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Chapter 2

Contrast-Enhanced Ultrasonography (CEUS) of Liver Masses — Principles, Clinical Applications, Drawbacks

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/55500

1. Introduction

Ultrasonography (US) is one of the most widely used imaging procedures. The main advantages of this investigation over others include it being non-invasive and safe, with no radiation exposure. In addition, its images are provided in "real time", delivering dynamic images with both anatomical and functional information. The images acquired by ultrasonography are sectional and easy to understand. The method is accurate, without distortion. The major disadvantage of ultrasonography is that it is operator dependent, requiring a large number of examinations performed personally in order to reach a high level of proficiency [1]. Additional issues include poorer performance if gas, adipose tissue or bony structures come between the transducer and the region of interest. A number of artifacts, such as reverberations and false reflections, may interfere with the acquisition of the ultrasound image, and need to be recognized and avoided.

Ultrasonography is practiced on a daily basis, both by physicians and specialized personal. Now it is widely accepted that a good correlation of the ultrasonographic data with clinical information is necessary in order to achieve an optimal performance [2]. The proposal that access to US should become generalized and be practiced by every physician within their specialty as a way of completing the clinical examination is increasingly voiced [3]. Liver ultrasonography has been recognized for a long time as an application of US efficient in detecting diffuse liver conditions, hepatic tumors, vascular abnormalities, post-traumatic lesions as well as in guiding interventional procedures [4, 5, 6, 7, 8, 9].

Ultrasonography is a multimodal examination, meaning that the final report and basis for the diagnosis, is a complex one, obtained through multiple procedures. Each procedure brings specific data in relation to the underlying principle of operation. The main US component is bidimensional ultrasonography ("grey scale" ultrasound). It consists of sectional images,

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presented on a grey scale, with each shade of grey representing a density (in fact, an acoustic impedance). "Grey scale" ultrasonography is a dynamic examination that allows the overall evaluation of the liver, with measurements of the hepatic lobes, identification of liver segments, as well as characterization of texture and echogenicity (in relation with the degree of fat infiltration and fibrosis). Grey scale US also enables the detection and evaluation of normal anatomical structures (bile ducts, vessels) and of pathological elements (mainly liver masses). Elastography, an additional component, realizes a quantitative and qualitative (using color coding) characterization of the elasticity of the liver parenchyma [10, 11, 12]. The Doppler procedure represents the basis for evaluating the flow within liver vessels. There is also the spectral version of this application which provides quantitative data (direction of flow, flow velocities, debits, etc) and a color coded version that gives information regarding the presence and the direction of blood flow in the region of interest [13, 14]. Ultrasonography using intravenous (i.v.) contrast agents (CEUS) is a procedure that observes the blood flow in a reference region by revealing the harmonic echoes [15]. Recently, a number of other applications have been developed, many of them based on the mathematical processing of the image. These are meant to optimize the information, enabling quantification, for example, and even allow an automatization of the US diagnosis [16]. Generally speaking, ultrasonography is often the first imaging exploration performed after the clinical exam. As a method, it has proven its value in many respects, including in the detection of liver tumors. In its standard form, however, it is not sensitive enough to characterize and establish the nature of these lesions, despite the many technical advances that have been made [17].

2. The principles and physics of contrast enhanced ultrasonography

The use of contrast in ultrasonography represents a huge advance for this investigation. Even though Doppler ultrasound has a certified role and is the recognized technique for detecting vascular abnormalities in large vessels, it is only after the introduction of contrast agents that we can talk about an exact and reproducible evaluation of microcirculation with the help of ultrasound.

Contrast enhanced ultrasonography (CEUS) consists of injecting gas 'microbubbles' into the systemic circulation. The contrast agent (CA) used is made of small bubbles close in size to red blood cell. These microbubbles contain low soluble gases encapsulated into a biocompatible membrane which may have variable composition – lipids, proteins or biopolymers. The membrane can be either rigid or flexible with a thickness between10-200 nm [18]. Basically, like in any other contrast based imaging procedure, the CEUS exam consists of a "bolus" administration of the contrast media through a superficial peripheral vein. Due to their extremely small size, the microbubbles pass through the pulmonary circulation and then disseminate into the systemic circulation through the arterial blood stream. The contrast agent remains in the blood stream for about 4-5 minutes. There is also a parenchymal phase at the level of the liver and spleen because the contrast agent is captured by the reticuloendothelial system and/or it becomes adherent to the hepatic sinusoids [19]. Unlike the contrast agents used for CT or MRI, the gas used for CEUS is eliminated through the air-ways 10-15 minutes

http://dx.doi.org/10.5772/55500

after administration, while the substances that make up the membrane are eliminated through the kidney or metabolized by the liver. The contrast media used in ultrasonography have no toxicity and the technique is less harmful to patients when compared with other investigations.

The contrast enhanced examination is based on the emission of harmonic echoes by the CA when this passes through an ultrasound beam that has a mechanical index of 0.09 – 0.11. The mechanical index (MI) represents a value that is directly correlated with the biological effect of the ultrasounds upon the tissues. This index is variable depending on the ultrasound machine, but it is basically conditioned by the acoustic power of the ultrasounds beam. The acoustic power (AP), measured in Pascals, represents the energy of the sound beam acting on a target, for example a group of red cells or the contrast agent inside the blood stream. Usually, at high values of the AP, up to MegaPa, the micro bubbles are "broken" and an irregular, non-linear signal is generated. At low values of the AP (30-70 kPa) the microbubbles vibrate in a particular, non-linear manner, producing alternating contractions and relaxations, thus generating harmonic echoes.

The ultrasound equipment produces a separation of the harmonic echoes generated by the CA within the blood stream from the echoes generated by the surrounding tissues. This separation may be realized by modulating the phase and the amplitude of the US beam. There are multiple US generating techniques within the transducer that generate harmonic echoes within the CA. Techniques of pulse inversion ("Pulse Inversion", "Power Pulse Inversion", "Cadence Contrast Pulse Sequencing") perform a "subtraction" of the tissue echoes by alternative emission of pulses found in an inversed phase. A "Vascular Recognition Imaging" technique introduces the Doppler principle in the analysis of the returned signals, allowing a color coding of the red cells in relation to their direction of flow.

Practically, CEUS consists of an injection of a contrast agent, prepared at the time of use, into a cubital vein. This is followed by a bolus of 10 cc saline solution. The region of interest, previously identified during the "grey scale" exam, is continuously observed on the monitor. The monitor may be divided into two identical, real-time images, one using fundamental, "grey scale", echoes and the other one using harmonic echoes obtained by exposure to a sound beam with a low mechanical index (0.09 – 0.11). The examination continues for 90 seconds. After this time the exploration may be intermittent. CEUS is focused on a single region of interest, usually a mass. The exploration of another mass requires either a "breaking" of the bubbles inside the mass, performed with special software or using the CFM technique, or a repetition of the CEUS exam after another contrast administration focused on the second lesion. There are no risks for the patient, so the injection of the CA can be repeated as often as needed.

Using CEUS in the exploration of the liver has special features that arise from the double vascularity of this organ – through the portal vein (two thirds) and through the arterial system (one third). The sequence of blood entering the liver is first arterial (up to 30 seconds) and then portal (30 to 90 seconds, with little variation). This vascular discrimination (similar to the one obtained by contrast CT or MRI) allows for gathering information regarding the circulatory bed (types of feeding vessels, tumor circulatory volume) of a tumor. The presence of arterio-venous communications is characteristic for the neoplastic circulation and in CEUS is expressed by the "wash-out" process. This phenomenon begins at the end of the arterial phase

and/or during the venous phase, is persistent and is characteristic for neoplastic processes in 90 % of cases [20]. There are studies that correlate the wash-out speed of the tumor with its aggressiveness, attributing CEUS a prognostic value.

An important component of the CEUS exam is represented by the quantitative analysis of the data. This consists of a representation in time of the acoustic impedance variation in one or more predetermined regions of interest. A graphic is obtained that can be correlated with hemodynamic parameters, like the time of maximum systolic ascent in the region of interest, the volume of the circulatory bed, presence and scale of the arteriovenous shunts, etc. All these elements are indicators for the quality of a specific circulatory bed [21].

The advantages of the CEUS technique are summarized in Table 1 and include the lack of ionizing radiation exposure, the non invasive character of the method, as well as very good spatial and temporal resolution [22]. The method is safe for patients, with very few cases of anaphylaxis having been reported (about 0.001% of the total number of investigations). It is therefore recommended in some centres as the firstline procedure for assessment of liver nodules. Contrast CT not only exposes the patient to ionizing radiation, but iodine based contrast agents can be toxic and produce allergic reactions. CT scan imaging may also be less sensitive, "losing" or failing to capture the early arterial phase in highly vascular tumors.

• very good spatial resolution;
• high temporal resolution – it is a "real time" examination;
• it reveals very slow blood flow or stagnant blood streams;
• non-ionizing examination;
• lack of anaphylaxis;
• the contrast agent is eliminated through the air-ways;
• can be repeated as often as needed

Table 1. Advantages of the CEUS examination

It should also be recognized that CEUS exploration has a number of limitations, as summarized in Table 2. It is dependent on expensive and sophisticated equipment that raises the cost of the investigation. The harmonic image is depending on good quality 2D image. Deeper lesions are harder to visualize and attenuation may represent a limit in detecting tumors located further from the transducer. Last, but not least the investigation is operator dependent and often the information that is obtained must be correlated with the clinical data and biochemical functional information.

• expensive and sophisticated equipment;
• high cost of the exploration compared with the standard investigation;
• operator dependent;
• it depends on a good quality 2D image;
• low quality information in case of attenuation like in liver steatosis;
• it investigates a single region of interest;

Table 2. Limitations of CEUS examination

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3. CEUS and the assessment of benign liver tumors

The imaging/ultrasonographic contribution to the detection of benign liver tumors is not insignificant. Benign lesions are numerous, affecting about 20% of the population [23]. They are frequently detected following ultrasonography, which is widely available and represents a common investigation in any abdominal complaint. CEUS exploration can distinguish between benign and malignant tumors and consequently can halt the diagnostic algorithm when a mass detected by 2D ultrasonography is characterized by CEUS as being benign. In this way the numbers of investigations is optimal and the patient's discomfort is significantly reduced. There a multiple benign liver masses, however, and not all of them have CEUS characteristic features. Their ultrasonographic aspect is often similar and their discrimination may require additional criteria [24]. Among the lesions that present specific circulation patterns which can be defined when analyzed by CEUS are cysts, hemangiomas, adenoma and benign focal hyperplasia (table 3).

Tumor	Arterial phase	Portal phase	Delayed phase	2D feature
Cyst	No uptake	No uptake	No uptake	Transsonic
Hemangioma	"Ring-like" peripheral uptake	Centripetal enhancement resembling "buds"	Complete uptake	Hyperechoic Well-defined Compressibility "Mirror" effect
Focal nodular hyperplasia	Central enhancement with a "spoked wheel" distribution of the CA	Complete enhancement with an isoechoic appearance compared with liver parenchyma	Isoechoic aspect when compared with the liver parenchyma	Echoic scar in the centre of the lesion Arterial signal in the centre of the tumor
Adenoma	Inhomogeneous uptake	Discrete wash-out Iso or hypoechoic aspect compared to liver parenchyma	Discrete wash-out, Iso or hypoechoic aspect compared to liver parenchyma	Hypoechoic nodule Non-cirrhotic liver

(*) The information presented in the table is referring to typical situations. In practice, there are variations of the 2D or CEUS aspects that require further investigations

Table 3. CEUS and 2D ultrasonographic features in cases of benign liver lesions. (*)

Liver hemangioma. It is the most frequently encountered benign tumor of the liver. It is most often found in women and has a prevalence of about 0.4 – 7.4 % in the population [25]. The mass consists of a vascular, capillary or venous, bundle, rich in fibrotic bands and with no capsule. It may be frequently associated with other benign tumors like cysts or adenomas. Hemangiomas are usually asymptomatic (in very rare cases, when extremely large they may cause a distension of the liver capsule and thrombocytopenia) and have a slow, self-limiting

development. In most cases there is just one lesion, but there is also a multicentric type. The grey scale US appearance of hemangiomas is fairly characteristic: a well circumscribed, hyperechoic liver mass, with a slightly hypoechoic centre or periphery (figure 1).

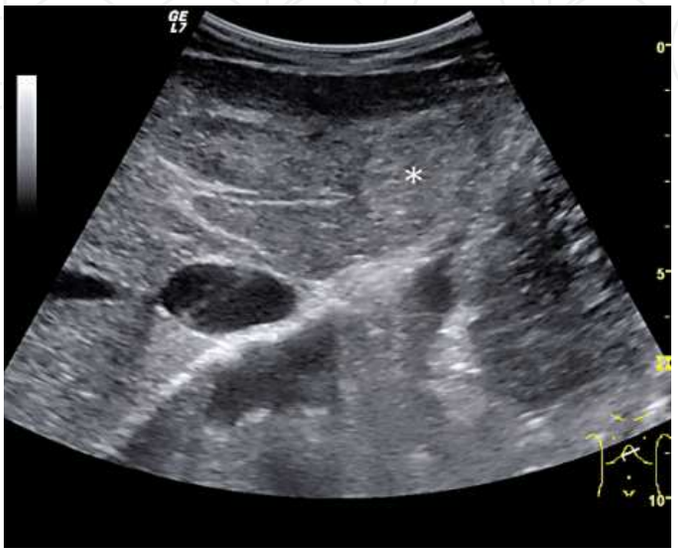
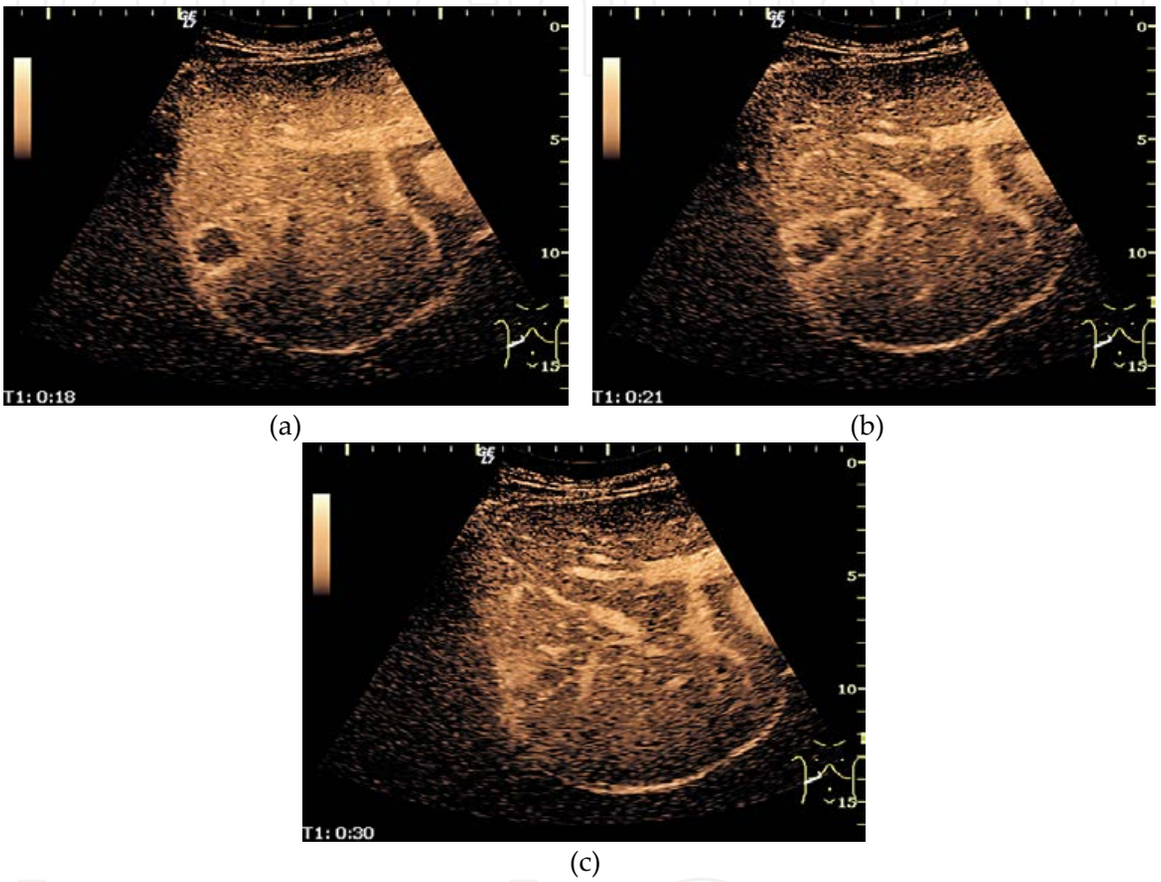


Figure 1. Liver hemangioma. The lesion is found within the left lobe (asterisk) and has a characteristic appearance on "grey scale" ultrasound: well circumscribed, hypoechoic nodule with irregular margins.

Hemangiomas do not cause vascular or biliary ducts invasion. But they may produce an effect of posterior acoustic enhancement. On closer inspection the operator can observe this effect by changing the aspect of the transducer in combination with profound compression. When the hemangioma is located in contact with the diaphragm it can generate a "mirror" effect that leads to a reproduction of the image in the lung parenchyma. Hemangiomas do not usually show signal on the Doppler investigation as flow velocities inside them are very low. Additionally, in many cases intratumoral ischemia or fibrotic scars will develop. Often, the ultrasonographic diagnostic criteria are clear enough and in most situations the conventional ultrasound which first detects the nodule, is sufficient to characterize the lesion. But there are circumstances when 2D ultrasound is not sufficient for tumor characterization and thus CEUS is needed. In the presence of severe steatosis as well as in patients undergoing chemotherapy for various neoplastic conditions, the appearance of a hemangioma may alter and become "atypical". Also in patients with liver cirrhosis, a hemangioma may be misinterpreted for a hepatocellular carcinoma or a large regeneration nodule. Extremely large hemangiomas may have a heterogeneous structure due to possible hemorrhage or ischemia developed inside the lesion, which can alter their appearance. Last but not least, CEUS can be very useful in reassuring both operator and patient that a nodule accidentally found during an ultrasound exam is benign.

http://dx.doi.org/10.5772/55500

The appearance of a hemangioma on CEUS is characterized by a peripheral, ring-like, clear enhancement during the arterial phase (figure 2a). This process is continuous and slow and is followed the appearance of contrast "buds" inwardly oriented (figure 2b). In the end, after several minutes of observation, a complete enhancement of the hemangioma is observed (figure 2c). Therefore a pattern of progressive and centripetal enhancement of a nodule is the characteristic feature for the diagnosis of hemangioma [26].



(a) (b)

(c)

Figure 2. Liver hemangioma. a. CEUS performed during the arterial phase (18 seconds since contrast media injection) shows a well defined "ring" around the nodule. b. The appearance of the contrast "buds" suggests the centripetal character of CA progression. c. At the end of the arterial phase there is complete enhancement of the lesion with contrast agent.

The uptake may take variable amounts of time, from tens of seconds to several minutes (even tens of minutes), depending on the size of the lesion and the type of circulatory bed (figure 3a; figure 3b; figure 3c).

A particular type of hemangioma is the arterialized type. It is characterized by accelerated, complete uptake during the arterial phase. It corresponds to circulatory alterations characterized by an important arterial flow. In this situations a differential diagnosis with hypervascular metastases or HCC is difficult and thus a correlation with other imaging techniques is mandatory [27].

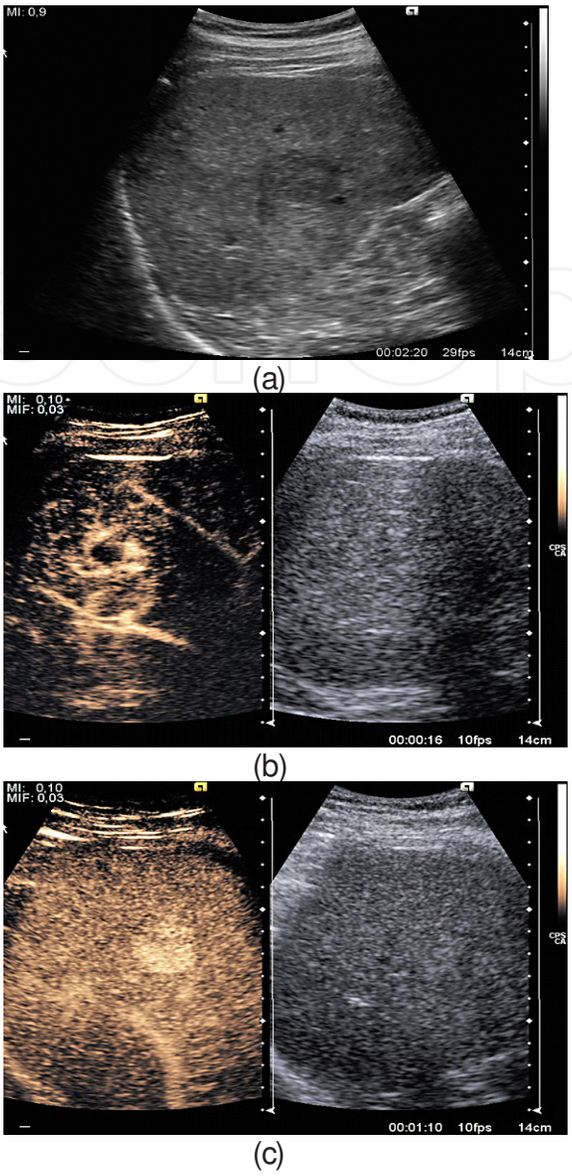


Figure 3. a. "Atypical" liver hemangioma. This is the case of a female patient undergoing chemotherapy for breast cancer. There is increased echogenicity of the liver suggesting therapy induced dystrophy. In the middle of the right lobe there is a hypoechoic, solid lesion that raises the possibility of a liver metastasis. b. CEUS exam shows a "ring" enhancement of the lesion during the arterial phase (16th second). c. CEUS exam reveals a complete enhancement of the nodule at the end of the portal phase (70th second). The enhancement process was centripetal (from periphery towards the centre). The diagnosis is certainly of hemangioma. The case demonstrates the role of the CEUS in patients undergoing oncologic treatments who present liver nodules.

Liver cysts. Liver cysts are serous collection circumscribed by cuboidal epithelium. They are frequently encountered during 2D ultrasound, especially in women. Usually they measure less than 20 mm and can present as single or multiple lesions. An involvement of the entire liver is rare. The grey scale US aspect of cysts is that of a well defined, transsonic lesion with posterior acoustic enhancement. The walls of a cyst are very thin and often difficult to distinguish. Inside the cyst there may be thin septa and sometimes deposits. Cysts show no signal on the CFM (color flow mode) interrogation. A hydatid cyst additionally presents