Ultrasound: Contrast agents add new dimension to sonography

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Microbubbles of air or other gases are ideally suited as echo-enhancers because of two factors: The high difference in acoustic impedance at gas fluid/tissue interfaces provides strong acoustic backscatter; and gas microbubbles approximately 1 to 5 microns in size resonate in the acoustic beam at frequencies used in diagnostic ultrasound. This "lucky coincidence" substantially increases the echo-enhancing potential of microbubbles.

An additional and usually undesirable physical property of microbubbles is attenuation of the ultrasound beam, which occurs at high microbubble concentrations. Attenuation increases disproportionately with concentration and can be a problem, particularly in contrast-enhanced echocardiography. In extreme cases, it can transiently obscure the structures being examined. In the last decade, several pharmaceutical companies have developed a variety of stabilized microbubble contrast agents for ultrasound, all of which have several common features. Most importantly, the bubbles in these agents are protected by a stabilizing layer or shell consisting of various chemicals that allow the bubbles to withstand several passes through the pulmonary and peripheral capillary systems. After intravenous injection, they achieve enhancement of the entire vascular system, including the left heart and large and small arteries, as well as peripheral veins and the portal venous systems. The duration of enhancement after a bolus injection varies from agent to agent, but is on the order of two to 10 minutes. This can be prolonged for as long as necessary by infusing the agents. Another common property of all ultrasound contrast agents is their size distribution of about 1 to 7 microns, which ensures that there is no embolization of the capillaries. All microbubble contrast agents are essentially blood-pool agents because they do not leave the intravascular space, which makes them fundamentally different from x-ray or MR agents. Some agents, however, have been shown to be taken up by the reticuloendothelial system (RES) and have liver-specific properties. The gas contained by the agents is exhaled via the lungs over the course of several minutes following the injection. The shells or protective layers vary in their chemical constituency and undergo different metabolic pathways. All the echo-enhancing agents have been shown to be extremely safe in clinical trials, with safety profiles that compare favorably with iodinated contrast agents. Almost no substantial adverse events have been reported.

Commercial Development
The history of echo-enhancers goes back to the mid-1960s, when Joyner first observed enhancement of intracardiac echoes during saline injections. Gramiak and Shah published the first report on contrast echocardiography using intracardiac injections of indocyanine green solutions in 1968. The observed echo-enhancing effect was due to tiny air bubbles introduced with the injected fluid. Since Joyner's discovery, cardiologists have routinely used microbubbles in injected solutions introduced by agitation or sonication for the detection of right-to-left shunts in echocardiography. Japanese investigators used carbon dioxide as an echo-enhancer in the liver. They injected CO2 into the hepatic artery during visceral angiography to enhance gray-scale ultrasound signals from normal liver parenchyma and liver tumors. The ultrasound examination had to be performed shortly after the injection on the angiography table. This technique, called "echocarbography," produced some encouraging results, particularly in relation to lesion detection, but its clinical use was limited by its invasive nature. The first commercially available contrast agent was Echovist (Schering AG, Berlin), a galactose-based agent consisting of air microbubbles. These bubbles are not protected, however,
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The use of contrast agents in focal liver lesions has also been studied by several investigators. Functional dynamic data. Early results have been encouraging. Contrast-enhanced scans, such as the three-dimensional morphology of the tumor vascularity and enhancement of the left ventricle and is used in echocardiography, e.g., to improve a left ventricular border detection. However, enhancement of the arterial system is weak and its use in radiology is limited.

The first agent to provide clinically useful vascular enhancement in a radiological context is Levovist (Schering AG). It is also a galactose-based agent, with air bubbles protected by a thin layer of palmitic acid. This protective layer ensures capillary passage, and the agent provides marked enhancement of Doppler signals from large and small vessels up to 20 decibels, as well as gray-scale enhancement of the cardiac chambers and large vessels. Levovist is commercially available in most European and several other countries.

Several newer contrast agents in clinical development use gases other than air, such as perfluorocarbons. The advantage of these gases is that they are stronger enhancers than air and are less soluble in water (and plasma). They not only provide stronger Doppler enhancement but also have a longer duration—about 10 minutes after a bolus injection. Examples of these newer "third-generation" agents are EchoGen (Sonus Pharmaceuticals, Bothell, Washington, U.S.), Imagent (Alliance, San Diego), FSO69 (Molecular Biosystems), MRX115 (ImaRx Pharmaceuticals, Tucson, U.S.) and BR1 (Bracco, Milan). Several of these agents not only achieve Doppler enhancement but also enhance gray-scale echoes from parenchyma of highly vascular organs such as the kidney or liver.

**Clinical Applications**

The main application of ultrasound contrast agents in radiology is the enhancement of Doppler signals in both large and small vessels. In larger vessel territories where Doppler examinations are often difficult—such as renal arteries, intracranial vessels, and the portal venous system, including TIPS (transjugular intrahepatic portosystemic shunts)—contrast agents enable visualization of vessels that are often inaccessible or only partially accessible to Doppler. The sensitivity and specificity of renal artery stenosis detection by ultrasound can be improved with echo-enhancing agents. In transcranial Doppler, visualization of the entire circle of Willis is substantially improved, and intracranial aneurysms can often be detected, as can vascular intracranial tumors. Because demonstration of flow within TIPS is often difficult with Doppler ultrasound, contrast enhancement is particularly useful in this application (Figure 1). A study of 20 patients undergoing TIPS has shown that the number of completely assessable shunts improved from eight precontrast to 19 post-Levovist.

Enhancement of Doppler signals from relatively small vessels within tumors is another clinical application of contrast agents that has aroused considerable scientific interest. Color Doppler ultrasound is the only widely available noninvasive imaging modality that has sufficient spatial resolution to demonstrate the abnormal morphology of small vessels within tumors. This is often limited, however, by the weak Doppler signals from such vessels, which usually have low flow. Contrast agents can overcome this limitation, and malignant tumors in particular often display dramatic vascularity on color Doppler ultrasound after contrast enhancement. Furthermore, the architecture of malignant tumor vascularity is often irregular, tangled, and chaotic. In principle, these features can be used to improve the differential diagnosis of solid tumors. The potential of this application of echo-enhancers has been studied in several body organs, with some encouraging results. Kedar et al studied 34 patients with breast masses using color Doppler ultrasound pre- and post-Levovist. They found that sensitivity and specificity for malignancy increased from 88.9% and 87.5% pre-Levovist to 100% and 100% respectively post-Levovist.

Inspired by these promising results, we studied 20 patients with indeterminate breast lesions using power Doppler ultrasound and the newer and more potent perfluorocarbon agent, EchoGen. Like Kedar et al, using morphological criteria we were able to improve the sensitivity from 82% to 100% (Figure 2), but specificity decreased from 89% pre-EchoGen to 56% post-EchoGen because several benign lesions also displayed marked hypervascularity after contrast administration. This suggests that simple evaluation of the degree of vascularity may not be sufficient to fully exploit the potential of the technique. Our work has therefore focused on extracting further information from contrast-enhanced scans, such as the three-dimensional morphology of the tumor vascularity and functional dynamic data. Early results have been encouraging.

The use of contrast agents in focal liver lesions has also been studied by several investigators.
Because of the large variety of focal liver lesions (such as hepatocellular carcinoma, metastasis, focal nodular hyperplasia [FNH], and hemangioma) and the dual blood supply of the liver, assessment of liver lesions with contrast-enhanced color Doppler is much more complex, however. The data in the literature are slightly patchy and at times contradictory, but typical features of some pathologies are emerging, and we have repeatedly applied them in our clinical practice. Hepatocellular carcinomas are almost invariably hypervascular centrally and peripherally after contrast administration (Figure 3), and any liver lesion displaying these features must be regarded with great suspicion, although some benign lesions such as FNH and adenomas may behave in a similar fashion. The clinical history is often extremely helpful in this respect. Focal fatty change/focal fatty sparing are good examples of benign lesions that by definition will not display abnormal vascularity, and contrast agents are extremely helpful in confirming their diagnosis.

We have studied several hemangiomas with different contrast agents and have generally found that demonstration of vessels in hemangiomas less than 3 cm in diameter is rare, while larger hemangiomas usually display peripheral vessels after contrast administration. Most metastases of common tumors such as colorectal or pancreatic primaries typically show only a mild degree of peripheral vascularity, whereas hypervascular metastases (e.g., from neuroendocrine tumors or renal cell carcinomas) often display vascularity throughout after contrast. Follow-up of anticancer treatment is another promising area for contrast-enhanced Doppler ultrasound of tumor vessels. Anticancer drugs, as well as radiotherapy, generally affect cell metabolism and blood supply soon after the start of treatment, whereas shrinkage of the tumor bulk occurs several weeks later. Imaging tumor vascularity with contrast-enhanced Doppler should allow much earlier assessment of treatment response than the conventional imaging criterion of reduced tumor size. Preliminary results appear to support this theory. Cosgrove et al studied 20 patients with carcinoma of the prostate and found a marked reduction of vascularity in patients undergoing hormone therapy compared with those not in treatment. Several Italian groups have used contrast-enhanced Doppler of malignant liver lesions to guide and monitor percutaneous ablation procedures.14

**Functional Imaging**

Because microbubble echo-enhancers are blood-pool agents, they can be used as intravascular tracers to dynamically study blood flow in body organs or tumors. The real-time nature of ultrasound, combined with its high spatial resolution, makes the combination of ultrasound and microbubble agents ideally suited to functional kinetic studies of physiological indices such as transit times and, potentially, perfusion. Reliable quantification of microbubble concentration is a prerequisite for meaningful functional studies, however. Quantification of microbubble concentration based on ultrasound signal changes is a complex task because of the highly nonlinear image processing algorithms of ultrasound scanners.

Our work at the Hammersmith Hospital, in collaboration with the Department of Medical Physics at the Royal Marsden Hospital, Sutton, U.K., has focused on this area. We have developed a computer-based system that allows accurate quantification of relative microbubble concentrations with power Doppler in vivo. Similarly, we have quantified relative microbubble concentrations with spectral Doppler in vivo, and we will report on this topic at the Radiological Society of North America (RSNA) meeting in December. Like contrast-enhanced MRI, kinetic studies of tumors (of the breast, for example) can be performed with Doppler ultrasound and echo-enhancers. The fundamental difference between the two techniques is that gadolinium chelates rapidly leave the intravascular space and diffuse into the interstitial space, and thus the dynamic time-intensity curves obtained with MRI are heavily influenced by the abnormal endothelial permeability of the tumor vessels within the tumor. Conversely, microbubble agents are confined to the intravascular space, and when used for dynamic studies, would seem an attractive technique for assessing indices of microcirculation independent of the interstitium, such as perfusion and transmit times.

Along with the morphological changes of malignant tumor vascularity, blood flow within malignant tumors is known to be abnormal. Flow can be accelerated due to arteriovenous shunts. On the other hand, small tumor vessels often lack normal smooth muscles and therefore have a lax tone and are unusually capacious, which can produce abnormally slow flow. Blind-ending vessels further complicate the picture. Flow in malignant tumor vasculature is known to have considerable spatial and temporal variation.15 All these features are potentially accessible to dynamic studies with ultrasound contrast agents and should be reflected in time-intensity curves. The work in this field is still in its infancy, but several groups worldwide have taken up this approach.

We applied the technique in 20 patients with breast lesions in the previously mentioned study, and
found a statistically significant longer enhancement in cancers compared with benign lesions. Furthermore, we observed a difference in the shape of the time-intensity curves. While the majority of benign lesions showed a simple monophasic contrast washout, most carcinomas displayed a more complex multiphasic washout, with one or several smaller peaks interspersed between the peak enhancement and the return to baseline. These features appear to reflect the flow abnormalities in cancers described above. Our results suggest that the best sensitivity and specificity will result from a unified approach combining anatomical and such functional data.9

Functional imaging with ultrasound contrast agents can also be used in other areas, such as studying the perfusion of entire organs rather than individual tumors. Correas et al have presented exciting experimental work on renal artery stenosis.16 They demonstrated impressive changes of the time-intensity curves obtained with gray-scale ultrasound from the renal parenchyma with increasing degrees of renal artery narrowing. This novel technique may result in a valuable clinical contribution to the unresolved problem of the assessment of renal artery disease with ultrasound.

Our group at Hammersmith is using functional Doppler studies with Levovist to assess liver blood flow changes in cirrhotic patients with extremely encouraging results, indicating that contrast-enhanced Doppler can reliably differentiate between cirrhosis and noncirrhotic diffuse liver disease (study to be presented at RSNA ‘97).

**Nonlinear Techniques**

The actual behavior of microbubbles in a sound wave is a highly complex process. Apart from simple backscatter, a variety of other effects occur on insonation, including harmonic resonance, microbubble disruption, and stimulated acoustic emission (SAE). Although usually discussed as separate phenomena, they actually represent aspects of a spectrum of nonlinear effects that occur as increasing sound pressure is applied to microbubbles.

The sound emitted by an insonated microbubble contains harmonics, just as a musical instrument produces overtones. At low sound pressures, microbubbles in a sound field undergo alternative expansions and contractions of equal sizes, and this strongly increases the backscattered signal, which is at the same frequency as the insonated signal. As the sound pressure is increased, these rhythmic size changes cease to be equivalent, and harmonic signals are emitted. When Levovist is insonated at 3 MHz, it produces not just an echo at 3 MHz, but a second harmonic signal at 6 MHz; subharmonic and higher order harmonic signals are also produced.

Modern broad-bandwidth transducers are capable of sending signals at a lower frequency while listening for returning signals at a higher, second harmonic frequency. The echoes produced by a microbubble are thus preferentially received while echoes from tissue are relatively suppressed; this technique is called (second) harmonic imaging. The result (not the principle) is similar to that of digital subtraction angiography.

Harmonic imaging can be used in both gray-scale and Doppler ultrasound. In gray-scale, areas of tissue enhanced with microbubbles will appear relatively bright, and larger vessels will be greatly enhanced (hyperechoic) against a relatively suppressed hypoechoic background. It is particularly useful for detecting contrast in small vessels, for example, when assessing myocardial perfusion. Similarly, harmonic imaging can be used to enhance the parenchyma of solid organs such as the kidney and liver, which do not usually show significant gray-scale enhancement with most agents using conventional (fundamental) imaging.

When harmonic Doppler ultrasound is used, the amount of clutter, or undesired artifactual signals from moving tissue, and flash artifacts can be greatly reduced. Thus, it can be very useful in Doppler studies of moving tissues such as the myocardium or the left lobe of the liver, and in our experience it particularly complements power Doppler, in which such artifacts are a particular problem.

Harmonic imaging is not without its problems, however. The second harmonic signal from many microbubble agents is weaker than the fundamental signal. With Levovist, the signal of the second harmonic peak is 13 decibels weaker than that of the fundamental.17 Generation of high-quality harmonic ultrasound images is not a simple task, and intensified efforts by the equipment manufacturers are required.

The second nonlinear phenomenon of clinical importance is microbubble disruption. It has been known for some time that the emitted sound at diagnostic energies can disrupt microbubbles, so it can be helpful to perform contrast studies using low transmit powers.

Intermittent imaging techniques are also useful in some situations for the same reasons. Intermittent imaging, with or without second harmonic imaging, has been shown to improve the demonstration of normal and abnormal myocardial perfusion,18 and to improve gray-scale enhancement of the liver.19 More speculatively, it appears possible to use this effect to create positive and negative boluses within blood vessels, and arteriovenous transit times can then be assessed.20
Another potential application that has attracted great interest is therapy, because it is possible to use microbubbles as drug-delivery vehicles. By inducing bubble destruction through insonation, local drug delivery can be achieved.\(^{21}\) The third important nonlinear effect, particularly at high transmit powers--but still within the diagnostic range--is SAE, which is a specific transient nonlinear microbubble response to insonation associated with the display of wide-frequency high-intensity Doppler shifts.\(^{22}\) On spectral Doppler, it appears as superadded wide-frequency signals and on color Doppler as a characteristic color mosaic effect obtainable from all tissues that contain a sufficiently high number of microbubbles, regardless of whether they are flowing or static.

The effect is caused by microbubble disruption or destruction. It has been best described with SHU 563 (Schering AG), a novel encapsulated agent undergoing clinical trials. This agent has another interesting property, apart from producing strong SAE signals: After an initial blood-pool phase, it accumulates in the liver and spleen, where it is taken up by the RES and can be used for SAE imaging. It therefore has liver-specific properties with lesions such as metastases standing out as focal color voids against a background diffuse polychromatic SAE signal. This promises to increase the sensitivity of liver lesion detection with ultrasound, similar to the recent results with liver-specific MR agents.\(^{23}\)

Intriguingly, data from the Hammersmith indicate that Levovist also has a liver-specific "late" phase during which it also produces SAE. It can be used to improve lesion conspicuity, and we have encountered several cases of previously undetected metastases made visible by SAE with Levovist (Figure 4).\(^{24}\)

**Conclusion**

Echo-enhancing agents represent the most important innovation in ultrasound since the advent of color Doppler. In radiology, they are most commonly used for examination of larger vessels to rescue failed Doppler studies and for the enhancement of otherwise invisible tumor vessels to aid differential diagnosis. They add a new functional dimension to ultrasound, with many promising potential applications. The advent of agents capable of parenchymal gray-scale enhancement and/or liver-specific effects may revolutionize abdominal ultrasound. Once such agents become widely available, they could become an integral part of ultrasound in some common applications, including looking for focal liver lesions, analogous to the use of contrast agents in liver CT. They also have an exciting potential for imaging myocardial perfusion.

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