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Characterization of unifocal liver lesions with pulse inversion harmonic imaging after Levovist injection: preliminary results

M. Bertolotto, L. Dalla Palma, E. Quaia, M. Locatelli

Istituto di Radiologia dell'Università, Ospedale di Cattinara, I-34149 Trieste, Italy

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Abstract. The aim of this study was to evaluate capabilities of pulse inversion harmonic imaging (PIHI) in characterization of unifocal liver lesions. We evaluated with PIHI (HDI5000, ATL, Bothell, Wash.) and spiral CT 46 consecutive patients with a single liver lesion identified by fundamental US [7 hepatocellular carcinomas (HCC), 2 cholangiocarcinomas, 7 focal nodular hyperplasias (FNH), 17 hemangiomas and 13 metastases]. The PIHI was performed before and 30 s, 2 and 4 min after bolus administration of Levovist (2.5 g, 300 mg/ml). Scans were digitally stored and reviewed using a dedicated software. Hepatocellular carcinoma was hyperechoic on 30-s scan, and hypoechoic ($n = 5$) or isoechoic ($n = 2$) on 2-min scan. Cholangiocarcinoma had inhomogeneous persistent enhancement. Focal nodular hyperplasia was hyperechoic ($n = 5$) or isoechoic ($n = 2$) on 30-s scan, hyperechoic ($n = 4$), isoechoic ($n = 2$) or slightly hypoechoic ($n = 1$) on 2-min scan. Large hemangioma revealed peripheral enhancement on 30-s scan which extended centripetally on 2-min scan. Small hemangioma appeared isoechoic on 2-min scan in all but two cases in which they were hypoechoic on 2-min scans and hyperechoic on 4-min scan. Metastasis was hypoechoic on all scans, 70 % with rim enhancement. Similar changes in enhancement pattern have been observed at spiral CT.

The 30-s and the 2-min scans revealed a conclusive importance in characterization of HCC, cholangiocarcinoma, and large hemangioma. The 2-min scan often furnished enough information for characterization of small hemangioma and metastasis. The 4-min scan allowed characterization of two hemangiomas which appeared hypoechoic on 2-min scans. In the other cases it did not provide further information. Diagnosis of FNH is usually reached with Colour Doppler US; PIHI should be used when colour Doppler is biased by artefacts or when colour Doppler findings are not characteristic. Our results seem to show that PIHI could be a valuable alternative diagnostic approach to spiral CT for unifocal liver lesion characterization. This hypothesis needs to be confirmed with an increased number of lesions.

Key words: Liver – Tumours – Ultrasound – Contrast media – Liver – Pulse inversion harmonic imaging

Correspondence to: L. Dalla Palma

Introduction

Although US is considered to be a powerful technique in identifying liver lesions, its capabilities in lesion characterization is low. Colour Doppler evaluation often allows diagnosis of focal nodular hyperplasia (FNH) [1], and can improve characterization of other undetermined liver lesions, giving information on their vascularity [2, 3, 4]. Moreover, colour Doppler sensitivity improves using latest-generation digital US apparatus or US contrast agents [5, 6]. Despite better recognition of vascular signals in liver lesions, a significant overlapping still exists between the appearance of benign and malignant lesions, and a wide range of sensitivity and specificity is reported by different authors [2, 3, 4, 7, 8].

Recently, it has been demonstrated that the interaction between the US beam and the US contrast agents is extremely complex, and that the diagnostic capabilities of these substances may go far beyond enhancement of Doppler signals. Indeed, when properly insonated, the microbubbles of the US contrast agents collapse producing a high-intensity, broadband transient signal which can be detected using contrast specific US imaging techniques [9, 10].

Pulse inversion harmonic imaging (PIHI), also named wide-band harmonic imaging, is a new contrast-specific imaging technique. It works by sending two trains of pulses out of phase to each other, and summing the returning echoes. The signal from tissues cancels,

whereas the signal from the collapsing microbubbles is recorded. Contrary to colour Doppler, the signal produced by microbubble collapse is related to microbubble concentration and does not depend on blood-flow velocity. As a consequence, very slow blood flow in capillaries and stationary blood in hepatic sinusoids can be detected as well as faster-moving blood.

The diagnostic capabilities of US contrast agents using contrast-specific imaging techniques have been demonstrated in the clinical practice, since several authors [11, 12, 13, 14, 15] report high sensitivity of these techniques in detection of liver metastases. It is conceivable that dynamic evaluation of lesion echogenicity after US contrast agent administration may improve liver lesion characterization as well [16, 17].

In clinical practice undetermined liver lesions are often characterized with spiral CT based on characteristic enhancement pattern [18, 19, 20, 21, 22, 23, 24, 25].

The aim of this study was to evaluate the diagnostic capabilities of PIHI in characterizing unifocal liver lesions in patients investigated previously with colour Doppler US and with spiral CT, which was considered the imaging gold standard.

Materials and methods

Patients

Forty-six consecutive patients with a single liver lesion identified by fundamental US were evaluated by colour Doppler US, spiral CT and PIHI.

Hepatocellular carcinoma (HCC) was diagnosed in 7 patients (5 men and 2 women; age range 50–76 years, mean age 66 years): 5 were cirrhotic and 2 non-cirrhotic. Diagnosis was biopsy proven in 6 of 7 patients, and in the remaining patient diagnosis of recurrent HCC has been done based on clinical and US findings. The patient had had alcoholization of a biopsy-proven HCC 8 months before and presented with another lesion and elevation of serum alpha-fetoprotein over 400 ng/ml. For the purpose of this study the features of the lesion which underwent alcoholization were not considered.

Peripheral cholangiocarcinoma was diagnosed in 2 patients (1 man, 86 years; 1 woman, 54 years). Diagnosis was biopsy or surgically proven.

Focal nodular hyperplasia (FNH) was diagnosed in 7 patients (all women; age range 32–48 years, mean age 36 years). Diagnosis was biopsy proved in one case; in the other 6 patients it was based on typical imaging findings at colour Doppler US and spiral CT [1, 19, 20, 22, 24].

Hemangioma was diagnosed in 17 patients (8 men and 9 women; age range 33–76 years, mean age 55 years). Diagnosis was made basing on typical findings at spiral CT [18, 20, 22, 23, 24] and, in 3 patients, on characteristic US appearance as well.

Metastasis was diagnosed in 13 patients (8 men and 5 women; age range 41–80 years, mean age 71 years) with a known primary tumour (9 gastrointestinal, 2 lung, 1 breast, 1 melanoma) based on biopsy ($n = 3$), anamnesis, typical CT findings and follow-up.

Colour Doppler ultrasonography

The present study was performed with a commercially available US digital apparatus (HDI-5000, ATL, Bothell, Wash.) using a broadband 2- to 5-MHz transducer. In each patient a baseline fundamental US examination was repeated to confirm the previously reported US findings, then colour Doppler evaluation and spectral analysis of intralesional vessels were performed. Proprietary settings were used specifically designed to image liver. Colour Doppler parameters were optimized to detect slow flow velocities (pulse repetition frequency 700 Hz, wall filter medium, flow optimization low). The colour Doppler gain was manipulated until colour noise first became evident and then slightly lowered (1 dB) to clean the image.

Pulse inversion harmonic imaging

After a suitable acoustic window was identified to cover all the liver volume in one to two scans with minimal blind areas, the US apparatus was set for PIHI. The PIHI was performed using a CSI-3 harmonic preset, low frame rate (5 Hz) and high mechanical index (MI 1.1–1.3). Using these parameters microbubble destruction occurs and a high-intensity transient wideband signal is produced. All imaging parameters were set first and then kept unchanged during the different scans before and after Levovist injection. A bolus of 2.5 g Levovist (SH U 508A, Shering, Berlin, Germany) was injected at a concentration of 300 mg/ml with a 10- to 20-ml normal saline flush. To characterize the liver lesion one or two fast scans (one for the right liver and one for the left liver) covering the entire liver volume were performed before Levovist injection and after, with delays of 30 s, 2 min and 4 min.

Spiral CT

Within 10 days after PIHI, all patients were evaluated by precontrast and triphasic spiral CT (5-mm slice thickness, 7-mm table feed, 5-mm scan reconstruction), which was considered to be the imaging gold standard.

The CT scans were acquired before contrast agent injection and 30 s, 90 s and 3 min after administration of 100–120 ml of nonionic contrast material (Iomeron 300, Bracco, Milan, Italy) at a rate of 3 ml/s.

Evaluation of images

Raw data of scans were stored digitally in a magneto-optical disk and reviewed off-line using specifically designed software (HDIlab, ATL, Bothell, Wash.). This software allows measuring the original signal intensity values of a region of interest from the raw data before logarithmic compression and postprocessing.

Subjective evaluation

Corresponding images from scans obtained before and after US contrast agent injection were subjectively compared by two operators who did not know results of the other imaging modalities. Operators evaluated independently echogenicity and conspicuity of single lesions, before and after contrast agent injection, in comparison with surrounding liver parenchyma. As regards echogenicity, lesions were subjectively scored as hypoechoic, isoechoic or hyperechoic. Conspicuity, namely the ability to identify single lesions from the surrounding liver parenchyma, was subjectively scored as good, reduced or poor. Since in some patients with only one lesion recognized with fundamental US multiple lesions were detected after contrast agent injection, and with spiral CT, the number of visible lesions was evaluated as well.

Objective evaluation

Corresponding images from scans obtained before and 30 s, 2 and 4 min after US contrast agent injection were compared by measuring for each lesion and for the surrounding liver parenchyma the original signal intensity value from raw data. Regions of interest (ROI) of the same size (25 mm^2) were placed inside the lesion and in a region of adjacent liver parenchyma free of vessels and artefacts. Since the amount of bubble destruction, and therefore echogenicity, depends on depth and focalization of US beam, ROIs inside lesion and inside liver parenchyma were placed at the same depth. In lesions smaller than 2 cm, one measure was done. In lesions larger than 2 cm with different enhancement in the centre and at the periphery, measurements were done in the areas with different contrast enhancement and the intensity values were considered separately. In the other lesions larger than 2 cm, two or more measurements were done in the centre and at the periphery and intensity values were averaged.

In order to estimate objectively lesion conspicuity, a "conspicuity index" was calculated from the difference, in absolute value, between the signal intensity measured into the lesion and within the liver parenchyma. The conspicuity index was measured before and 30 s, 2 and 4 min after US contrast agent injection.

All calculations of the signal intensity values were performed using a linear scale, and then the results were transformed in logarithmic scale [logarithmic intensity = $10 \times \log_{10}$(linear intensity)] to reduce the wide range of variation of the measured values and match intensity differences which are perceivable by the human eye as different grey levels. The transformed values were presented as average ± standard deviation.

Results

Liver parenchyma

The echogenicity of the liver parenchyma subjectively increased from the 30-s to the 2-min scan and subjectively decreased at 4-min scan. The data were confirmed at quantitative evaluation (Table 1).

Hepatocellular carcinoma

There were seven well-circumscribed lesions 2–7 cm in diameter. At fundamental US one was hyperechoic, three were hypoechoic and three (Fig. 1) were isoechoic.

Colour Doppler examination revealed hypervascularity of 5 of 7 lesions, two with a fine network of arterial vessels surrounding the tumour, and three with peripheral and intralesional arterial vessels. Two lesions appeared avascular.

At spiral-CT examination all HCC appeared hyperdense on 30-s scan. Two of seven HCCs were hyperdense also on 90-scan; all were hypodense on 3-min scan.

At PIHI (Fig. 1) all HCC appeared subjectively hyperechoic on 30-s scan; 5 were hypoechoic and 2 isoechoic on 2-min scan. On 4-min scan the lesions had the same echogenicity as on the non-enhanced scans. The data were confirmed at quantitative evaluation (Table 1).

Subjective and objective evaluation of lesion conspicuity showed better visibility of HCC on contrast-enhanced scans (Table 2).

Table 1. Average signal intensity in logarithmic scale (dB) of liver parenchyma and of different liver lesions at pulse inversion harmonic imaging (PIHI) before and 30 s, 2 min and 4 min after US contrast agent injection. *HCC* hepatocellular carcinoma; *FNH* focal nodular hyperplasia

	Basal	30-s	2-min	4-min
Liver parenchyma ($n = 46$)	14 ± 4	20 ± 5	24 ± 6	20 ± 5
HCC ($n = 7$)	13 ± 6	25 ± 6	19 ± 7	15 ± 6
Cholangiocarcinoma ($n = 2$)	15 ± 1	20 ± 5	23 ± 7	18 ± 2
FNH ($n = 7$)	13 ± 3	25 ± 3	26 ± 4	22 ± 5
Large angioma ($n = 7$)[a]	16 ± 4	20 ± 7	24 ± 4	23 ± 7
Small angioma ($n = 10$)	15 ± 8	17 ± 6	20 ± 6	18 ± 7
Metastasis ($n = 13$)	12 ± 5	14 ± 5	12 ± 5	12 ± 5

Table 2. Average conspicuity index in logarithmic scale (dB), measuring the echogenicity of different liver lesions in comparison with surrounding liver parenchyma before and 30 s, 2 min and 4 min after US contrast agent injection. Conspicuity index is defined as the difference, in absolute value, between the signal intensity measured within the lesion and within the liver parenchyma

	Basal	30-s	2-min	4-min
HCC ($n = 7$)	13 ± 7	26 ± 8	26 ± 4	21 ± 4
Cholangiocarcinoma ($n = 2$)	15 ± 1	23 ± 8	28 ± 9	26 ± 4
FNH ($n = 7$)	12 ± 6	24 ± 5	23 ± 6	20 ± 7
Large angioma ($n = 7$)[a]	17 ± 6	22 ± 11	20 ± 5	19 ± 6
Small angioma ($n = 10$)	18 ± 7	15 ± 7	12 ± 9	11 ± 7
Metastasis ($n = 13$)	10 ± 7	22 ± 6	29 ± 6	23 ± 5

[a]Intensity values measured at periphery of lesion

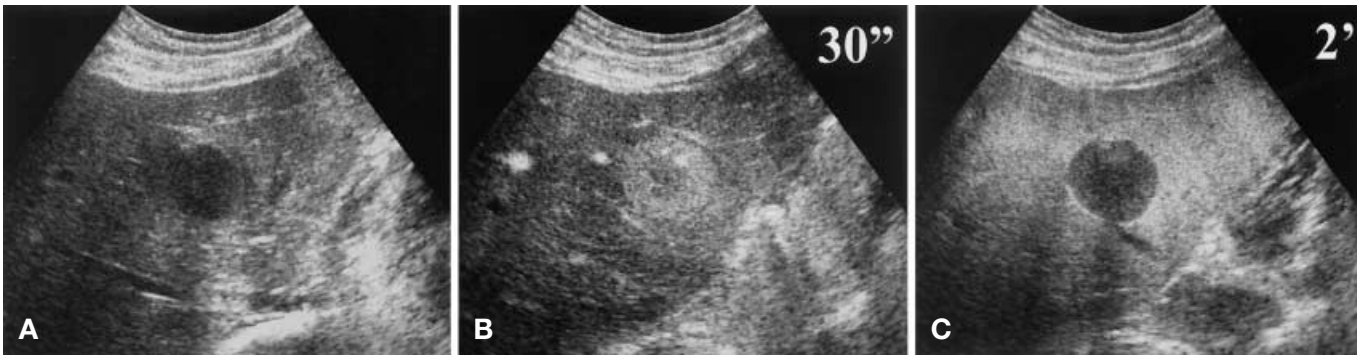


Fig. 1 A–C. Contrast-enhanced US pattern of hepatocellular carcinoma (HCC). Corresponding images of the same lesion obtained with **A** fundamental US and with **B** 30-s pulse inversion harmonic imaging (PIHI) and **C** 2-min PIHI after bolus Levovist injection. The lesion is hypoechoic on the fundamental scan, hyperechoic on 30-s scan and hypoechoic on 2-min scan.

Peripheral cholangiocarcinoma

There were two lesions, 9–12 cm in diameter. At fundamental US they were inhomogeneously isoechoic with lobulated margins (Fig. 2). Colour Doppler examination revealed hypervascularity with prevalence of arterial vessels both at the periphery and at the centre.

At spiral CT examination inhomogeneous contrast enhancement of the lesions was found, with maximum enhancement during the 90-s and 3-min scans. One patient presented intralesional hypoattenuating areas, due to tumour necrosis, and 4 small (0.5–1 cm) peripheral satellite lesions which were not appreciable with fundamental US.

At PIHI (Fig. 2) the lesions showed inhomogeneous contrast enhancement, but remained hypoechoic in comparison with the surrounding liver parenchyma.

Fig. 2 A–C. Contrast-enhanced US pattern of peripheral cholangiocarcinoma. Corresponding images of the same lesion obtained with **A** fundamental US and with **B** 30-s PIHI and **C** 2-min PIHI after bolus Levovist injection. The lesion is inhomogeneously isoechoic on the fundamental scan, with lobulated margins. Inhomogeneous contrast enhancement is appreciable on 30-s and 2-min scans, but lesion remains hypoechoic in comparison with the surrounding liver parenchyma. Two small satellite lesions *(arrows)* are visible on 2-min scan

The data were confirmed at quantitative evaluation (Table 1).

Subjective and objective evaluation of lesion conspicuity showed better lesion visibility on contrast-enhanced scans which was maximum on 2-min scan (Table 2). Areas with reduced enhancement, due to tumour necrosis, and multiple satellite lesions were detected in 1 patient after contrast agent injection, with maximum conspicuity on 2-min scan.

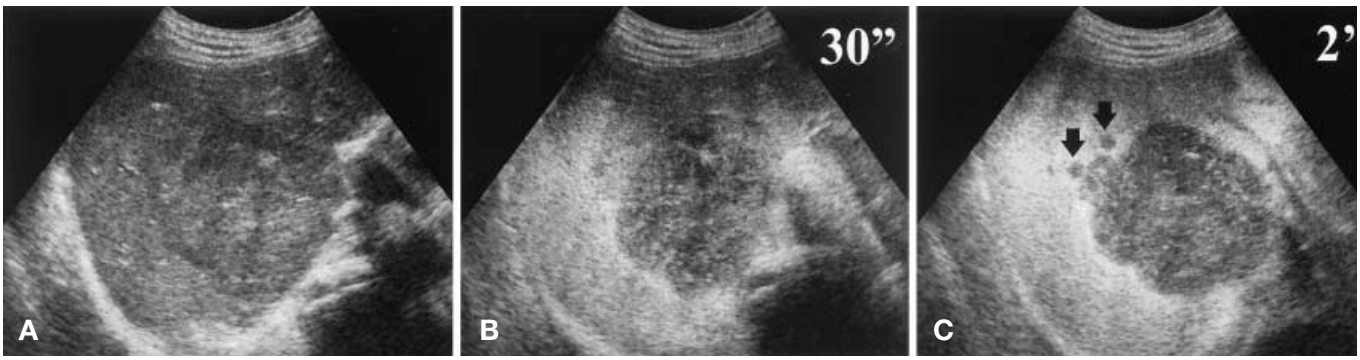
Focal nodular hyperplasia

There were seven well-circumscribed lesions 1.6–7.5 cm in diameter. At fundamental US four were hypoechoic and three isoechoic (Fig. 3).

Colour Doppler examination was characteristic in 6 of 7 cases, revealing a central arterial vessel with low resistance flow radiating towards the periphery of the lesion. In the remaining patient colour Doppler examination was hampered by motion artefacts and the characteristic spoke-wheel appearance was not clearly detected.

At spiral-CT examination all FNH were hyperdense on 30-s scan; four were hyperdense also on 90-s scan. On 3-min scan 6 of 7 FNH were hypodense and 1 of 7 was isodense. Central scar was demonstrated in 2 cases.

At PIHI (Fig. 3) five FNH appeared subjectively hyperechoic and two isoechoic on 30-s scan; four were hyperechoic, two were isoechoic and one slightly hypoechoic on 2-min scan; six were isoechoic and one hypoechoic on 4-min scan. In 1 patient a central vessel with spoke-wheel appearance was seen on 30-s scan, and in another patient hypoechoic stellate pattern was seen on 2-min scan. The data were confirmed at quantitative



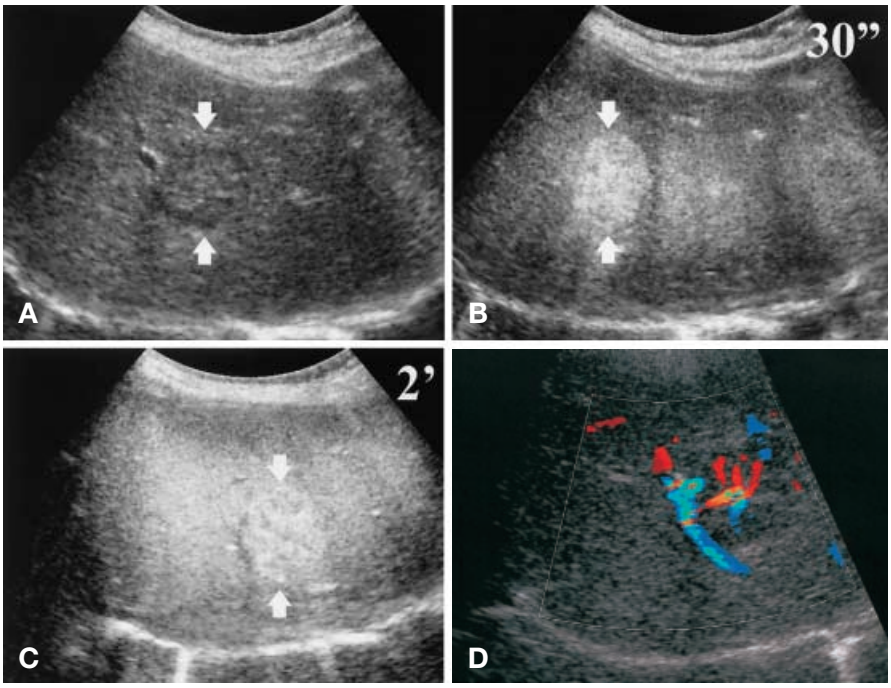


Fig. 3 A–D. Colour Doppler and contrast-enhanced US pattern of focal nodular hyperplasia (FNH). Corresponding images of the same lesion *(arrows)* obtained with **A** fundamental US and with **B** 30-s PIHI and **C** 2-min PIHI after bolus Levovist injection. The lesion is isoechoic on the fundamental scan and becomes hyperechoic on 30-s and 2-min scans. **D** Colour Doppler imaging shows a central arterial vessel radiating towards the periphery

evaluation (Table 1) which demonstrated in all FNH contrast enhancement on 2-min scan higher than the enhancement observed in HCC.

Subjective and objective evaluation of lesion conspicuity showed better lesion visibility on contrast-enhanced scans (Table 2).

Large hemangioma

There were seven large hemangiomas (4–10 cm in diameter, mean 6 cm). At fundamental US all hemangiomas were inhomogeneous (Fig. 4) with posterior acoustic enhancement; three were hyperechoic, two isoechoic and two hypoechoic.

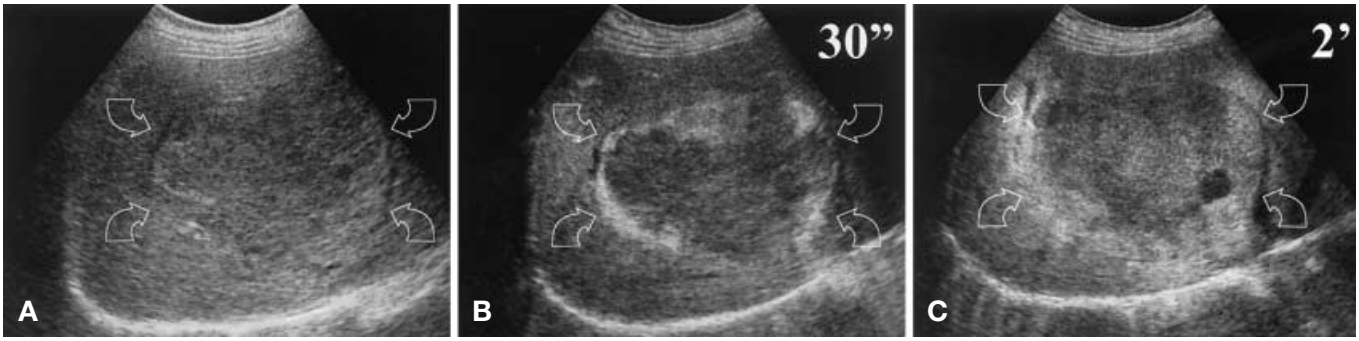
Colour Doppler examination revealed in 4 cases peripheral vascular spot signals with low-velocity arterial and venous flows, and in one case, central vascular signals with the same spectral characteristics were demonstrated as well.

At spiral CT all large hemangiomas revealed peripheral globular enhancement on the 30-s scan which became gradually confluent on the 90-s and 3-min scans filling the lesion from the periphery towards the centre.

At PIHI (Fig. 4) all large hemangiomas revealed peripheral enhancement on 30-s scan which extended centripetally in the 2-min scan. In 6 of 7 patients the centre of the lesion remained hypoechoic, in comparison with the peripheral portion, whereas in the remaining patient the lesion enhanced homogeneously. On 4-min scan a similar enhancement pattern was seen. Data were confirmed at quantitative evaluation (Table 1).

Subjective and objective evaluation of lesion conspicuity showed better visibility on contrast-enhanced scans which was maximum on 30-s scan due to sharply demarcated peripheral enhancement (Table 2).

Fig. 4 A–C. Contrast-enhanced US pattern of large hemangioma. Corresponding images of the same lesion *(arrows)* obtained with **A** fundamental US and with **B** 30-s PIHI and **C** 2-min PIHI after bolus Levovist injection. The lesion is inhomogeneously isoechoic on the fundamental scan. Peripheral globular enhancement is appreciable on 30-s scan which extends centripetally in the 2-min scan



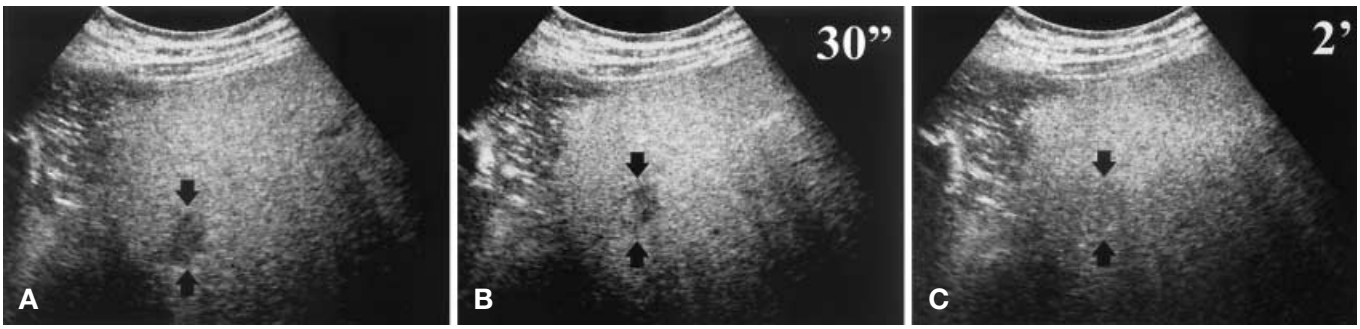


Fig. 5 A–C. Contrast-enhanced US pattern of small hemangioma. Corresponding images of the same lesion *(arrows)* obtained with **A** fundamental US and with **B** 30-s PIHI and **C** 2-min PIHI after bolus Levovist injection. On the fundamental scan the lesion is hypoechoic in bright liver. On 30-s scan the lesion is partially isoechoic, but a portion remains hypoechoic and becomes isoechoic on 2-min scan

Small hemangioma

There were ten small hemangiomas (1–2.5 cm in diameter, mean 1.6 cm). At fundamental US six of ten lesions were hyperechoic, two were isoechoic and two were hypoechoic in bright liver (Fig. 5). No vascular flows were detected at colour Doppler analysis.

At spiral CT all but two lesions enhanced on 30 s, 90-s and 3-min scans. Two lesions enhanced only on 90 ′s scan. Seven hemangiomas showed homogeneous contrast enhancement, whereas the other three showed a central filling defect on 30-s scan which was filled by iodinated contrast agent on 90-s and 3-min scan.

At PIHI four small hemangiomas were subjectively hyperechoic on 30-s scan, six subjectively isoechoic. Two lesions had a hypoechoic portion on 30-s scan which became isoechoic on 2-min scan (Fig. 5). All but two small hemangiomas appeared isoechoic on 2-min scan; two were hypoechoic. On 4-min scan two hemangiomas appeared hyperechoic, seven isoechoic and one hypoechoic. The two small hemangiomas which were hypoechoic on 2-min scan became isoechoic ($n = 1$) or hyperechoic ($n = 1$) on 4-min scan. The data were confirmed at quantitative evaluation (Table 1).

Subjective and objective evaluation of lesion conspicuity showed worse lesion visibility on contrast-enhanced scans in all but 2 cases (Table 2). In particular, on 2-min scan, most (8 of 10) small hemangiomas were almost indistinguishable from surrounding liver parenchyma.

Metastasis

There were 13 lesions 1.5–6 cm in diameter (mean 2.8 cm). At fundamental US 1 was hyperechoic, 3 isoechoic and 9 hypoechoic (Fig. 6).

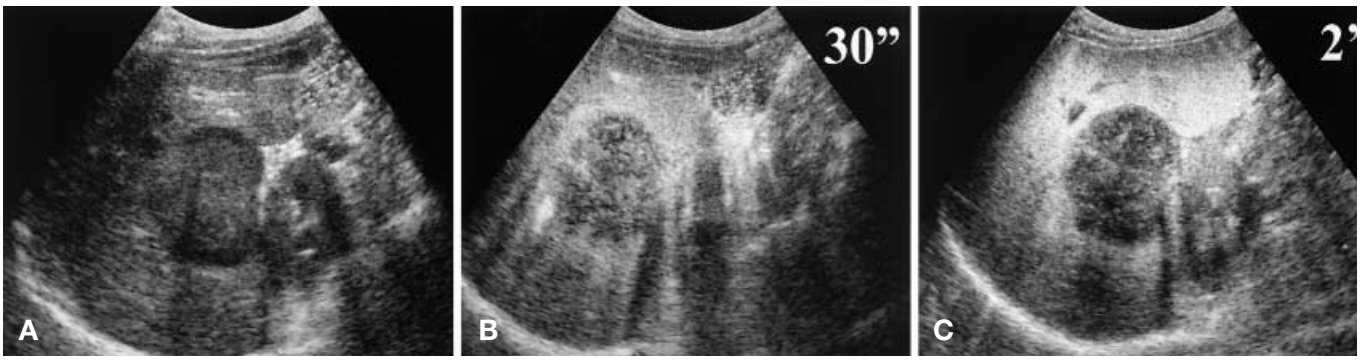
Colour Doppler examination revealed peripheral and intralesional arterial vessels in 2 lesions and peripheral vascular spot signals in 1 lesion. The remaining 10 lesions appeared avascular.

At spiral CT metastases appeared in all scans hypodense with peripheral enhancement. In 5 of 13 cases, spiral CT revealed multiple small (3–5 mm) additional metastases which were not visible on fundamental US.

At PIHI (Fig. 6) all metastases were hypoechoic on 30-s and 2-min scans. They revealed a peripheral rim of enhancement in 9 of 13 cases. Measurement of lesion and liver echogenicity confirmed that metastases had lower contrast enhancement in comparison with the surrounding liver parenchyma (Table 1). A low enhancement peak was observed on 30-s scan, followed by rapid reduction. It was higher for metastases which displayed colour signals on colour Doppler examination.

Subjective and objective evaluation of lesion conspicuity showed better lesion visibility on contrast-en-

Fig. 6 A–C. Contrast-enhanced US pattern of solitary metastasis. Corresponding images of the same lesion obtained with **A** fundamental US and with 30-s PIHI and **C** 2-min PIHI after bolus Levovist injection. The lesion appears hypoechoic on all scans. A low contrast enhancement is appreciable on 30-min scan



hanced scans which was maximum on 2-min scan (Table 2).

Multiple small (3–5 mm) additional metastases which were not visible on fundamental US were detected in 5 of 13 patients.

Discussion

In this study we evaluated echogenicity time changes of liver parenchyma, different liver primary tumours and solitary liver metastases with PIHI following bolus administration of Levovist.

Although our main goal was to establish whether PIHI was useful in characterizing liver lesions, we observed that this techniques improved detection of most lesions as well, except for small hemangiomas. Increased lesion conspicuity was subjectively observed and demonstrated by conspicuity index measurements. This finding is particularly important in assessing multifocality in HCC, cholangiocarcinoma and metastasis.

It results from our study that liver normal parenchymal echogenicity increases from the 30-s to the 2-min scan and then decreases at 4-min scan. We disagree with other authors [11, 15], however, who observed a longer contrast persistence, of at least 5 min. A difference in imaging technique can explain this discordance. Whereas these authors performed only one scan several minutes after Levovist injection, we performed three scans at different time intervals. As a consequence, a large amount of microbubbles are destroyed before the 4-min scan. In our material the observed lower contrast enhancement of the liver parenchyma on 4-min scan relies largely on this different technique, not on hemodynamic differences. As a consequence, using the imaging protocol of the present study, attention must be paid in interpretation of lesion echogenicity on 4-min scan.

The 30-s and 2-min scans appeared to be the most important in characterizing HCC, cholangiocarcinoma and large hemangioma. In HCC the two scans revealed hyperechogenicity followed by hypoechogenicity; in cholangiocarcinoma inhomogeneous, persistent enhancement; in large hemangiomas globular peripheral enhancement followed by centripetal progression.

In our opinion, the 2-min scan often furnished enough information for characterization of small hemangioma and metastasis, documenting in the former similar, and in the latter lower, signal enhancement relative to that of the liver parenchyma.

In our material PIHI appeared to be a valid diagnostic technique for characterization of HCC revealing early contrast enhancement which rapidly subsided in all cases. The same behaviour was observed with spiral CT. Colour Doppler showed different patterns.

We observed only two peripheral cholangiocarcinomas, which are too few to draw conclusions about the role of PIHI; however, a similar enhancement pattern was observed at spiral CT, with inhomogeneous enhancement, persisting also on late scans. This enhancement is considered at spiral CT diagnostic for this tumour [25]. Moreover, PIHI was able to detect satellite lesions in 1 patient, as did spiral CT.

In our experience, using latest-generation digital US apparatus with high Doppler sensitivity, colour Doppler examination allowed confident diagnosis of FNH in most cases. Pulse inversion harmonic imaging should be considered complementary to colour Doppler. It can have a diagnostic role in cases in which colour Doppler analysis cannot be performed properly because of moving artefacts, or in lesions without the characteristic spoke-wheel vascular pattern. In our opinion, the 2-min scan allows enough information to characterize this lesion when hyperechogenicity in comparison with the surrounding liver parenchyma is seen. Indeed, this enhancement pattern has not been detected in other lesions. Ultrasonography generally seems to be a reliable modality in diagnosing FNH.

In all 7 cases of large hemangiomas PIHI revealed peripheral globular enhancement on 30-s scan, with progressive extension towards the centre of the lesion at 2- and 4-min scans. Similar enhancement dynamics were observed with spiral CT. Whereas PIHI provides an enhancement pattern which allows lesion characterization, colour Doppler investigation was not specific, because two lesions were avascular. Moreover, also identification of peripheral ($n = 4$) or both peripheral and central ($n = 1$) colour spots was not specific, since it can be observed also in metastases [3, 4, 7, 8].

In our series of ten small hemangiomas they appeared with characteristic US pattern in six cases as strongly hyperechoic, well-circumscribed, homogeneous lesions. However, hyperechoic metastases exist, and small hemangiomas may appear isoechoic or hypoechoic in a bright liver, or may display atypical features such as inhomogeneities. Small hemangiomas with atypical US appearance are indistinguishable from other small benign and malignant lesions. Colour Doppler analysis does not provide useful information, since no vascular signals are usually detected in these lesions, and spiral CT or magnetic resonance imaging are needed to reach diagnosis.

According to our results, PIHI may aid characterization of small hemangiomas with atypical US appearance by demonstrating enhancement which persists or increases on the late scans. In our series eight of ten small hemangiomas became almost isoechoic to the surrounding liver parenchyma on 2-min scan. Occasionally, they are still hypoechoic on 2-min scan (2 cases in our series) but become isoechoic or hyperechoic on 4-min scan. This delayed enhancement pattern can also be observed with spiral CT, and is due to very slow flow within the lesion. In this case at 2-min scan the pattern of small hemangiomas and metastases is similar. To differentiate the two lesions we need the 4-min scan which shows a hyperechoic pattern for hemangiomas and a hypoechoic pattern for metastasis.

In our series of patients with metastases PIHI was characteristic, revealing at 2-min hypoechoic lesions, in 70 % of cases with peripheral rim enhancement. This finding, in any case, must be supported by the clinical pattern. Conversely, colour Doppler findings were not

diagnostic, revealing either avascular lesions, or a non-specific intralesional vascular pattern.

Besides typical enhancement pattern, in 5 of 13 patients with single liver lesions PIHI identified multiple lesions, leading to diagnosis of diffuse metastatic disease. This finding is in agreement with previous studies published by us and by other authors [11, 12, 14, 15] in which a dramatic increase in the number of lesions detected has been demonstrated with PIHI and other contrast-specific US techniques, in comparison with fundamental US. Therefore, we could consider this technique alternative to spiral CT in evaluation of patients with metastatic disease.

The one major limitation of this study was the number of patients: due to the small case numbers, our results should be considered preliminary; more cases are needed to confirm them and assess sensitivity of the technique. Furthermore, some lesions, such as metastases, did not have biopsy. However, we believe that this limitation does not bias our results, since a confident diagnosis has been made on the basis of well-established imaging criteria, clinics, anamnesis and follow-up.

In conclusion, grey-scale and colour Doppler US often allow characterization of small hemangiomas, FNH and metastases; however, liver lesions may be difficult to characterize and spiral CT is needed to reach the diagnosis. We obtained with PIHI enhancement patterns which are characteristic for the different liver lesions and similar findings have been reported on a preliminary experience by other authors [17]. If our results are confirmed by further investigation, it is conceivable that differential diagnosis among different unifocal liver lesions will improve consistently, complementing colour Doppler US with PIHI.

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