplasia with SonoVue (Bracco Pharmaceuticals) in pulse inversion.

CONCLUSION

There is a tremendous amount of research underway in the clinical applications of ultrasonic contrast imaging. Many of the major advances in the field during the past decade have come from the equipment manufacturers, led by Philips Ultrasound, because the bubble properties are fixed once they enter clinical trials. Because of the length of time required to develop or even change an existing contrast agent, clinical utility will have to be proved with existing agents. This will undoubtedly require yet more improvements to the imaging equipment until ultrasonic contrast agents become used widely during routine clinical situations. However, judging from the improvements seen during the past decade, there is little doubt that these improvements will be forthcoming and that Philips Ultrasound will continue in a leadership role in this rapidly emerging market.

REFERENCES

1. Gramiak R, Shah PM. Echocardiography of the aortic root. *Invest Radiol* 1968;3:356–366.

2. Kremkau FW, Gramiak R, Carstensen EL, et al. Ultrasonic detection of cavitation at catheter tips. *Am J Roentgenol Radium Ther Nucl Med* 1970;110:177–183.
3. Becher H, Zahler K, Grube E, et al. [Improving color Doppler echocardiography of the right heart chambers following intravenous injection of SHU 454.] *Z Kardiol*. 1988;77:227–232. Erratum. *Z Kardiol*. 1988;77:398.
4. Fritzsch T, Schartl M, Siegert J. Preclinical and clinical results with an ultrasonic contrast agent. *Invest Radiol*. 1988;23:5.
5. Angeli E, Carpanelli R, Crespi G, et al. Efficacy of SH U 508 A (Levovist) in color Doppler ultrasonography of hepatocellular carcinoma vascularization. *Radiol Med (Torino)*. 1994;87(suppl 1):24–31.
6. Feinstein SB, Cheirif J, Ten CF, et al. Safety and efficacy of a new transpulmonary ultrasound contrast agent: initial multicenter clinical results. *J Am Coll Cardiol* 1990;16:316–324.
7. Fritzsch T, Hauff P, Heldmann F, et al. Preliminary results with a new liver specific ultrasound contrast agent. *Ultrasound Med Biol* 1994; 20:137.
8. Goldberg BB, Liu JB, Burns PN, et al. Galactose-based intravenous sonographic contrast agent: experimental studies. *J Ultrasound Med* 1993;12:463–470.
9. Burns PN, Powers JE, Hope Simpson D, et al. Harmonic imaging: principles and preliminary results. *Angiology* 1996;47:S63–S74.
10. Burns PN, Powers JE, Hope Simpson D, et al. Harmonic power mode Doppler using microbubble contrast agents: an improved method for small vessel flow imaging. *Proc IEEE UFFC* 1995:1547–1550.
11. Blomley MJ, Albrecht T, Cosgrove DO, et al. Improved imaging of liver metastases with stimulated acoustic emission in the late phase of enhancement with the US contrast agent SH U 508A: early experience. *Radiology* 1999;210:409–416.
12. Leen E, McArdle CS. Ultrasound contrast agents in liver imaging. *Clin Radiol* 1996;51(suppl 1):35–99.
13. Leighton TG. *The Acoustic Bubble*. London: Academic Press; 1994.
14. Walker KW, Pantely GA, Sahn DJ. Ultrasound-mediated destruction of contrast agents. Effect of ultrasound intensity, exposure, and frequency. *Invest Radiol* 1997;32:728–734.
15. Villarraga HR, Foley DA, Aeschbacher BC, et al. Destruction of contrast microbubbles during ultrasound imaging at conventional power output. *J Am Soc Echocardiogr* 1997;10:783–791.
16. Berne RM, Levy MN. *Cardiovascular Physiology*. 2nd ed. St. Louis: CV Mosby; 1972.
17. Porter T, Xie F. Transient myocardial contrast following initial exposure to diagnostic ultrasound pressures with minute doses of intravenously injected microbubbles: demonstration and potential mechanisms. In: Nanda N, Schlief R, Goldberg B, eds. *Advances in Echo Imaging Using Contrast Enhancement*. 2nd ed. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1996.
18. Porter TR, Xie F, Kricsfeld D, et al. Improved myocardial contrast with second harmonic transient ultrasound response imaging in humans using intravenous perfluorocarbon-exposed sonicated dextrose albumin. *J Am Coll Cardiol* 1996;27:1497–1501.
19. Wilson SR, Burns PN, Muradali D, et al. Harmonic hepatic US with microbubble contrast agent: initial experience showing improved characterization of hemangioma, hepatocellular carcinoma, and metastasis. *Radiology* 2000;215:153–161.
20. Heckemann RA, Cosgrove DO, Blomley MJ, et al. Liver lesions: intermittent second-harmonic gray-scale US can increase conspicuity with microbubble contrast material—early experience. *Radiology* 2000;216:592–596.
21. Kim TK, Choi BI, Hong H, et al. Improved imaging of hepatic metastases with delayed pulse inversion harmonic imaging using a contrast agent SH U 508A: preliminary study. *Ultrasound Med Biol* 2000; 26:1439–1444.
22. Hamiltion MF, Blackstock DT. *Nonlinear Acoustics*. San Diego, CA: Academic Press; 1998.
23. Averkiou MA, Roundhill DN, Powers JE. New imaging technique based on the nonlinear properties of tissues. *Proc IEEE Ultrason Symp* 1997;2:1561–1566.
24. Hirooka Y, Goto H, Ito A, et al. Recent advances in US diagnosis of pancreatic cancer. *Hepatogastroenterology* 2001;48:916–922.
25. Blomley M, Albrecht T, Wilson S, et al. Improved detection of metastatic liver lesions using pulse inversion harmonic imaging with Levovist: a multicenter study. *Radiology* 1999.
26. Burns PN, Wilson SR, Simpson DH. Pulse inversion imaging of liver blood flow: improved method for characterizing focal masses with microbubble contrast. *Invest Radiol* 2000;35:58–71.
27. Hope Simpson D, Chin CT, Burns PN. Pulse inversion Doppler: a new method for detecting nonlinear echoes from microbubble contrast agents. *IEEE Trans Ultrason Ferroelectrics Freq Control* 1999;46: 372–382.
28. Folkman J. Tumor angiogenesis. *Cancer*. New York: Plenum; 1979: 355–388.
29. Folkman J, Beckner K. Angiogenesis imaging. *Acad Radiol* 2000;7: 783–785.
30. Bassingthwaighte J. Physiology and theory of tracer washout techniques for the estimation of myocardial blood flow: flow estimation from tracer washout. *Prog Cardiovasc Dis* 1977;20:165–189.
31. Voci P, Heidenreich P, Aronson S, et al. Quantitation of renal blood flow by contrast ultrasonography: preliminary results. *Cardiologia* 1989;34:1001–1006.
32. Tiemann K, Becher H, Köster J, et al. Quantification of tissue perfusion by means of bubble destruction using harmonic power Doppler imaging. *Circulation* 1998;98:I570.
33. Wei K, Jayaweera AR, Firoozan S, et al. Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. *Circulation* 1998;97:473–483.
34. Averkiou M, Bruce M, Powers J, inventors; ATL Ultrasound, assignee. *Ultrasonic Diagnostic Imaging With Contrast Agents*. USA patent no. 5,833,613. 1998.
35. Wilson SR, Burns PN. Liver mass evaluation with ultrasound: the impact of microbubble contrast agents and pulse inversion imaging. *Semin Liver Dis* 2001;21:147–159.
36. Leen E. The role of contrast-enhanced ultrasound in the characterisation of focal liver lesions. *Eur Radiol* 2001;11(suppl 3):E27–E34.
37. Albrecht T, Barr R, Blomley M, et al. Seeking consensus: contrast ultrasound in radiology. *Invest Radiol* 2002;37:205–214.
38. Robbin ML. Ultrasound contrast agents: a promising future. *Radiol Clin North Am* 2001;39:399–414.
39. Blomley MJ, Albrecht T, Cosgrove DO, et al. Stimulated acoustic emission to image a late liver and spleen-specific phase of Levovist in normal volunteers and patients with and without liver disease. *Ultrasound Med Biol* 1999;25:1341–1352.
40. Harvey CJ, Blomley MJ, Eckersley RJ, et al. Hepatic malignancies: improved detection with pulse-inversion US in late phase of enhancement with SH U 508A—early experience. *Radiology* 2000;216:903–908.
41. Wermke W, Gassmann B. *Tumor Diagnostics of the Liver With Echo Enhancers, Color Atlas*. Berlin: Springer Verlag; 1998.