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Original Article

Efficacy of contrast enhanced grey scale ultrasound in characterisation of hepatic focal lesions: A pilot study

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ABSTRACT

Background: Contrast enhanced ultrasound (CEUS) has recently gained widespread acceptance as an adjunct to conventional grey scale ultrasound. The present pilot study was undertaken to evaluate the efficacy of this technique in characterisation of hepatic focal lesions.

Methods: Adult patients who had at least one focal liver lesion underwent ultrasound evaluation in regular and contrast mode before and after intravenous administration of sulphur hexafluoride. The diagnoses were confirmed by comparison with a reference standard (multidetector CT), response to treatment or pathological correlation.

Results: The rate of correct diagnosis for unenhanced ultrasound was 54%, CEUS was 72% and multidetector CT (MDCT) was 92%. A comparison of unenhanced ultrasound versus CEUS using the McNemar test yielded a *p* value of 0.0704 (>0.05). However, comparison of CEUS versus MDCT using the McNemar test yielded a *p* value of 0.0265 (<0.05). Additionally, comparison of unenhanced ultrasound versus MDCT using the McNemar test yielded a *p* value of <0.0001 .

Conclusion: CEUS increases diagnostic efficacy over unenhanced ultrasound but does not have any significant advantages over MDCT. Currently it may be used as a problem solving tool in atypical haemangiomas, echogenic focal liver lesions, contrast sensitivity and to avoid multiple studies utilising ionising radiation.

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Introduction

Ultrasound is a widely available imaging technique which is particularly useful in non-invasive evaluation of abdominal solid organs. In recent years contrast enhanced ultrasound (CEUS) techniques have added another facet to conventional grey scale ultrasound. This technique shows tissue perfusion and patterns of enhancement in various phases after intravascular injection of a microbubble contrast agent. Like conventional grey scale ultrasound it is free from the risks associated with ionising radiation and it has the advantage over iodinated contrast media that it has no risk of nephrotoxicity.¹

Very little work has been carried out in this fascinating modality due to the fact that till very recently ultrasound contrast agents (UCAs) had not been licenced for use in our country. These agents are tiny bubbles of gas in a supporting shell. The characterisation of liver focal lesions is an established use of CEUS. The present study was a pilot study to evaluate and characterise hepatic focal lesions using contrast harmonic imaging with the UCA sulphur hexafluoride.

Materials and methods

Subject population: The subjects were the patients who had been referred for a contrast enhanced ultrasound study after detection of a focal lesion in the liver in a previous ultrasound study.

Inclusion criteria: Adult patients in the age group of 20–70 years who had at least one hepatic focal lesion detected in the liver in a previous ultrasound study were included in the study. Availability of informed consent for the intravenous administration of contrast media was essential for inclusion. **Exclusion criteria:** UCAs have been associated with ventricular ectopic beats and have been known to cause increased capillary permeability in animal models. Moreover, adequate information regarding safety in pregnancy is not available. Patients with diffuse liver disease, cardiac disease and pregnant women were therefore excluded from the study. Patients who had iodinated contrast administration in the previous 48 h, lithotripsy in the previous 72 h and liver biopsy in the previous 24 h were also excluded from the study.

Procedure and imaging: Ultrasound imaging was carried out before and after IV administration of sulphur hexafluoride in regular and contrast mode. Relevant frozen images and cine loops were recorded. Patients were monitored for 30 min after completion of imaging. A provisional diagnosis was made on the basis of unenhanced and contrast images.

Baseline ultrasound: All subjects underwent a baseline scan documenting the liver focal lesion and its characteristics including dimensions, shape, number, margins, echogenicity, posterior enhancement, shadowing and calcification, if any.

Contrast administration: All patients received sulphur hexafluoride intravenous contrast media. Sulphur hexafluoride (SonoVue, Bracco Imaging SpA, Milan) is available as a lyophilised powder in vials which are reconstituted with 5 ml saline. The reconstituted solution has 8 µl sulphur hexafluoride in microbubbles per ml. Each patient received 2.5 ml of this solution followed by a 10 ml saline flush.

Contrast enhanced ultrasound: Coded harmonic contrast imaging was carried out on a Logiq P5 ultrasound scanner (GE Healthcare). Routine imaging was carried out using a convex probe (transmitting frequency 4.0 MHz, mechanical index 0.1) and focus set at the region of interest. Using the timer video clips were recorded in DICOM format.

Follow up/confirmation of diagnosis: Confirmation of the diagnosis was by further imaging (by a reference standard) or response to treatment or by pathological correlation.

Reference standard: The reference standard for the study was triple phase multidetector contrast enhanced computed tomography.

Image reading: All images were read by an onsite investigator and a blinded remote investigator. The images were evaluated using established criteria.² The diagnosis was arrived at by consensus in case there was a discrepancy between the two readings. Investigators described the final diagnosis and allotted one of the following five groups – hepatocellular carcinoma, metastasis, haemangioma, other benign lesion and other malignant lesion.

Results

A total of 50 patients of hepatic focal lesions were evaluated by contrast enhanced ultrasound using the contrast agent sulphur hexafluoride. There were 27 male patients and 23 female patients in an age range of 26–69. There were 16 cases of hepatocellular carcinoma, 16 cases of metastases, 9 cases of haemangioma, 7 cases of other benign lesions and 2 cases of other malignant lesions. The various diagnoses arrived at by different modalities (unenhanced ultrasound, contrast enhanced ultrasound and multidetector CT) are summarised in [Table 1](#). Observers also collated the rate of correct diagnosis in cases of malignant lesions and benign lesions. The findings are summarised in [Table 2](#).

As has been summarised above the rate of correct diagnosis for unenhanced ultrasound was 54%, CEUS was 72% and MDCT was 92%. A comparison of unenhanced ultrasound versus CEUS using the McNemar test yielded a *p* value of 0.0704 (>0.05). However, comparison of CEUS versus MDCT using the McNemar test yielded a *p* value of 0.0265 (<0.05). Additionally, comparison of unenhanced ultrasound versus MDCT using the McNemar test yielded a *p* value of <0.0001 .

As is clear from the foregoing the correct rate of diagnosis was greater for CEUS as compared to unenhanced ultrasound. However this difference was not statistically significant and may have arisen due to chance. Similarly the correct rate of diagnosis was greater for MDCT as compared to CEUS. This difference was statistically significant. However, the correct rate of diagnosis was greatest for MDCT as compared to unenhanced ultrasound. This difference was markedly statistically significant.

Discussion

Ultrasound contrast agents are composed of small gas bubbles which enhance echo from blood. Specialised imaging techniques are required for CEUS which employ a low Mechanical

Index (MI) which reduces rupture of these bubbles due to ultrasound energy while increasing contrast by suppressing echoes from background tissues. Ultrasound contrast agents (UCAs) have been undergoing continuous refinement in the past few decades. Free gas bubbles gave way to encapsulated gas bubbles stabilised by shells. Commercially available UCAs currently are – Optison (GE Healthcare, Milwaukee) which is perfluoropropane stabilised with an albumin shell, SonoVue (Bracco Imaging SpA, Milan) – sulphur hexafluoride in a phospholipid shell, Definity (Lantheus Medical Imaging, Billerica, Mass) – perfluoropropane with a flexible bilipid shell and Sonazoid (Daiichi Sankyo, Tokyo) – perfluorobutane with a lipid shell. These shells increase the time before which the gas diffuses into solution thereby increasing time available for study.³

No significant adverse effects have been reported for UCAs and the incidence for allergic events is also lower than that for iodinated contrast.⁴

A panel of experts of the European Federation of Societies for Ultrasound in Medicine and Biology has formulated guidelines for the use of UCAs in various clinical situations and has recommended the following indications for their use in liver ultrasound: (1) characterisation of focal lesions detected in patients without chronic liver disease, (2) characterisation of focal lesions detected in surveillance programs of chronic liver disease, (3) staging and follow up of cancer patients and (4) monitoring of local ablative treatment.⁵

Various workers have evaluated the use of UCAs in characterisation of hepatic focal lesions.^{6–8} All studies rely on the evaluation of blood flow patterns on CEUS⁹ in addition to information from grey scale studies. While some workers have stressed on the perfusion patterns in differentiating benign from malignant lesions^{10,11} others have characterised specific lesions¹² or focussed on the differential diagnosis of benign lesions.^{13–15}

The commonest benign focal lesions encountered are haemangiomas. These are usually hyperechoic but may occasionally show variable echogenicity in which case there may be a diagnostic dilemma. On CEUS they typically show peripheral nodular enhancement in puddles starting in the arterial phase which follows a centripetal enhancement extending into the portal venous phase and may extend to complete filling in.^{6–9} Focal nodular hyperplasias (FNH) are subtle isoechoic lesions which show intense arterial enhancement in the arterial phase and occasional arteries arranged in a spoke wheel pattern and a feeding vessel. Enhancement extends into the portal venous phase except for

Table 2 – Rate of correct diagnosis in characterisation of hepatic focal lesions (benign vs malignant).

	US	CEUS	MDCT	Total
Overall	36 (72%)	43 (86%)	50 (100%)	50
Malignant	23 (67.6%)	30 (88.2%)	34 (100%)	34
Benign	13 (81.2%)	13 (81.2%)	16 (100%)	16

Table shows the rate of correct diagnosis in characterisation of hepatic focal lesions as benign or malignant. The total number of cases is shown with the percentage in parentheses.

a central region representing the scar.^{7–9,13,14} They need to be differentiated from hepatic adenomas which are usually hypoechoic lesions which show intense arterial phase enhancement which persists into the portal venous phase but is nonhomogenous.^{8,13,14} Liver abscesses show enhancement only of the wall and septa in all phases without any central enhancement. Simple cysts do not show any enhancement at all, while focal fatty change and focal fatty sparing typically do not show any differential enhancement.^{2,8}

Malignant focal lesions are characterised by a phenomenon known as “washout”,¹² where the lesion shows arterial phase enhancement greater than the liver and portal venous phase enhancement less than the liver. This is in contrast to the sustained enhancement of benign lesions. Hepatocellular carcinomas show this kind of enhancement with non enhancing areas representing necrosis. Also, there may be enhancing vessels in a bizarre distribution and a thrombus may be visualised in the portal vein. All metastases show enhancement only for a very short period of time followed by washout. Even hypovascular and cystic metastases show rim enhancement in the arterial phase.^{6–9}

Based on these studies algorithms for the evaluation of focal liver lesions have been developed.¹⁶ These algorithms basically rely on portal phase enhancement. A sustained enhancement in the portal phase is taken as indicative of a benign aetiology. If this is associated with an arterial phase enhancement less than the liver with peripheral nodularity and progressive centripetal “filling in” a diagnosis of haemangioma is offered (Fig. 1). A homogenous arterial phase enhancement greater than that of the liver is considered indicative of a focal nodular hyperplasia (FNH).

Portal phase enhancement less than the liver is considered indicative of a malignant lesion. If this is seen after intense arterial phase enhancement (washout) it is likely to represent a malignant lesion such as hepatocellular carcinoma (HCC) (Fig. 2) or a hypervascular metastasis (Fig. 3). Poor enhancement in the arterial phase is likely to be due to a non-HCC malignancy such as cholangiocarcinoma.

As described above, in addition to the intensity of enhancement, the pattern of enhancement also gives a clue to the diagnosis. Peripheral nodular enhancement with centripetal progression is seen in haemangiomas, diffuse arterial phase enhancement is seen in focal nodular hyperplasia and malignancy and sparse or rim enhancement in non-HCC malignancy. Thus the differential diagnosis takes into account the intensity as well as pattern of enhancement.

Catalano et al¹⁷ have surmised after an extensive review that a homogeneously hypoechoic lesion in the portal phase on

Table 1 – Rate of correct diagnosis in characterisation of hepatic focal lesions.

	US	CEUS	MDCT	Total
HCC	8 (50%)	12 (75%)	16 (100%)	16
Metastases	6 (37.5%)	10 (62.5%)	13 (81.3%)	16
Haemangioma	7 (77.7%)	8 (88.9%)	9 (100%)	9
Other benign	5 (71.4%)	5 (71.4%)	7 (100%)	7
Other malignant	1 (50%)	1 (50%)	1 (50%)	2
Total	27 (54%)	36 (72%)	46 (92%)	50

Table shows the rate of correct diagnosis in characterisation of hepatic focal lesions. The total number of cases is shown with the percentage in parentheses.

Fig. 1 – An iso to hypoechoic focal lesion in the liver with post contrast images showing peripheral enhancement (arrow) with progressive centripetal filling in (arrowheads) suggestive of haemangioma.

CEUS should be considered malignant till proved otherwise. Thus to differentiate malignant from benign lesions could be one of the major uses of CEUS. Xu et al⁶ came to the same conclusion with regards to small focal liver lesions and also surmised that CEUS was most useful for diagnosis of HCC, FNH and haemangioma.

While CEUS imaging characteristics of common hepatic lesions have been well studied those of rare lesions like lipoma and peliosis hepatis require further study.¹⁸ There is good concordance between CEUS and CT or MR imaging¹⁹ as also increased sensitivity and specificity with a reduction in the number of indeterminate diagnoses.⁷ In the present study the endeavour was to study the characterisation of hepatic focal lesions with contrast enhanced ultrasound and compare them with the reference standard, multidetector CT.

There was a difference in the rate of correct diagnosis with CEUS as compared to unenhanced ultrasound. This is expected as CEUS gives additional information as compared to unenhanced ultrasound, viz. vascular and flow information. Although this information can be obtained to a certain extent by Doppler studies in the large vessels, Doppler is of little efficacy in the smaller vessels. Moreover, Doppler gives virtually no information as far as solid organ perfusion is concerned. In addition, CEUS also gives better spatial and temporal resolution of the vessels per se as compared to Doppler imaging.

In our study CEUS was able to correctly characterize 88.9% of haemangiomas as compared to unenhanced ultrasound which correctly characterized 77.7% and MDCT which correctly characterized 100% of haemangiomas. This result is

similar to Catalano et al.¹⁷ Other benign lesions also showed similar results.

Real time ultrasound using contrast is likely to characterise haemangiomas with much greater accuracy as the contrast typical imaging features, namely peripheral globular pooling of contrast material followed by gradual perfusion (filling in) of the entire lesion is well appreciated with a contrast study. Therefore it is likely that characterization of an atypical haemangioma would be one of the important applications of CEUS. This is especially useful as haemangiomas are the most frequently encountered benign tumour and need to be differentiated from hypervascular metastases among other lesions.

As regards HCC CEUS had a 75% diagnostic accuracy compared to unenhanced scans which had 50% diagnostic accuracy. Similarly metastases showed 62.5% diagnostic accuracy compared to unenhanced scans which had a 37.5% diagnostic accuracy.

Similar results have been obtained by other workers^{8,11} who have concluded that CEUS improves diagnostic confidence. However, in our study this difference, though present, was not statistically significant ($p > 0.05$). It is possible that this is due to the small sample size as this was a pilot study.

As regards efficacy as compared to the reference standard, in our study MDCT clearly had higher diagnostic efficacy which was statistically significant ($p < 0.05$). Moreover MDCT clearly scored over unenhanced ultrasound ($p < 0.0001$). In this regard our results are at variance with other workers^{18,19} who have reported that CEUS is more efficacious than MDCT for

Fig. 2 – Post contrast images in a case of hepatocellular carcinoma showing intense homogenous arterial phase enhancement (long arrow) with non enhancing anechoic areas (short arrow) within suggestive of necrosis.

Fig. 3 – Post contrast images of multiple hepatic focal lesions (arrowheads) showing increased enhancement of the liver parenchyma relative to the focal lesions in the portal venous phase (washout) suggestive of multiple metastases.

the evaluation of focal liver lesions. It is possible that to an extent these results may be due to equipment limitations.

It is important to realize that CEUS will add to the findings of unenhanced ultrasound because CEUS examinations also start with analysis of unenhanced images. This is also important because the low MI technique currently employed results in the suppression of background images and therefore correlation has to be made with the unenhanced images.

Therefore it is necessary to consider CEUS as complementary to unenhanced scans and not as a separate modality in itself.

Based on the above the possible applications of CEUS of liver could be in evaluation of atypical haemangiomas, evaluation of multiple echogenic focal liver lesions, diagnostic dilemmas – HCC/metastases, known sensitivity to iodinated contrast media, monitoring of chemo-embolisation, screening for hepatic metastases and surveillance programmes in patients with chronic liver disease.

In all cases CEUS would be used as a complementary modality and as an adjunct to other modalities. Further studies would be required to further establish the role of this promising technique. In addition studies would also be required to establish the role of this technique in detection of focal liver lesions, as also in patients with diffuse liver disease, aspects which were beyond the scope of the present study.

An advantage of CEUS is the lack of exposure to ionizing radiation which makes it an attractive modality especially in cases where multiple studies may be required.

It has been reported that referrals for CEUS increase with adoption of the technology and introduction of UCAs in routine use positively impacting patient management.²⁰

The authors faced numerous technical challenges during the conduct of this study. CEUS is a technique which utilises a low mechanical index (MI). As a result there is loss of tissue resolution in the contrast mode. Inability to visualise contrast and non contrast modes simultaneously meant that investigators had to be trained to orient themselves to the few landmarks still visible (e.g., diaphragm) in the contrast mode. The low MI contrast mode was used with existing presets in order to maximise reproducibility of the study. Existing guidelines of the American Institute of Ultrasound in Medicine²¹ were used for uniformity of technical factors like frame rates and focal zones. A trained assistant was also required as the UCA has to be administered followed by a saline flush while the investigator keeps the region of interest in focus and simultaneously triggers the contrast timer on the screen. This is more so because CEUS is a dynamic examination carried out in quiet respiration. As with any contrast administration, informed consent was obtained and the patient was observed for at least one hour subsequent to the administration of UCA for contrast reactions.

Conclusion

Contrast enhanced ultrasound is a promising new modality which is likely to complement conventional grey scale ultrasound in the future. It is essential to incorporate this modality into the diagnostic algorithm in teaching and referral hospitals. Though currently the high cost of ultrasound contrast media preclude its routine use in liver applications, the

likelihood of this cost coming down with increased adoption and availability due to the economics of scale as happened in the case on non-ionic iodinated and Gadolinium based MR contrast media suggest an increased role for this modality in the future.

Conflicts of interest

All authors have none to declare.

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