CONTRAST-ENHANCED ULTRASOUND: PRINCIPLES OF CLINICAL UTILISATION

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ANDREW HOLLOWAY and MIKE HERRTAGE discuss the merits of ultrasound contrast agents, which include increased signalling and more precise tissue sampling techniques

CONVENTIONAL greyscale and Doppler ultrasonography are non-invasive techniques that, by virtue of their crosssectional nature and ability to detect blood flow, have had a considerable impact on the imaging assessment of small animal patients.

Despite these advantages, the broadly similar attenuation properties of normal and diseased tissues may, in certain instances, limit identification and characterisation of pathology. Furthermore, the weak echoes and physical characteristics of blood flow restrict the various Doppler techniques to the assessment of macrovascular structures.

Ultrasound contrast agents (UCAs) overcome these limitations by substantially increasing the signal generated within the tissues in which they accumulate and contrast. Furthermore, by acting as blood pool agents, UCAs demonstrate microvasculature – thus permitting perfusion studies and functional imaging.

UCAs are gases stabilised by encapsulation to form microbubbles. Interaction of these microbubbles with ultrasound waves produces significantly increased signals (backscattered echoes). The first-generation UCAs (stabilised or encapsulated air, such as Levovist; Schering AG) have been superseded by a second generation of UCAs (containing sulphur hexafluoride or perfluorocarbons, such as SonoVue; Bracco, or Definity – Bristol-Myers, US), which, with a more

uniform microbubble size and better intravascular stability, allows them to persist in the circulation for longer.

The ideal features of UCAs include uniformity in microbubble size and small enough (less than 8µm in diameter) to remain in the microcirculation without being filtered by the lung.

They should also have the stability to persist in circulation long enough (five to 30 minutes) to allow clinical examination, and exhibit physiologically inert and non-toxic chemical characteristics. UCAs must have an affinity to accumulate in certain tissues (such as the liver and spleen), and have acoustic properties – thus allowing interaction with the incident ultrasound wave to produce an increased tissue signal.

The increased signal generated by UCAs relates to nonlinear oscillation and resonance of the microbubbles when interacting with the ultrasound waves. The acoustic pressure or energy (mechanical index) of the incident wave is an important feature of this interaction.

At low energies, the microbubbles behave in a linear fashion – in the same way as tissue – with echoes produced around the fundamental (transmitted) frequency.

At a low-to-medium mechanical index (MI: less than 0.2) the bubbles oscillate in a nonlinear fashion, generating large numbers of harmonic echoes (multiples of the fundamental frequency), which produce the contrast image. Although tissue also produces harmonic echoes, these are considerably weaker and fewer in number than those produced by the UCAs.

At a higher MI (more than 0.5), as employed in conven- tional B-mode and Doppler examinations – and some contrast-enhanced ultrasound techniques, such as interval delay imaging – the microbubble capsule is disrupted or “burst”, resulting in a marked transient increase in signal.

To take advantage of the large amount of backscatter produced by UCAs, contrast-specific imaging techniques use multiple pulses of differing phase, polarity and amplitude to filter out or subtract the signal from tissue not containing a contrast agent.

These imaging techniques are usually proprietary and require specific broad-bandwidth transducers and specialised software. Therefore, contrast-enhanced ultrasonography is usually limited to high-end ultrasound machines, although the technology is increasingly available – at a not inconsiderable cost – on portable units. In this article, the images are examples of pulsed inversion harmonic imaging (PIHI, HDI 5000 SonoCT, Philips, Eindhoven, The Netherlands) and contrast-tuned harmonic imaging (CnTI, MyLab 30; Esaote, Florence, Italy). Although the general principles of UCA use are broadly similar, the peculiarities of each UCA and the variation in the type of insonation technique must be considered before undertaking any study.

The majority of abdominal imaging studies using second generation UCAs are performed using a

low-MI (0.08-0.12) continuous imaging technique.

The recommended dose or volume of contrast agent varies, but, for most small animals, a dose range of 0.5ml to 2ml of SonoVue (the authors' comments relate specifically to SonoVue as this is the only UCA with which they have practical experience) is usually adequate, allowing two to three studies per examination, per reconstituted vial.

In humans, the practical advantages of using contrastenhanced ultrasound include the relatively low cost of contrast ultrasound examinations; comparable sensitivity and specificity to computed tomography and magnetic resonance imaging for detecting metastatic disease; and the absence of ionising radiation[1], [2]. However, the cost of UCAs remains substantial (Sono- Vue costs approximately £30 per vial), and the short activity life (six to eight hours for SonoVue) following reconstitution may limit widespread use in veterinary imaging. UCAs are not licensed for use in small animals, although they have been widely used (primarily in dogs) in both experimental and clinical settings with no reported reactions to date.

Clinical application

• Liver

UCAs demonstrate affinity for certain organs, such as the liver, in which they persist. The reason for this accumulation is not clear, but is suspected to be associated with accumulation within the hepatic sinusoids or incorporation within Kupffer cells. As a result, three phases of liver enhancement – arterial, early and delayed portovenous phases – can be recognised (Figure 1). The clinical utility of UCAs is particularly related to the perfusion characteristics demonstrated in the latter two phases.

A continuous, low-MI imaging technique is usually employed in contrast-enhanced examinations of the liver. The use of contrast ultrasonography in dog[3]-[4] and cat5 livers has been most widely reported in the localisation and characterisation of nodular hepatic lesions – in particular, the differentiation of benign primary nodular disease from metastatic or primary hepatic malignancy.

In general, benign lesions, including lipid granulomas, tend to demonstrate variable enhancement during the arterial and early portovenous phases (hypo, iso or hyperechoic), with similar enhancements to normal liver during the late portal phase (Figures 2 and 3).

Malignant lesions (Figures 4 and 5) characteristically show a rapid and complete contrast wash out and appear hypoechoic, compared to the enhanced liver, during the late portovenous phase. These characteristics are related to tumoral neoangiogenesis from the hepatic artery, and the absence of normal hepatic sinusoidal architecture.

Haemangiosarcoma metastases, particularly relevant in veterinary patients, may not demonstrate

enhancement at any stage (Figure 6). The imaging characteristics during the early phases of liver enhancement generally appear to be of little clinical significance in the assessment of metastatic disease. Although macrovascular patterns, such as the “basket pattern” associated with hepatocellular carcinoma and the “spoke-wheel pattern” typical of nodular hyperplasia, may be of significance in humans with primary hepatic masses, the validity of extrapolating these features to the dog and cat is uncertain.

As noted, much of the clinical experience in the veterinary field relates to nodules or nodular masses, and assessment of large complex or lobar masses should be approached with caution, as these may have areas of haemorrhage or necrosis that confound the diagnosis. Careful correlation with the fundamental images and anticipated histopathological findings is necessary, as predominantly cystic lesions may demonstrate rapid wash out, and nonenforcement of haematomas may mimic malignant disease (Figures 7 and 8).

In veterinary clinical practice, contrast ultrasonography of the liver should be employed primarily to assess lesion margination and extent, and to improve lesion detection (number and conspicuity of lesions[6]).

Isoechoic or poorly marginated solid components of masses with larger cystic or necrotic regions may not be recognised on fundamental imaging. Contrast-enhanced ultrasonography may then be used to guide biopsy to avoid sampling non-representative regions of such mass lesions.

Equally, isoechoic or poorly marginated metastatic nodules may be difficult to recognise on fundamental imaging, and contrast-enhanced ultrasound is reported to increase the number of metastases identified[6].

These factors are particularly relevant where exploratory surgery is being considered. The findings of the contrast-enhanced examination and aspirate or biopsy results should not be interpreted in isolation, but considered together to determine if they are representative. Two to three UCA boluses are usually required to ensure a satisfactory assessment of all liver segments.

The quality of the later examinations is usually superior due to UCA persistence in the liver. The technique is dependent on operator experience, and all studies should be acquired as cineloops for review.

Most transducers capable of contrast-enhanced imaging are of either curvilinear or linear construction, and poorly suited to the subcostal window due to the large diameter of the former, and the limited field of view at depth of the latter.

The use of contrast-enhanced ultrasound in the diagnosis of portosystemic shunts (PSS) has been described[7]. Shunting vessels are not recognised as such, but the generation of time-intensity curves of hepatic perfusion demonstrate a shorter time to peak liver enhancement when compared

to normal dogs, due to the marked increase in hepatic arterialisation associated with PSS (Figure 9).

The effect of general anaesthesia on hepatic perfusion has been reported, but further assessment of the effects of age, body size and sedation on hepatic perfusion characteristics is still needed.

• Spleen

The spleen demonstrates an early arterial phase of enhancement with a patchy or mottled appearance[8]. The late parenchymal phase results in more homogeneous enhancement, and should be used to assess any changes[8].

Contrast ultrasonography has been reported to be useful to discriminate between benign (excluding haematoma) and malignant lesions[9].

Benign lesions are characterised by enhancement at a rate and intensity similar to that of a normal spleen. Malignant tumours are characterised by a hypoechoic appearance during the late parenchymal phase, with rapid enhancement (wash in) a feature of lymphoma and soft-tissue sarcomas (Figure 10). Extensive non-perfused regions during all phases are a feature of haemangiosarcoma (Figure 11).

The diagnosis of lymphoma is usually facilitated by identifying concurrent lymphadenopathy or organomegaly – cytology is usually diagnostic. Therefore, contrast-enhanced ultrasound should be reserved for those cases with disease limited to the spleen (suspected stage-four disease) and/or to support equivocal cytological findings.

Differentiation between haematoma and haemangiosarcoma is not possible10. UCAs may be useful to confirm and differentiate splenic torsion or infarction (Figure 12) from splenitis infiltrative disease, where the conventional B-mode findings are not typical for the appearance of vascular compromise.

Contrast-enhanced ultrasound has been employed in children to evaluate for traumarelated subscapular haemorrhage (“fracture”) of the spleen to avoid exposure to ionising radiation, and may be useful in similar settings following trauma in cats and dogs.

• Other structures

The use of contrast-enhanced ultrasound has been reported in the characterisation of pancreatic disease in humans[11]. The utility and relevance of the technique in canine pancreatitis has not been demonstrated, but may be of value in identifying extensive or irreversible pancreatic necrosis.

Contrast ultrasonography of the diseased pancreas in the cat demonstrated increased perfusion

and vascularity compared to normal cats, according to one study[12]. In this study, however, colour Doppler – rather than the multipulse filtering techniques described above – were used to demonstrate changes.

Contrast-enhanced ultrasound of the feline pancreas may be limited by transducer size and operating frequency, as well as the low inherent frequency generated by the microbubbles themselves.

Further investigation is required to determine whether differentiation between inflammatory, benign nodular changes and neoplastic disease is possible using this technique. Insulinoma, in common with other neuroendocrine tumours, may demonstrate strong enhancement during the arterial phase, with rapid wash out of contrast media.

In the authors' experience, this pattern is not invariable and, as has been demonstrated by CT, minimally or non-enhancing insulinoma masses may also be observed. Therefore, the primary utility of contrast-enhanced ultrasound in assessing patients with insulinoma should be the evaluation of the liver for metastatic disease, rather than the identification of primary pancreatic masses.

Contrast-enhanced ultrasonography of neoplastic superficial lymph nodes has been reported to better define the distribution of vessels, which may characterise lesion morphology[13]. This may assist with the staging of disease or demonstrate sentinel lymph node involvement, but in the clinical setting, contrast-enhanced ultrasound should complement existing staging techniques (thoracic radiographs, abdominal radiography and fine-needle aspirate). In future, there may be value in using the technique to quantitatively monitor the response to chemotherapy or radiotherapy by demonstrating change in tumour vascular volume or angiogenesis.

Practically, contrast-enhanced ultrasonography can be used to confirm vascularity within suspected tumour thrombi (Figure 13), and may be useful for identifying suitable regions for biopsy of superficial masses associated with swelling or haemorrhage, and in which an underlying tumour is suspected (Figure 14).

Contrast-enhanced ultrasonography should always precede aspiration or biopsy procedures, both to guide needle placement and to avoid a non-diagnostic study, due to the potential artefacts of postsampling haemorrhage.

Conclusions

Contrast-enhanced ultrasonography is a valuable, minimally invasive technique particularly suited to the identification and characterisation of liver and splenic nodular mass lesions.

The technique may assist in identifying suitable areas for tissue sampling. The technique's value

for the evaluation of other organs and diseases requires further verification. The requirements for specialised equipment, transducers and software, the dependence on operator experience and the cost of contrast ultrasound media must be recognised as significant limitations.

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