Progress Report

New perspectives for the use of contrast-enhanced liver ultrasound in clinical practice

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Abstract

The introduction of second-generation microbubble ultrasound contrast agents and the development of contrast specific ultrasound techniques have improved the ability of contrast enhanced ultrasound in detecting and characterising liver lesions, offering new perspectives for its exploitation in clinical hepatology. Indeed, several studies have demonstrated a high diagnostic accuracy in focal lesion characterisation (85–96%) in patients either with or without underlying chronic liver disease.

This review article describes the basic principles of contrast enhanced ultrasound, defines the different vascular features of benign and malignant liver lesions, and assesses its clinical impact in different clinical scenarios, according to the guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology, contrast enhanced ultrasound enables the characterisation of focal liver lesions, regardless of the presence or absence of underlying chronic liver disease. Contrast enhanced ultrasound is also useful in staging and follow-up of cancer patients and in monitoring local ablative treatment. Contrast enhanced ultrasound is expected to be considerably increased and replace many computed tomography and magnetic resonance imaging examinations in near future, according to the European Federation of Societies for Ultrasound in Medicine and Biology guidelines. Therefore, it is necessary to take measures in order to meet the demand for an increasing number of these procedures.

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1. Introduction

B-mode ultrasound (US) is the first choice liver imaging technique in view of its safety (lack of radiation exposure), widespread availability and low cost. Unfortunately, the ability of conventional US in discriminating between normal and abnormal liver tissue and in characterising focal abnormalities of liver echo-texture is limited, making the use of computed tomography (CT) scanning or magnetic resonance imaging (MRI) mandatory in many liver disorders.

The introduction of US microbubble contrast agents and the development of contrast-specific US techniques have improved the ability of US of detecting and characterising liver lesions, offering new perspectives for its exploitation in clinical hepatology. The use of US contrast agents was initially based on digital processing of non linear backscattered signals produced by the breaking of microbubbles of the first generation US contrast agents when insonated at a high acoustic power (expressed also as mechanical index, MI). As a result, the signals originating from microbubble destruction must be explored by an intermittent imaging modality. More recently, contrast-specific software and technologies have been developed in order to analyse harmonic signals originat-
ing from the insonation of second-generation contrast agents, such as SonoVue® (Bracco, Italy), by using low MI. These agents allow producing images, which are based on nonlinear acoustic effects of microbubbles. The second-generation microbubbles are characterised by a flexible shell that allows them to vibrate in response to an US beam generated at a low acoustic power, the so-called low MI imaging mode. The oscillations make them several thousand times more reflective than normal body tissues, so that they enhance both grey scale images and flow-mediated Doppler signals in real time. The microbubbles are taken up by the liver and are able to reach the capillary beds without being destroyed; they can thus enhance liver vessels, but not the parenchyma, as they do not leak out of the vessels [1–4]. Several contrast-specific US technologies, operating at low acoustic pressure, have been introduced in clinical practice and allow a continuous real-time imaging of liver parenchyma during vascular perfusion. For this reason, this technique has also been named ‘perfusional contrast-enhanced angiosonography’, in order to be distinguished from previous techniques based on intermittent imaging.

With continuous imaging of a region of interest, changes in the parenchymal or tumoral blood supply over time can be assessed. Contrast enhanced ultrasound (CEUS) of the liver provides different parenchymal or tumoral enhancement on the different phases of contrast enhancement of the liver, which are summarised in Table 1. It is related to the unique blood vessel network of the liver by the hepatic arterial and portal venous supply.

Elimination of microbubbles occurs partly in the liver (shell and stabilising agents) and partly in the lungs (air or gas).

### Table 1

<table>
<thead>
<tr>
<th>Phase</th>
<th>Start (s)</th>
<th>End (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial phase</td>
<td>10–0</td>
<td>25–5</td>
</tr>
<tr>
<td>Portal-venous phase</td>
<td>30–5</td>
<td>120</td>
</tr>
<tr>
<td>Late phase</td>
<td>&gt;120</td>
<td>Bubble disappearance</td>
</tr>
</tbody>
</table>

3. Characterisation of focal liver lesions occasionally detected in patients without known chronic liver disease

The incidental detection of a liver lesion that needs to be characterised is one of the most common clinical issues, as US is the first choice imaging investigation for a number of abdominal disorders and the prevalence of benign liver lesions in the general population is high. Focal liver lesions (FLL) are found incidentally during more than 50% of autopsies, hemangiomas being the most common (up to 20%), followed by focal nodular hyperplasia (3%) [7]. Small liver tumours detected in asymptomatic patients are usually benign even in patients with a history of malignancy, especially when the diameter of the lesion is below 15 mm [8].

CEUS characterisation of liver lesions is based on the comparison of enhancement level of the lesion to normal liver parenchyma during all the three vascular contrast phases, i.e. arterial, portal-venous and late phase.

Blood supply of malignant liver lesions is, in fact, nearly completely provided by arteries and AV shunts are frequently present; the washout in most liver malignancies is much quicker compared to normal liver parenchyma. Benign solid lesions are often best detected and characterised during the arterial phase of the contrast agent, as they may vanish in later phases.

The main US features of liver lesions are summarised in Table 2, which shows that all common benign liver lesions have unique enhancing features that enable reliable characterisation by CEUS.

In contrast, conventional unenhanced US is not able to characterise with certainty any kind of benign lesions in every patient, even hemangioma: these lesions, in fact, can be characterised by unenhanced US with high reliability in asymptomatic patients, who have no underlying chronic hepatic disease, but, in patients who are at risk of hepatocellular carcinoma (HCC), it may fail in half of the cases [9–11].

The typical contrast kinetics of the two most common benign tumours can be seen in Figs. 1 and 2. Fig. 1 depicts the typical peripheral nodular enhancement in the arterial phase, followed by centripetal filling, in a hemangioma and Fig. 2 illustrates hyperenhancement of focal nodular hyperplasia during both the arterial and late phases.

The main difference between benign and malignant lesions is that during the late phase all benign lesions, except enhanced liver US which have a clear cut impact in clinical practice as delineating four different clinical scenarios:

1. characterisation of focal lesions occasionally detected in patients without known chronic liver disease;
2. characterisation of focal lesions detected in surveillance programs of chronic liver diseases;
3. staging and follow-up of cancer patients;
Table 2
Main US features of liver lesions during the three contrast phases (E = enhancement)

<table>
<thead>
<tr>
<th>Liver lesion</th>
<th>Arterial phase</th>
<th>Portal venous phase</th>
<th>Late phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal fatty changes</td>
<td>Iso-E</td>
<td>Iso-E</td>
<td>Iso-E</td>
</tr>
<tr>
<td>Cyst</td>
<td>No E</td>
<td>No E</td>
<td>No E</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Peripheral-nodular E + No central E, small lesions: complete rapid centripetal E</td>
<td>Partial/complete centripetal filling</td>
<td>Complete E, non-enhancing central areas</td>
</tr>
<tr>
<td>Adenoma</td>
<td>Complete, hyper-E, areas of no E (hemorrhage)</td>
<td>Iso-E, areas of hyper-E, or no E (hemorrhage)</td>
<td>Iso-E, no E in central areas (hemorrhage)</td>
</tr>
<tr>
<td>FNH</td>
<td>Complete, hyper-E, early spoke-wheel sign, centrifugal filling, feeding artery, hyper-E, hypo-E in central scar</td>
<td>Iso/hyper-E, hypo-E in central scar</td>
<td>Iso/hyper-E, hypo-E in central scar</td>
</tr>
<tr>
<td>Abscess</td>
<td>Rim-E, no central E, enhanced septa Hyper-E, liver segment, hyper/iso-E of rim, no central E, hypo-E in central scar rim, enhanced septa, hypo-E of rim, no central E</td>
<td>Hypo-E, areas of non-E</td>
<td>Hypo/no-E</td>
</tr>
<tr>
<td>Hypervascularised metastases</td>
<td>Complete, hyper-E, chaotic vessels, hypo-E</td>
<td>Hypo-E, areas of non-E</td>
<td>Hypo/no-E</td>
</tr>
<tr>
<td>Hypovascularised metastases</td>
<td>Complete rim-E, areas of non-E</td>
<td>Hypo-E, areas of non-E</td>
<td>Hypo/no-E</td>
</tr>
</tbody>
</table>

Fig. 1. Typical contrast kinetics of a hemangioma at perfusional CEUS with SonoVue®. Peripheral nodular enhancement in the arterial phase, followed by centripetal filling.

cysts (which never enhance) and thrombosed hemangiomas exhibit iso-enhancement or slight hyperenhancement as compared to surrounding liver tissue, whereas malignant liver lesions exhibit frank hypoenhancement or do not enhance at all. The specificity of this criterion for the characterisation of FLL ranges from 95 to 100% [12–14]. The reason for this difference is that nutrition of malignant tumours is provided exclusively by arterial vessels; there is no portal venous supply. CEUS can provide very useful information as it can depict small arterial vessels less than 100 μm in diameter, compared to CT or angiography.

Indeed, in a large study in 686 patients with 694 FLLs [15], the accuracy of CEUS for characterising FLLs was similar to that of CT/MRI, with a concordance of 94.5% (metastases 95.3%, hemangioma 97%, focal nodular hyperplasia (FNH) 90%). Another study by Quaia [5] documented an increased overall diagnostic accuracy of CEUS in comparison to conventional US (85 versus 49% for reader 1, 88 versus 51% for reader 2) and a higher diagnostic confidence (0.968 versus 0.820 for reader 1, 0.978 versus 0.831 for reader 2).

Liver metastases exhibit different degrees of vascularisation. Those showing homogeneous enhancement in

Fig. 2. Typical pattern of focal nodular hyperplasia at perfusional CEUS with SonoVue®. Appearance of the lesion at conventional sonography is depicted in the left frame, whereas in the subsequent frames, from left to right, the arterial, portal and late phases are shown. The lesion appears markedly and intensely hyperechoic in the arterial phase, with a feeding artery, and remains still, although slightly hyperenhancing during the late phase.
the arterial phase are termed hypervascular and usually derive from neuroendocrine tumours (carcinoids), islet cell tumours (insulinoma/gastrinoma), choriocarcinoma/ovarian cancer, carcinoma of the thyroid and kidney, melanoma and sarcomas, whereas hypovascular lesions (those without homogeneous enhancement in the arterial phase) usually derive from adenocarcinomas (gastrointestinal tract, lung) or squamous cell carcinomas. However, such differentiation according to vascularity does not always give useful information about origin of the tumours. For instance, carcinomas of the breast and lymphomas may produce both hyper and hypovascularised liver metastases. Examples of hypervascular and hypovascular metastases are illustrated in Figs. 3 and 4.

Another issue, that perfusional CEUS may address, is to correctly identify the number of lesions that are actually present. However, for this purpose, the technique, although markedly more sensitive than conventional US, is clearly less sensitive than CT scan and MRI, which are able to provide a more comprehensive overview of liver parenchyma.

4. Characterisation of focal lesions detected in surveillance programmes of liver cirrhosis

HCC represents the major cause of death in cirrhotic patients and its incidence is rising in western countries, ranging from 2.7 to 3.2 per 100,000 [16]. For these reasons surveillance of patients with chronic liver disease and particularly with cirrhosis is requested for the early diagnosis of this neoplasm at a stage when curative treatments can still be performed [17–20].

Surveillance with US and AFP has now become a well established practice, both in western countries and in Asia [21–23]. Follow-up schedules are variable, but intervals of six months are most frequently used, based on the available data on doubling times of HCC [24], with the aim of detecting tumours below 3 cm in diameter.

There are few data about actual sensitivity of conventional US within screening programs. It should be outlined that in a study prospectively comparing US and CT in a screening program [25], the sensitivity of CT resulted significantly higher than that of US (88 versus 59%). However, for practical and economical reasons, and for the possible false positive results of CT, US is still considered the first choice screening tool. Apart the issue of screening, data derived from the analysis of the explanted livers seem to confirm the low sensitivity of conventional US, particularly for small nodules [26]. The detection of a definite small nodular lesion within a cirrhotic liver at conventional US examination remains a difficult challenge and requires operators’ expertise and some favorable technical conditions: first the US beam should reach the nodule, and second the ultrasonic properties of the nodule should be different from those of the surrounding cirrhotic parenchyma. The liver atrophy and the interposition of bowel gases reduce the accessibility of the liver parenchyma. The distortion and attenuation of the
US beam due to fibrosis, fatty infiltration and micro/macro nodules limits the study of the deep liver segments and makes the differential diagnosis of small changes of the echo-pattern difficult. Large regenerative and dysplastic nodules do not have specific features at conventional US. Colour Doppler US might be useful for the characterisation of FLL in cirrhosis, as most of HCCs exhibit arterial Doppler signals [27], but the sensitivity of the Doppler method in depicting vascular abnormalities within a tumour mass is lower than ideal [28].

The problem of recall procedures and diagnostic confirmation of HCC were discussed at the Barcelona-2000 EASL conference [19] and some issues were pointed out:

1. The detection of hypo or hyperechoic nodule at conventional US should always raise the suspicion of HCC
2. Pathological studies have shown that half of the nodules <1 cm in size do not correspond to HCC; therefore, a reasonable protocol in these case is to repeat US every 3 months, until the lesion grows to >1 cm, at which point additional diagnostic techniques can be applied.
3. When the nodule does not exceed 2 cm, biopsy is recommended, since the imaging techniques do not have sufficient accuracy (based on their vascular patterns) to distinguish HCC from other benign or malignant lesions.
4. In nodules >2 cm, a non-invasive diagnosis can be achieved by coincident findings of at least two radiological techniques showing arterial hypervascularisation.

CEUS was not considered in the diagnostic work-up, since enough data on its diagnostic accuracy were not available at that time. At present, it is recognised that HCCs exhibit specific kinetics of the US contrast agent in more than 90% of the cases, with strong enhancement during the arterial phase of CEUS followed with a rapid wash-out [29–32]. During the delayed phase, they are usually echo-poor compared to the surrounding parenchyma (Fig. 5), except for well-differentiated lesions that can remain isoechoic. The differential diagnosis between regenerating nodules and HCC may be feasible, as the former exhibit synchronous enhancement to the surrounding parenchyma, and they typically remain isoechoic during portal and delayed phases. Well-differentiated HCC may sometimes lack the hypervascular arterial pattern and the hypovascular late appearance [33]. CEUS has also shown a significantly higher sensitivity, in comparison to colour and Power

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Fig. 5. Small nodule, 1.5 cm in diameter, located in segment VII (white arrow) detected during the surveillance program of cirrhosis. This lesion was almost isoechoic compared to the surrounding parenchyma at conventional B-mode sonography (A). No abnormal vascularity was detected using colour-Doppler US examination (B, white arrow). Perfusional CEUS with SonoVue® shows a strong enhancement during the arterial phase (C, white arrow) and a wash out becomes apparent during the delayed phase, making the lesion hypoechoic (D, white arrow).
Doppler, in displaying arterial vascularity of HCC [27]. CEUS may, therefore, be an effective modality for FLL characterisation and particularly for HCC, with a sensitivity ranging from 92 to 94% and a specificity of 87–96% [33–35].

Based on these results, the guidelines provided by the EFSUMB document [6] enable to define new indications for CEUS in the setting of diagnostic confirmation of HCC in liver cirrhosis. Accordingly, also the guidelines on management of HCC, of the American Association for the Study of Liver Disease, published in November 2005, now also include CEUS, among the techniques able to achieve a diagnosis of malignancy [36]. This technique may, in fact, represent a useful tool for immediate characterisation of any nodular lesion or suspicious focal change detected by conventional US, thus, limiting the use of other more sophisticated techniques for achieving coincident findings about vascular alterations and reducing the delay for treatment. A recent study [37] has shown that, despite the fact that the relative sensitivities of perfusional CEUS and helical CT in assessing arterial hypervasculaarity of small (3 cm) HCCs are not significantly different (88% for CEUS versus 77% for CT), in some nodules the vascular pattern at perfusional CEUS was different from that at helical CT (with more nodules positive for early arterial enhancement only at CEUS). This discrepancy may be explained by the different vascular distribution of US and CT contrast agents, by the capacity of perfusional CEUS to detect hypervascularity lasting for only a short time or occurring very early, thanks to the continuous real time working modality, or by both.

5. Staging and follow-up of cancer patients

According to EFSUMB guidelines, six CEUS should be performed in all cancer patients referred for liver US for the search of metastases, unless clear-cut disseminated disease is detected by unenhanced US. The reasons for this strong recommendation are that CEUS increases the ability of the US technique to detect liver metastases substantially, by visualising the arterial enhancement and the portal and late wash-out of tumours, and that the management and prognosis of the patient depend heavily on the early detection of metastases, as well as their number and location. Some studies, using first generation contrast agents, have shown that the accuracy of CEUS is comparable to that of spiral CT and in some cases it can detect lesions not visible on CT [38–40]. More recently, using a second generation contrast agent (SonoVue®), the appearance of liver metastases was characterised (homogeneous enhancement in 38.1%, rim-like enhancement in 52.4%, marked hypoenhancement in the late phase (76.2%) [41] and a higher sensitivity of CEUS in comparison with conventional and Duplex Doppler US was demonstrated [42,43]. Some studies [43,44] have confirmed that the accuracy of CEUS with SonoVue® is comparable to that of spiral CT and MRI with a liver contrast agent.

Another application of CEUS in the field of oncology is the monitoring of response to chemotherapy. Following chemotherapy, the acoustic properties of the hepatic parenchyma change, making comparisons with previous examinations difficult and inaccurate. This issue is no longer important with CEUS, as the evaluation is based mainly on the enhancement of the arterial supply vessel network of the tumour, even though missing arterial enhancement does not always preclude disease progression [45].

Finally, in the field of staging of cancer patients, the high sensitivity of CEUS in characterising malignant portal vein thrombosis in relation to HCC has to be mentioned [46].

6. Monitoring of local ablative treatment

Percutaneous ablation has emerged as a viable therapeutic option for patients with limited hepatic malignant disease when surgery is not an option, and is becoming a valid alternative to partial heptectomy for small HCC lesions [47–49]. The administration of the US contrast agent can provide additional important information throughout the procedure: it improves delineation and conspicuousness of lesions poorly visualised by unenhanced US, facilitating targeting and the positioning of the needles or electrodes [50]. After ablation with percutaneous ethanol injection or radiofrequency devices, CEUS is able to assess immediate and delayed efficacy of treatment (Fig. 6) [51,52], allowing immediate repositioning of the needle in case of incomplete treatment (Fig. 6). Per-procedural CEUS reduces the number of partial necrosis from 16.1 to 5.1% in experienced hands [51]. Its use is also increasing for monitoring delayed efficacy, and a diagnostic accuracy comparable to that of spiral CT has been recently demonstrated in the evaluation at one month from the procedure [53].

7. The impact of CEUS on US Units

The implementation of EFSUMB guidelines will result in a considerable increase in the request for CEUS procedures. Consequently, US units will have to update their equipment, provide proper training to the physicians performing US examinations and take into account the cost of introduction of CEUS in daily practice. Whether the eventual cost saving, associated with a reduced request of CT or MRI imaging of the liver after CEUS, could counterbalance the cost of the examination, should be investigated by a pharmacoeconomic analysis. However, we must emphasise that CEUS will replace many, but not all CT and MRI investigations. These techniques still offer a more comprehensive assessment of the liver parenchyma, which is essential for the planning
of surgery or any other kind of intervention. Furthermore, budgeting will have to make allowances for the fact that experience with CEUS in clinical practice is still limited and its optimal use in a number of clinical situations remains to be defined.

In conclusion, CEUS has the potential to become the liver imaging modality of choice for early detection and characterisation of FLL and US units need to take measures to ensure that they can meet the demand for an increasing number of these procedures.

**Practice points**

- Occasional finding of a space-occupying liver lesion is quite common at ultrasound (US) examination. Definite characterisation of these lesions as benign or malignant is almost impossible based on their pattern at conventional real time ultrasonography.
- Different enhancement and wash out patterns after i.v. contrast agents administration may allow characterisation of these lesions at multislice CT scan and MRI.
- Recent advances in US equipment technology and the development of microbubble US contrast agents have now provided new clues for this purpose. In particular the second generation of US contrast agents allow a continuous real time monitoring of vascular perfusion of the liver. This particular development of contrast-enhanced liver ultrasound has been named “Contrast-enhanced perfusional angiosonography”.
- Some definite points have been established using this technique regarding the characterisation of liver lesions. Wash out of the US contrast agent during the portal and parenchymal phases is considered strongly suggestive for malignancy (either primary or secondary), while early arterial enhancement may be found both in some benign (focal nodular hyperplasia, adenoma) and malignant conditions (HCC, metastases).
- Contrast enhanced perfusional angiosonography may therefore be applied for the immediate characterisation of any liver mass following its detection at US examination, thus avoiding in many cases the use of more sophisticated and expensive techniques and the need for a guided biopsy.
Research agenda

- Comparison with other imaging modalities and validated clinical assessment.
- Evaluation of possible diagnostic improvement using different modalities for US contrast administration (bolus vs. continuous infusion).
- Testing the relative advantages and disadvantages of new US contrast agents.

Conflict of interest statement
None declared.

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