Microbubble-based scans reach beyond liver

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Ultrasound is the most commonly used abdominal imaging modality. The addition of color and spectral Doppler imaging has been particularly beneficial. When ultrasound findings are nonspecific, however, patients are generally referred to CT or MRI.

A contrast-enhanced ultrasound examination could alleviate the need for these more expensive imaging investigations, and a number of micro-bubble-based agents exist. The predominant agent used in Europe is SonoVue (Bracco). Other available agents include Definity (Bristol-Myers Squibb) and Optison (GE Healthcare). All microbubbles are filled with gas; sulfur hexachloride in the case of SonoVue, perfluoropropane in the case of Definity. The gas-filled bubbles are smaller than red blood cells, so they will undergo pulmonary recirculation. When injected intravenously, the micro-bubbles remain in the blood pool for up to six minutes.¹

Technological advances, particularly the advent of harmonic and pulse-inversion imaging, have contributed to improvements in microbubble-based imaging. All major manufacturers of ultrasound equipment offer add-on software packages that allow for contrast-enhanced imaging, albeit at an extra cost. Microbubble contrast agents have an excellent safety profile and can be used in patients with renal impairment.² Many clinical radiology departments across Europe now use micro-bubble contrast agents for ultrasound scans of the liver. Published guidelines are available on the characterization of focal liver lesions using contrast-enhanced ultrasound,³⁴ and good concordance with CT and MRI has been demonstrated.⁵

The extension of contrast-enhanced ultrasound into other abdominal structures outside of the liver is on the horizon, though the potential role for microbubble agents in these organs is not as well appreciated at present. The agents may be used to depict disease processes in the spleen, kidneys, gallbladder, bowel, and pancreas.

KIDNEY IMAGING

The kidneys normally are readily accessible on ultrasound. The combination of real-time imaging and patient cooperation yields the best views. Adding microbubble contrast to the renal examination is a logical step if the features of any abnormality require further elucidation. Several renal pseudotumors may mimic genuine tumors on imaging.⁶ The column of Bertin, for example, comprises non-reabsorbed polar parenchyma of the subkidneys that fuse to form a normal kidney. It may be misdiagnosed as a renal mass on ultrasound, though its location between overlapping regions of two renal sinus systems, the presence of normal renal tissue, and the observation of a smooth surface contiguous with adjacent parenchyma should be reassuring. The same misdiagnosis can occur in cases of fetal lobulation and lobar dysmorphism. Ultrasound contrast agents may be of particular value in these patients. The immediate depiction of normal-functioning renal tissue can reassure both the patient and the examining physician (Figure 1). Suspicious areas remain isoreflective to normal renal parenchyma. They exhibit a rapid increase in enhancement during the arterial phase and subsequent wash-out in the later phase, identical to normal tissue.⁷ It is worth remembering that patterns of contrast enhancement in organs with a single afferent blood supply are different from those seen in the liver, which has a unique dual afferent blood supply.

Complex renal cysts account for 10% of renal cell carcinomas, and it is thus vital to diagnose these correctly. The Bosniak renal cyst classification system is an established method of assessing renal cystic lesions from CT findings.⁸ Ultrasound alone is of limited value in these cases. The use of microbubble contrast agents can be an effective addition to the imaging workup when dealing with complex renal cysts, and this approach may supersede the role of CT and MRI. The
vascularity of renal cyst walls can be assessed, allowing the suspect lesion to be characterized and its potential malignancy evaluated. Newer imaging techniques make it possible to visualize microbubbles in real-time within the tiny capillaries that supply the cysts' fine septae and walls (Figure 2).

Researchers have shown that the Bosniak renal cyst classification is also applicable to contrast-enhanced ultrasound. Replacement of contrast-enhanced CT with micro-bubble ultrasound imaging for complex renal cyst follow-up will have a substantial impact on patient morbidity. The potential for nephrotoxicity from iodinated contrast and the long-term risks associated with ionizing radiation are eliminated.

Renal cell carcinoma is the most common malignant tumor of the kidney. Diagnosis is traditionally established by unenhanced CT followed by contrast-enhanced CT during the corticomedullary and nephrographic phases. Tumor detection is maximal during the nephrographic phase. Microbubble contrast agents are an effective tool for assessing tumor vascularity. A heterogeneous pattern of enhancement is more common than a homogeneous pattern, unlike the pattern seen in normal renal tissue. A renal tumor enhances more than the adjacent parenchyma, and it enhances maximally in the arterial phase (20 to 60 seconds after a bolus injection). Contrast-enhanced ultrasound may also evaluate hypovascular solid renal tumors that enhance less than normal renal parenchyma.

Care should be taken in the rare case of patients with multiple focal renal infarcts, which do not enhance with microbubble contrast. Unenhanced ultrasound shows the infarcts as wedge-shaped, low-reflective areas. This illustrates the importance of performing a baseline ultrasound examination prior to contrast administration in all patients.

Ultrasound is an established screening tool for renal artery stenosis, a treatable cause of secondary hypertension. The examination is often time-consuming and operator-dependent, however. Micro-bubble enhancement has been shown to improve the detection of renal artery stenosis and reduce the rate of technical failure. Angiography remains the reference standard. Renal vein examinations using microbubble contrast could potentially be used to differentiate thrombus from tumor thrombus, which shows strong enhancement.

**SPLENIC ASSESSMENT**

Ultrasound is the most frequently used imaging modality for splenic assessments. The addition of microbubble contrast can help diagnose a wide variety of abnormalities, including congenital variations, acquired focal lesions (benign and malignant), abscesses, infarctions, and the effects of trauma.

Accessory spleens found in 10% to 30% of the population can be single or multiple. Most occur at the splenic hilum, though they can also be found in the splenorenal or gastrosplenic ligaments. Histopathology of an accessory spleen is similar to that of the parent spleen, as is appearance on ultrasound. Microbubble contrast demonstrates the vascular hilum clearly and shows the sinusoidal blood flow occurring at identical times within the spleen and splenunculus. These imaging features are of value in distinguishing a splenunculus from a pancreatic tail mass or an abnormal lymph node.

Splenic cysts are either primary (parasitic or epithelial) or traumatic. They are normally avascular but may contain debris or demonstrate wall calcification. Microbubble contrast outlines the smooth contour of the cyst and can differentiate the cyst from a solid lesion. Hydatid cysts are the exception. These may have high re-flectivity and demonstrate peripheral but not internal enhancement. Benign solid lesions of the spleen include hemangiomas, lymphangiomas, and hamartomas. Cavernous hemangiomas, the most common, are typically detected as an incidental finding measuring less than 2 cm across. Cavernous hemangiomas are characteristically well defined, highly reflective lesions that enhance centripetally with microbubble contrast. This is particularly the case for larger lesions.

Splenic metastases are due mainly to lymphoma and melanoma, although other malignancies can spread to the spleen. Most have low reflectivity and, with microbubble contrast, peripheral irregular enhancement. Additional lesions not seen on the baseline examination are often identified when contrast is added. Differentiation from splenic abscesses may be difficult, though demonstration of enhancing septations and a relevant clinical history can help in such cases (Figure 3).

Solid organ injury in blunt abdominal trauma may be imaged reliably with contrast-enhanced ultrasound, though CT is the investigation of choice. An initial FAST (focused assessment with sonography for trauma) evaluation is often performed in the emergency department to rule out obvious solid organ injury and the presence of free fluid.

Baseline ultrasound imaging features of splenic trauma include subcapsular hematoma, intrasplenic...
foci of iso- or low reflectivity, and lacerations. These injuries may not be apparent on B-mode imaging in an acute setting. Micro-bubble contrast agents in-crease the conspicuity of these abnormalities, especially complex lacerations, which are visualized surrounded by the enhancing parenchyma (Figure 4). The ability to identify solid organ injury in the emergency setting allows patients to be triaged efficiently. Microbubble contrast-enhanced ultrasound can improve the detection of injury in the spleen, liver, and kidneys.\textsuperscript{15}

**ADDITIONAL APPLICATIONS**

Microbubble contrast can help differentiate highly reflective bile sludge from a possible tumor or polyp. Biliary sludge shows neither tumor vessels nor tumor enhancement (Figure 5),\textsuperscript{16} but inflammatory polyps, adenomas, and carcinomas can demonstrate both intralesional vessels and enhancement. Assessment of tumor vessels on contrast-enhanced ultrasound may be useful for distinguishing gallbladder carcinoma from other polypoidal gallbladder lesions. Caution must be taken because the appearances can overlap. Contrast-enhanced ultrasound is also superior to unenhanced color Doppler ultrasound when evaluating the vascularity of gallbladder wall disease. Microbubble contrast demonstrates marked enhancement in the gallbladder wall in acute cholecystitis.

Contrast-enhanced ultrasound can be used to assess the pancreas, bowel, and ovaries as well.\textsuperscript{17-19} The evaluation of pancreatic tumors, particularly cystic tumors and ductal adenocarcinoma, is promising. Intense enhancement may signal the presence of a small insulinoma in the pancreas.\textsuperscript{20} Intense enhancement to thickened bowel wall may indicate ongoing inflammatory changes due to Crohn's disease. It may be more important, however, to search for areas of bowel wall with no enhancement, as these areas are likely to be ischemic.\textsuperscript{21}

Microbubble contrast can be used to assess the integrity of an endovascular abdominal aortic stent-graft. This is reported to be the most sensitive method of detecting subtle leaks that result in endotension (persistent or recurrent pressurization of the aneurysm sac).\textsuperscript{22}

**SAFETY POINTS**

The incidence of hypersensitivity or adverse events appears to be much lower with the microbubble agents used for ultrasound than with iodine-based CT contrast. Ultrasound is also free from ionizing radiation. Reports of the adverse effects of MR contrast agents, coupled with the claustrophobic nature of MR imaging, make contrast-enhanced ultrasound even more attractive.\textsuperscript{23} A review of 23,188 investigations using microbubble contrast revealed the incidence of adverse events to be 0.0086%. These events were predominantly minor, such as itching, nausea, dizziness, headache, mild hypotension, and a sense of warmth.\textsuperscript{2} Arrhythmia effects have been reported when using ultrasound contrast during cardiac investigations. These are thought to be attributable to QT prolongation and the induction of premature ventricular contractions.\textsuperscript{24}

**FUTURE PERSPECTIVE**

Contrast-enhanced ultrasound is not performed widely, despite the wealth of scientific data demonstrating the usefulness of microbubble agents. The technique is employed by enthusiastic practitioners at a number of centers, but the overall number of users is growing slowly. Obstacles may be difficult to overcome. In the U.K., for example, ultrasound is perceived as a noninvasive examination, and the need to administer an injection is a major psychological hurdle. Most sonographers operate single-handed. A contrast-enhanced examination would require two practitioners, raising staffing issues.

Radiologists may prefer to direct a CT or MRI examination remotely and report at their convenience. Ultrasound does not lend itself to this practice. Hands-on imaging is the only way to fully appreciate the nuances of the examination and attain the correct conclusion. If the addition of contrast to ultrasound imaging resulted in a definitive answer, and patients were no longer referred for further examinations, then arguments relating to lack of time could perhaps be resolved. Radiologists may then look at the technique more favorably.

Ultrasound can demonstrate anatomy and pathology with high resolution, and the addition of microbubble-based contrast aids in the diagnosis of disease and subsequent follow-up. The role of such agents outside of the liver is clearly useful. Operators should be encouraged to take this step before requesting further imaging with CT or MRI.

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References


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