

## Contrast Enhanced Ultrasound for the diagnosis of liver hemangiomas in clinical practice

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### Abstract

**Background and aim:** Contrast enhanced ultrasound (CEUS) has a well established place in the characterization of focal liver lesions (FLL). The aim of this paper was to evaluate the usefulness of CEUS in the assessment of liver hemangiomas. **Material and method:** We included in a prospective study all the CEUS examinations performed during a 13 months period for the evaluation of de novo FLL, using a Siemens Acuson S2000TM Ultrasound System, following an intravenous bolus of 2.4ml SonoVue®. CEUS was considered conclusive for hemangioma if a typical pattern was present following contrast (centripetal fill in during the arterial phase, hyperenhanced lesion during venous and late phases). **Results:** During September 2009 - October 2010, 413 CEUS examinations were performed in our department for the evaluation of de novo FLL. Out of the 413 cases, based on standard ultrasound, 43 were suspected hemangiomas, 125 were uncharacteristic lesions and 245 were suspected for other types of lesions (metastases, focal nodular hyperplasias, hepatocellular carcinomas etc). Out of the 413 de novo FLL, 64 cases (15.5%) were diagnosed as hemangiomas by CEUS (typical CEUS pattern). MRI diagnosed 7 additional hemangiomas in inconclusive CEUS cases, so 90.1% (64/71) of the hemangiomas were diagnosed by CEUS alone. Out of the 125 uncharacteristic lesions on standard ultrasound, 29 cases were diagnosed after CEUS as hemangiomas. Thus, CEUS diagnosed additional 40.8% (29/71) hemangiomas as compared to standard ultrasound, without the need of more expensive imaging methods. **Conclusion:** CEUS is a reliable method for the diagnosis of hemangiomas, also allowing a precise characterization of FLL. This method diagnosed additional 40% hemangiomas in comparison with standard ultrasound (for atypical ultrasound hemangiomas) and finally, CEUS diagnosed correctly 90% of this type of lesions, all with typical enhancement pattern according to the EFSUMB guidelines.

**Keywords:** Contrast Enhanced Ultrasound, focal liver lesions, hemangiomas

### Rezumat

**Introducere:** Ecografia cu substanță de contrast (CEUS) are deja un loc bine stabilit în evaluarea leziunilor focale hepatice (LFH). Scopul acestei lucrări este evaluarea utilității CEUS pentru investigarea hemangioamelor hepatice. **Material și metodă:** Studiul nostru a fost unul prospectiv incluzând toate examinările prin CEUS efectuate în clinica noastră timp de 13 luni pentru evaluarea LFH de novo. Examinarea a fost făcută cu un ecograf Siemens Acuson S2000TM după injectarea în bolus a 2,4 ml SonoVue®. Evaluarea CEUS a fost considerată diagnostică pentru hemangiomi dacă după administrarea substanței de contrast formațiunea a avut comportament tipic conform ghidului EFSUMB din 2008 (în faza arterială captare centripetă, leziune hipercaptantă în fazele portală și parenchimatooasă). **Rezultate:** În perioada Septembrie 2009 - Octombrie 2010, în departamentul nostru au fost efectuate 413 CEUS pentru evaluarea LFH de novo. În urma ecografiei standard, 43 din cele 413 cazuri au fost suspectate a fi hemangioame, 125 au fost leziuni necaracteristice și în 245 de cazuri a fost suspectat alt diagnostic (metastaze, hiperplazie nodulară focală, hepatocarcinom, etc). Din cele 413 LFH de novo, 64 cazuri (15,5%) au fost diagnosticate prin CEUS ca hemangioame (comportament tipic CEUS). În cazurile în care CEUS nu a fost diagnostică, evaluarea RMN a mai diagnosticat 7 hemangioame, astfel încât 90,1% (64/71) din hemangioame au fost diagnosticate prin CEUS singură. Din cele 125 leziuni necaracteristice la ecografia standard, 29 cazuri au fost diagnosticate prin CEUS ca hemangioame. În consecință, CEUS a diagnosticat în plus 40,8% (29/71) hemangioame în comparație cu ecografia standard, fără a fi nevoie de metode imagistice mai scumpe. **Concluzie:** CEUS este o metodă care permite caracterizarea precisă și diagnosticul hemangioamelor. Prin această metodă am diagnosticat 40% hemangioame în plus față de ecografia standard, prin CEUS singură fiind diagnosticate corect 90% din hemangioame, toate având captare tipică pentru acest tip de leziune, conform cu ghidul EFSUMB.

**Cuvinte cheie:** ecografie cu substanță de contrast, leziuni focale hepatice, hemangioame

Received 09.01.2011 Accepted 27.02.2011

Med Ultrason

2011, Vol. 13, No 2, 95-101

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### Introduction

Hemangiomas are the most common benign liver tumors [1], with a prevalence varying from 1-2% [2] to 20% [3], the female to male ratio ranging from 2:1 to 5:1 [4]. It accounts for 0.4-20% of all hepatic tumors, up to 7% of them being found in autopsy [5]. Hemangiomas are often solitary, but multiple lesions may be present in

both the right and left lobe of the liver, in up to 40 percent of patients [6]. They range in diameter from a few millimeters to over 20 cm. The majority are small (<5 cm), those larger than 5 cm being referred to as giant hemangiomas [7].

The etiology of hepatic hemangiomas is not completely understood. They are considered to be vascular malformations or hamartomas of congenital origin, which enlarge by ectasia, rather than by hyperplasia or hypertrophy. Hormonal influence over tumor growth is suggested by enlargement during pregnancy and estrogen and progesterone therapy and regression after withdrawal of therapy [8,9].

From a pathological point of view, hemangiomas are well circumscribed lesions, often surrounded by a thin capsule [10]. The cut surfaces exhibit a red-brown appearance with a spongy consistency that may show hemorrhage, scarring, or calcification. Microscopically, the tumor is composed of cavernous vascular spaces of varying sizes lined by a single layer of flat endothelium and filled with blood. The vascular compartments are separated by thin fibrous septae and may contain thrombi. Large hemangiomas may develop a collagenous scar or fibrous nodule as thrombosis occurs. Rarely, there may be focal stromal calcification and ossification [11].

The vast majority of hemangiomas are asymptomatic, typically discovered incidentally during an imaging test performed for unrelated conditions or at laparotomy. Lesions >4 cm are more likely to cause symptoms [12]. The most common symptoms are abdominal pain and right upper quadrant, discomfort or fullness. Less common symptoms include nausea, anorexia and early satiety, which may develop with large hemangiomas due to compression of adjacent organs [13]. Acute abdominal pain can result from thrombosis or bleeding within the tumor and associated stretching and inflammation of Glisson's capsule. Discomfort from an acute thrombosis can last up to three weeks and be associated with fever and abnormal liver function tests [14].

The typical ultrasonographic appearance of a hemangioma is that of a hyperechoic, well defined lesion, with or without small central regions with decreased echogenicity [15,16]. Another appearance also highly suggestive of hemangioma is that of a hypoechoic or isoechoic mass with a hyperechoic periphery [17]. In patients with fatty infiltration of the liver, they may appear hypoechoic due to the bright signal from the surrounding parenchyma. Blood flow within the hemangioma can be demonstrated by color Doppler in only 10 to 50 percent of hemangiomas, thus color Doppler does not improve the accuracy of ultrasound [18]. Unfortunately, some malignant liver lesions have similar ultrasonographic pat-

terns and therefore other imaging modalities are required for confirmation, especially in high risk patients, such as de novo focal liver lesions (FLL) in cirrhotics and in individuals with a history of malignancy.

Imaging methods used for confirmation are contrast enhanced computer tomography (CT), contrast enhanced magnetic resonance imaging (MRI), Technetium-99m pertechnetate-labeled red blood cell pool study and, in recent years, contrast enhanced ultrasonography (CEUS).

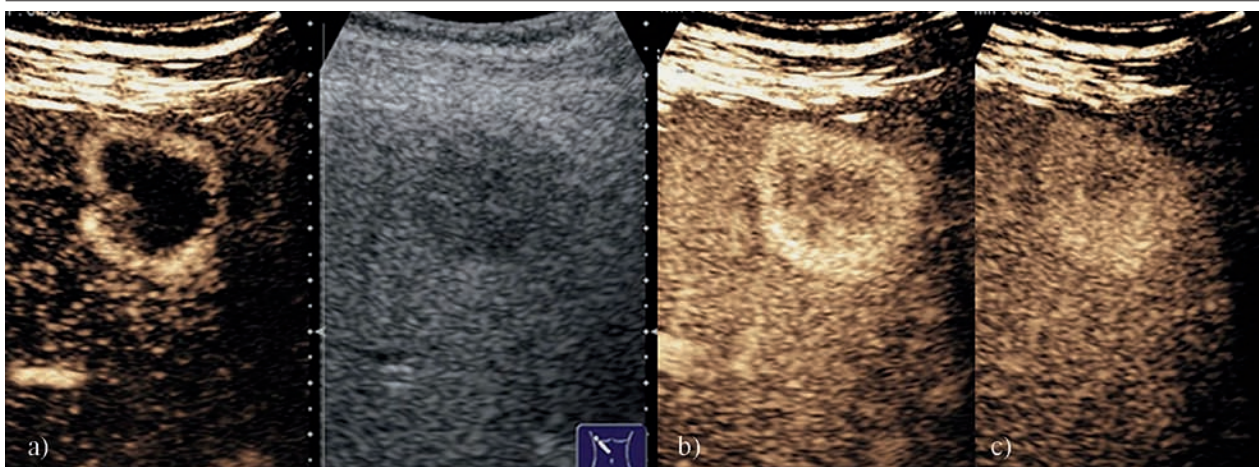
**The aim** of this paper was to evaluate, in our experience, the usefulness of CEUS in daily clinical practice, for the evaluation of liver hemangiomas.

### Material and methods

We performed a prospective study that included all the CEUS examinations performed during a 13 months period for the evaluation of de novo FLL. In all the cases in which standard ultrasound was not sufficient for a correct diagnosis, we performed CEUS, interpreted according to the EFSUMB Guidelines [19]. Following CEUS, we divided the patients in two groups: one in which CEUS evaluation was conclusive and no other diagnostic methods were needed; and another in which CEUS was inconclusive and other diagnostic methods were performed (contrast CT or MRI, or biopsy of the lesions). CEUS was considered conclusive for hemangioma if a typical pattern was present following contrast (centripetal fill-in during the arterial phase, hyperenhanced lesion during venous and late phases) according to the EFSUMB guidelines 2008 (fig 1) [19].

Exclusion criteria for performing CEUS were: subjects with acute cardiac infarction, with class III/IV cardiac insufficiency, with rhythm disorders and pregnant women. The study was approved by the Local Ethics Committee. After informed consent was obtained, CEUS was performed and all patients were monitored for adverse events, until four hours after the procedure. The clinical status, blood pressure and heart rate were followed-up.

Four experienced ultrasonographers, who were aware of the patients' clinical histories, performed US scanning by means of a Siemens Acuson S2000™ Ultrasound System with a 3.5 MHz convex array probe. A baseline survey examination, including a color/power Doppler analysis, was performed (fig 2-4). Once set, the US scan parameters - such as focal zone and time gain compensation - were not changed throughout the study. A low frame rate (5 Hz) and a very low mechanical index (MI) < 0.08, were used for real-time imaging. One focus was positioned below the level of the lesion. Each examination lasted about 5 min after bolus injection.



**Fig 1.** CEUS examination in a patient with liver hemangioma: a – arterial phase, centripetal, nodular filling; b – portal phase, hyper-enhanced lesion; c – late phase, hyperenhanced lesion



**Fig 2.** Typical ultrasonographic appearance of a hemangioma: hyperechoic, well defined lesion



**Fig 3.** Ultrasonographic appearance highly suggestive of hemangioma: hypoechoic mass with a hyperechoic periphery.

The US contrast agent used in the present study was SonoVue® (Bracco, Italy), a perfluoro gas containing agent, provided as a sterile, lyophilized powder contained in a septum-sealed vial. A white, milky suspension of sulphur hexafluoride (SF6) microbubbles was obtained by adding 5 ml of physiological saline (0.9% sodium chloride) to the powder (25 mg), followed by hand agitation. Each patient received an intravenous bolus injection of SonoVue® for each lesion to be characterized (usually 2.4 ml). To characterize the lesion, the hemodynamic behavior of SonoVue® enhancement during the arterial phase (15-30 seconds), portal venous (30-120 seconds) and late vascular phases (120-300 seconds) was evaluated. All sonographic examinations were digitally recorded.

All patients agreed to undergo CEUS examination and the study was approved by the local ethical committee.



**Fig 4.** Atypical hemangioma in a patient with fatty infiltration of the liver: hypoechoic image due to the bright signal from the surrounding parenchyma.

Data from the patients were collected in a Microsoft Excell file. Summarized descriptive statistics were provided for continuous variables (mean and range), and percentages were calculated for categorical data.

## Results

During September 2009 - October 2010, 413 patients with de novo FLL were evaluated by CEUS in our department (204 women, 209 men, mean age  $59.1 \pm 11.8$  years).

Out of the 413 cases, based on standard ultrasound, 43 were suspected hemangiomas, 125 were uncharacteristic lesions and 245 were suspected for other types of lesions (metastases, focal nodular hyperplasias, hepatocellular carcinomas etc). Out of the 43 suspected hemangiomas on standard US, 35 had a typical CEUS aspect of hemangioma, 2 were diagnosed after CEUS as focal nodular hyperplasias, one as liver metastasis, one as hepatocellular carcinoma, while 4 had an uncharacteristic CEUS aspect.

Out of the 125 uncharacteristic lesions on standard ultrasound, following CEUS 29 were diagnosed as hemangiomas (typical CEUS enhancement pattern) (fig 5).

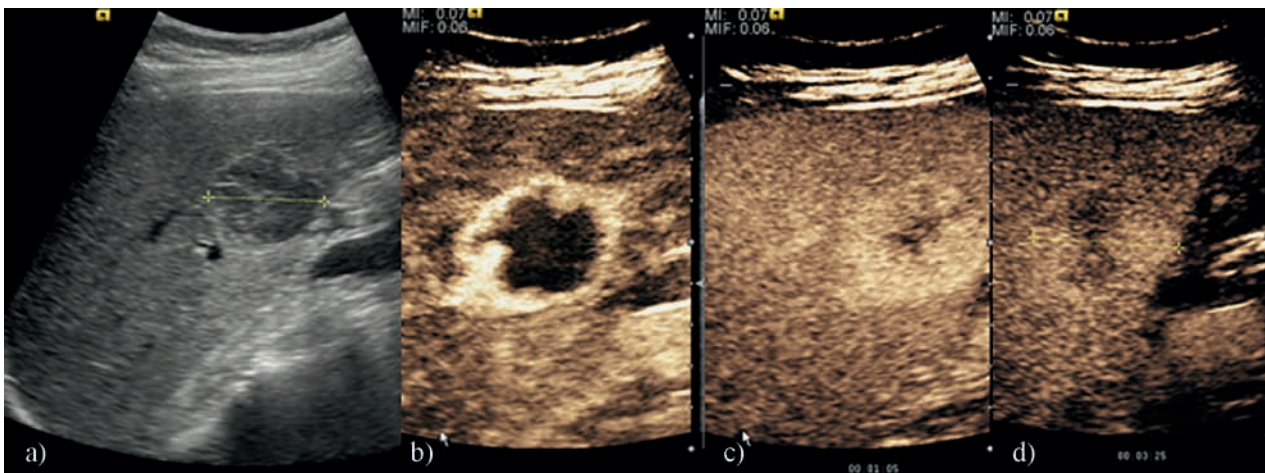
Out of the 413 de novo FLL, 64 cases (15.5%) were diagnosed as hemangiomas by CEUS (typical CEUS pattern). MRI diagnosed 7 additional hemangiomas in inconclusive CEUS cases, so 90.1% (64/71) of the hemangiomas were diagnosed as such by CEUS alone.

Out of the 125 uncharacteristic lesions on standard ultrasound, 29 cases were diagnosed after CEUS as hemangiomas. Thus, CEUS diagnosed additional 40.8% (29/71) hemangiomas as compared to standard ultrasound, without the need of more expensive imaging methods.

## Discussions

As we mentioned above, hemangiomas are frequently discovered during a “routine” ultrasound examination performed for unrelated pathology. The question still under debate is what to do with a patient with “typical” ultrasound appearance of a hepatic hemangioma, since it overlaps with the sonographic aspect of hepatocellular carcinoma and liver metastases. All patients with a history of liver disease or known or suspected of extrahepatic malignancy should undergo a confirmatory examination, while in patients with no evidence of liver disease or extrahepatic malignancy and “typical” appearances of hemangioma on ultrasound, an acceptable alternative is to repeat the ultrasound at three to six months to document stability. Also, patients with a possible hepatic hemangioma who subsequently develop liver disease or extrahepatic malignancy require further evaluation [20].

Until recently, contrast enhanced CT and MRI were considered the best second-line imaging methods to be used for the confirmation of the ultrasound diagnosis of hemangioma. MRI especially has emerged as a highly accurate, non-invasive technique for diagnosing hemangiomas with a sensitivity of approximately 90% and a specificity of 91-99% [21]. The typical MRI appearance is a smooth, well-demarcated homogeneous mass that has low signal intensity on T1-weighted images and is hyperintense on T2-weighted images [21]. The presence of intratumoral fibrosis results in areas of low intensity on T2-weighted images. Administration of gadolinium results in early peripheral discontinuous nodular or globular enhancement on arterial phase imaging with progressive centripetal enhancement or “filling-in” on



**Fig 5.** Atypical hemangioma: a – standard ultrasound, inhomogeneous hypoechoic lesion with hyperechoic septa and margins in a patient with newly discovered colonic cancer; b – arterial phase, centripetal, nodular filling; c – portal phase, hyperenhanced lesion; d – late phase, hyperenhanced lesion

delayed scans similar to that seen on CT scanning [20].

Technetium-99m pertechnetate-labeled red blood cell pool studies (99mTc-RBC pool studies) show initial hypoperfusion during arterial flow, which is followed by a gradual increase of tracer peaking 30 to 50 minutes after the injection. Retention of the isotope within the lesion remains on delayed images. Sensitivity for lesions >2 cm in size varies from 69 – 92%, while specificity approximates 100% [22].

Considering the high performance of imaging methods for the diagnosis of hemangiomas that can diagnose up to 95% of the cases [23], biopsy is not warranted in those typical cases. According to the guidelines released by the American College of Radiology, liver biopsy should be performed only in indeterminate (after contrast CT/MRI) liver lesions >1 cm in diameter, in patients with a history of malignancy or of chronic liver disease [24]. Several studies have been published regarding the safety of liver biopsy, either fine needle aspiration biopsy or core biopsy, for the diagnosis of atypical hemangiomas. Surprisingly, once the typical vascular hemangiomas are excluded, there is little risk of a significant complication from the atypical variety, the reason being that thrombosis or fibrosis in the lesion, which makes the imaging appearance atypical, also reduces the potential for bleeding complications [25]. Ultrasound-guidance, normal bleeding parameters, suitable trajectory planning via a small cuff of normal liver may all contribute to the low complication rate [26].

In the latter years, the value of CEUS for FLL characterization was demonstrated in well known multicentre studies performed in Germany and France, each one including more than 1000 lesions. Also, it was proven that CEUS is a cost-efficient method of evaluation. A study published by Giesl [27] who performed a cost-minimization analysis of CEUS as compared to multi-phase CT as the diagnostic standard for diagnosing incidental FLL, concluded that CEUS was the more cost-effective method in all scenarios in which CEUS examinations were performed at specialized centers, and that with an expected 40,000 new incidental FLL detected each year in Germany, the total savings would reach 4,000,000 Euros/year.

Regarding the diagnostic performance of CEUS for the diagnosis of hepatic hemangioma, published data showed very good results. The German multicentre study [28] included 1,349 patients with FLL discovered in standard US that could not be characterized by standard US alone, and in which CEUS was compared with a diagnostic “gold standard”: biopsy in more than 75% of the lesions, spiral contrast CT or contrast MRI, CEUS correctly diagnosed 82.2% of the hemangiomas. The mul-

ticentre French study (STIC) [29] included 874 patients with 1034 FLL. CEUS was compared to contrast spiral CT, contrast MRI or liver biopsy, considered to be the “gold standard”. For the diagnosis of the most frequent FLL (hemangioma, FNH, metastases and HCC), the sensitivities were 85.4%, 82.5%, 79.3% and 69.8% respectively, and the specificities were 93.7%, 94.3%, 92.5% and 94.7% respectively.

In a multinational study [30] that included 134 patients with one FLL detected in baseline ultrasound (US) and in which second line imaging methods included CEUS, contrast-enhanced CT and/or dynamic contrast-enhanced MRI, the sensitivities and specificities of CEUS for the identification of focal nodular hyperplasia (FNH) and hemangioma were 100% and 87%, resulting in an accuracy of 94.5%.

In our study 90.1% of the hemangiomas were diagnosed by CEUS alone, without the need of an additional imaging method, all of them having typical enhancement pattern according to the EFSUMB guidelines. Out of the 125 uncharacteristic lesions on standard ultrasound, 29 cases were diagnosed after CEUS as hemangiomas, thus CEUS diagnosed additional 40.8% hemangiomas (29/71) in comparison with the gray scale examination.

However, even if in most cases, after contrast administration, hemangiomas have a typical filling and enhancement pattern; in some cases CEUS is inconclusive. In a recently published paper that analyzed unclear FLL after CEUS in the German multicentre study [31], the authors evaluated the causes of CEUS misdiagnosed cases. In this study, 31 benign lesions, from which 9 biopsy proven hemangiomas, were classified as malignant by CEUS and 86 lesions were unclear after CEUS (67 benign lesions iso- or hypoenhancing during the late phases, from which 20 hemangiomas). The authors suggest that the causes of hypo or isoenhancement of the hemangiomas in the late phases of CEUS could be the continuous insonation of the lesion which leads to bubble destruction, especially in the near field, or over a long sonication time. In our study, from the 7 hemangiomas additionally diagnosed by MRI, 3 were declared inconclusive after CEUS due to hypoenhancement in the late phase, even if in the arterial phase the filling pattern was rather typical, 3 were declared inconclusive due to isoenhancement in the late phase and 1 was unenhancing in all the vascular phases.

The aim of our study was not to assess the performance of CEUS for the diagnosis of hemangioma, already demonstrated in several studies mentioned above. Since the diagnostic accuracy of CEUS for the characterization of FLL is comparable to that of contrast CT [32] and contrast MRI [33], the aim of our study was only to evaluate

the usefulness of CEUS in daily clinical practice for the assessment of hemangiomas, CEUS being considered as a gold standard method when a typical enhancement pattern was present.

### Conclusion

CEUS is a reliable method for the diagnosis of hemangiomas, also allowing a precise characterization of FLL. This method diagnosed an additional 40% hemangiomas in comparison with standard ultrasound (for atypical ultrasound hemangiomas) and finally, CEUS diagnosed correctly 90% of this type of lesions, all with typical enhancement pattern according to the EFSUMB guidelines.

**Conflict of interest:** none

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