HEPATOBILIARY-PANCREAS

Tommaso Vincenzo Bartolotta
Massimo Midiri
Emilio Quaia
Michele Bertolotto
Massimo Galia
Filippo Cademartiri
Roberto Lagalla

Liver haemangiomas undetermined at grey-scale ultrasound: contrast-enhancement patterns with SonoVue and pulse-inversion US

T. V. Bartolotta · M. Midiri · M. Galia ·
R. Lagalla
Department of Radiology,
University of Palermo,
Via Del Vespro 127,
90127 Palermo, Italy

E. Quaia · M. Bertolotto
Department of Radiology, Cattinara
Hospital, University of Trieste,
Strada di Fiume 447,
34149 Trieste, Italy

F. Cademartiri
Department of Radiology,
Erasmus Medical Center,
Dr. Molenwaterplein, 40,
3015 Rotterdam, The Netherlands

T. V. Bartolotta (✉)
Via Del Carabiniere 32,
90146 Palermo, Italy
e-mail: tv_bartolotta@yahoo.com
Tel.: +39-91-6552330
Fax: +39-91-6552337

Abstract The objective of this study was to describe the spectrum of contrast-enhancement patterns of hepatic haemangiomas undetermined at grey-scale ultrasound (US) on SonoVue-enhanced pulse-inversion (PI) US. Twenty patients (11 women, nine men) with 35 haemangiomas (size range: 1–7 cm; mean: 3.1 cm) undetermined at baseline US underwent PI at low M.I. (0.05–0.08) after i.v. injection of SonoVue. All haemangiomas were confirmed by typical helical computed tomography (CT) and/or magnetic resonance imaging (MRI) findings. US examinations were videotaped and then reviewed by two experienced radiologists blinded to the final diagnosis. Readers evaluated by consensus the baseline echogenicity and the dynamic enhancement pattern of each lesion, in comparison with adjacent liver parenchyma. After administration of SonoVue, 31/35 (88%) haemangiomas showed peripheral hyperechoic nodules in the arterial phase, followed by progressive centripetal fill-in, which was complete in 25/35 cases and incomplete in 6/35 cases. Three out of 35 (9%) haemangiomas showed rapid and complete fill-in in the arterial phase, which persisted in the portal and delayed phases. Finally, 1/35 haemangiomas (3%) showed a rim of arterial contrast enhancement with progressive and complete centripetal fill-in in portal-venous and delayed phases. In conclusion, PI after the administration of SonoVue enabled the depiction of typical contrast-enhancement patterns in haemangiomas undetermined at baseline US.

Keywords Liver · Haemangiomas · Liver neoplasms · US · Ultrasound · Contrast media · Pulse inversion harmonic imaging

Introduction

Haemangiomas are the most common benign tumours of the liver, with a prevalence ranging from 1–2% to 20% among the general population and a higher incidence in females than in males (ratio 2:1–5:1) [1]. The differential diagnosis between haemangiomas and other hepatic tumours is of clinical relevance since haemangioma, although frequently an incidental finding of abdominal ultrasound (US), is rarely symptomatic or requires treatment [2].

Grey-scale US is commonly used as a first-line imaging modality in the diagnostic work-up of patients with suspected liver disease, but unfortunately US does not have a high specificity for the characterization of hepatic tumours [3]. This is particularly important in the case of haemangiomas, as these tumours may present with an atypical appearance on baseline US [2, 4].

Colour Doppler analysis is of limited value, as it is unable to detect with adequate sensitivity the extremely slow flows within the venous pools characterising the macroscopic pathological structure of hepatic haemangio-

mas [5, 6]. Power Doppler has a higher sensitivity in detecting slow flows compared with colour Doppler. However, it is limited by its high sensitivity to motion artefacts, particularly when echo-amplifier contrast media are used with consequent appearance of blooming artefacts [7].

Recently, new ultrasound techniques, such as pulse inversion (PI) harmonic imaging, have been developed that are extremely sensitive to non-linear effects of US interaction with microbubble contrast agents [8]. Some studies have demonstrated that PI with a first-generation, air-based contrast agent (SH U 508A) is helpful in diagnosing hepatic haemangiomas [9, 10], including those assessed as atypical at baseline US [11].

SonoVue is a new, second-generation, stabilised microbubble preparation containing sulphur hexafluoride. This latter is a low solubility, isotonic and does not contain antigenic potential gas [12]. Early report showed that SonoVue could enable the identification of some specific contrast-enhancement patterns in different focal liver lesions [13, 14].

The objective of this study was to describe the enhancement patterns of hepatic haemangiomas assessed as atypical at conventional grey-scale ultrasound with PI and SonoVue and to assess the potential of this method for characterising these lesions.

Materials and methods

Patients and lesions

Twenty patients (11 women, nine men; age range 31–72 years, mean 54 years) with 35 hepatic haemangiomas (size range 1–7 cm, mean 3.1 cm) previously diagnosed at US entered this prospective study.

None of the haemangiomas presented the typical ultrasound findings: hyperechoic lesions with homogeneous echotexture, well-defined margins and posterior wall shadowing [3] and all lesions had been previously detected and characterized by both spiral computed tomography (CT) (15/35) and magnetic resonance imaging (MRI) (20/35) and, in one case (1/35), also by scintigraphy using red cells labelled with Technetium-99 m.

Ethical Committee permission was obtained and all patients gave their full informed consent before the contrast-enhanced US examination. The procedure followed was in accordance with the Declaration of Helsinki as revised in 1989.

Standard of reference

The final diagnosis was made respectively by means of typical helical CT (n=35) and MRI findings (n=20). Both CT and MR studies were performed with the acquisition of non-enhanced and contrast-enhanced images including hepatic arterial-dominant phase (25–35 s from injection of intravenous bolus of contrast material), portal venous-dominant phase (60–80 s) and late phase (2–5 min). Strict imaging criteria were employed including nodular peripheral enhancement followed by centripetal fill in, change to isointensity on MRI and isodensity on CT with the blood vessels on contrast enhanced images, high signal intensity on T2-weighted images, and lack of interval 6–12 months increase in size [15–17].

US technique

Scanning was performed by one experienced radiologist using an HDI 5000 unit (ATL, Bothell, Wash., USA) provided with a C5-2 convex array probe and PI imaging software. A baseline survey examination, including a colour/power Doppler analysis, was performed. Once set, the US scan parameters—such as focal zone and time gain compensation—were not changed throughout a study. The US contrast agent used in the present study was SonoVue (Bracco, Milan, Italy) injected intravenously as a bolus in 2.4 ml (equivalent to a 0.003 ml/kg for 70 kg body weight), followed by 5 ml of normal saline flush, by using a 20- or 22-gauge peripheral intravenous cannula [18]. A low frame-rate (5 Hz) and a very low mechanical index (MI=0.05–0.08) were used. Each exam lasted about 5 min after bolus injection.

In patients with multiple lesions a 2.4-ml further bolus of SonoVue was administered for each lesion, with an interval time at least of 15 min to allow for contrast clearance of the previous contrast injection. Furthermore, before a new injection was performed, the entire liver was scanned at least 1 minute with high MI (1.3) in order to destroy microbubbles, so actually absolutely no contrast agent was appreciable either in the liver parenchyma or haemangiomas before starting a new examination [19].

Image analysis

All examinations were videotaped and then reviewed by two radiologists experienced in contrast-enhanced US studies of the liver blinded to the final diagnosis. The two readers evaluated by consensus the echogenicity of each lesion, in comparison with adjacent liver parenchyma. Readers also evaluated the dynamic enhancement pattern of each lesion in comparison with adjacent liver parenchyma at 25–30 s (arterial phase), 55–60 s (portal-venous phase), and 235–240 s (delayed phase) after the beginning of SonoVue injection.

The following parameters were considered:

- Baseline echogenicity of the lesions, divided into typical (hyperechoic lesions with homogeneous echo-

texture and well-defined margins) and atypical (hypo-echoic, isoechoic and mixed lesions);

– Echotexture of the lesions, divided into homogeneous and inhomogeneous;

– Changes in the echogenicity and enhancement patterns after contrast injection, subjectively classified as [10]:

  – peripheral globular: enhancing peripheral nodular areas;

  – rim-like: continuous ring of peripheral enhancement;

  – hyperechoic;

  – isoechoic;

  – hypoechoic.

Homogeneity and progression of enhancement were also evaluated.

Statistical analysis

The Student t-test was used to assess statistically significant differences in contrast-enhancement pattern between haem-angiomas with different size and/or echotexture. A P value less than 0.05 was considered statistically significant.

Results

Results are summarized in Tables 1, 2, and 3.

The liver echogenicity subjectively increased after administration of SonoVue with a peak of enhancement achieved in the portal-venous (60 s) phase after contrast agent injection, and then subjectively decreased starting from 240 s. On average, contrast enhancement of the liver parenchyma was subjectively appreciable for 5 min.

No adverse events or side effect were recorded during or immediately after the injection of SonoVue.

On conventional US, 21/35 haemangiomas were located in otherwise normal liver and had highly inhomogeneous echotexture, mainly hypoechoic (n=11), hyperechoic (n=8) or isoechoic (n=2), respectively. In seven patients, 14/35 haemangiomas were located in a "bright liver" and appeared mainly hypoechoic (n=11) or slightly hyperechoic (n=3). In these latter cases, fatty change of the liver was confirmed by means of baseline CT attenuation values (at least 10 HU lower than the spleen) [20]. Colour Doppler imaging showed peripheral spots of colour signals in 5/35

Table 1 Analysis of contrast enhancement pattern of 35 hepatic haemangiomas after SonoVue administration

No. of lesions	Arterial phase	Portal-venous phase	Delayed phase
25	Nodular peripheral	Centripetal fill-in	Complete fill-in
6	Nodular peripheral	Centripetal fill-in	Incomplete fill-in
3	Hyperechoic	Iso-hyperechoic	Iso-hyperechoic
1	Peripheral rim-like	Centripetal fill-in	Complete fill-in

Table 2 Analysis of contrast enhancement pattern of 35 hepatic haemangiomas after SonoVue administration and correlation with lesion size

Size range (cm)	No. of lesions	Arterial phase	Portal-venous phase	Delayed phase
<2.1	10	Nodular peripheral	Centripetal fill-in	Complete fill-in
	3	Hyperechoic	Iso-hyperechoic	Iso-hyperechoic
	1	Peripheral rim-like	Centripetal fill-in	Complete fill-in
2.1–3	6	Nodular peripheral	Centripetal fill-in	Complete fill-in
3.1–4	9	Nodular peripheral	Centripetal fill-in	Complete fill-in
	2	Nodular peripheral	Centripetal fill-in	Incomplete fill-in
>4	4	Nodular peripheral	Centripetal fill-in	Incomplete fill-in

Table 3 Analysis of contrast enhancement pattern of 35 hepatic haemangiomas after SonoVue administration and correlation with baseline echogenicity

Baseline echogenicity	No. of lesions	Arterial phase	Portal-venous phase	Delayed phase
Isoechoic	1	Nodular peripheral	Centripetal fill-in	Complete fill-in
	1	Nodular peripheral	Centripetal fill-in	Incomplete fill-in
Hypoechoic	15	Nodular peripheral	Centripetal fill-in	Complete fill-in
	3	Nodular peripheral	Centripetal fill-in	Incomplete fill-in
	3	Hyperechoic	Iso-hyperechoic	Iso-hyperechoic
	1	Peripheral rim-like	Centripetal fill-in	Complete fill-in
Hyperechoic	9	Nodular peripheral	Centripetal fill-in	Complete fill-in
	2	Nodular peripheral	Centripetal fill-in	Incomplete fill-in

(14%) haemangiomas with both arterial and venous flows at pulsed Doppler analysis.
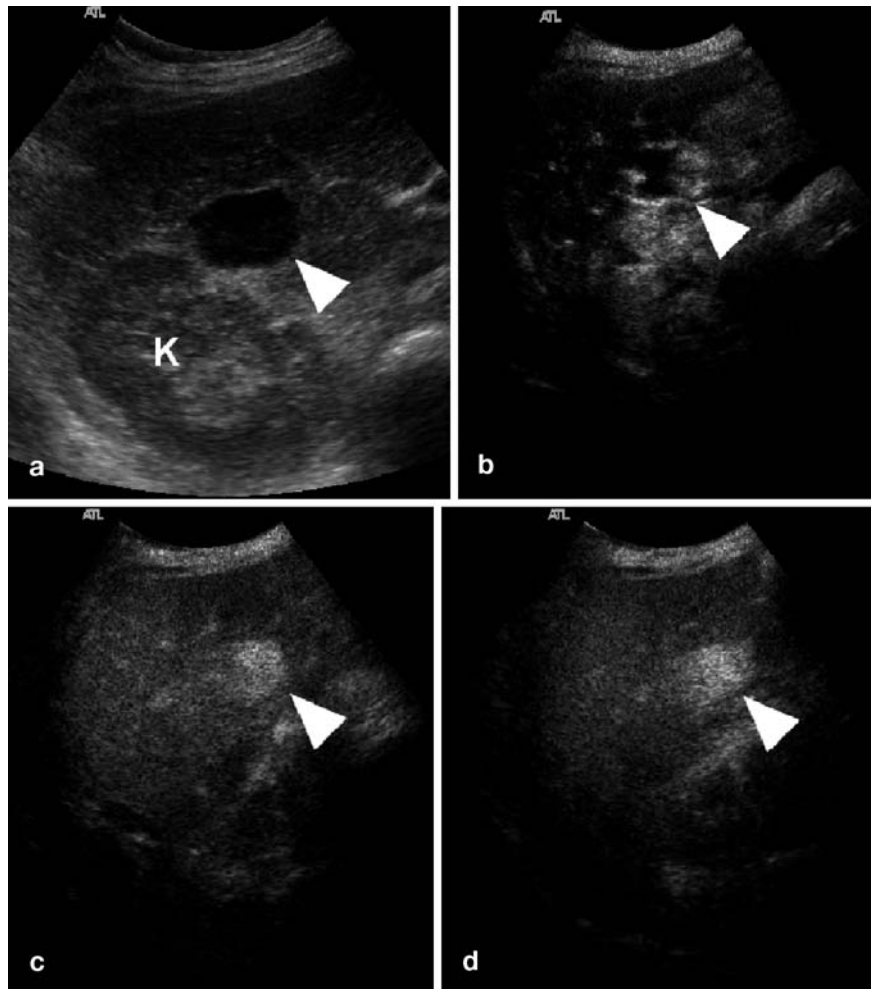
Overall, after administration of SonoVue, 31/35 (88%) haemangiomas showed peripheral hyperechoic nodules in the arterial phase, followed by progressive centripetal fill-in, which was complete in 25/35 cases (Fig. 1) and incomplete in the remaining six cases. Three out of 35 (9%) haemangiomas showed rapid and complete fill-in in the arterial phase, which persisted in the portal and delayed phases (Fig. 2). Finally, 1/35 haemangiomas (3%) showed a rim of arterial contrast enhancement with progressive and complete centripetal fill-in in portal-venous and delayed phases (Fig. 3) (Table 1).

The size of the haemangiomas was less than 2.1 cm (mean size: 1.5 cm) in 14/35 (40%) cases and these lesions showed, respectively, nodular peripheral (n=10), hyperechoic (n=3) and rim-like (n=1) contrast enhancement pattern in the arterial phase (Table 2). Six out of 35 (17.2%) haemangiomas ranged from 2.1 to 3 cm in size (mean size, 2.7 cm) and showed a nodular peripheral contrast-enhancement pattern. Eleven of 35 (31.4%) haemangiomas ranged
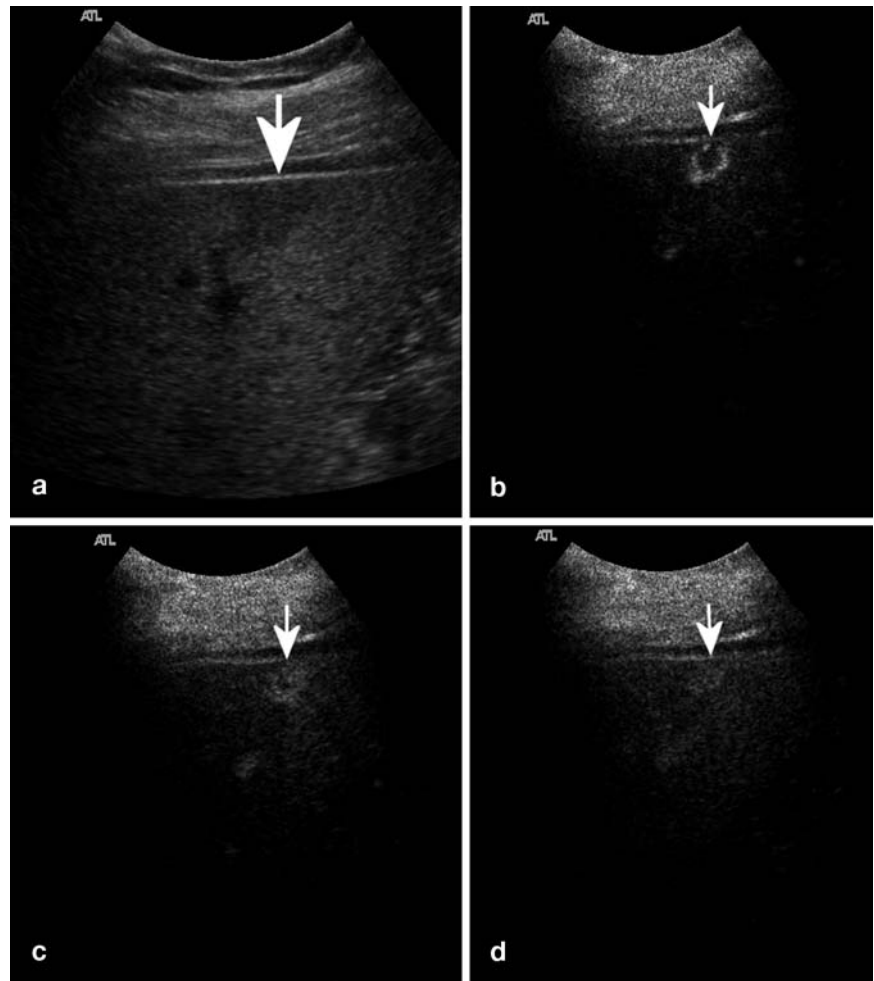
from 3.1 to 4 cm (mean size, 3.7 cm) and showed peripheral hyperechoic nodules in the arterial phase, followed by progressive centripetal fill-in. Finally, 4/35 (11.4%) haemangiomas were larger than 4 cm (mean size: 5.2 cm) and showed peripheral hyperechoic nodules in the arterial phase, followed by progressive but incomplete centripetal fill-in.

Eighteen out of 22 (82%) hypoechoic haemangiomas showed peripheral hyperechoic nodules in the arterial phase, followed by progressive centripetal fill-in which was complete in 15/22 haemangiomas and incomplete in the remaining three cases. Three of 22 (14%) hypoechoic haemangiomas showed a rapid and complete fill-in in the arterial phase, which persisted in the portal and delayed phases. One of 22 (4%) haemangiomas showed a rim of arterial contrast enhancement with progressive and complete centripetal fill-in in portal-venous and delayed phases. Nine out of 11 (82%) hyperechoic haemangiomas showed peripheral hyperechoic nodules in the arterial phase, followed by progressive and complete centripetal fill-in, whereas it was incomplete in the remaining two cases. Both

Fig. 1 a Oblique ascending right subcostal baseline image in a 44-year-old woman shows a strongly hypoechoic lesion (*arrowhead*) in the V–VI hepatic segment (*K* kidney). b On the oblique ascending right subcostal image obtained in the arterial phase (25 s after SonoVue injection) the lesion shows peripheral globular enhancement (*arrowhead*); c, d in the portal-venous and delayed phases (60 and 240 s after SonoVue injection, respectively) a progressive and complete centripetal fill-in is showed (*arrowhead*)

Fig. 2 a Oblique right intercostal baseline image in a 51-year-old man shows an hypoechoic ill-defined 1-cm mass (*arrow*) in the subcapsular region of the VI hepatic segment. **b** Oblique right intercostal image obtained in the arterial phase (25 s after SonoVue injection) shows a peripheral rim of enhancement (*arrow*). **c, d** Oblique ascending right subcostal images obtained in the portal-venous phase and in the delayed phase (60 and 240 s after SonoVue injection, respectively) depict a progressive and complete centripetal fill-in (*arrow*)

isoechoic haemangiomas showed peripheral hyperechoic nodules in the arterial phase, followed by progressive and centripetal fill-in, which was complete in one case and incomplete in the other one (Table 3).

No statistically significant differences were found in contrast-enhancement pattern between haemangiomas with different size and/or echotexture.

Discussion

Worldwide, US is the most commonly used imaging modality to screen for focal liver lesion. Unfortunately, US findings are often non-specific, thus making challenging the task of characterization [21]. In particular hepatic haemangiomas—in a percentage difficult to quantify, but undoubtedly significant, being estimated at 20–40% of cases —may not show on grey-scale US the typical hyperechoic oval pattern with homogeneous or slightly inhomogeneous echotexture, well-defined margins and posterior wall shadowing [2, 4, 22]. This complicates the differential diagno-

sis, especially in patients with neoplasms or chronic hepatic diseases, such as liver cirrhosis, in whom the ultrasound finding of a focal hepatic lesion, even with haemangioma-like characteristics, calls for the use of additional examinations such as CT or MRI, with resulting higher costs and longer times for correct patient management [23, 24].

On grey-scale US scan atypical haemangiomas often display an inhomogeneous internal echotexture, partly hypoechoic and with a hyperechoic peripheral rim of varying thickness [22]. This morphostructural appearance, recurring four times in our series, though suggestive of haemangioma according to several authors, gives rise to problems of differential diagnosis with both benign (hepatocellular adenomas) and malignant lesions (metastases), particularly those from islet cell neoplasms of the pancreas [2, 4]. In large haemangiomas is often appreciable a markedly inhomogeneous echotexture, which is related to thrombo-haemorrhagic episodes, cystic degeneration, fibrosis or hyalinisation and calcium deposit [4]. In particular, the term "giant haemangioma" refers to lesions larger than 4 cm in diameter, though some authors use this

Fig. 3 a Oblique ascending subcostal baseline image of the right liver lobe in a 55-year-old man shows a subtle hypoechoic oval lesion (*arrow*) in the VI hepatic segment. **b** The arterial-phase image (25 s after SonoVue injection) shows early, homogeneous and complete fill-in (*arrow*). **c** The lesion appears as a slightly hyperecoic mass and **d** substantially isoechoic with respect to surrounding liver parenchyma in the portal-venous and delayed phases (60 and 240 s after SonoVue injection, respectively) (*arrow*)
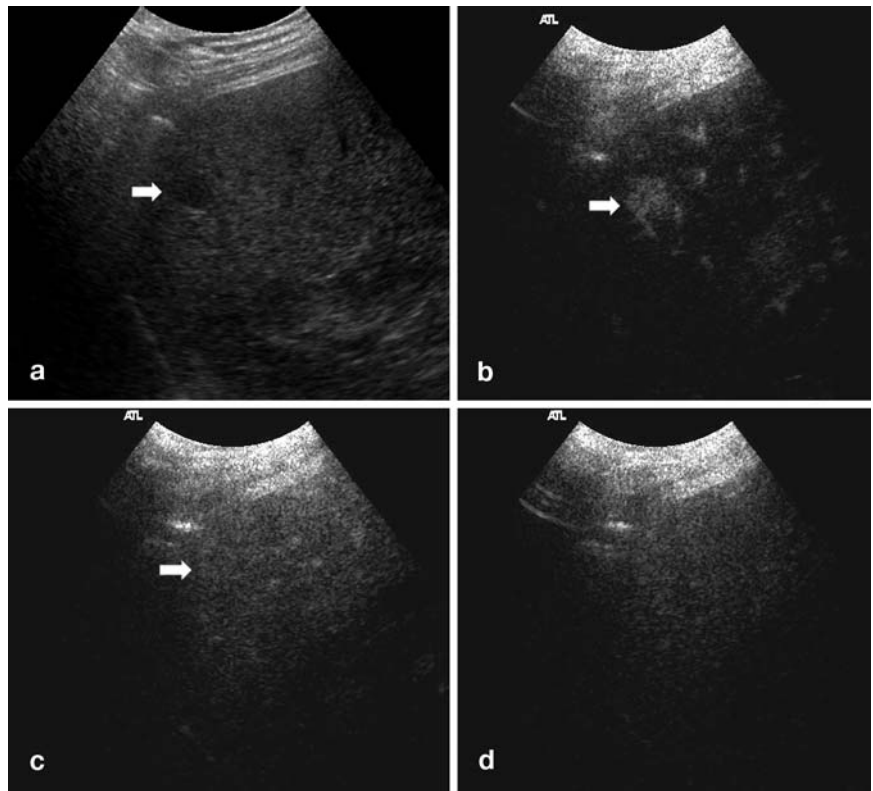
term only for haemangiomas larger than 6 cm or even 12 cm in diameter [4]. In our study, if we consider 4 cm as the cut-off diameter, 4/35 (11%) haemangiomas could be defined as giant. The differential diagnosis of haemangiomas with an inhomogeneous echotexture is extensive, and includes all tumoral lesions showing varying degrees of inhomogeneity, but above all a central scar. Benign neoplasms include focal nodular hyperplasias and hepatocellular adenomas with haemorrhagic intralesional component; malignant neoplasms include hepatocellular and fibrolamellar carcinomas and cholangiocarcinomas [4].

Integration with colour Doppler is of limited value in evaluating haemangiomas, except for the demonstration of absent or poor intralesional vascularization. In fact, due to both the size of the vascular structures examined and the extremely low flow velocities (0.03–0.08 cm/s) colour Doppler is quite insensitive in the detection of the venous flows that characterise the anatomo-pathological structure of haemangiomas [6, 25, 26]. Moreover, the presence of motion artefacts, both macroscopic—of cardiac origin in lesions located in the left segments in cranial subcapsular sites—and microscopic, but not negligible for Doppler effect purposes, along with the difficulty of studying lesions deep located in the hepatic parenchyma or small-sized lesions make the Doppler analysis often unsatisfactory and thus inconclusive for the differential diagnosis [6]. In our series, conventional colour Doppler imaging showed peripheral spots of colour signals in 5/35 (14%) haemangiomas with both arterial and venous flows at pulsed Doppler analysis.

The use of contrast media does not appear to have significantly improved the performance of colour Doppler in characterizing hepatic haemangiomas [7, 27]. First-generation microbubble-based contrast agents used in combination with grey-scale US techniques, which are very sensitive to non-linear behaviour of microbubbles, have lead to a better depiction of both micro and macro-vasculature of focal hepatic masses, thus improving US reliability in the assessment of liver tumours, including liver haemangiomas [9, 10, 19, 28–34]. In a study PI US with SH U 508A allowed the characterization of haemangiomas which did not present the typical ultrasound appearance by demonstrating contrast-enhancement patterns already observed on CT or MRI [11, 35]. Nevertheless, the relatively short half-life of first-generation air-based contrast agents, such as Levovist, does not allow adequate time for liver imaging; in adjunction, the wall rigidity of air-based microbubbles requires intermittent ultrasound at high US output imaging (MI>0.5) with limited scanning planes [36]. This makes the examination technically difficult and unsuitable for an exhaustive study of the entire liver parenchyma in the various contrast phases [37].

More recently, a second-generation microbubble-based contrast agent (SonoVue) became commercially available. SonoVue is a blood pool ultrasonographic contrast agent

based on a stabilised microbubble preparation containing sulphur hexafluoride with a phospholipidic shell. This latter is a low solubility, isotonic and does not contain antigenic potential gas, which shows a strong harmonic response even at low US output (0.1<MI<0.5) [18, 36, 38, 39]. These features enable the radiologist to perform continuous imaging at low acoustic power instead of intermittent imaging at high acoustic power and to scan the entire liver in all the vascular phases, providing an easier and more accurate depiction of tumour vascularity [40–44]. Despite the recommended MI of 0.3–0.5 [41], we have chosen a lower output power in our study in order to minimize microbubble disruption, as previously reported in a study of the kidney [45]. Our results demonstrate the feasibility of SonoVue-enhanced US of the liver even at very low MI (0.05–0.08).

On average, contrast enhancement of the liver parenchyma after SonoVue injection was subjectively appreciable for 5 min, lasting more than reported for the first-generation contrast agent Levovist [9]. In our series, comprising exclusively haemangiomas with atypical features on conventional US, 32/35 (91%) haemangiomas displayed the "typical" arterial-phase enhancement pattern of peripheral hyperechoic nodules (31/35) or a continuous peripheral rim of enhancement (1/35) previously detected at CT and MRI [15–17, 35]. We believe that this latter sign, though ascribed by some authors to haemangiomas only [10, 30], requires further study, particularly in relation to similar findings documented by US and CT regarding metastases and abscesses [17, 31]. Nonetheless a sign of benignity may be provided by the analysis of the subsequent vascular (portal and delayed) phases in which progressive centripetal fill-in was seen in all 32/35 haemangiomas. Such fill-in was complete in 26/32 cases and incomplete in 6/32 cases. Incomplete fill-in, detected in our series mostly in larger haemangiomas (4 cm or more), is at least in part referable to the technique used in the present study, since US scans were performed a maximum of 5 min after bolus injection, given the half-life of SonoVue. Incomplete fill-in was confirmed in two cases also by CT in late acquisitions (15 min), whereas typical complete centripetal fill-in was confirmed in late CT or MR acquisitions in the remaining four cases. However, it must be underlined that centripetal fill-in of haemangiomas may require even more than 15 min on CT and/or MRI [35].

In our experience, in a limited but non-negligible number (3/35, 8.6%) of small haemangiomas (diameter <2 cm) the typical globular peripheral enhancement pattern of the arterial phase could not be documented; instead, there was rapid uptake of contrast with consequent hyperechogenicity, that was appreciable also in subsequent phases. However, such semeiological features, though reported in the literature as indicating possible capillary haemangiomas on CT and MRI, represent an atypical pattern and may cause interpretation problems, thus requiring

further diagnostic studies, including scintigraphy if the lesion is larger than 2 cm in diameter or MRI with superparamagnetic contrast agents or even, with adequate clinical justification, biopsy [11, 46].

When considering the correlation between the lesion size and the contrast-enhancement pattern, in our series haemangiomas sized less than 2.1 cm showed three different patterns of contrast enhancement in the arterial phase (nodular peripheral, rim-like, and hyperechoic), whereas larger lesions showed only nodular peripheral contrast enhancement followed by centripetal fill-in, either complete or partial. Centrifugal enhancement pattern of the haemangioma on dynamic contrast-enhanced CT and MR imaging was also described [47]. This atypical inside-out pattern of hepatic haemangioma was never seen in our series, as well as reversal of echogenicity after contrast administration, but these are quite rare contrast-enhancement patterns of the haemangioma [41, 47].

In our series, nodular peripheral contrast enhancement followed by centripetal fill-in was most frequently observed, but no statistically significant differences were found in contrast-enhancement pattern between haemangiomas with different size and/or echotexture.

The previously described veil enhancement pattern of the haemangiomas was never observed in our series [29, 41]. This could probably be related to the different technique used in the present work (continuous, low-MI imaging), instead of "interval-delay" high-MI imaging described in those latter studies.

In clinical practice the presence of diffuse liver disease, such as steatosis, may largely alter grey-scale US appearance of hepatic tumours [48]. In a study carried out with a first-generation contrast agent, diffuse liver steatosis masked contrast enhancement of FNH, thus hampering a reliable characterization [19]. In our series haemangiomas located in "bright" fatty liver showed typical contrast-enhancement patterns. Furthermore, fatty liver itself showed contrast enhancement after administration of SonoVue. Our findings suggest that second-generation contrast agents allow a reliable characterization of focal liver tumours even in fatty liver, but further studies in larger series are needed to address this issue.

This study has some inherent limitations. Firstly, the final diagnosis was established without pathological evaluation. However, many authors accept that a diagnosis of haemangioma can be confidently made when clinical, biochemical, and typical imaging criteria are met [4, 35]. Another potential limit of this study is that comparison of baseline and CEUS images could be, at least in part, system dependent, hence further studies with different equipment should be considered.

In summary, our study showed that PI after the administration of SonoVue enables the depiction of typical contrast-enhancement patterns in most hepatic haemangiomas undetermined at conventional grey-scale US, thus providing useful clues for the characterization of these benign

hepatic tumors. Second-generation contrast agents, such as SonoVue, was proved to be effective to this purpose and safe to our patients. It is conceivable that CEUS will expand its role in the differential diagnosis of hepatic tumours, especially in patients with unsuspected incidental mass found at US scan.

References

1. Mergo PJ, Ros PR (1998) Benign lesions of the liver. Radiol Clin North Am 36:319–331
2. Moody AR, Wilson SR (1993) Atypical hepatic hemangioma: a suggestive sonographic morphology. Radiology 188:413–417
3. Harvey CJ, Albrecht T (2001) Ultrasound of focal liver lesions. Eur Radiol 11:1578–1593
4. Vilgrain V, Boulous L, Vullierme MP et al (2000) Imaging of atypical hemangiomas of the liver with pathological correlation. Radiographics 20:379–397
5. Hosten N, Puls R, Bechstein WO, Felix R (1999) Focal liver lesions: Doppler ultrasound. Eur Radiol 9:428–435
6. Perkins AB, Imam K, Smith WJ, Cronan JJ (2000) Color and power Doppler sonography of liver hemangiomas: a dream unfulfilled? J Clin Ultrasound. 28:159–165
7. Kim TK, Han JK, Kim AY et al (1999) Hepatic hemangiomas using a sonographic contrast agent (Levovist) and Power Doppler ultrasonography. J Ultrasound Med 18:737–743
8. Burns PN, Wilson SR, Simpson DH (2000) Pulse inversion imaging of liver blood flow: improved method for characterizing focal masses with microbubble contrast. Invest Radiol 35:58–71
9. Bertolotto M, Dalla Palma L, Quaia E et al (2000) Characterization of unifocal liver lesions with pulse inversion harmonic imaging after Levovist injection: preliminary results. Eur Radiol 10:1369–1376
10. Quaia E, Bertolotto M, Dalla Palma L (2002) Characterization of liver hemangiomas with pulse inversion harmonic imaging. Eur Radiol 12:537–544
11. Bartolotta TV, Midiri M, Galia M et al (2003) Atypical liver hemangiomas: contrast-enhancement patterns with SH U 508A and pulse-inversion US. Radiol Med 106:320–328
12. Schneider M, Arditi M, Barrau M et al (1995) BRI: a new ultrasonographic contrast agent based on sulphur hexafluoride-filled microbubbes. Invest Radiol 30:451–457
13. Quaia E, Degobbis F, Tona G et al (2004) Differential patterns of contrast enhancement in different focal liver lesions after injection of the microbubble US contrast agent SonoVue. Radiol Med 107:155–165
14. Nicolau C, Catala V, Vilana R, Gilabert et al (2004) Evaluation of hepatocellular carcinoma using SonoVue, a second generation ultrasound contrast agent: correlation with cellular differentiation. Eur Radiol 14:1092–1099
15. Hanafusa K, Ohashi I, Himeno Y et al (1995) Hepatic hemangioma: findings with two phase CT. Radiology 196:465–469
16. Semelka RC, Brown ED, Ascher SM et al (1994) Hepatic hemangiomas: a multi-institutional study of appearance on T2-weighted and serial gadolinium-enhanced gradient-echo MR images. Radiology 192:401–406
17. Nino-Murcia M, Olcott EW, Jeffrey RB et al (2000) Focal liver lesions: pattern-based classification scheme for enhancement at arterial phase. Radiology 215:746–751
18. Leen E, Angerson WJ, Yarmenitis S et al (2002) Multi-centre clinical study evaluating the efficacy of SonoVue (BR1), a new contrast agent in Doppler investigation of focal hepatic lesions. Eur J Radiol 41:200–206
19. Bartolotta TV, Midiri M, Scialpi M, Sciarrino E, Galia M, Lagalla R (2004) Focal nodular hyperplasia in normal and fatty liver: a qualitative and quantitative evaluation with contrast-enhanced ultrasound. Eur Radiol 14:583–591
20. Foley D, Jochem RJ (1991) Computed tomography. Focal and diffuse liver disease. Radiol Clin North Am 29:1213–1222
21. Ros PR (2000) Benign liver lesions. Eur Radiol 10 (Suppl 2):S175–S184
22. Farrell MA, Charboneau JW, Reading CC (2000) Sonographic–pathologic correlation of the hyperechoic border of an atypical hepatic hemangioma. J Ultrasound Med 20:169–170
23. Brancatelli G, Federle MP, Blachar A et al (2001) Hemangioma in the cirrhotic liver: diagnosis and natural history. Radiology 219:69–74
24. Caturelli E, Pompili M, Bartolucci F et al (2001) Hemangioma-like lesions in chronic liver disease: diagnostic evaluation in patients. Radiology 220:337–342
25. Bollinger A, Putti P, Barras JP et al (1974) Red blood cell velocity in nailfold capillaries of men, measured by a television microscopy technique. Microvasc Res 7:61–72
26. Young LK, Yang WT, Chan KW et al (1998) Hepatic hemangiomas: quantitative color power US angiography—facts and fallacies. Radiology 207: 51–57
27. Strobel D, Krodel U, Martus P et al (2000) Clinical evaluation of contrast-enhanced color Doppler sonography in the differential diagnosis of liver tumors. J Clin Ultrasound 28:1–13
28. Dill-Macky MJ, Burns PN, Khalili K et al (2002) Focal hepatic masses: enhancement patterns with SH U 508 A and pulse-inversion US. Radiology 222:95–102
29. Wilson SR, Burns PN, Muradali D et al (2000) Harmonic hepatic US with microbubble contrast agent: initial experience showing improved characterization of hemangioma, hepatocellular carcinoma, and metastasis. Radiology 215:153–161
30. Kim TK, Choi BI, Han JK et al (2000) Hepatic tumors: contrast agent-enhancement patterns with pulse-inversion harmonic US. Radiology 216:411–417
31. Tanaka S, Ioka T, Oshikawa O et al (2001) Dynamic sonography of hepatic tumors. Am J Roentgenol 177:799–805
32. Von Herbay A, Vogt C, Haussinger D (2002) Pulse Inversion sonography in the early phase of the sonographic contrast agent Levovist: differentiation between benign and malignant focal liver lesions. J Ultrasound Med 21:1191–2000
33. Sidhu PS, Shaw AS, Ellis SM et al (2004) Microbubble ultrasound contrast in the assessment of hepatic artery patency following liver transplantation: role in reducing frequency of hepatic artery arteriography. Eur Radiol 14:21–30
34. Klein D, Jenett M, Gassel HJ et al (2004) Quantitative dynamic contrast-enhanced sonography of hepatic tumors. Eur Radiol 14:1082–1091
35. Horton KM, Bluemke DA, Hruban RH et al (1999) CT and MR imaging of benign hepatic and biliary tumors. Radiographics 19:431–451

36. Correas JM, Bridal L, Lesavre A et al (2001) Ultrasound contrast agent: properties, principles of action, tolerance, and artifacts Eur Radiol 11:1316–1328

37. Dalla Palma L, Bertolotto M (1999) Introduction to ultrasound contrast agents: physics overview. Eur Radiol 9 (Suppl 3):S338–S342

38. Madjar H, Prömpeler HJ, Del Favero C et al (2000) A new Doppler signal enhancing agent for flow assessment in breast lesions. Eur J Ultrasound 12:123–130

39. M Schneider (1999) SonoVue, a new ultrasound contrast agent. Eur Radiol 9 (Suppl 3):S347–S348

40. Lencioni R, Cioni D, Bartolozzi C (2002) Tissue harmonic and contrast agent and contrast-specific imaging: back to gray scale in ultrasound. Eur Radiol 12:151–165

41. Leen E (2001) The role of contrast-enhanced ultrasound in the characterisation of focal liver lesions. Eur Radiol 11:27–34

42. Nicolau C, Catala V, Bru C (2003) Characterization of focal liver lesions with contrast-enhanced ultrasound. Eur Radiol 13 (Suppl 3):N70–N78

43. Albrecht T, Oldenburg A, Hohmann J et al (2003) Imaging of liver metastases with contrast-specific low-MI real-time ultrasound and SonoVue. Eur Radiol 13 (Suppl 3):N79–N86

44. Quaia E, Bertolotto M, Forgacs B et al (2003) Detection of liver metastases by pulse inversion harmonic imaging during Levovist late phase: comparison with conventional ultrasound and helical CT in 160 patients. Eur Radiol. 13:475–483

45. Tranquart F, Correas JM, Martegani A et al (2004) Feasibility of real time contrast enhanced ultrasound in renal disease. J Radiol 85:31–36

46. Bartolotta TV, Midiri M, Galia M et al (2001) Benign hepatic tumors: MRI features before and after superparamagnetic iron oxide administration. Radiol Med 101:219–229

47. Kim S, Chung JJ, Kim MJ et al (2000) Atypical inside-out pattern of hepatic hemangiomas. Am J Roentgenol 174:1571–1574

48. Konno K, Ishida H, Sato M et al (2001) Liver tumors in fatty liver: difficulty in ultrasonographic interpretation. Abdom Imaging 26:487–491